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RESPIRATORY EPIDEMIOLOGY

Asthma, asthma control and risk of acute myocardial infarction: HUNT study

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Abstract

Asthma, a chronic inflammatory airway disease, shares several common pathophysiological mechanisms with acute myocardial infarction (AMI). Our aim was to assess the prospective associations between asthma, levels of asthma control and risk of AMI. We followed 57,104 adults without previous history of AMI at baseline from Nord-Trøndelag health study (HUNT) in Norway. Self-reported asthma was categorised as active asthma (i.e., using asthma medication) and non-active asthma (i.e., not using asthma medication). Levels of asthma control were defined as controlled, partly controlled, and uncontrolled based on the Global Initiative for Asthma guidelines. AMI was ascertained by linking HUNT data with hospital records. A total of 2868 AMI events (5.0%) occurred during a mean (SD) follow-up of 17.2 (5.4) years. Adults with active asthma had an estimated 29% higher risk of developing AMI [adjusted hazard ratio (HR) 1.29, 95% CI 1.08–1.54] compared with adults without asthma. There was a significant dose–response association between asthma control and AMI risk, with highest risk in adults with uncontrolled asthma (adjusted HR 1.73, 95% CI 1.13–2.66) compared to adults with controlled asthma (p for trend < 0.05). The associations were not explained by smoking status, physical activity and C-reactive protein levels. Our study suggests that active asthma and poor asthma control are associated with moderately increased risk of AMI. Further studies are needed to evaluate causal relationship and the underlying mechanisms and to clarify the role of asthma medications in the risk of AMI.

Keywords Myocardial infarction · Heart attack · Cardiovascular disease · Asthma · Asthma control

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Introduction

Despite a better understanding of risk factors, acute myocardial infarction (AMI) is still the number one global cause of death and is expected to rise by 36% in the next 15 years reaching 23.6 million deaths per year [1]. A significant proportion of the mortality cannot be explained by known risk factors alone [2].

One potential risk factor for AMI is asthma, a chronic inflammatory airway disease, affecting 7.6% of adults and causing half a million hospitalisation a year in the US alone [3]. Chronic systemic inflammation as indicated by higher levels of inflammatory biomarkers have been reported in adults with asthma, with the highest levels in symptomatic and severe asthma patients [4, 5]. At the same time, elevated inflammatory markers have been shown to predict future cardiovascular events including AMI [6]. Furthermore, the use of beta2-agonists, the most common prescribed asthma medication, has been shown to increase heart rate and decrease potassium concentrations potentially increasing the risk of AMI [7]. Lastly, asthma and AMI share similarities in symptoms such as fatigue and dyspnoea [8].

The association between asthma and cardiovascular disease (CVD) was proposed as early as the 1970s [9]. Since then, several research reports have confirmed the association between asthma and the risk of CVD, with particularly higher risk in those with persistent asthma defined as current asthma medications use, presence of asthma exacerbations or recent hospitalisation for asthma [10–15]. However, research of the association between asthma and AMI is limited and, to our knowledge, no previous studies have assessed the association between levels of asthma control and AMI.

Therefore, we used a large well-defined population cohort with a long follow-up to assess the association between asthma, levels of asthma control and AMI.

Methods

Study design and population

Nord-Trøndelag Health Study (HUNT) is Norway's largest population health cohort that started in 1984–1986 (HUNT1) with two follow-up examinations in 1995–1997 (HUNT2) and 2006–2008 (HUNT3). The study population consisted of adults aged 20 years and older living in Nord-Trøndelag county, with socio-demographic characteristics representative of Norway [16].

We included 78,964 adults that participated in either HUNT2 or HUNT3 examinations as questions on asthma were not included in HUNT1. Of the total sample, 28,160 individuals (35.7%) participated only in HUNT2, 37,069 individuals (46.9%) participated in HUNT2 and HUNT3 and 13,735 individuals (17.4%) participated only in HUNT3. Of the 78,964 participants, 23,726 individuals (30.0%) were invited to the follow-up in Lung Study (a sub-study of HUNT) taken from a random HUNT sample and symptom sample that reported attacks of wheezing or breathlessness during the last 12 months or asthma history or having ever used asthma medication at HUNT baseline (Figure S1). Out of the 23,726 invited individuals, 16,115 (67.9%) participated. HUNT Lung Study was used to asses asthma history, asthma medication use and symptoms with the use of questionnaire as well as to perform spirometry testing [16].

Of the 78,964 total participants, 85 (0.1%) were excluded because of missing asthma information at baseline and 67 participants (0.1%) who reported history of asthma at HUNT2, but not at HUNT3. To reduce the possibility of undiagnosed asthma, we excluded participants who did not report to have asthma, but reported to be taking specific asthma medication at baseline (n = 761 [1.0%]). To minimise misdiagnosed COPD as asthma, we excluded adults with asthma who had also self-reported COPD at baseline (n = 1016 [1.3%]). Furthermore, participants who were diagnosed with AMI before start of follow-up or self-reported AMI at baseline (n = 2527 [3.2%]) were excluded. Lastly, we excluded 17,404 participants (22.0%) with at least one missing potential confounder (smoking status n = 1574 [2.0%], physical activity n = 12,895 [16.3%], alcohol use n = 2420 [3.1%], education n = 4090 [5.2%], diabetes n = 119 [0.15%], BMI n = 131 [0.2%]), leaving a total of 57,104 out of 78,964 participants (72.3%) included in this study (Fig. 1).

Asthma

Self-reported asthma was ascertained using the HUNT2 and HUNT3 baseline and Lung Study question "Have you ever had asthma?". Asthma status was then stratified into two self-reported groups. Active asthma was defined as those with an affirmative answer to all the following: "Have you ever had asthma?" and "In the past 12 months, have you used asthma medication?" at the HUNT baseline questionnaire. Those who answered positively to "Have you ever had asthma?" but negatively to "In the past 12 months, have you used asthma medication?" were classified as having non-active asthma.

Asthma control

We matched the HUNT Lung Study questions on asthma symptoms with asthma control assessment from the Global Initiative for Asthma (GINA) Global Strategy for Asthma

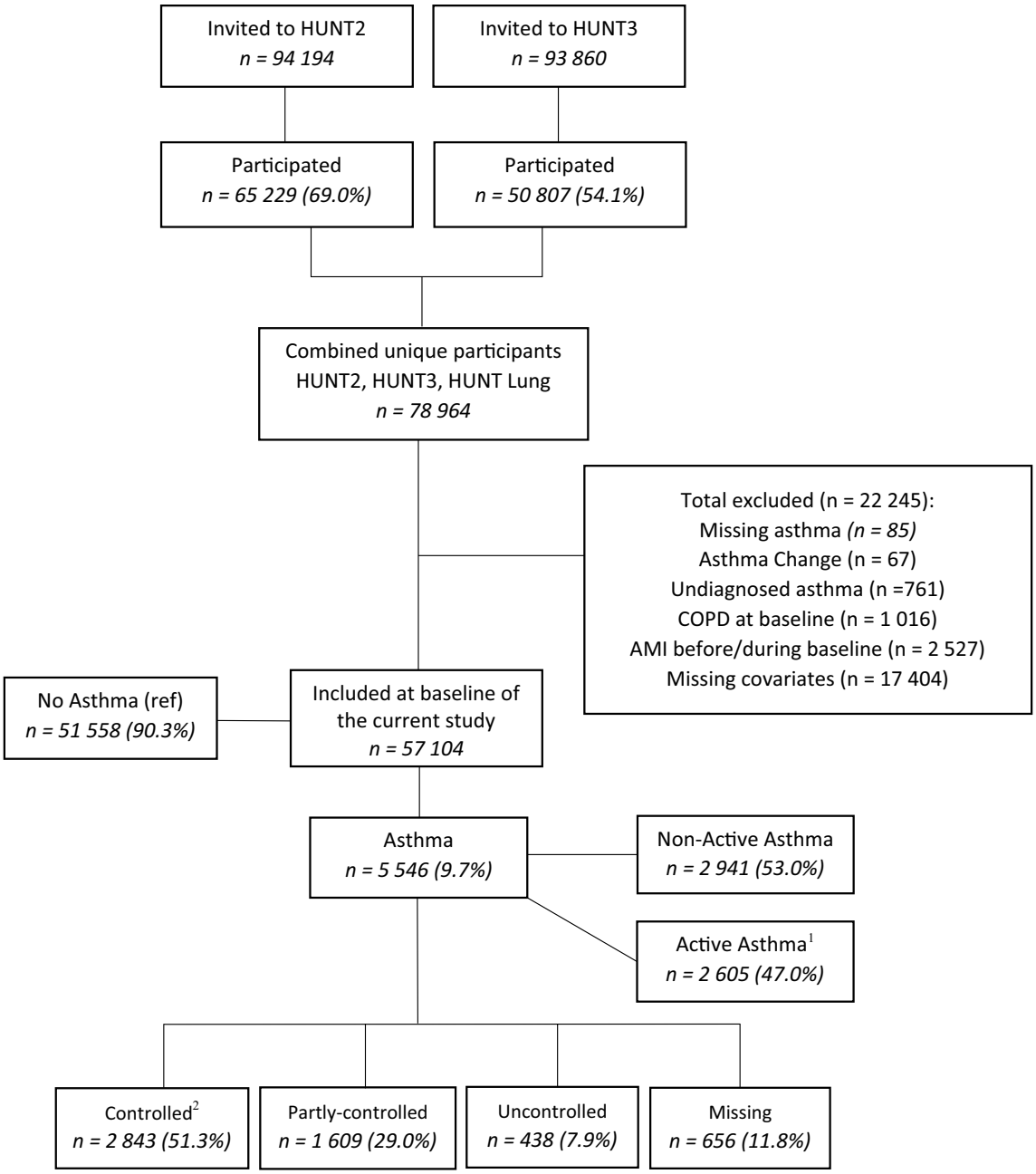

Fig. 1 Flowchart of the participants. [1]Based on current asthma medication use at baseline. [2]Asthma control based on the GINA Global Strategy for Asthma Management and Prevention guidelines

Management and Prevention [17] (Supplementary Table 1). Asthma control was categorised into controlled, partly controlled and uncontrolled asthma based on the following characteristics: daytime symptoms (2 times per week or less or more than 2 times/week), night awakenings (none or any), the need for reliever medication (2 times/week or less or more than 2 times/week) and limitation of activities (none or any). Participants categorised in the controlled asthma group reported no such asthma characteristics, participants in the partly controlled asthma group reported 1–2 characteristics and individuals categorised in the uncontrolled asthma group reported 3 or more characteristics.

Acute myocardial infarction ascertainment

Incidence of AMI was ascertained by linking HUNT data with hospital records from the two hospitals in Nord-Trøndelag County between 1995 and 2017 based on International Statistical Classification of Diseases and Related Health Problems, 9th Revision (ICD-9) code 410 and 10th

Revision (ICD-10) codes I21 and I22. AMI was defined and diagnosed by the caregiving cardiologists and physicians according to the European Society of Cardiology/American College of Cardiology consensus guidelines [18]. Criteria for AMI included: specific clinical symptoms according to case history information, changes in blood levels of cardiac enzymes, and electrocardiogram changes as defined in American and European consensus guidelines. For all diagnosed AMIs the caregiving cardiologists and physicians had to register additional information as type, localization, ECG findings, laboratory findings, as well as coronary angiograms findings in the regional register. If the cardiologists or physicians judged the event to not be a valid AMI, the event was deleted from the registry. A small part of the AMI diagnoses (2%) from medical records have been manually validated [19] and an ongoing validation study (unpublished) found that that 92% of the cases (n = 1194) was type 1 AMI, implying that the underlying pathological process is plaque erosion, fissuring, or rupture with thrombus formation.

Covariates

A self-administrated questionnaire was used in both HUNT2 and HUNT3 to assess participants' smoking status (never, former and current), physical activity (inactive, low, medium and high), alcohol use (abstainers, light, moderate and heavy drinkers) and education (< 10, 10–12, > 12 years). Pack-years of smoking was calculated as: pack-years = (number of cigarettes a day × years of smoking)/20. A detailed description of the covariates can be found elsewhere [20]. During interviews, self-reported medical history of common chronic diseases including diabetes and COPD (HUNT3 only) was assessed, while validated atrial fibrillation, heart failure and stroke cases were identified from hospital records.

Body mass index (BMI) was calculated by dividing body weight (kg) by height (m) squared (kg/m^2) and categorized into 4 categories (underweight < 18.5, normal 18.5–25, overweight 25–30, obese > 30). Waist to hip ratio was calculated by dividing waist circumference by hip circumference. Systolic and diastolic blood pressures were measured using a Dinamap 845XT (Critikon) machine for a total of three times; the average of the second and the third measurements was used in the analyses. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of blood pressure lowering medication. Total cholesterol, high density lipoprotein (HDL) and triglycerides were measured in non-fasting fresh serum samples using Hitachi 911 Autoanalyzer (Hitachi) in HUNT2 and Architect cSystems ci8200 (Abott Diagnostic) in HUNT3. Both machines measure lipid levels according to the same principles providing very similar values. LDL levels were not measured in our study, thus total cholesterol/HDL ratio was used to asses lipid profile. FEV1/FVC ratio was calculated from forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) measurements during spirometry test using MasterScope Version 4.1 (Jaeger) taken during Lung Study. We used FEV1/FVC z-score of less than − 1.64 to identify airway obstruction according to the Global Lung Function Initiative (GLI)-LLN method [21]. High-sensitivity C-reactive protein (hsCRP) was measured during HUNT3 fasting baseline visit using latex immunoassay methodology (Reagent kit; 6K2640 CRP Vario (Abbot, Clinical Chemistry, USA)) with CV: 1.5% in the low range (5.8 mg/l) and 1.7% in the high range (12.8 mg/l). Information on self-reported current asthma medication use, i.e. short acting beta2-agonists (SABA), long acting beta2-agonists (LABA) and inhaled corticosteroid (ICS), was obtained from the Lung Study Questionnaire. Medication use was classified as no current use or current use of beta2-agonist or ICS based on the regular use in the last 6 months in HUNT2 and use in the last 12 months in HUNT3.

Statistical analyses

Baseline characteristics were presented as means and SDs for continuous variables and as numbers and percentages for the categorical variables. To investigate the prospective association between asthma, asthma control and risk of AMI we used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). HUNT2 baseline was the earliest date of participation and all participants were followed-up for AMI until the examination at which AMI was first diagnosed, death, emigration or at the end of follow-up (December 30, 2016) whichever came first. We fitted cause-specific models, thus participants with competing events (deaths) were censored at the time of the event [22]. Where adults participated at more than one examination, we updated their information by splitting survival data.

We have split a survival data, using a time-varying covariate approach, by creating a second observation on the same participant at the time of change (HUNT3). For example, if a participant had controlled asthma at HUNT2 (1997) and partly-controlled asthma at HUNT3 (2007), then their person-years would contribute to the controlled asthma group until HUNT3 and then afterwards to the partly-controlled asthma group until event date or end of follow-up. We did this for all variables that changed status between HUNT2 and HUNT3 including asthma, asthma control, medication and the potential confounders. We have illustrated this in Figure S2.

Potential confounders were chosen based on previous literature and plausibility assessment of their association with asthma and AMI. A minimally adjusted model included age and sex (Model 1). In a fully adjusted model (Model 2) we controlled for traditional cardiovascular disease risk factors including smoking status, physical activity, alcohol

consumption, education, BMI, total cholesterol/HDL ratio, hypertension and diabetes. Some of the confounding variables might act as effect modifiers; therefore, we have also evaluated effect modification by gender, smoking history (ever vs. never smoker) and physical activity levels (inactive/low vs. moderate/high) by performing stratified analyses and by assessing interaction terms.

Furthermore, we assessed possible mediating factors that could potentially contribute to the association between asthma and AMI. In these mediation analyses, we compared HRs of asthma and risk of AMI from Model 2 with and without inclusion of current use of short acting beta2-agonists (SABA) or long acting beta2-agonist (LABA) and current use of inhaled corticosteroids (ICS).

We assessed "dose–response" associations and calculated a p value for trend between asthma control and AMI by treating asthma control as a continuous variable in the model. In doing so, we assumed a linear relationship between asthma control and AMI based on the previously knowledge. We used chronological age as the time scale in our analyses. We tested for multicollinearity by assessing the correlation coefficient between variables in our models as well as performing variance inflation analysis (VIF). Variables with VIF > 10 were excluded from the model (W/H ratio) or transformed (BMI from continuous to categorical) [23]. The proportionality of hazards were tested using log–log curves and the Schoenfeld test. Variables that showed evidence against proportionality in the formal test ($p < 0.05$) were treated as time varying covariates (smoking status and total cholesterol/HDL ratio).

Sensitivity analysis

In a sensitivity analysis, we adjusted for self-reported comorbidities at baseline including stroke, heart failure, atrial fibrillation, hypo-, and -hyperthyroidism, rheumatoid arthritis, angina pectoris, fibromyalgia, ankylosing spondylitis, epilepsy and osteoporosis. In a separate analysis we adjusted for hsCRP levels that were measured in HUNT3 participants only, as higher levels have been reported in symptomatic asthma patients [24] as well as being associated with AMI. Thirdly, we excluded participants who had been diagnosed with atrial fibrillation, stroke or heart failure at baseline or during follow-up. To minimise misdiagnosed COPD or heart failure as asthma, we therefore excluded adults with asthma who had all of the following: post-bronchodilator FEV1/forced vital capacity (FVC) z score less than − 1.64, a history of smoking tobacco, and a diagnosis of asthma that occurred after the age of 40 years. We also performed multiple imputation by chained equations [25] for missing physical activity (n = 9715) to assess impact of missing data on the results. We excluded those only participating at HUNT2, i.e., those who did not attend HUNT3 and consequently did not have updated data on asthma status. Because smoking is a strong risk factor for both asthma and AMI, we excluded current and former smokers. We have also adjusted for smoking pack-years after imputing missing data to assess potential residual confounding by smoking.

We performed the data analyses using Stata 13.1 for Windows 10 (StataCorp). The study received ethics approval from the Regional Committee for Medical Research Ethics. All study participants gave informed written consent.

Results

Sample description

A total of 57,104 individuals were used for the main analysis, out of which 2868 participants (5.0%) were diagnosed with AMI during a mean follow-up of 17.2 ± 5.4 years contributing a total of 981,602 person-years. The prevalence of asthma in the study was 9.7% (n = 5546), out of which 2605 (47%) had active asthma and 2941 (53%) had non-active asthma. Asthma prevalence was slightly higher at HUNT3 follow-up than at HUNT2 (9.7% vs. 7.8%) (supplementary material). Amongst the 57,104 participants, individuals with active asthma at baseline were older, had higher BMI and hsCRP levels and more likely to be females, have lower education and have diabetes than individuals without asthma (Table 1). In contrast, those with non-active asthma were younger, had lower BMI and blood pressure, were more likely to be males, have higher physical activity and achieved education level than those with active asthma. The prevalence of controlled asthma, partly controlled asthma and uncontrolled asthma amongst participants with asthma were 2843 (51.3%), 1609 (29.0%) and 438 (7.9%), respectively with 656 missing values (11.8%).

Association of asthma with AMI

After adjustment for potential confounders (Model 2), participants with active asthma had an estimated 29% increased risk of AMI compared to those without asthma (HR 1.29, 95% CI 1.08–1.54). In contrast, higher AMI risk was not observed in adults with non-active asthma compared to those without asthma (HR 0.95, 95% CI 0.80–1.13) (Table 2).

Association of asthma control with AMI

After adjustment for potential confounders (Model 2), participants with uncontrolled asthma had a higher AMI risk compared to participants with controlled asthma (HR 1.73, 95% CI 1.13–2.66) (Table 2). The risk of AMI was not significantly higher amongst participants with partly-controlled asthma (HR 1.28, 95% CI 0.96–1.70). There was

Table 1 Baseline characteristics of asthma groups in 57,104 participants

Characteristic	No asthma (n = 51,558)	Active asthma (n = 2605)	Non-active asthma (n = 2941)
Female	27,526 (53%)	1540 (59%)	1531 (52%)
Smoking			
Never	23,248 (45%)	1007 (39%)	1278 (44%)
Former	13,552 (26%)	834 (32%)	768 (25%)
Current	14,758 (29%)	764 (29%)	895 (30%)
Physical activity			
Inactive	9665 (19%)	541 (21%)	535 (18%)
Low	14,760 (28%)	728 (28%)	807 (28%)
Medium	21,112 (41%)	1019 (39%)	1189 (40%)
High	6021 (12%)	317 (12%)	410 (14%)
Alcohol use			
Abstainers	16,859 (33%)	925 (35%)	950 (32%)
Light	26,755 (52%)	1315 (51%)	1530 (52%)
Moderate/Heavy	7944 (15%)	365 (14%)	461 (16%)
Education			
< 10 years	15,093 (29%)	874 (33%)	806 (27%)
10–12 years	24,013 (47%)	1194 (46%)	1416 (48%)
> 12 years	12,452 (24%)	537 (21%)	719 (25%)
BMI			
Under/normal	21,677 (42%)	949 (37%)	1127 (38%)
Over	21,878 (42%)	1046 (40%)	1253 (43%)
Obese	8003 (16%)	610 (23%)	561 (19%)
Asthma medication			
Beta2-agonist use	0 (0%)	1635 (65%)	0 (0%)
ICS use	0 (0%)	970 (40.0%)	0 (0%)
Diabetes mellitus	1112 (2.2%)	81 (3.1%)	75 (2.6%)
Hypertension	19,307 (38%)	1097 (42%)	997 (34%)
Age (years)	46.3 ± 15.8	47.1 ± 16.3	43.7 ± 15.8
SBP (mm/Hg)	134.1 ± 20.4	135.1 ± 20.1	132.4 ± 19.7
DBP (mm/Hg)	78.3 ± 12.1	79.4 ± 11.9	77.2 ± 12.2
Total C:HDL	4.44 ± 1.55	4.46 ± 1.48	4.49 ± 1.60
Triglycerides (mmol/L)	1.67 ± 1.09	1.75 ± 1.09	1.72 ± 1.13
C-reactive protein (μg/mL)[a]	2.58 ± 5.56	3.10 ± 6.16	2.89 ± 5.7

Values are mean ± SD or n (%)

BMI body mass index, *W/H ratio* waist to hip ratio, *Total cholesterol/HDL* total cholesterol to high density lipoprotein ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

[a]hsCRP measured in HUNT3 only (n = 37,888)

a significant trend with increasing AMI risk as the level of asthma control decreased (p for trend 0.007).

Other analyses

Amongst 5546 participants with asthma, 1635 individuals (29.5%) currently used beta2-agonists, 2748 participants (49.5%) did not use beta2-agonist and 1163 (21.0%) had missing data. Similarly, 970 individuals (17.5%) currently used ICS, 3320 participants (59.9%) did not use ICS and 1256 (22.7%) had missing data. In the mediation analysis, adjustment for current beta2-agonists use did not change the absolute risk of AMI in all asthma groups (< 10% change) (Table 3). However, the risk of AMI attenuated in active asthma group (adjusted HR 1.15, 95% CI 0.82–1.60) and uncontrolled asthma group (adjusted HR 1.59, 95% CI 0.97–2.61) after adjustment of current ICS use. Also, we found no strong evidence for statistical interaction (p value > 0.100) between asthma or asthma control and sex, smoking or physical activity levels.

Table 2 Associations between asthma, asthma control and the risk of AMI during 17.2 years of follow-up amongst 57,104 participants

Group	N	No. of cases (%)	Model 1	Model 2
Asthma status				
No asthma	51,558	2591 (5.0%)	Reference	Reference
Non-active asthma	2941	127 (4.3%)	0.99 (0.83–1.18)	0.95 (0.80–1.14)
Active asthma	2605	150 (5.8%)	1.30 (1.09–1.55)	1.29 (1.08–1.54)
Asthma control				
Controlled asthma	2843	113 (4.0%)	Reference	Reference
Partly controlled asthma	1609	98 (6.1%)	1.34 (1.01–1.78)	1.28 (0.96–1.70)
Uncontrolled asthma	438	27 (6.2%)	1.67 (1.10–2.54)	1.73 (1.13–2.66)
p for trend			0.005	0.007

Hazard ratios and 95% confidence intervals were derived from Cox proportional hazards models

Model 1 adjusted for age and sex

Model 2 adjusted for age, sex, BMI, smoking status, alcohol use, physical activity, education level, total cholesterol/HDL ratio, hypertension and diabetes mellitus

Table 3 Mediation analysis for current medicaiton use in the associations between asthma, asthma control and the risk of AMI

	Current beta2-agonist use (n = 55,941)*			Current ICS use (n = 55,848)*		
	Model 2 only adjusted HR[a]	Model 2 + mediator adjusted HR[b]	Absolute change (%)[e]	Model 2 only adjusted HR[c]	Model 2 + mediator adjusted HR[d]	Absolute change (%)[e]
Asthma status						
No asthma	Reference	Reference		Reference	Reference	
Non-active asthma	0.92 (0.75 – 1.12)	0.92 (0.76–1.13)	0	0.66 (0.48–0.92)	0.67 (0.48–0.93)	1
Active asthma	1.30 (1.09 – 1.55)	1.30 (0.98–1.73)	0	1.28 (1.06–1.54)	1.15 (0.82–1.59)	− 13
Asthma control						
Controlled	Reference	Reference		Reference	Reference	
Partly controlled	1.28 (0.95–1.72)	1.25 (0.89–1.74)	− 4	1.33 (0.93–1.90)	1.21 (0.84–1.74)	− 12
Uncontrolled	1.72 (1.12–2.66)	1.64 (0.98–2.74)	− 9	1.90 (1.19–3.04)	1.59 (0.97–2.61)	− 31
p for trend	0.009	0.067		0.007	0.069	

ICS inhaled corticosteroid

*n represents sample size of the analysis after excluding missing data on either current beta2-agonist use or current ICS use amongst adults with asthma. Current use defined as use in the last 6 months at HUNT2 baseline and last 12 months at HUNT3 baseline. Current beta2-agonist users n = 1635 (29.5%) and missing n = 1163 (21.0%) amongst adults with ever asthma at baseline; Current ICS users n = 970 (17.5%) and missing n = 1256 (22.7%) amongst adults with ever asthma at baseline

[a]Adjusted for Model 2; participants with missing current beta2-agonist medication use information excluded

[b]Adjusted for model 2 and current beta2-agonist use

[c]Adjusted for Model 2; participants with missing current ICS medication use information excluded

[d]Adjusted for model 2 and current ICS use

[e]Mediation was assessed as the absolute change between model 2 only adjusted HR and model 2 + mediator adjusted HR

Sensitivity analyses

The associations between asthma, asthma control and AMI remained consistent after adjusting for comorbidities and hsCRP levels (n = 37,888) at baseline and after excluding other prevalent and incident CVD events before censoring (n = 5117) (Table S4). Excluding those with asthma and COPD characteristics (n = 155) slightly increased the risk of AMI in the uncontrolled asthma group (HR 2.04, 95% CI 1.31–3.18) compared to the main analysis (HR 1.73, 95% CI 1.13–2.66). Similarly, the risk was increased after excluding those who participated only at the HUNT2 examination (n = 18,886) in the uncontrolled asthma group (HR 2.18, 95% CI 1.17–4.05) compared to the main analysis (HR 1.73, 95% CI 1.13–2.66). Imputing missing physical activity data (n = 9478), excluding former and current smokers (n = 31,571) or adjusting for smoking pack-years did not change the results (Table S5).

Discussion

In this large prospective study including 57,104 adults free from AMI at baseline, we found that individuals with active asthma, defined as current asthma medication users, were at higher risk of developing AMI compared with individuals without asthma. In addition, adults with uncontrolled asthma symptoms were at higher AMI risk compared with those who had their symptoms under control. The associations were not explained by cardiovascular disease risk factors, somatic comorbidities, hsCRP levels and remained similar in male and female and in physically active individuals or those with no smoking history.

To the best of our knowledge, one previous study has specifically investigated the association between asthma and AMI and it found consistent results with ours. In this population-based case–control study with 543 cases and controls, active asthma, described as asthma-related events and health care contact for asthma within 1 year of AMI date, was associated with 2.3-fold increased risk of AMI (adjusted OR 2.33, 95% CI 1.12–4.82) [13]. However, the study was of retrospective design, had a relatively small sample consisting of 46 cases and 19 controls in active asthma group, and did not adjust for all known cardiovascular disease risk factors such as physical activity level.

In line with our study, two of the previous studies found stronger associations of asthma and cardiovascular disease in adults reporting reoccurring asthma symptoms such as wheezing and shortness of breath [12, 14]. Our study is first to find a relation between asthma symptoms control and AMI risk. Considering that asthma control has been reported to be suboptimal in 56.5% of patients [26], our findings might have important implication for health care. However, results should be interpreted with caution due to smaller sample size and thus less precise estimates in the asthma control analysis.

Previous Copenhagen prospective study found stronger AMI risk in current smokers with asthma (HR 3.2, 95% CI 1.8–5.8) than never smokers with asthma (HR 1.3, 95% CI 0.8–2.0) compared to never smokers without asthma [27]. However, in our study, increased AMI risk remained the same in never smokers, while adjustment for smoking pack-years had no impact on the results. The increased AMI risk among current smokers could be due to the higher prevalence of COPD as a result of misdiagnosed COPD as asthma or asthma-COPD overlap. In contrast to our study, the authors of Copenhagen study did not control for COPD, chose never smokers as a reference group and had few AMI events and a short follow-up of 4.5 years, all of which could explain the difference in findings.

It has been hypothesised that asthma medication use could partly explain the association between asthma and CVD [10, 13, 14]. GINA 2019 guidelines recommend the use of low dose ICS and formoterol (LABA) as-needed instead of SABA as-needed as the first line of approach for asthma management followed by higher dosages and frequency in more severe asthma cases [28]. A meta-analysis of randomized placebo-controlled trials of beta2-agonist (LABA) use alone found 154% increased risk of adverse cardiovascular events, including AMI, within 3–6 months [7]. On the other hand, one previous study did not find higher AMI risk [29] among ICS users, while one study found a protective effect [30]. In our study, we found the highest risk of AMI in the active and uncontrolled asthma groups, characterized by prevalent asthma medication use. However, excess AMI risk in the participants with asthma, was not explained by current beta2-agonist and only partly explained by current ICS use. The higher AMI risk in current medication users may reflect confounding by indication, as medication is prescribed during times of asthma exacerbations, where increased risk of adverse outcomes is already seen. A limitation of our study is that we could not differentiate between asthma symptom severity and medication use. Also, we could not investigate the degree of adherence to the asthma treatment. In previous studies, a higher adherence has been associated with fewer asthma exacerbations [31]. Further studies are needed to evaluate the impact of different types and combinations of asthma medication use on AMI risk while considering asthma severity and adherence to asthma treatment.

Chronic inflammation, a hallmark of asthma, might play a role in the association between asthma and AMI. During asthma attack, airway inflammatory response, driven by T helper type 2 cells (Th2), is often followed by systemic inflammation [32]. Systemic inflammation as measured by inflammatory biomarkers such as hsCRP and IL-6 have been associated with vascular events. Alternatively, the presence of asthma-triggered inflammatory platelet-activating factor (PAF), largely responsible for airway hyperresponsiveness in asthma, could also contribute to increased AMI risk in asthma patients [33]. In our study, adjusting for hsCRP levels did not change the association. However, we could not explore the role of inflammation in the associations fully, because we did not have data on any other biomarkers such as IL-6 that could represent upstream inflammatory pathway [34]. Additionally, we did not have information on anti-inflammatory drug use such as aspirin, statin or leukotriene receptor antagonists to examine if anti-inflammatory treatments in patients with asthma would mitigate the association between asthma and AMI as found in a previous study [35]. Future studies are needed to asses this.

Our large population-based study is one of the first to investigate association between asthma, asthma control and AMI. This study has several strengths including a large cohort of men and women with long follow-up, information

on a wide range of confounders, high participation rate and carefully reviewed hospital and register information. All variables including asthma, asthma control and confounders were measured in both HUNT2 and HUNT3 for most of the participants allowing us to take into account potential changes in participants' lifestyle habits or exposure status over time. Furthermore, Lung Study questionnaire allowed us to incorporate strict exclusion criteria and perform multiple sensitivity analysis increasing the robustness of our findings. Also, multiple questions on asthma symptoms and medication use in Lung Study allowed us to investigate the impact of symptomatic and active asthma versus passive and controlled asthma on the risk of AMI.

We recognise several limitations of this study. Residual confounding might exist due to the observational nature of the data limiting causal inference. However, for residual confounding to be influencing our results considerably a potential confounder would have to be strongly associated with both asthma and AMI and be unrelated to the confounders already included in our models. In some of the cases, asthma and COPD directly overlap [36], or asthma can be misdiagnosed as heart failure or other chronic lung conditions that share similar symptoms. However, we addressed this by excluding participants with self-reported COPD and potentially undiagnosed asthma in main analysis and performing sensitivity analysis excluding adults with COPD characteristics. Also, we had considerable amount of missing data for physical activity; however, there was no difference in asthma prevalence between missing and non-missing groups and imputing the missing data did not change the results. Furthermore, our study population consists of relatively young adults with low AMI incidence and the implications for healthcare may be not applicable to the older, higher risk groups.

We did not have spirometry reversibility data to define asthma severity and relying on the self-reported asthma questionnaires, could have resulted in misclassification of the exposure. However, questions on self-reported asthma have been shown to have good specificity, positive predictive value and give prevalence estimate close to those obtained by clinical judgement in both in younger and older adults [37, 38]. Furthermore, the prevalence of asthma in our study is in line with The World Health Survey data [39] and Norway general practitioner data [40]. Therefore, this gives us little reason for misclassification concerns.

Another drawback of this study is that the way AMI were diagnosed and reported could have changed over time including change in the advent of cTn assays, ICD coding or in the universal MI definition which potentially could have led to underreporting of AMI cases. However, the AMI cases in our study have been thoroughly evaluated by caregiving cardiologists and physicians in the hospitals on multiple criteria following European Society of Cardiology/American College of Cardiology consensus guidelines [18]. This should ensure high specificity, while the potential low sensitivity of AMI should not bias our effect estimates [41].

In our study, a part of participants changed their asthma status from no asthma to asthma between HUNT2 and HUNT3, which represents a longer follow-up time and older age at the HUNT3 examination among those who participated at both examinations. Also, asthma prevalence in our study was higher in HUNT3 only participants, which is in line with the increased asthma prevalence from 7 to 18% between 1985 and 2008 in children in Norway [42]. Also, majority of those who changed from no asthma to asthma in our study reported asthma onset age higher than participation age when they reported no asthma, indicating little concern for recall bias in this group. In addition, asthma management and asthma medication use, and lifestyle habits have changed over long follow-up time due to new public health policies that have been introduced in Norway. However, by performing sensitivity analysis excluding those who participated at HUNT2 only without follow-up data at HUNT3 and using time-varying covariate approach we have partly accounted for these differences between HUNT2 and HUNT3.

In summary, we observed higher AMI risk amongst adults with active asthma, indicated by current asthma medication use, and in adults with asthma that is uncontrolled and symptomatic irrespective of hsCRP levels, smoking history, physical activity levels or gender. Given the high prevalence of asthma and high burden of AMI, clinicians should be aware of this connection. However, the observed association does not prove a causal relationship since the association could still be due to residual confounding. Future studies should assess causal relationship, elucidate the mechanisms of how active and symptomatic asthma increases the risk of AMI and study the role of asthma medication use and inflammation in adults with asthma.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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