

Associations of Asthma and Asthma Control With Atrial Fibrillation Risk

Results From the Nord-Trøndelag Health Study (HUNT)

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 [Supplemental content](#)

IMPORTANCE Asthma, a chronic inflammatory airway disease, and atrial fibrillation (AF) share several common pathophysiological mechanisms. Research on the association between asthma and atrial fibrillation is lacking, and to our knowledge, no previous studies have assessed the dose-response association between levels of asthma control and AF.

OBJECTIVE To assess the association between asthma, levels of asthma control, and AF.

DESIGN, SETTING, AND PARTICIPANTS This prospective population cohort analyzed data on adults from a second and third iteration of the survey-based Nord-Trøndelag Health Study (HUNT) in Norway. All included participants were free from AF at baseline. Atrial fibrillation was ascertained by linking HUNT data with hospital records from the 2 hospitals in Nord-Trøndelag County. Data analysis was completed from May 2017 to November 2017.

EXPOSURES Self-reported asthma was categorized into 3 groups: those who had ever had asthma, those who self-report being diagnosed with asthma, and those who had active asthma. Asthma control was defined according to Global Initiative for Asthma guidelines and was categorized into controlled, partly controlled, and uncontrolled cases.

MAIN OUTCOMES AND MEASURES Atrial fibrillation.

RESULTS A total of 54 567 adults were included (of whom 28 821 [52.8%] were women). Of these, 5961 participants (10.9%) reported ever having asthma, 3934 participants (7.2%) reported being diagnosed with asthma, and 2485 participants (4.6%) reported having active asthma. During a mean (SD) follow-up of 15.4 (5.8) years, 2071 participants (3.8%) developed AF. Participants with physician-diagnosed asthma had an estimated 38% higher risk of developing AF (adjusted hazard ratio, 1.38 [95% CI, 1.18-1.61]) compared with participants without asthma. There was a dose-response association between levels of asthma control and risk of AF with the highest risk for AF in participants with uncontrolled asthma (adjusted hazard ratio, 1.74 [95% CI, 1.26-2.42]; *P* for trend < .001).

CONCLUSIONS AND RELEVANCE Asthma and lack of asthma control were associated with moderately increased risks of AF in a dose-response manner. Further studies are needed to explore the underlying mechanisms and clarify causal pathways between asthma and AF.

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a lifetime risk of 26%.¹ Atrial fibrillation is emerging as a growing epidemic² and is associated with adverse cardiovascular outcomes, such as an estimated 2-fold increased risk of stroke and cardiovascular mortality.³ Therefore, further investigations of novel risk factors of the disease are highly warranted.

One potential novel risk factor for AF is asthma, a chronic inflammatory airway disease that affects as many as 30 million individuals in Europe.⁴ High levels of systemic inflammation biomarkers have been reported in both adults with uncontrolled asthma and patients with AF.⁵⁻⁷ Furthermore, short-acting and long-acting β_2 -agonists are the most common prescribed asthma symptom reliever medication, which has been shown to influence heart rate and increase the risk of arrhythmias.⁸ These observations underpin the need for novel investigations of asthma and AF.

Several research articles have linked asthma with the risk of coronary heart disease, stroke, and heart failure.⁹⁻¹² Furthermore, there is evidence that reduced forced expiratory volume in the first second (FEV₁), an indicator of airway obstruction, is associated with higher risk of AF.^{13,14} However, research of the association between asthma and AF is limited, apart from a single study that found asthma to be associated with 1.2-fold increased risk of AF.¹⁵ To our knowledge, no previous studies have assessed the dose-response association between levels of asthma control and AF. Therefore, in the current study, we used a large, well-described population cohort with a long follow-up period and information on a large number of potential confounders to assess the association between asthma, levels of asthma control, and AF.

Methods

Study Design and Population

The Nord-Trøndelag Health Study (called *Helseundersøkelsene i Nord-Trøndelag* in Norwegian, or HUNT) is Norway's largest population health study, consisting of 3 iterations of surveys: HUNT1 (1984-1986), HUNT2 (1995-1997), HUNT3 (2006-2008), and the ongoing HUNT4 (2017-2019). At each survey, all adults aged 20 years and older in Nord-Trøndelag County were invited. A detailed description of HUNT can be found elsewhere.¹⁶

The study received approval from the Regional Committee for Medical Research Ethics. All study participants gave informed written consent.

We used data from HUNT2 and HUNT3 because information on asthma was not collected in HUNT1. A total of 65 229 individuals (69.0% of those invited) and 50 807 individuals (54.1% of those invited) participated in HUNT2 and HUNT3, respectively. The total sample for this study consisted of 78 964 individuals. Of the total sample, 28 160 individuals (35.7%) participated only in HUNT2, 37 069 individuals (46.9%) participated in both HUNT2 and HUNT3, and 13 735 individuals (17.4%) participated only in HUNT3. Of the 78 964 individuals, 23 726 (30.0%) answered yes to at least 1 question on asthma, asthma symptoms, and asthma medication use. These

Key Points

Question What is the association between asthma, levels of asthma control, and atrial fibrillation?

Findings In this cohort study of 54 567 participants, diagnosed asthma was associated with a 38% increased risk of atrial fibrillation, and there was a dose-response association between levels of asthma control and atrial fibrillation.

Meaning Lack of asthma control was associated with moderately increased risk of atrial fibrillation; given poor asthma control in general population, the observed association has clinical and public health importance.

individuals were invited to the Lung Study (a substudy of HUNT), and 16 115 individuals (67.9%) participated.¹⁷

Of the 78 964 total participants, 85 (0.1%) were excluded because of missing information on asthma at baseline, and 67 participants (0.08%) were excluded because they had reported ever having asthma at HUNT2 but not at HUNT3. In addition, we excluded participants who did not have asthma but reported using asthma-associated medication and/or have asthma symptoms (eg, wheezing and/or dyspnea) at baseline ($n = 6517$ [8.3%]). To minimize self-reported asthma misclassification as chronic obstructive pulmonary disease (COPD), we excluded participants who had all 3 of the following: a post-bronchodilator FEV₁/forced vital capacity (FVC) z score less than -1.64 , a history of smoking, and a diagnosis of asthma that occurred after the age of 40 years ($n = 336$ [0.4%]). Lastly, we excluded individuals who were diagnosed with AF at or before baseline ($n = 347$ [0.4%]) and those with missing covariates ($n = 17 045$ [21.6%]), leaving a total of 54 567 of 78 964 participants (69.1%) for the baseline analyses of this study (Figure).

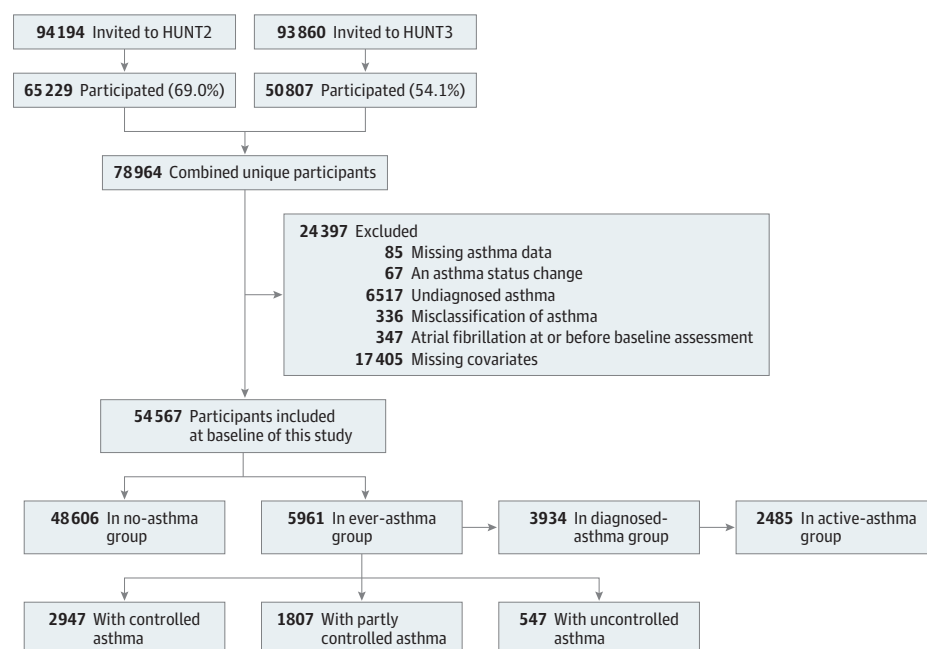
Asthma

Self-reported asthma was categorized into 3 self-reported asthma groups (ever asthma, diagnosed asthma, and active asthma), based on the answers to HUNT Baseline and Lung Study Questionnaires. The category called *ever asthma* was used to capture all cases and was defined as those who answered yes to "Do you have or have you ever had asthma?" Those with an affirmative answer to this question and to the question, "Have you been diagnosed as having asthma by a doctor?" were classified in a category termed *diagnosed asthma*. Lastly, those who answered yes to previous questions and to the question, "In the past 12 months, have you used asthma medication?" were categorized in the group *active asthma*. Therefore, those in the active asthma category must have answered yes to all 3 questions (eTable 1 in the Supplement): (1) "Do you have or have you ever had asthma?" (2) "Have you been diagnosed as having asthma by a doctor?" and (3) "In the past 12 months, have you used asthma medication?"

Asthma Control

We selected HUNT Lung Study questions on asthma symptoms and medication use to match the asthma control assessment questions from the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention

Figure. Flowchart of the HUNT Participants



(eTable 2 in the [Supplement](#)).¹⁸ The ever asthma group was further categorized as having controlled, partly controlled, and uncontrolled asthma, based on 4 characteristics: daytime symptoms (2 times per week or less or more than 2 times per week), night awakenings (none or any), the need for reliever medication (2 times per week or less or more than 2 times per week), and limitation of activities (none or any). Participants in the controlled asthma group had no asthma characteristics, while individuals with partly controlled asthma had 2 or less of these characteristics, and individuals with uncontrolled asthma had 3 or more of the characteristics (eTable 3 in the [Supplement](#)).

Atrial Fibrillation Ascertainment

Atrial fibrillation was ascertained by linking the HUNT data with hospital records from the only 2 hospitals in Nord-Trøndelag County. Cardiologists identified potential AF cases based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* code I48. The sensitivity of a hospital discharge diagnosis of AF was 73.7%, the specificity was 99.7%, the positive predictive value was 66.2%, and the negative predictive value was 98.4%.¹⁹ The medical records were then reviewed and the patient was considered as having AF if an electrocardiogram could be classified as AF or atrial flutter, according to the standard criteria based on the American College of Cardiology consensus guidelines.²⁰ If an electrocardiogram was not in the digital medical record, the written records were further reviewed for electrocardiographic interpretation and, in doubtful cases, the information was evaluated separately by specialists in cardiology (J.P.L.) and internal medicine (H.E.) and then discussed in a consensus meeting.¹⁹ In this study, cases in which an electrocardiographic scan was not taken, but patients had been de-

scribed as having irregular heartbeats or periods of fast, irregular pulse were never regarded as constituting a diagnosis of AF.

Covariates

Detailed information on participant demographics, anthropometrics, lifestyle factors, and health were collected in questionnaires, interviews, and clinical examinations.¹⁶ A self-administrated questionnaire was used to assess participants' smoking status (never, former, and current), physical activity, alcohol use, and years of education (<10 years, 10-12 years, and >12 years). Physical activity was categorized according to hours of physical activity per week into 4 groups: inactive (1 hour or less light physical activity and no hard activity), low (more than 1 hour of light activity and less than 1 hour of hard activity), medium (1 to 2 hours of hard activity, regardless of light activity level), and high (3 hours or more of hard activity, regardless of light activity level). Alcohol was categorized according to participants' wine, beer, and spirits consumption as abstainers (0 drinks per day), light drinkers (between 0 and 0.5 drinks per day), moderate drinkers (between 0.5 and 1 drink per day), or heavy drinkers (>1 drink per day). During interviews, a medical history of common chronic diseases was assessed, which included diabetes, stroke, heart failure, myocardial infarction, hypothyroidism, hyperthyroidism, and rheumatism. Use of short-acting and long-acting β_2 -agonist was assessed in the Lung Study Interview and participants were classified as never having used these or as current users.

Body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared. Waist-to-hip (W/H) ratio was calculated by dividing waist circumference in centimeters by hip circumference in centimeters. We measured FEV₁ and FVC in accordance with the American Tho-

Table 1. Baseline Characteristics of HUNT2 and HUNT3 Participants

Characteristic (N = 54 567)	Ever Asthma, No. (%)	
	No (n = 48 606)	Yes (n = 5961)
Female	25 564 (52.6)	3257 (54.6)
Smoking		
Never	22 162 (45.6)	2371 (39.8)
Former	13 119 (27.0)	1788 (30.0)
Current	13 325 (27.4)	1802 (30.2)
Physical activity		
Inactive	8910 (18.3)	1194 (20.0)
Low	13 880 (28.6)	1637 (27.5)
Medium	20 102 (41.4)	2369 (39.7)
High	5714 (11.8)	761 (12.7)
Alcohol use		
Abstainers	15 987 (32.9)	2070 (34.7)
Light	25 225 (51.9)	3014 (50.6)
Moderate/heavy	7394 (15.2)	877 (14.7)
Education		
<10 y	14 385 (29.6)	1872 (31.4)
10-12 y	22 435 (46.2)	2812 (47.2)
>12 y	11 786 (24.2)	1277 (21.4)
Age, mean (SD), y	46.6 (15.9)	46.0 (16.1)
BMI, mean (SD)	26.1 (4.0)	27.0 (4.6)
W/H ratio, mean (SD)	0.84 (0.08)	0.86 (0.08)
C-reactive protein, mean (SD), $\mu\text{g/mL}$	2.4 (5.3)	3.2 (7.4)
Diabetes mellitus	1081 (2.2)	189 (3.2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HUNT, The Nord-Trøndelag Health Study; W/H, waist-to-hip.

racic Society criteria in HUNT2²¹ and the European Respiratory Society–American Thoracic Society criteria in HUNT3,²² with quality control methods described elsewhere.¹⁷

High-sensitivity C-reactive protein (hsCRP) was measured from serum samples taken during the HUNT3 baseline medical visit only. Measurements were obtained using latex immunoassay methodology (Abbott Laboratories).

Statistical Methods

Baseline characteristics were presented as means and SDs for continuous variables and as numbers and percentages for the categorical variables for the group with no asthma (the reference group) and the ever-asthma group. To investigate the prospective association between asthma, asthma control, and risk of AF, we used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% CIs. Risk time was calculated for each of the asthma groups from baseline until the examination at which AF was first diagnosed, death, emigration, or asthma status change during follow-up or at the end of the follow-up period (November 30, 2015), whichever came first. We assessed dose-response association and calculated a *P* value for trend between asthma control and AF by treating asthma control as a continuous variable in the model. We used chronological age as the time scale in our analysis. We tested the proportionality of hazards using log-log curves and the Schoenfeld

test. Variables that showed evidence against proportionality in the formal test (*P* < .05) were treated as time-varying covariates in our models.

Selection of covariates was based on prior knowledge of their association with asthma and AF. A minimally adjusted model included age and sex (model 1). In a fully adjusted model, we controlled for traditional cardiovascular disease risk factors including smoking status, physical activity, alcohol consumption, education, BMI, W/H ratio, and diabetes (model 2). Waist-to-hip ratio was used as a potentially better indicator of central obesity than BMI.²³ We tested for effect measure modification by sex, age (dichotomized by age < 60 years – mean AF incidence age), BMI (< 25), smoking status (ever or never), and physical activity (inactive or active) by performing stratified analysis and assessing interaction terms in multivariate models.

Furthermore, we assessed possible mediating factors that could potentially explain the association between asthma and AF. In these mediation analyses, we compared the varying HRs of asthma and risk of AF from the fully adjusted models (model 2) with and without inclusion of β_2 -agonists use and hsCRP levels.

Sensitivity Analysis

We repeated the analyses after the exclusion of the first 5 years of the follow-up period to address the possibility of reverse causation. In further sensitivity analysis, we excluded participants who had self-reported comorbidities at baseline or diagnosed myocardial infarction or heart failure (from 2007) during follow-up, which could influence the association between asthma and AF. Lastly, to minimize misdiagnosed heart failure or COPD as asthma, we excluded those who were diagnosed with asthma at the age of 40 years or older.

We performed data analysis using Stata 13.1 for Windows 10 (StataCorp). Data analysis was completed from May 2017 to November 2017.

Results

The cumulative prevalence of ever asthma, diagnosed asthma, and active asthma were 10.9% (n = 5961 of 54 567), 7.2% (n = 3934), and 4.6% (n = 2485), respectively. Among the 54 567 participants (including 28 821 women [52.8%]), individuals with asthma, compared with individuals without asthma, had higher BMIs at baseline (group with no asthma: mean [SD] BMI, 26.1 [4.0]; ever-asthma group: 27.0 [4.6]) and lower rates of completing more than 12 years of education (group with no asthma: n = 11 786 of 48 606 [24.2%]; ever-asthma group: n = 1277 of 5961 [21.4%]). Individuals with asthma also had greater likelihood of diabetes at baseline than individuals without asthma (group with no asthma: n = 1081 [2.2%]; ever-asthma group: n = 189 [3.2%]), female sex (group with no asthma: n = 25 564 [52.6%]; ever-asthma group: n = 3257 [54.6%]), and former smoking (group with no asthma: n = 13 119 [27.0%]; ever-asthma group: n = 1788 [30.0%]) or current smoking (group with no asthma: n = 13 325 [27.4%]; ever-asthma group: n = 1802 [30.2%]; Table 1).

The prevalence of controlled asthma, partly controlled asthma, and uncontrolled asthma were 5.4% (n = 2947 of 54 567), 3.3% (n = 1807), and 1.0% (n = 547), respectively. Among 54 567 participants, a total of 2071 (3.8%) were diagnosed with AF during a mean (SD) follow-up time of 15.4 (5.8) years.

Association of Asthma With AF

After adjustment for sex and age (model 1), participants categorized in the ever-asthma group at baseline had higher risk of developing AF compared with those with no asthma (HR, 1.30 [95% CI, 1.13-1.48]) (Table 2). In comparisons, participants with diagnosed asthma had an estimated 42% increased risk (HR, 1.42 [95% CI, 1.21-1.67]), and those with active asthma had an 81% increased risk (HR, 1.81 [95% CI, 1.51-2.16]). After further adjustment for potential confounders (model 2), the association remained similar (Table 2).

Association of Asthma Control With AF

There was a dose-response association of asthma control and risk of AF (*P* for trend <0.001). After adjustment for sex and age (model 1), participants with uncontrolled asthma at base-

line had an estimated 74% increased risk of developing AF compared with the participants with no asthma (HR, 1.74 [95% CI, 1.25-2.41]). The risk of AF was lower in participants with partly controlled asthma (HR, 1.42 [95% CI, 1.16-1.73]) and those with controlled asthma (HR, 1.19 [95% CI, 0.98-1.45]). In the fully adjusted model (model 2), the HRs were essentially the same (Table 2).

We found no strong evidence for statistical interaction between asthma or asthma control and sex, age, BMI, smoking and physical activity. Estimated HRs did not change after adjustment for hsCRP in the fully adjusted models (model 2) (Table 3). After adjustment for β 2-agonists use, there was only a small change in HRs (<10%) for the asthma groups. A total of 1362 participants used β 2-agonist medications; of these, 618 used β 2-agonists alone, and 1148 used a combination of β 2-agonists and inhaled corticosteroids.

Sensitivity Analyses

Excluding participants who only completed the first 5 years of follow-up (n = 320) and participants with comorbidities (n = 8016), including those with myocardial infarction (n = 3759) and heart failure (n = 1218) and those who were di-

Table 2. Associations Between Asthma, Asthma Control, and the Risk of Atrial Fibrillation Among 54 567 Participants During 15.4 Years of Follow-up

Status	Patients, No.	Person-Years, No.	Atrial Fibrillation, No. (%)	Hazard Ratios (95% CI) ^a	
				Model 1 ^b	Model 2 ^c
Asthma					
No asthma	48 606	752 149	1806 (3.7)	1 [Reference]	1 [Reference]
Ever	5961	89 883	265 (4.5)	1.30 (1.13-1.48)	1.27 (1.10-1.46)
Diagnosed	3934	56 192	199 (5.1)	1.42 (1.21-1.67)	1.38 (1.18-1.61)
Active	2485	31 889	150 (6.0)	1.81 (1.51-2.16)	1.76 (1.47-2.10)
Asthma control ^d					
Controlled	2947	44 267	108 (3.7)	1.19 (0.98-1.45)	1.16 (0.95-1.41)
Partly controlled	1807	27 974	101 (5.6)	1.42 (1.16-1.73)	1.40 (1.14-1.71)
Uncontrolled	547	8329	38 (7.0)	1.74 (1.25-2.41)	1.74 (1.26-2.42)

^a Hazard ratios (95% CI) were derived from Cox proportional hazards models. The group that reported no asthma served as the reference group for both asthma status and asthma control status.

^b Model 1 adjusted for age and sex.

^c Model 2 adjusted for age, sex, BMI, smoking status, alcohol use, physical activity, education level, waist-to-hip ratio, and diabetes mellitus.

^d *P* value for trend < .001.

Table 3. Mediation Analysis for the Associations Between Asthma, Asthma Control, and the Risk of Atrial Fibrillation Among 54 567 Participants During 15.4 Years of Follow-up

Status	Use of β 2-Agonists (n = 52 477) ^a			C-Reactive Protein (n = 30 332) ^b		
	Model 2 Adjusted HR ^c	Model 2 With Mediator-Adjusted HR ^d	Change in HR, % ^e	Model 2 Adjusted HR ^c	Model 2 With Mediator-Adjusted HR ^d	Change in HR, % ^e
Asthma						
Ever	1.17 (1.00 to 1.38)	1.09 (0.90 to 1.34)	-7	1.18 (0.99 to 1.41)	1.18 (0.99 to 1.41)	0
Diagnosed	1.19 (0.99 to 1.43)	1.11 (0.87 to 1.41)	-7	1.39 (1.12 to 1.72)	1.39 (1.12 to 1.72)	0
Active	1.50 (1.22 to 1.85)	1.60 (1.61 to 2.20)	6	1.51 (1.19 to 1.92)	1.51 (1.19 to 1.92)	0
Asthma control						
Controlled	0.95 (0.74 to 1.23)	0.95 (0.74 to 1.23)	0	1.08 (0.84 to 1.40)	1.08 (0.84 to 1.40)	0
Partly controlled	1.26 (1.00 to 1.58)	1.31 (0.97 to 1.77)	4	1.62 (1.16 to 2.27)	1.61 (1.15 to 2.26)	1
Uncontrolled	1.64 (1.15 to 2.33)	1.78 (1.09 to 2.88)	8	1.95 (1.10 to 3.46)	1.93 (1.09 to 3.42)	1

Abbreviation: HR, hazard ratio.

^a Self-assessed long-acting or/and short-acting β 2-agonists use at baseline among participants with asthma (n = 1362 [22.8%]).

^b High-sensitivity C-reactive protein was measured in HUNT3 only.

^c Model 2 adjusted HR for age, sex, BMI, smoking status, alcohol use, physical activity, education level, waist-to-hip ratio, and diabetes, with exclusion of

missing values in the respective covariates (β 2-agonists and high-sensitivity C-reactive protein).

^d Adjusted for model 2 and the respective covariate.

^e Mediation was assessed as the percentage change in the HRs between the adjusted HR for model 2 and adjusted HR for model 2 after mediator adjustment.

agnosed with asthma at the age of 40 or older ($n = 1128$) did not change the associations of asthma with risk of AF (eTable 4 in the [Supplement](#)). Likewise, associations of asthma control with risk of AF did not change.

Discussion

In this large population-based study of more than 50 000 individuals, we found an increased risk of AF in individuals with asthma compared with individuals without asthma, with the highest risk in those with active or uncontrolled asthma. Similarly, we found a positive dose-response association between levels of asthma control and AF risk. The association was not explained by cardiovascular risk factors or somatic comorbidities. Moreover, we found no clear evidence for a mediating effect of hsCRP levels or the use of β_2 -agonist medications.

To the best of our knowledge, only 1 previous population-based study¹⁵ has investigated the association between asthma and AF, and it found consistent results with ours. In this population-based study of 7439 cases and 10 075 controls utilizing the Taiwan National Health Insurance database, asthma was associated with a 20% increased risk of AF, whereas the risk of new-onset AF was higher among those with current use of corticosteroids and bronchodilators.¹⁵ However, no adjustments for cardiovascular disease risk factors were made and the authors did not investigate asthma control.

In line with our study, previous research found stronger associations of asthma and cardiovascular disease in individuals taking medication or having reoccurring asthma symptoms.^{9,12,15} In a multicenter prospective study, asthma participants reporting wheeze attacks with shortness of breath had a greater risk for stroke compared with participants with asthma without these symptoms.¹² We observed the strongest associations in individuals with uncontrolled asthma exhibiting all 4 asthma characteristics and the weakest association in those with controlled asthma. Considering the high prevalence of patients with moderate to severe asthma who have uncontrolled symptoms, these findings have important implications for health care.²⁴

We recognize that medication use is one of the potential explanations for the association between asthma and AF. Asthma medication is the first line of approach for asthma control.¹⁸ GINA recommends the use of low-dose inhaled corticosteroids together with short acting β_2 -agonists (SABAs) for asthma control, followed by addition of long-acting β_2 -agonists (LABAs) if symptoms persist.¹⁸ The use of high doses of β_2 -agonists for asthma has been shown to increase the risk of arrhythmias.⁸ Also, as many as 98% of patients with severe asthma have electrolyte disturbances associated with the use of β_2 -agonists, a well-known cause of cardiac arrhythmia.²⁵ However, in our study, the higher AF risk among individuals with active and uncontrolled asthma was not explained by β_2 -agonist use. Discriminating between asthma symptoms or severity and medication use would be challenging in observational studies, because asthma treatment guidelines recommend long-acting β_2 -agonists use in steps 3 to 5, where increased rates of disease-associated outcomes are seen. In this

study, more than 90% of participants who are using asthma medication reported still experiencing multiple asthma symptoms, representing the most severe asthma group. It is likely that participants without asthma medication use have passive asthma that has been diagnosed a long time ago, and their symptoms are under control without the need of reliever medication. More in-depth studies looking at asthma symptoms and medication use, including frequency and dosage, with serial follow-up methods, are needed.

Shared inflammatory pathways of asthma and AF might also play a role in the association between the 2 conditions. It was originally thought that asthma exerts an inflammatory response driven T helper cells-type 2 with inhaled innocuous allergens; however, it is now considered to be highly heterogeneous.²⁶ Episodes of acute inflammatory reactions are often accompanied by an underlying chronic inflammation, even in the absence of continuous allergen exposure. More specifically, the inflammatory response in asthma involves the activation and recruitment of inflammatory cells and release of inflammatory mediators, creating a cycle of chronic inflammation.²⁷ Chronic inflammation has been linked with AF, partly because of the higher levels of various inflammatory proteins, including C-reactive protein and interleukin 6 in patients with AF.²⁸ However, the role of inflammation as a causal factor in the development of AF remains debatable, and this study did not find any mediating effect of hsCRP in the association between asthma and AF. Additionally, we did not have information on anti-inflammatory drug use to examine if these treatments would mitigate the association between asthma and AF.

There are other plausible mechanisms for an increased risk of AF. Dysfunction of the airway autonomic nervous system may be involved in the airway hyperresponsiveness observed in patients with asthma.²⁹ Similarly, dysfunction of the autonomic nervous system may induce significant and heterogeneous changes of atrial electrophysiology, causing cardiac arrhythmia.³⁰ However, we did not evaluate autonomic nervous system function of our participants, and more research is needed to assess this possible link.

This large, population-based study is, to our knowledge, the first to examine the dose-response association between asthma control and cardiovascular disease in general. This study has several strengths, including a large, stable cohort of men and women, long follow-up, a high participation rate, and carefully revised hospital and register information. Information on many potential confounders enabled us to perform extensive statistical adjustment for these factors. Furthermore, the Lung Study questionnaire allowed us to incorporate strict exclusion criteria and perform multiple sensitivity analysis, increasing the robustness of our findings. Lastly, questions on asthma symptoms and medication use enabled us to assess the dose-response association between asthma control and AF, which strengthens the evidence of an association between asthma and AF.

Limitations

Despite its obvious strengths, our study also has several limitations. First, the observational nature of the data limits causal inference with a possibility of residual confounding. However, to influence our results, the unmeasured con-

founder would have to be strongly associated with both asthma and AF and be generally unassociated with the other potential confounders included in our models.

Second, we did not have a full data set on heart failure, an important comorbidity of AF. Excluding participants with self-reported heart failure at HUNT3 and those diagnosed with heart failure starting in 2007 did not change the results, however.

Finally, sleep apnea could worsen asthma symptoms throughout the day, while asthma itself can affect sleep apnea with nighttime awakenings and difficulty breathing, making it a potential confounder. Unfortunately, we do not have data on sleep apnea in HUNT2, so we could not explore these associations. It should be noted that in our study, all of the participants in the uncontrolled asthma group reported having night awakenings because of asthma, which could indicate poorer sleep quality.

One major problem with epidemiological studies of asthma is the lack of a gold standard for asthma diagnosis. In our study, we did not have asthma diagnosis data from hospital records or full post bronchodilator testing for asthma and instead relied on self-reported asthma questionnaires, which may have resulted in misclassifications. However, questions on self-reported asthma and physician-diagnosed asthma has been shown to have good specificity and positive predictive value and to give prevalence estimates close to those obtained by clinical judgment in both younger and older adults.³¹⁻³³ More specifically, an Italian study of adults aged 20 to 44 years has shown a specificity of 97.5% for participants who reported ever having asthma and 99.7% for participants with current asthma (defined as self-reported asthma attacks in the last 12 months and/or current use of asthma medication).³³ Furthermore, questions on self-

reported current asthma slightly underestimated the prevalence of current asthma.^{31,33}

Finally, the prevalence of asthma in our study is in alignment with the World Health Survey data³⁴ and Norway general practitioner register data.³⁵ Therefore, the high specificity and potential underestimation of the association in the validation studies gives us little reason for misclassification concerns.

Some people with asthma may still be undiagnosed or diagnosed with other chronic lung conditions, such as COPD, and heart failure that share similar symptoms. However, to improve the specificity of the definition of asthma, we excluded participants with potentially undiagnosed asthma who reported having asthmalike symptoms and asthma medication use for the group without asthma, while excluding participants with COPD characteristics from the groups with asthma. We further performed sensitivity analysis to minimize the possibility of COPD and heart failure by excluding adults with late-onset asthma.

Conclusions

In summary, in this large, well-described cohort, asthma and asthma control was associated with increased risk of AF in a dose-response manner. Given the high prevalence of asthma, clinicians should be aware of this connection and closely examine AF risk factors in this patient group. Further investigation is warranted into the underlying mechanisms of this association, including asthma medication use and inflammation, to clarify the causal pathways between asthma, asthma control, and atrial fibrillation.

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