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# Asthma, asthma control and risk of atrial fibrillation: the HUNT study

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## Key Points

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

**Findings:** In this prospective cohort that included 54 567 participants, diagnosed asthma was associated with 38% increased atrial fibrillation risk 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.

## ABSTRACT

**Importance** Asthma, a chronic inflammatory airway disease, and atrial fibrillation (AF) share several common pathophysiological mechanisms. Research of the association between asthma and atrial fibrillation is lacking and 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 utilized data on 54 567 adults from a second and third survey "The Nord-Trøndelag Health Study" in Norway free from AF at baseline.

**Exposures** Self-reported asthma was categorized into three groups: ever asthma, diagnosed asthma and active asthma. Asthma control was defined according to the Global Initiative for

Asthma guidelines and was categorized into controlled, partly controlled and uncontrolled asthma.

**Main Outcome and Measure** AF was ascertained by linking HUNT data with hospital records from the two hospitals in Nord-Trøndelag.

**Results** During a mean follow-up of 15.4 ± 5.8 years, 2 071 (3.8%) participants developed AF. Participants with physician diagnosed asthma had an estimated 38% higher risk of developing AF (adjusted HR 1.38, 95% CI 1.18-1.61) compared to participants without asthma. There was a dose-response association between levels of asthma control and risk of AF (p for trend <0.001) with the highest risk for AF in participants with uncontrolled asthma (adjusted HR 1.74, 95% CI 1.26–2.42).

**Conclusions and Relevance** Asthma and lack of asthma control was associated with moderately increased risk of atrial fibrillation in a dose-response manner. Further studies are needed to explore the underlying mechanisms to clarify the causal pathways between asthma and atrial fibrillation.

## BACKGROUND

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a lifetime risk of 26% (1). AF is emerging as a 'growing epidemic' (2), 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, affecting 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 and long acting beta2-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 reports link asthma with the risk of coronary heart disease, stroke and heart failure (9-12). Furthermore, there is evidence that reduced forced expiratory volume (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 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 (HUNT) is Norway's largest population health study consisting of three surveys: HUNT1 (1984-1986), HUNT 2 (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).

We used data from HUNT2 and HUNT3 as information on asthma was not collected in HUNT1. A total of 65 229 (69.0% of those invited) and 50 807 (54.1%) individuals participated in HUNT2 and HUNT3, respectively. Our total sample consisted of 78 964 individuals. Of the total sample, 28 160 individuals participated only in HUNT2, 37 069 individuals participated in both HUNT2 and HUNT3 and 13 735 individuals participated only in HUNT3. Out of the 78 964 individuals, 23 726 answered "yes" to at least one of the questions on asthma, asthma symptoms and asthma medication use and were invited to the Lung Study (a sub-study of HUNT) and 16 115 individuals participated (17).

Of the 78 964 participants, 85 were excluded due to missing information on asthma at baseline and 67 participants who reported ever asthma at HUNT2, but not at HUNT3. In addition, we excluded participants who do not have asthma, but reported to be using asthma related medication or/and have asthma-like symptoms (wheezing and/or dyspnea) at baseline (n

= 6 517). In order to minimize self-reported asthma misclassification as chronic obstructive pulmonary disease (COPD), we excluded participants who had all three of the following: post-bronchodilator FEV1/FVC z-score lower than -1.64, history of smoking and were diagnosed with asthma after the age of 40 years old (n = 336). Lastly, we excluded individuals that were diagnosed with AF at or before baseline (n = 347) and those with missing covariates (n = 17 045), leaving a total of 54 567 participants for the baseline analyses of this study (Figure 1).

*Asthma*

Self-reported asthma was categorized into three self-reported asthma groups: *'Ever Asthma',* *'Diagnosed Asthma',* and *'Active asthma'* based on the answers to HUNT Baseline and Lung Study Questionnaires. *'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 as *'Diagnosed Asthma'*. Lastly, those who answered *'yes'* to previous questions and to *'In the past 12 months, have you used asthma medication?'* were categorized as *'Active Asthma'*. Therefore, those with "*Active asthma"* must have answered "yes" to all three questions: 1) "Do you have or have you ever had asthma?" and 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 (18). The *'Ever Asthma'* group was further categorized as controlled, partly-controlled and uncontrolled asthma based on the following four

characteristics: daytime symptoms (≤2 times/week or >2 times/week), night awakenings (none or any), the need for reliever medication (≤2 times/week or >2 times/week) and limitation of activities (none or any). Participants in the controlled asthma group had no asthma characteristics, while partly-controlled and uncontrolled asthma individuals had 2 or less and 3 or more of the characteristics, respectively (supplementary table 2).

*Atrial Fibrillation ascertainment*

AF was ascertained by linking the HUNT data with hospital records from the only two hospitals in Nord-Trøndelag County. Cardiologists identified potential AF cases based on International classification of Diseases version 10 (ICD-10) code I48. The sensitivity and specificity of a hospital discharge diagnosis of AF was 73.7%, specificity 99.7%, positive predictive value (PPV) 66.2%, and negative predictive value (NPV) 98.4% (19). The medical records were then reviewed and patient was considered as having AF if electrocardiogram could be classified as AF or atrial flutter according to the standard criteria based on the American College of Cardiology consensus guideline (20). If an ECG scan was not in the digital medical record, the written records were further reviewed for ECG interpretation and, in doubtful cases, the information was evaluated separately by specialist in cardiology and internal medicine, and then discussed in a consensus meeting (19). In the cases where an ECG was not taken at all, but patients had described irregular heartbeats or periods of fast, irregular pulse, it was never considered as AF in our study.

*Covariates*

Detailed information on participants' 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, 10–12, >12 years). Physical activity was categorized according to hours of physical activity per week into four groups: inactive (≤1h light physical activity and no hard activity), low (>1h light and <1h hard), medium (1-2h of hard regardless of light activity) and high (≥3h of hard regardless of light activity). Alcohol was categorized according to participants' wine, beer and spirits consumption as abstainers, 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, medical history of common chronic diseases was assessed, which included diabetes, stroke, heart failure, myocardial infarction, hypo-, and –hyperthyroidism and rheumatism. Use of short and long-acting beta2-agonist was assessed in the Lung Study Interview and classified as never or current users.

Body mass index (BMI) was calculated by dividing body weight (kg) by height (m) squared ($kg/m^2$). Waist hip ratio (W/H ) was calculated by dividing waist circumference (cm) by hip circumference (cm). Forced Expiratory Volume in the first second ($FEV_1$) and Forced Vital Capacity (FVC) were measured in accordance with the ATS-criteria in HUNT2 (21) and the ATS-ERS criteria in HUNT3 (22) with quality control methods described elsewhere (17).

High sensitivity C-reactive protein (hsCRP) was measured from serum samples taken during HUNT3 baseline medical visit only. Measurements were obtained using latex immunoassay methodology (Abbot, Clinical Chemistry, USA).

*Statistical Methods*

Baseline characteristics were presented as mean and standard deviation for continuous variables and number and percentage for the categorical variables for no asthma (reference) and ever asthma groups.

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% confidence intervals (CIs). Risk time was calculated for each of the asthma groups from baseline until the examination at which AF was first diagnosed, death, emigration, asthma status change in follo-up or end of follow-up (30$^{th}$ November 2015), whichever came first. We assessed dose-response association (p 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 Schoenfield's test. Variables that showed evidence against proportionality in the formal test ($p < 0.05$) were treated as time varying covariates in our models.

Selection of covariates was based on prior knowledge on 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). W/H ratio was used as a potentially better indicator of central obesity than BMI (23).

We tested for effect measure modification by gender, age (dichotomized by <60y – mean AF incidence age), BMI (<25kg/m$^2$), smoking (ever and never smoker) and physical activity (inactive and 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 this mediation analyses we compared HR of asthma and risk of AF from the fully adjusted models (Model 2) with and without inclusion of beta2-agonists use and high-sensitive C-reactive protein levels.

*Sensitivity Analysis*

We repeated the analyses after the exclusion of the first five years of follow-up 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 that could influence the relationship between asthma and AF. Lastly, to minimize misdiagnosed heart failure or COPD as asthma, we excluded those that were diagnosed with asthma at the age of 40 or older.

We performed data analysis using Stata 13.1 for Windows 10 (StataCorp, College Station, TX, USA). The study received approval from the Regional Committee for Medical Research Ethics. All study participants gave informed written consent.

**RESULTS**

The cumulative prevalence of ever asthma, diagnosed asthma and active asthma were 10.9%, 7.2% and 4.6%, respectively. Among the 54 567 participants, individuals with asthma at baseline had higher BMI, lower education and were more likely to have diabetes, to be females and former or current smokers than individuals without asthma (Table 1).

The prevalence of controlled asthma, partly-controlled and uncontrolled asthma were 5.4%, 3.3% and 1.0%, respectively. Among 54 567 participants, a total of 2 071 (3.8%) were diagnosed with AF during a mean follow-up of 15.4 ± 5.8 years.

*Association of asthma and AF*

After adjustment for sex and age (Model 1), participants with ever asthma at baseline had higher risk of developing AF compared to those without asthma (HR 1.30, 95% CI 1.13 – 1.48) (Table 2). In comparisons, participants with diagnosed and active asthma had an estimated 42% (HR 1.42, 95% CI 1.21 – 1.67) and 81% (HR 1.81, 95% CI 1.51 – 2.16) increased risk, respectively. After further adjustment for potential confounders (Model 2), the association remained similar (Table 2).

*Association of asthma control and 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 baseline had an estimated 74% increased risk of developing AF compared to 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 or controlled asthma: HR 1.42, 95% CI 1.16 – 1.73 and HR 1.19, 95% CI 0.98 – 1.45, respectively. 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 (p for interaction >0.10).

Estimated HRs did not change after adjustment for hsCRP in the fully adjusted models (Model 2) (Table 3). After adjustment for beta2-agonists use, there was only a small change in HRs (<10%) for the asthma groups. A total of 1362 participants used beta2-agonist, 618 used beta2-agonists alone and 1148 a combination of beta2-agonists and inhaled corticosteroids.

*Sensitivity Analyses*

Excluding the first five years of follow-up (participants n = 320), participants with comorbidities (n = 8016) including myocardial infarction (n = 3759) and heart failure (n = 1218) or those that were diagnosed with asthma at the age of 40 or older (n = 1128) did not change the associations of either asthma or asthma control with risk of AF (supplementary table 4).

## DISCUSSION

In this large population-based study including more than 50 000 individuals, we found an increased risk of AF in individuals with asthma, compared to 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 beta2-agonist.

To the best of our knowledge, only one previous population-based study has investigated the association between asthma and AF, and found consistent results with ours. In this population-based study of 7 439 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 CVD 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 CVD 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 to participants with asthma, but without these

symptoms (12). We observed the strongest associations in individuals with uncontrolled asthma exhibiting all four asthma characteristics and weakest association in those with controlled asthma. Considering the high prevalence of patients with moderate to severe asthma that have uncontrolled symptoms these findings have important implications for healthcare (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 usage of low dose ICS together with short acting beta2-agonists (SABA) for asthma control followed by addition of long acting beta2-agonists (LABA) if symptoms persist (18). Use of high doses of beta2-agonists for asthma has been shown to increase the risk of arrhythmias (8). Also, as high as 98% of severe asthma patients have electrolyte disturbances related to the use of beta2-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 beta2-agonist use. Discriminating between asthma symptoms or severity and medication use would be challenging in observational studies, because asthma treatment guidelines recommend long acting beta2-agonists use in steps 3–5, where increased rates of disease-related outcomes are seen. In our study, over 90% of participants who are using asthma medication still experience 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, medication use including frequency and dosage with serial follow-up are needed.

Shared inflammatory pathways of asthma and AF might also play a role in the association. It was originally thought that asthma exerts Th2-driven inflammatory response to

inhaled innocuous allergen; 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 to AF, partly due to the higher levels of various inflammatory proteins including C-reactive protein (CRP) and IL-6 in patients with AF (28). However, the role of inflammation as a causal factor in the development of AF remains debatable and we did not find any mediating effect of hsCRP in the relationship between asthma and AF. Additionally, we did not have information on anti-inflammatory drug use to examine if anti-inflammatory treatments would mitigate the association between asthma and AF.

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

Our large population-based study is first to examine the dose-response association between asthma control and CVD in general. This study has several strengths including a large stable cohort of men and women with long follow-up, 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 relationship between asthma control and AF strengthening the evidence of an association between asthma and AF.

Despite its obvious strengths, our study also has several limitations. Firstly, the observational nature of the data limits causal inference with a possibility of residual confounding. However, to be influencing our results the unmeasured confounder would have to be strongly associated with both asthma and AF and be generally unrelated to the other potential confounders included in our models. Secondly, we did not have full dataset on heart failure, an important comorbidity of AF. Excluding participants with self-reported heart failure at HUN3 and those diagnosed from 2007 did not change the results. Lastly, 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 cannot explore these associations. It should be noted that in our study, all of the participants in uncontrolled asthma group had night awakening due to 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 relied on self-reported asthma questionnaires, which may have resulted in misclassification. However, questions on self-reported asthma and physician diagnosed asthma has been shown to have good specificity and positive predictive value and give prevalence estimate close to those obtained by clinical judgment in both younger and older adults (31-33). More specifically, an Italian study of adults aged 20-44 years old has shown a specificity of 97.5% for ever-asthma and 99.7% for 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 current-asthma prevalence (31, 33). Lastly, the prevalence of asthma in our study is in-line with The World Health Survey data (34) and Norway GP 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 potentially undiagnosed asthma participants with asthma-like symptoms and asthma medication use for the non-asthma group while excluding participants with COPD characteristics in the asthma groups. We further performed sensitivity analysis minimizing the possibility of COPD and heart failure by excluding adults with late-onset asthma.

In summary, in this large, well-described cohort, asthma and asthma control was associated with increased risk of atrial fibrillation 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 into the underlying mechanisms including asthma medication use and inflammation to clarify the causal pathways between asthma, asthma control and atrial fibrillation is warranted.

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*Statement of interest*

None declared.

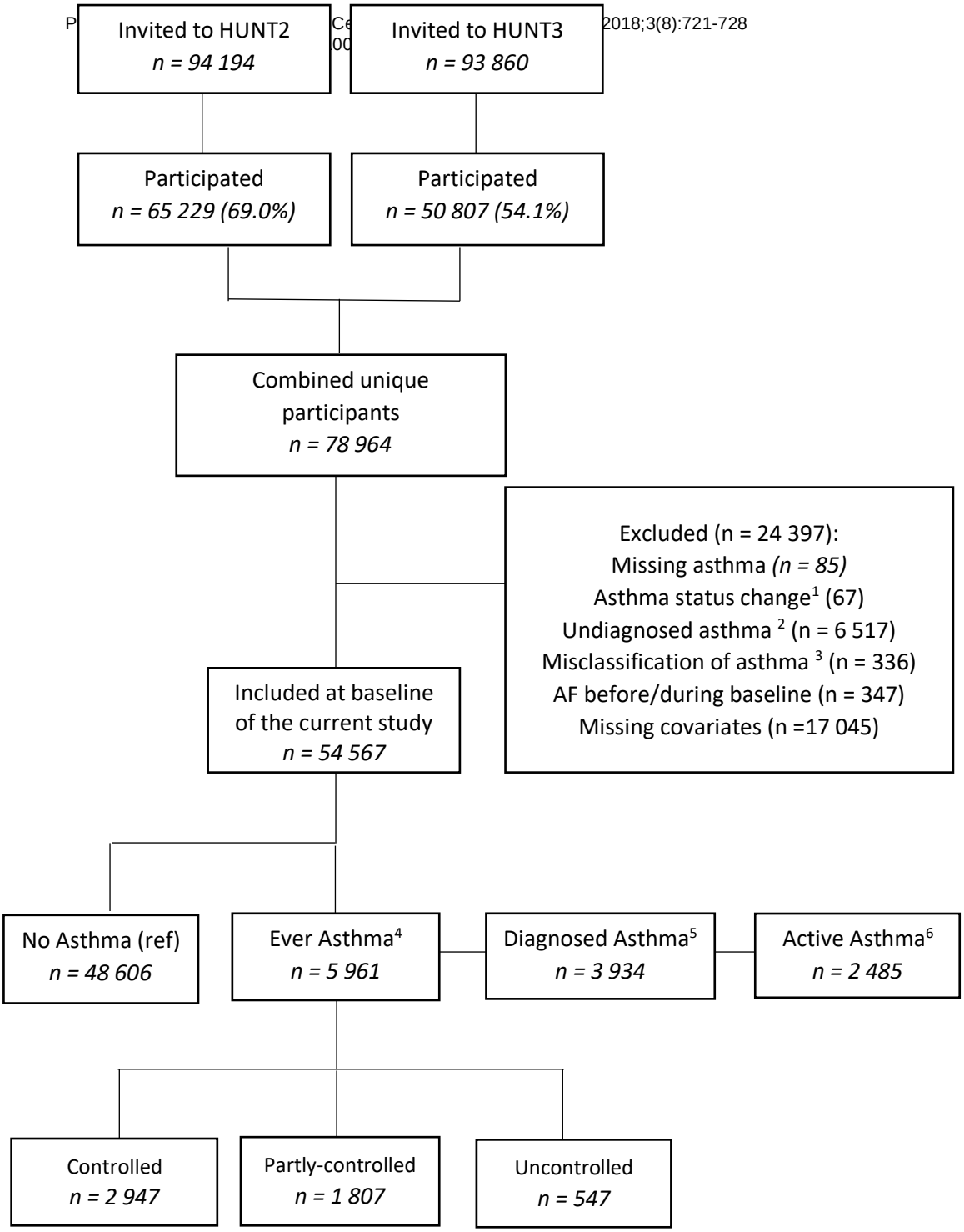


*Figure 1 Flowchart of the participants*

[1] Change of asthma status during follow-up (asthma to non-asthma)

[2] Potentially undiagnosed: do not have asthma at baseline or follow-up, but are taking asthma related medication or have asthma symptoms at baseline

[3] Possible misclassification of reported asthma as COPD: FEV1/FVC z-score lower than -1.64, current/ex-smokers and diagnosed asthma at >40 years old

[4] All participants that answered yes to 'Have you ever had asthma?'

[5] Only those that answered yes to above and 'Have you been diagnosed as having asthma by doctor?'

[6] Only those that answered yes to above and 'In the past 12 months, have you used asthma medication?

Asthma control based on the GINA Global Strategy for Asthma Management and Prevention

*Table 1. Baseline characteristics of 54 567 HUNT2 and HUNT3 participants*

| **Characteristic** | Ever Asthma | |
|---|---|---|
| | No (n = 48 606) | Yes (n = 5 961) |
| **Female** | 25 564 (53%) | 3 257 (55%) |
| **Smoking** | | |
| Never | 22 162 (46%) | 2 371 (40%) |
| Former | 13 119 (27%) | 1 788 (30%) |
| Current | 13 325 (27%) | 1 802 (30%) |
| **Physical activity** | | |
| Inactive | 8 910 (18%) | 1 194 (20%) |
| Low | 13 880 (29%) | 1 637 (27%) |
| Medium | 20 102 (41%) | 2 369 (40%) |
| High | 5 714 (12%) | 761 (13%) |
| **Alcohol use** | | |
| Abstainers | 15 987 (33%) | 2 070 (35%) |
| Light | 25 225 (52%) | 3 014 (50%) |
| Moderate/Heavy | 7 394 (15%) | 877 (15%) |
| **Education** | | |
| <10y | 14 385 (30%) | 1 872 (31%) |
| 10-12y | 22 435 (46%) | 2 812 (47%) |
| >12y | 11 786 (24%) | 1 277 (21%) |
| **Age (y)** | 46.6 ± 15.9 | 46.0 ± 16.1 |
| **BMI (kg/m$^2$)** | 26.1 ± 4.0 | 27.0 ± 4.6 |
| **W/H ratio** | 0.84 ± 0.08 | 0.86 ± 0.08 |
| **C-reactive protein (µg/mL)** | 2.4 ± 5.3 | 3.2 ± 7.4 |
| **Diabetes Mellitus** | 1 081 (2.2%) | 189 (3.2%) |

Values are mean ± SD or n (%)

Abbreviations: BMI, body mass index; W/H ratio, waist to hip ratio

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Table 2. Associations between asthma, asthma control and the risk of AF during 15.4 years of follow-up among 54 567 participants

| | N | Person-years, y | No. of cases (%) | Model 1 | Model 2 |
|---|---|---|---|---|---|
| **Asthma** | | | | | |
| No asthma (ref) | 48 606 | 752 149 | 1 806 (3.7%) | Reference | Reference |
| Ever asthma | 5 961 | 89 883 | 265 (4.5%) | 1.30 (1.13 – 1.48) | 1.27 (1.10 – 1.46) |
| Diagnosed asthma | 3 934 | 56 192 | 199 (5.1%) | 1.42 (1.21 – 1.67) | 1.38 (1.18 – 1.61) |
| Active asthma | 2 485 | 31 889 | 150 (6.0%) | 1.81 (1.51 – 2.16) | 1.76 (1.47 – 2.10) |
| **Asthma control[1]** | | | | | |
| No asthma (ref) | 48 606 | 752 149 | 1 806 (3.7%) | Reference | Reference |
| Controlled asthma | 2 947 | 44 267 | 108 (3.7%) | 1.19 (0.98 – 1.45) | 1.16 (0.95 – 1.41) |
| Partly controlled asthma | 1 807 | 27 974 | 101 (5.6%) | 1.42 (1.16 – 1.73) | 1.40 (1.14 – 1.71) |
| Uncontrolled asthma | 547 | 8 329 | 38 (7.0%) | 1.74 (1.25 – 2.41) | 1.74 (1.26 – 2.42) |

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, W/H ratio and diabetes mellitus

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*Table 3. Mediation analysis for the associations between asthma, asthma control and the risk of AF during 15.4 years of follow-up among 54 567 participants*

| | beta2-agonists use[1] (n = 52 477) | | | C-Reactive Protein[2] (n = 30 332) | | |
|---|---|---|---|---|---|---|
| | Model 2 adjusted HR[3] | Model 2 + Mediator adjusted HR[4] | Change in HR (%)[5] | Model 2 adjusted HR[3] | Model 2 + Mediator adjusted HR[4] | Change in HR (%)[5] |
| **Asthma** | | | | | | |
| Ever asthma | 1.17 (1.00 – 1.38) | 1.09 (0.90 – 1.34) | -7 | 1.18 (0.99 – 1.41) | 1.18 (0.99 - 1.41) | 0 |
| Diagnosed asthma | 1.19 (0.99 – 1.43) | 1.11 (0.87 – 1.41) | -7 | 1.39 (1.12 – 1.72) | 1.39 (1.12 – 1.72) | 0 |
| Active asthma | 1.50 (1.22 – 1.85) | 1.60 (1.61 – 2.20) | 6 | 1.51 (1.19 – 1.92) | 1.51 (1.19 - 1.92) | 0 |
| **Asthma Control** | | | | | | |
| Controlled asthma | 0.95 (0.74 – 1.23) | 0.95 (0.74 - 1.23) | 0 | 1.08 (0.84 – 1.40) | 1.08 (0.84 – 1.40) | 0 |
| Partly controlled asthma | 1.26 (1.00 – 1.58) | 1.31 (0.97 – 1.77) | 4 | 1.62 (1.16 – 2.27) | 1.61 (1.15 – 2.26) | 1 |
| Uncontrolled asthma | 1.64 (1.15 – 2.33) | 1.78 (1.09 – 2.88) | 8 | 1.95 (1.10 – 3.46) | 1.93 (1.09 – 3.42) | 1 |

[1] Self-assessed long or/and short beta2-agonists use at baseline, n = 1362 (23%) among participants with asthma[2] High sensitivity C-reactive protein was measured in HUNT3 only

[3] Model 2 adjusted HR (age, sex, BMI, smoking status, alcohol use, physical activity, education level, W/H ratio and diabetes mellitus) with exclusion of missing values in the respective covariates (beta2-agonists and hsCRP).

[4] Adjusted for model 2 and the respective covariate

[5] Mediation was assessed as the % change in the HRs between model 2 adjusted HR and mediator plus model 2 adjusted

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