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Asthma, asthma control and risk of ischemic stroke: The HUNT study

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ABSTRACT

Background: Asthma, a chronic inflammatory airway disease, shares common pathophysiological mechanisms with ischemic stroke. The aim of the study is to assess the association between asthma, levels of asthma control and ischemic stroke risk in men and women and by smoking habits.

Methods: This prospective population-based cohort study utilized data on 58 712 adults from HUNT Study in Norway free from stroke. Self-reported asthma was categorized as ever asthma, non-active asthma and active asthma (i.e., being on asthma medication within 12 months of the baseline). Asthma control was defined according to the Global Initiative for Asthma questionnaire and was categorized into controlled and not controlled asthma. Stroke was ascertained by linking HUNT data with Nord-Trøndelag hospital records and the Norwegian Patient Registry.

Results: During a mean follow-up of 17.3 ± 5.3 years, 2619 participants (4.5%) had a first stroke. Not controlled asthma was associated with a modest increased risk of stroke (adjusted HR 1.34, 95%CI 1.03–1.73). Subgroup analyses revealed that the respective association was stronger among those with history of smoking (HR 1.48, 95%CI 1.10–2.00) and males (HR 1.55, 95%CI 1.12–2.16) while absent in non-smokers (HR 1.02, 95%CI 0.61–1.70) and females (HR 1.05, 95%CI 0.69–1.60). Likewise, active asthma was associated with similar increased stroke risk among smokers and males and absent in non-smokers and females.

Conclusions: Symptomatic and active asthma was associated with a modest increased relative risk for ischemic stroke in smokers and males. Future studies should clarify the difference in risks and mechanisms between different phenotypes of asthma.

1. Introduction

Stroke is the second leading cause of death globally and the leading cause of long-term and preventable disability [1]. Major risk factors such as smoking, hypertension and ageing population have been identified [1]. However, the burden of stroke is projected to rise and further understanding of risk factors of the disease is highly warranted.

Asthma is a chronic inflammatory airway disease, characterized by reversible airway obstruction, affecting as many as 30 million individuals in Europe [2]. Asthma is not curable, but rather managed by controlling the symptoms, with asthma medication as a first line approach [3]. However, beta2-agonist use has been shown to increase the risk of arrythmias [4,5], a major risk factor for stroke [6]. Furthermore, asthma and atherosclerosis share many common risk factors and pathophysiologic pathways linked to the chronic inflammatory response present in both diseases [7]. The presence of asthma is associated with prothrombotic factors and endothelial dysfunction that contribute to the development of atherothrombosis [8,9]. Also, smoking is a major risk factor for both stroke and lung disease [10,11], and smokers with asthma are known to have poorer symptom control and disease prognosis than non-smokers [12].

Several epidemiological studies have found a higher risk of stroke in adults with asthma compared to those without asthma [13–18]. However, most of previous studies could not distinguish between adult or

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child-onset asthma and did not address the possibility of misclassification between asthma and other lung diseases like COPD. In addition, no previous studies have assessed the association between levels of asthma control and stroke risk. Therefore, we used a large Norwegian population cohort to assess the associations between asthma, asthma control and stroke risk in men and women and by smoking habits.

2. Methods

2.1. Study design and population

All adults ≥20 years residing in Nord-Trøndelag County, Norway, received a postal invitation to participate in the HUNT Study. The HUNT study started in 1984–1986 and consists of four surveys, HUNT1 (1984–86), HUNT2 (1995–97), HUNT3 (2006–08) and HUNT4 (2017–2019). Information was collected by self-administered questionnaires and a clinical examination, which included blood sampling. A detailed description of HUNT can be found elsewhere [19,20].

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 individuals (54.1%) participated in HUNT2 and HUNT3, respectively, giving us a total sample 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%) were invited to HUNT Lung Study consisting of a random HUNT2 and HUNT3 sample and a symptom sample that included participants who reported attacks of wheezing or breathlessness during the last 12 months, a history of asthma or to ever have used asthma medication at baseline (Fig. S1). Of the invitees, 16 115 individuals (67.9%) participated completing additional interviews and questionnaires about asthma history, asthma symptoms, medication use and lung function [19] (Fig. 1).

We excluded participants with missing information on asthma (n = 93 [0.1%]) or those with missing information on at least one covariate (total n = 18 005 [22.8%]) with the following variables: physical activity n = 13 941 [17.7%], smoking status n = 1702 [2.2%], alcohol use n = 2678 [3.4%], education n = 4540 [5.8%], diabetes n = 124 [0.16%], BMI n = 919 [1.2%] and TotalC/HDL n = 953 [1.3%]. In addition, to minimize potential undiagnosed asthma, we excluded those

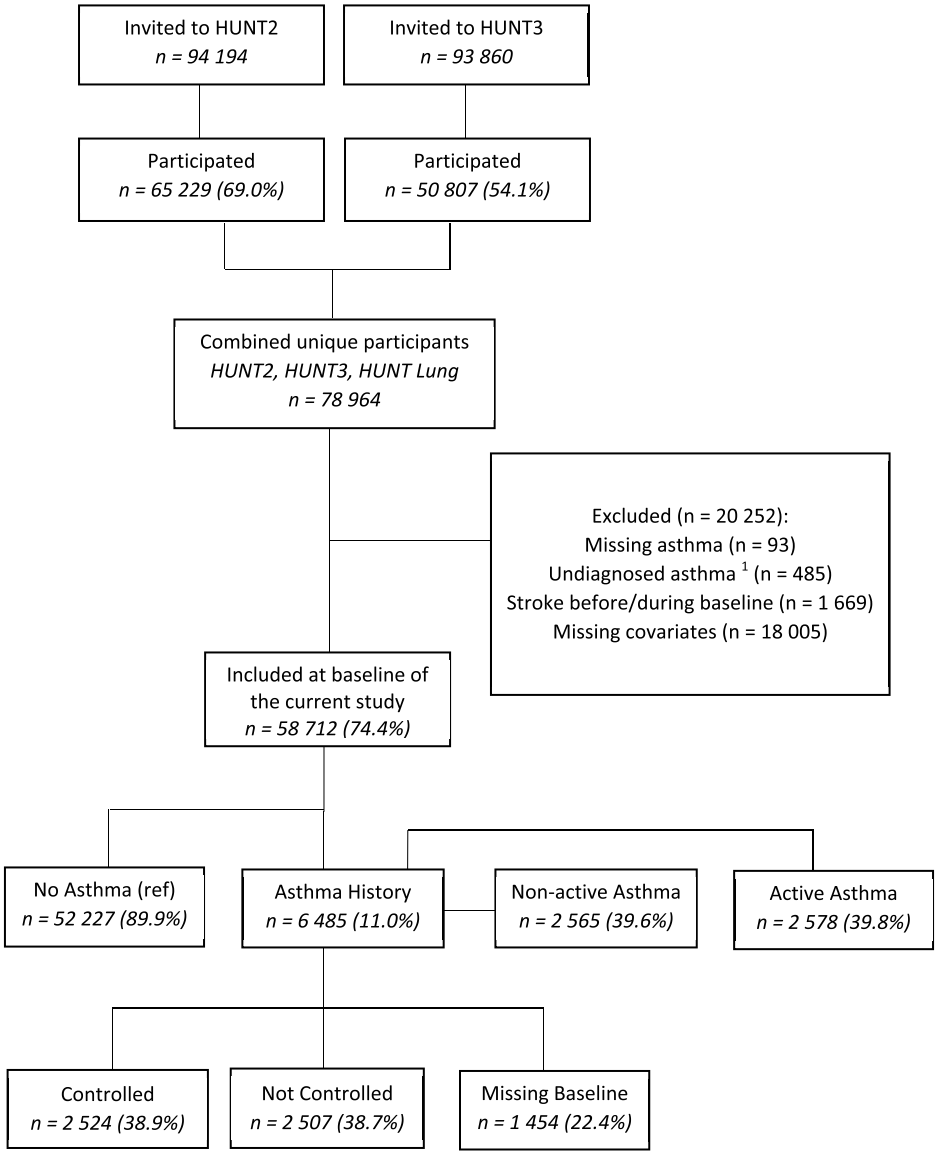

Fig. 1. Flowchart of the participants
[1] Based on asthma symptoms and medication use Asthma control based on the GINA Global Strategy for Asthma Management and Prevention guidelines.

who did not report asthma but had a history of taking medications prescribed for their asthma at baseline (n = 485 [0.6%]). Lastly, participants who had a history of stroke at baseline were excluded (n = 1669 [2.5%]) leaving a total of 58 712 participants (74.4%) included in the analyses (Fig. 1).

2.2. Asthma

Self-reported asthma status was ascertained using the HUNT baseline and the Lung Study questionnaires and stratified into three self-reported asthma groups ever asthma, active asthma and non-active asthma. Ever asthma was defined as those with an affirmative answer to "Have you ever had asthma?". Active asthma was defined as those with an affirmative and not missing answer to all the following: "Have you ever had asthma?" (no missing), "Have you been diagnosed with asthma by a doctor?" (missing n = 1395) and "In the past 12 months, have you used asthma medication?" (missing n = 993). In addition, those who answered positively to the first ever asthma question but answered negatively to the third asthma medication question were classified as having non-active asthma (i.e. having asthma but not actively using asthma medication). No frequency or dosage has been recorded for the medication question, while those with missing answers were excluded from respective asthma group analyses. We regarded current asthma medication use, which requires doctor prescription, as a more reliable proxy for asthma status (i.e. passive or active) than asthma symptoms that can change over short period of time.

2.3. 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 Management and Prevention 2016 [3] (Supplementary Table 3). Asthma control was categorized as controlled or not controlled asthma based on the following characteristics: daytime symptoms (2 times per week or less or more than 2 times/week, missing n = 807), night awakenings (none or any, missing n = 812), the need for reliever medication (2 times/week or less or more than 2 times/week, missing n = 807) and limitation of activities (none or any, missing n = 1085). Participants categorized in the controlled asthma group reported no such asthma characteristics and had no missing answers, while participants in the not controlled asthma group reported 1 or more characteristics. There were 1454 participants with missing on at least one of the asthma symptoms while 737 individuals had missing values for all the symptoms.

2.4. Stroke ascertainment

Incidence of ischemic stroke was ascertained by linking HUNT data with hospital electronic records from the two hospitals in Nord-Trøndelag County between 1995 and 2016. We used International Statistical Classification of Diseases and Related Health Problems, 9th Revision (ICD-9) codes 433 and 434 and 10th Revision (ICD-10) code I63 (all positions). Electronic medical records and diagnostic imaging of hospital admissions for stroke has been shown to have high sensitivity and positive predictive values [21,22].

2.5. Covariates

A self-administrated questionnaire was used to assess participants' smoking status (never, former and current), physical activity (inactive, low, medium and high), alcohol use (abstainers, light, moderate and heavy drinkers), education (<10, 10–12, >12 years) and medical history of common chronic diseases. Pack-years of smoking was calculated as: pack-years = (number of cigarettes a day * years of smoking)/20. Comorbidities such as diabetes and COPD were self-reported at baseline. A detailed description of these covariates can be found elsewhere [5].

Body mass index (BMI) was categorized into 4 categories (underweight <18.5, normal 18.5–25, overweight 25–30, obese >30). 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. 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) in a spirometry subsample of the HUNT Lung study (n = 11 622 within total sample and n = 4385 among those with asthma). 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. This cut-off value has been shown to be clinically acceptable and is recommended by The European Respiratory Society (ERS)/American Thoracic Society (ATS) [23,24]. C-reactive protein (CRP) was measured from serum samples taken during HUNT3 baseline medical visit using latex immunoassay methodology (Abbot). Information on self-reported asthma medication use was obtained from the Lung Study Questionnaire. Short acting beta2-agonists (SABA), long acting beta2-agonists (LABA) and inhaled corticosteroid (ICS) use was classified as non-current users or current users based on the regular use in the last 6 months in HUNT2 and use in the last 12 months in HUNT3.

2.6. Statistical analyses

Baseline characteristics were presented as means and SDs for continuous variables and as numbers and percentages for categorical variables. We used Cox proportional hazard models to estimate hazard ratios (HRs) to assess the prospective association between asthma, asthma control and risk of stroke. Risk time was calculated from baseline until the examination at which stroke was first diagnosed, death, emigration or to the end of follow-up (31st December 2016) whichever came first. We used a time-varying approach which means that for those participants that attended both HUNT2 and HUNT3 examinations and did not have stroke before HUNT3, we used HUNT3 data to update asthma status and the status of the potential confounders (Fig. S2).

A minimally adjusted model included sex, age and birth year cohort (birth calendar year in 5-year intervals) to account for the fact that the risk of stroke has decreased over time [25] (Model 1). In a fully adjusted model (Model 2), we controlled for traditional stroke risk factors including smoking status, physical activity, alcohol consumption, education, BMI, total cholesterol/HDL ratio, hypertension and diabetes. We also evaluated effect modification by gender, smoking (history of smoking versus no smoking history) and age of asthma onset (child versus adult) 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 stroke. We compared HRs of the asthma groups and risk of stroke from Model 2 with and without inclusion of current beta2-agonists use (short and long acting), inhaled corticosteroids and C-reactive protein levels, all of which could act as a mediator of the association.

We used attained age as the time scale in our analyses to account for age being a strong determinant of the disease in our study [26]. We tested for multicollinearity by assessing the correlation coefficient between variables in our models as well as performing variance inflation analysis (VIF) [27]. The proportionality of hazards was 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).

2.7. Sensitivity analysis

In a sensitivity analysis, we repeated our analysis after adjusting for self-reported chronic comorbidities at baseline including cardiovascular

disease (acute myocardial infarction, heart failure and atrial fibrillation), hypo-, and –hyperthyroidism, rheumatoid arthritis, angina pectoris, fibromyalgia, ankylosing spondylitis, epilepsy and osteoporosis. Secondly, we also excluded participants who had been diagnosed with acute myocardial infarction, heart failure or atrial fibrillation at baseline or during follow-up and before stroke event. Thirdly, to minimize misclassification between COPD or heart failure and asthma we excluded participants with asthma who had self-reported chronic bronchitis or emphysema at baseline or had all of the following: post-bronchodilator FEV1/forced vital capacity Z score lower than -1.64, a history of smoking tobacco, and a diagnosis of asthma that occurred after the age of 40 years. We also adjusted for smoking pack-years after imputing missing data to assess potential residual confounding by smoking. Lastly, we performed multiple imputation by chained equations [28] for missing physical activity (n = 9715) to assess any impact of missing data on the results.

We performed the data analyses using Stata 15 for Windows 10 (StataCorp). The study received ethics approval from the Regional Committee for Medical Research Ethics. All study participants gave informed written consent.

3. Results

A total of 58 712 individuals were used for the main analysis, out of which 2619 participants (4.5%) were diagnosed with ischemic stroke during a mean follow-up of 17.2 ± 5.4 years contributing a total of 1 008 091 person-years. The median age and stroke incidence were higher among males than females (46.4y. vs 44.5y. and 5.3% vs 3.8%). Of our study sample, 6485 adults (11.1%) reported asthma history at baseline while 2578 adults (4.4%) reported active asthma. Participants with asthma were more likely to be current smokers, have lower education, higher BMI and to have diabetes mellitus and COPD as well as higher CRP levels and lower FEV/FVC Z-Score than individuals without asthma (Table 1). In contrast, participants with non-active and controlled asthma were younger, less likely to be smokers, had higher education, lower BMI and lower prevalence of comorbidities than other asthma groups. In addition, participants with asthma and smoking history were more likely to have poorer asthma control, lower lung function and higher prevalence of comorbidities (Table S4). The prevalence of controlled asthma and not controlled asthma among participants with asthma was 2524 (38.9%) and 2507 (38.7%), respectively with 1454 missing values (22.4%).

3.1. Association of asthma and asthma control with stroke risk

After adjustment for potential confounders (Model 2), there was no association between ever asthma and non-active asthma and risk of stroke (HR 1.07, 95% CI 0.95–1.22 and HR 0.95, 95% CI 0.76–1.20, respectively). Participants with active asthma showed some evidence for increased risk of developing stroke compared with those without asthma (HR 1.17, 95% CI 0.97–1.41) (Table 2). Similarly, we found a small increased risk of stroke among participants with not controlled asthma compared to controlled asthma (HR 1.34, 95% CI 1.03–1.73).

3.2. Other analyses

Among 6485 participants with asthma, 2270 (35.0%) and 1394 individuals (21.5%) currently used beta2-agonists and ICS with 794 (12.2%) and 1394 (21.5%) missing values, respectively. Adjustment for beta2-agonists or ICS use increased the absolute relative risk for stroke by 29% in the active asthma group and 18% and 5%, respectively, in not controlled asthma group (Table 3). HRs did not change after adjustment for hsCRP levels (results not shown).

The relative risk for stroke was higher among adults with history of smoking in ever and active asthma groups (HR 1.17, 95% CI 1.01–1.35 and HR 1.31, 95% CI 1.06–1.62, respectively with p for interaction

Table 1
Baseline characteristics of asthma groups in 58 712 participants at baseline.

Characteristic	No asthma (n = 52 227)	Ever asthma (n = 6485)	Active asthma (n = 2578)	Controlled (n = 2524)	Not controlled (n = 2507)
Female	27 543 (53%)	3538 (55%)	1480 (57%)	1413 (56%)	1362 (54%)
Smoking					
Never	23 278 (45%)	2467 (38%)	894 (35%)	1052 (42%)	825 (33%)
Former	13 970 (27%)	1948 (30%)	879 (34%)	729 (29%)	853 (34%)
Current	14 979 (29%)	2047 (32%)	805 (31%)	743 (29%)	830 (33%)
Pack-Years[a]	6.63 ± 10.3	8.4 ± 11.9	9.5 ± 12.7	6.8 ± 10.6	10.6 ± 13.5
Physical activity					
Inactive	9753 (19%)	1300 (20%)	564 (22%)	431 (17%)	601 (24%)
Low	14 959 (29%)	1799 (28%)	735 (28%)	704 (28%)	725 (29%)
Medium	21 422 (41%)	2554 (39%)	995 (39%)	1041 (41%)	936 (37%)
High	6093 (12%)	809 (13%)	284 (11%)	348 (14%)	245 (10%)
Alcohol use					
Abstainers	17 138 (33%)	2232 (35%)	940 (36%)	770 (31%)	970 (39%)
Light	27 055 (52%)	3280 (51%)	1275 (50%)	1369 (54%)	1195 (47%)
Moderate/ Heavy	8034 (15%)	950 (14%)	363 (14%)	385 (15%)	342 (14%)
Education					
<10y	15 445 (30%)	2055 (32%)	915 (35%)	657 (26%)	950 (38%)
10-12y	24 238 (46%)	3030 (47%)	1179 (46%)	1252 (50%)	1129 (45%)
>12y	12 544 (24%)	1377 (21%)	484 (19%)	615 (24%)	428 (17%)
BMI					
Under/ Normal	21 879 (42%)	2372 (37%)	900 (35%)	940 (37%)	863 (35%)
Over	22 315 (43%)	2698 (42%)	1066 (41%)	1084 (43%)	1031 (41%)
Obese	8033 (15%)	1392 (21%)	612 (24%)	500 (20%)	588 (24%)
Asthma Medication[b]					
Beta2-agonist use	–	2114 (37%)	1758 (68%)	464 (18%)	1616 (65%)
ICS use	–	1234 (24%)	1626 (43%)	523 (21%)	1335 (53%)
Asthma Symptoms					
Daytime Symptoms	–	1411 (25%)	929 (36%)	–	1412 (57%)
Night Awakenings	–	905 (16%)	648 (25%)	–	906 (37%)
Limitations activities	–	464 (8.6%)	352 (14%)	–	464 (21%)
Diabetes Mellitus	1168 (2.2%)	200 (3.1%)	87 (3.4%)	57 (2.3%)	101 (4.0%)
Hypertension	19 588 (38%)	2509 (39%)	1105 (43%)	814 (32%)	1139 (45%)
Self-reported COPD	826 (1.6%)	1320 (20%)	781 (30%)	397 (16%)	767 (31%)
Asthma Duration (y)	–	22.2 ± 18.5	18.6 ± 15.9	24.8 ± 16.6	19.6 ± 16.9
Asthma onset (age)	–	26.4 ± 21.4	32.4 ± 20.8	21.4 ± 19.6	31.5 ± 21.7
FEV_1/FVC Z score[c]	-0.39 ± 0.98	-0.65 ± 1.08	-1.09 ± 1.30	-0.60 ± 1.00	-1.19 ± 1.37
Age (y)	46.5 ± 15.9	46.3 ± 16.0	48.5 ± 15.8	43.8 ± 14.6	49.7 ± 16.3
Total C:HDL	4.5 ± 1.6	4.51 ± 1.56	4.5 ± 1.5	4.5 ± 1.5	4.6 ± 1.6
Triglycerides (mmol/L)	1.7 ± 1.1	1.75 ± 1.12	1.8 ± 1.1	1.7 ± 1.1	1.8 ± 1.2

(continued on next page)

Table 1 (*continued*)

Characteristic	No asthma (n = 52 227)	Ever asthma (n = 6485)	Active asthma (n = 2578)	Controlled (n = 2524)	Not controlled (n = 2507)
C-reactive protein (μg/mL)[d]	2.6 ± 5.6	3.19 ± 6.37	3.3 ± 6.3	2.8 ± 5.4	3.7 ± 7.4

Values are mean ± SD or n (%).
Abbreviations: BMI, body mass index; Total C/HDL, total cholesterol to high density lipoprotein ratio.
[a] Calculated as: pack-years = (number of cigarettes a day * years of smoking)/20 (n = 55 542).
[b] Current use defined as use in the last 6 months at HUNT2 baseline for ICS and last month for beta2-agonist and last 12 months at HUNT3 baseline for both medications.
[c] Force expiratory volume/Forced vital capacity Z-score based on Global Lung Function Initiative (GLI)-LLN method measured in small subsample (n = 11 622).
[d] CRP measured in HUNT3 and a small subsample of HUNT2 cohort (total n = 41 835).

between asthma status and smoking history <0.100) as well as not controlled asthma group (1.48, 95% CI 1.10–2.00, p for interaction = 0.387) (Table 4). The risk of stroke was absent in participants with no smoking history in all asthma groups. Gender stratification revealed a stronger relative risk of stroke among males than females within the active asthma group (HR 1.31, 95% CI 1.03–1.66 p for interaction = 0.140) and the not controlled asthma group (HR 1.55, 95% CI 1.12–2.16, p for interaction = 0.216) (Table 4). Lastly, we found no strong changes in HRs or evidence for interaction between asthma groups and age of onset (child vs adult, p for interaction >0.200, missing age of asthma onset n = 1571) (results not shown).

3.3. Sensitivity analyses

The results for asthma and asthma control remained consistent after adjusting for self-reported comorbidities at baseline (n = 14 493), excluding participants with other prevalent and incident CVD events before censoring (n = 4912) (Table S6) or imputing missing data on physical activity (n = 9715) and adjusting for it (Table S6). Similarly, HRs did not change after excluding participants with asthma who either had self-reported COPD at baseline (n = 1320) or had all of the following (n for presence of all characteristics = 202): post-bronchodilator FEV1/forced vital capacity Z score lower than -1.64 (n = 803), a history of smoking tobacco (n = 4012), and a diagnosis of asthma that occurred after the age of 40 years (n = 941), with a total exclusion of 1425 participants. Excluding COPD cases (n = 1023) with the same criteria among those with history of smoking, increased HR in the active asthma group (HR 1.45, 95% CI 1.09–1.93) and the not controlled asthma group (HR 1.69, 95% CI 1.17–2.45) compared to the main analysis (HR 1.34, 95% CI 1.03–1.73 and HR 1.43, 95% CI 1.07–1.91) (Table S7). Lastly, adjusting for smoking pack-years among those with history of smoking did not change HRs.

4. Discussion

The results of this large prospective study show that participants with self-reported history of asthma and current asthma medication use

Table 2
Associations between asthma, asthma control and the risk of stroke during 17.2 years of follow-up.

	N	No. of cases (%)	Unadjusted	Model 1	Model 2
Asthma Status					
No asthma	52 227	2317 (4.4%)	Reference	Reference	Reference
Ever asthma	6485	302 (4.7%)	1.10 (0.97–1.25)	1.10 (0.97–1.25)	1.07 (0.95–1.22)
Non-active	2565	88 (3.7%)	0.98 (0.78–1.23)	0.97 (0.77–1.22)	0.95 (0.76–1.20)
Active asthma	2578	144 (5.6%)	1.20 (1.00–1.45)*	1.21 (1.00–1.45)*	1.17 (0.97–1.41)
Asthma control					
Controlled	2524	88 (3.5%)	Reference	Reference	Reference
Not controlled	2507	142 (5.7%)	1.39 (1.10–1.76)	1.39 (1.08–1.79)	1.34 (1.03–1.73)

Hazard ratios and 95% confidence intervals were derived from Cox proportional hazards models.
Model 1 adjusted for age, birth year cohort and sex.
Model 2 adjusted for age, birth year cohort, sex, BMI, smoking status, alcohol use, education level, total cholesterol/HDL ratio, hypertension and diabetes mellitus.
*p value = 0.051 and 0.048 for unadjusted and model 1, respectively.

Table 3
Mediation analysis for the associations between asthma, asthma control and the risk of stroke.

	Beta2-Agonist use (n = 57 918)[a]			ICS Use (n = 57 318)[a]		
	Model 2 adjusted HR[b]	Model 2 + Mediator adjusted HR[c]	Change (%)[f]	Model 2 adjusted HR[d]	Model 2 + Mediator adjusted HR[e]	Change (%)[f]
Asthma Status						
No asthma	Reference	Reference		Reference	Reference	
Ever asthma	1.00 (0.87–1.14)	1.00 (0.84–1.18)	0	1.10 (0.94–1.28)	1.15 (0.94–1.41)	5
Non-active asthma	–	–	–	–	–	–
Active asthma	1.16 (0.95–1.40)	1.45 (1.06–1.97)	29	1.13 (0.93–1.38)	1.42 (1.02–1.99)	29
Asthma Control						
Controlled	Reference	Reference		Reference	Reference	
Not controlled	1.32 (1.03–1.71)	1.50 (1.07–2.10)	18	1.28 (0.97–1.68)	1.33 (0.96–1.85)	5

[a] Beta2-agonist users n = 2270 (35.0%) and missing n = 794 (12.2%) among adults with asthma; ICS users n = 1241 (19.1%) and missing n = 1394 (21.5%) among adults with asthma. Current use defined as use in the last 6 months at HUNT2 baseline for ICS and last month for beta2-agonist and last 12 months at HUNT3 baseline for both medications.
[b] Adjusted for Model 2; participants with missing current beta2-agonist medication use information excluded.
[c] Adjusted for model 2 and current beta2-agonist use.
[d] Adjusted for Model 2; participants with missing current ICS medication use information excluded.
[e] Adjusted for model 2 and current ICS use.
[f] Mediation was assessed as the absolute change between model 2 only adjusted HR and model 2 + mediator adjusted HR.

Table 4
Stratification by smoking history and gender in the associations between asthma, asthma control and the risk of stroke.

Categories	Smoking History		P value*	Gender		P value*
	Never smokers (n = 25 751)	Ever smokers[a] (n = 32 961)		Female (n = 31 081)	Male (n = 27 631)	
Asthma Status						
No asthma	Reference	Reference		Reference	Reference	
Ever asthma	0.88 (0.69–1.11)	1.17 (1.01–1.35)	**0.052**	1.00 (0.83–1.22)	1.13 (0.96–1.33)	0.341
Non-active asthma	0.86 (0.58–1.30)	0.99 (0.75–1.31)	0.595	0.96 (0.67–1.38)	0.95 (0.70–1.29)	0.953
Active asthma	0.87 (0.59–1.30)	1.31 (1.06–1.62)	**0.098**	1.00 (0.74–1.35)	1.31 (1.03–1.66)	0.140
Asthma Control						
Controlled	Reference	Reference		Reference	Reference	
Not controlled	1.02 (0.61–1.70)	1.48 (1.10–2.00)	0.387	1.05 (0.69–1.60)	1.555 (1.12–2.16)	0.216

Hazard ratios and 95% confidence intervals were derived from Cox proportional hazards models.
Adjusted for age, birth year cohort, sex, BMI, smoking status, alcohol use, education level, total cholesterol/HDL ratio, hypertension and diabetes mellitus.
*P for interaction between asthma status and smoking history or gender.
[a] Ever smokers include former and current smokers.

and a history of smoking or presence of asthma symptoms have a modest increased risk of stroke. The association between asthma and stroke was absent among lifetime non-smokers suggesting the asthma-stroke association may in part be due to smoking or potential misclassification of COPD as asthma. In addition, associations were stronger in males than females, indicating modifying effect by gender.

Several previous studies have investigated the association between asthma and stroke [13–18]. A Taiwanese nationwide prospective study found a modest higher risk of stroke in a cohort of adults diagnosed with adult-onset asthma and a history of asthma medication use (HR 1.37, 95% CI: 1.27–1.48) compared to those without asthma [17]. Another large prospective study of 2 matched cohorts using an insurance database found a similar modest increased risk of stroke in adults with asthma (HR 1.20, 95% CI: 1.15–1.25) [16]. However, a recent large Korean case-control study did not find increased ischemic stroke risk among participants with asthma (HR 0.91, 95% CI 0.86–0.95) [18]. These studies did not address the possible misclassification of COPD as asthma, some did not have information on smoking status and asthma symptoms and some of the important potential confounders such as alcohol use, education and physical activity were missing.

In line with our study, a large prospective study found higher stroke mortality among current smokers (HR 1.97, 95% CI: 1.20–3.23) than non or ex-smokers (HR 0.87, 95% CI: 0.53–1.43) within the active asthma group [14]. Similarly, stroke risk slightly attenuated in participants with asthma after excluding lifetime smokers in a community cohort (HR 1.55, 95% CI:0.95–2.52 vs HR 1.26, 95% CI: 0.68–2.33) [15] and in Copenhagen prospective study [29]. We found evidence for interaction between smoking and asthma status with increased risk of stroke in adults with active and not controlled asthma and a history of smoking but not in lifetime non-smokers.

The prevalence of tobacco smoking is high in individuals with asthma and it is a significant risk factor for both stroke and asthma [10]. Active cigarette smoking interacts with asthma which causes more severe symptoms and frequent asthma exacerbations, accelerated decline in lung function, and adverse effects on clinical, prognostic and therapeutic outcomes [12,30]. It has been reported that impaired lung function is strongly associated with mortality and CVD risk including stroke [31,32]. In addition, participants with asthma and no smoking history reported no excess CVD risk compared to non-smokers without asthma within a Danish cohort [29]. In line with these findings, we observed more frequent asthma symptoms and medication use, poorer lung function and higher prevalence of comorbidities in smokers with asthma than non-smokers with asthma in our study. Also, excluding individuals with history of smoking diminished stroke risk in those reporting recent asthma symptoms. Therefore, it is highly likely that higher risk of stroke arises from tobacco smoking which combined with the presence of asthma may lead to multiple adverse outcomes and poorer prognosis. This enforces the idea that quitting smoking should be highly encouraged in those with asthma.

Obstructive lung diseases are characterized by airflow limitation and include both asthma and chronic obstructive pulmonary disease (COPD). In Norway, COPD was often called asthma at the time of HUNT2 study and we found that 35% of those with asthma and current smoking had self-reported COPD in our study. COPD is most prevalent among smokers and have been associated with increased risk of stroke [11]. In addition, asthma and COPD, although distinctive, share many similar features and often co-exists together termed as asthma-COPD overlap syndrome [33]. Those with asthma-COPD overlap are more likely to have worse respiratory symptoms, poorer quality of life, increased exacerbations and hospital admissions than those with asthma alone [33,34]. Therefore, we considered that the excess stroke risk in individuals with asthma and smoking may be partly due to asthma-COPD overlap or misclassification of COPD as asthma in smokers. In addition, previous study has shown that majority of the stroke risk in COPD patients is attributed to the history of smoking [35]. Although, in our study stroke risk slightly increased after excluding participants with self-reported COPD and COPD characteristics in smokers, the likelihood of misclassification remains.

In addition, we found higher risk of stroke in the not controlled asthma group compared to the controlled asthma group, characterized by the presence of at least one asthma symptom at baseline. In line with our findings, a previous prospective study found that participants reporting attacks of wheezing and shortness of breath had a greater risk for stroke compared to participants with asthma, but without these symptoms [15]. Poor asthma symptom control could be as a result of persistent smoking and suboptimal asthma treatment. Asthma medication, ICS with or without beta2-agonists (SABA or LABA), is the first line of approach for asthma control [36]. It has been reported that a good adherence to a combination of ICS with LABA or SABA treatment results in a better long-term asthma control and less hospital admissions and exacerbations and improved lung function [37–39].

On the other hand, an American prospective study found an increased stroke risk in asthma medication users, but not in non-users at baseline and during follow-up [16]. Beta2-agonists, the most common asthma medication, is considered to be a significant risk factor for incident atrial fibrillation [4], which in turn is associated with 4-fold increased risk of stroke [6]. However, beta2-agonists have also been shown to improve lung function and reduce symptoms eliminating night-time awakenings and exercise-induced asthma as well as improving quality of life [40–42]. Thus, the higher stroke risk in medication users may reflect confounding by indication, as medication is prescribed during times of asthma exacerbations and frequent symptoms. In our study, adjustment for current beta2-agonist use slightly increased the risk of stroke in active asthma and uncontrolled asthma groups, indicating a potentially protective effect. In addition, including asthmatics with symptoms of asthma in the past 12 months but not taking asthma medication to active asthma group did not change the results.

In our study, we observed higher relative risk for stroke among males than females within the active and not controlled asthma groups. Only one previous study detected gender differences, which found that females with adult-onset asthma had higher carotid intima media thickness [43] and relative risk for stroke than males in crude analysis [13]. However, the association was found in crude analysis and study had a very small sample size (stroke cases n = 19). The effect of hormones could alter the association between asthma and stroke due to oestrogen levels exerting modifying effects on inflammatory response and potential protecting against vascular inflammation and endothelial damage in pre-menopausal women in our study (median age of women in our study was 44.0y.) [44]. Also, in our study males had higher median age and overall incidence of stroke than females whereas it has been previously reported that the median age of first stroke is 4 years lower in males than females [45].

Other potential mechanism underlying the possible association between asthma and risk of stroke is a higher atrial fibrillation risk among adults with asthma, and especially active asthma [5,46]. Arrhythmias have been found to be a significant risk factors for stroke in observational studies [6,47]. Furthermore, it is speculated that asthma may predispose to atherosclerosis through pathophysiologic pathways linked to the chronic inflammatory response [48]. However, we did not find any mediating effect of hsCRP, an inflammatory biomarker, in the association between asthma and stroke.

Our study had several strengths. First, we utilized data from a large cohort with a long follow-up, extensive information on a wide range of confounders and on asthma medication use was available, the study also had a high participation rate and carefully reviewed hospital and register information. All variables including asthma, asthma control and confounders were measured both in HUNT2 and HUNT3 and updated in the analysis for most of the participants allowing us to take into account potential changes in participants' lifestyle habits or exposure status over time.

One of the limitations is that the observational nature of the data could have resulted in residual confounding. However, to influence our results, a potential unmeasured confounder would have to be strongly associated with both asthma and stroke and be unrelated to the confounders already included in our models.

We did not have clinical measures for asthma or COPD and had to rely on the self-reported questionnaires, which could have resulted in potentially non-differential misclassification of the exposure. However, it has been reported that questions on ever asthma and physician diagnosed asthma have high specificity (>90%) [49] and high positive predictive value that give prevalence estimates close to those obtained by clinical judgement [50]. In Norway, COPD was often labelled as asthma by the doctors up until the early 2000s, thus misclassification of COPD as asthma is likely. To partly address this, we excluded participants with self-reported COPD and with COPD characteristics within the asthma groups. However, spirometry data had high missing (n = 2100 among those with asthma) and self-reported COPD would not address substantial under-diagnosis.

The response rate was 69% in HUNT2 (n = 65 299), 54% in HUNT3 (n = 50 807), and 68% in the Lung Study (n = 16 115), which could have introduced selection bias. However, non-respondent studies were performed for HUNT2 and HUNT3 [19,51]. The main reasons for not attending the health survey were lack of time or having moved out of the county, while those in age group of 70 + commonly reported to have regular follow-up by a doctor or hospital and therefore did not need to attend the health survey in HUNT2 [52]. There were no difference for respiratory symptoms or asthma, while stroke was slightly more prevalent in non-responders in HUNT3 [51].

In summary, we observed increased stroke risk among adults with presence of asthma symptoms and those with asthma and a history of smoking with higher relative risk in male gender. Asthma and smoking interaction suggest poorer prognosis in smokers with asthma than non-smokers. The findings highlight the importance of smoking cessation in those with asthma. Future studies should clarify the difference in risks and mechanisms between different phenotypes of asthma.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Aivaras Cepelis: Conceived and designed the analysis, Performed the analysis, Wrote the paper. **Ben M Brumpton**: Conceived and designed the analysis, Wrote the paper. **Lars E Laugsand**: Performed the analysis, Wrote the paper, Other contribution. **Arnulf Langhammer**: Collected the data, Wrote the paper, Other contribution. **Imre Janszky**: Performed the analysis, Wrote the paper, Other contribution. **Linn B Strand**: Conceived and designed the analysis, Wrote the paper, Other contribution.

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Appendix A. Supplementary data

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