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Abstract: Back ground: Chronic airflow obstruction (CAO) is the primary characteristic of Chronic obstructive pulmonary disease (COPD) but is also seen in chronic asthma.
Objective: To compare the prevalence of CAO and possible risk factors between Tartu in Estonia, Reykjavik in Iceland and Uppsala in Sweden.
Methods: All participants underwent spirometry testing of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) before and after bronchodilation. CAO was defined as post-bronchodilator FEV1/FVC below lower limit of normal. Information on respiratory diseases and smoking status, was obtained through questionnaires administered by trained interviewers.
Results: 1,037 men and 956 women participated in the study. The prevalence of CAO was lower in women in Tartu compared to the other centres (4.9% vs. 13.4 and 8.7% in Reykjavik and Uppsala, respectively, p=0.002) while no difference was found for men. A similar picture was seen for the proportion of participants that had smoked 10 pack years or more which was much lower in Tartu for women than in Reykjavik and Uppsala, respectively (13.2% vs. 33.7 and 29.2%, p<0.001) (Figure 1). Of the participants with CAO the majority (57 to 67%) did not have a previous diagnosis of asthma or COPD.
Conclusion: The prevalence of CAO was lower in Estonian women than in women from Iceland and Sweden. The reason for this was probably that the Estonian women had smoked less than the female participants from Iceland and Sweden. The majority of those with CAO do not have a diagnosed lung disease.

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Dear Editor,

We have the privilege of submitting our manuscript" The prevalence of chronic airflow obstruction in three cities in the Nordic-Baltic region".

Chronic airflow obstruction (CAO) is the primary characteristic of chronic obstructive pulmonary disease (COPD) but is also seen in chronic asthma. Previous studies on prevalence of asthma, respiratory allergies and bronchial hyper responsiveness has shown a lower prevalence in eastern Europe compared to western Europe but it is less clear if this is also the case when it comes to CAO

The aim of this analysis was to see whether there is a difference in the prevalence of CAO and the possible risk factors between Tartu in Estonia, Reykjavik in Iceland and Uppsala in Sweden.

In the study we found that the prevalence of CAO was lower in women in Tartu compared to the other centres while no difference was found for men. The reason for this was probably that the Estonian women had smoked less than the female participants from Iceland and Sweden. The majority of those with CAO did not have a diagnosed lung disease. We believe that our study contributes to the understanding of CAO and especially in understanding geographical variation and gender difference. This manuscript could there be of interest to the readers of Respiratory Medicine

We hereby certify that this manuscript is not being submitted elsewhere and we look forward hearing from you.

Sincerely yours on behalf of the authors,
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Conflicts of interest

None of the authors have any conflicts of interest to declare in relation to the manuscript: “The prevalence of chronic airflow obstruction in three cities in the Nordic-Baltic region.”

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The prevalence of chronic airflow obstruction in three cities in the Nordic-Baltic region.

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ABSTRACT

Back ground: Chronic airflow obstruction (CAO) is the primary characteristic of Chronic obstructive pulmonary disease (COPD) but is also seen in chronic asthma.

Objective: To compare the prevalence of CAO and possible risk factors between Tartu in Estonia, Reykjavik in Iceland and Uppsala in Sweden.

Methods: All participants underwent spirometry testing of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) before and after bronchodilation. CAO was defined as post-bronchodilator FEV_1/FVC below lower limit of normal. Information on respiratory diseases and smoking status, was obtained through questionnaires administered by trained interviewers.

Results: 1,037 men and 956 women participated in the study. The prevalence of CAO was lower in women in Tartu compared to the other centres (4.9% vs. 13.4 and 8.7% in Reykjavik and Uppsala, respectively, p=0.002) while no difference was found for men. A similar picture was seen for the proportion of participants that had smoked 10 pack years or more which was much lower in Tartu for women than in Reykjavik and Uppsala, respectively (13.2% vs. 33.7 and 29.2%, p<0.001) (Figure 1). Of the participants with CAO the majority (57 to 67%) did not have a previous diagnosis of asthma or COPD.

Conclusion: The prevalence of CAO was lower in Estonian women than in women from Iceland and Sweden. The reason for this was probably that the Estonian women had smoked less than the female participants from Iceland and Sweden. The majority of those with CAO do not have a diagnosed lung disease.

Keywords: chronic airflow obstruction, COPD, asthma, smoking, gender difference

INTRODUCTION

Chronic airflow obstruction (CAO) is the primary characteristic of chronic obstructive pulmonary disease (COPD). COPD is a disease characterized by a progressive airflow limitation and an accelerated decline in lung function.[1] It is an important cause of morbidity and mortality worldwide and it is suggested that the rates of the disease are generally underestimated. [2] The ageing population of the world and the continuous smoking is a big part of the growing burden of COPD, [2, 3] but previous studies shows that it is not the only explanation. [4] An accurate estimation of the prevalence of CAO and its risk factors would be of great value to prevent a further increase. CAO is also seen in chronic asthma with remodeling of the airway. [5]

The prevalence of CAO and COPD in Europe ranges widely from 2.1 to 26.1 %. [6]. The reason behind this large difference is not fully known. The Burden of Lung Disease Initiative (BOLD) is an international study on the prevalence of CAO and COPD. [7, 8]. Previous studies on prevalence of asthma, respiratory allergies [9] and bronchial hyper responsiveness [10] has shown a lower prevalence in eastern Europe compared to western Europe but it is less clear if this is also the case when it comes to CAO.

The aim of this analysis was to see whether there is a difference in the prevalence of CAO and the possible risk factors between Tartu in Estonia, Reykjavik in Iceland and Uppsala in Sweden.

METHODS

Study design and participants

The report is based on data from BOLD, which is an international study on the prevalence of COPD and its rationale and design are described elsewhere [11]. The participants were adults aged 40 or older recruited through random sampling from the general population of Reykjavik, Iceland 2004-2005, Uppsala, Sweden 2006-2007 and Tartu, Estonia 2009.

Information was obtained about demographics, respiratory symptoms and diagnoses, pharmacological treatment, smoking status, occupational exposure and education level, through questionnaires administered by trained interviewers.

All participants underwent spirometry testing of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) before and after bronchodilation (200 µg salbutamol). The spirometry was conducted with the participant sitting in an upright position wearing a disposable mouth piece and a nose clip. FEV_1 and FVC values were obtained by spirometry using the NDD Easy One, ndd Medizintechnik, Zurich, Switzerland. Height and weight were measured and body mass index (BMI) was calculated as weight in kilograms divided by the square of height expressed in meters.

Serum concentrations of interleukin 6 (IL-6) and C-reactive protein (CRP) were measured at the University Hospital in Reykjavik. Blood was drawn from the antecubital vein of the seated subjects. Specimens were collected in SSTs from Greiner (Kremsmunster, Austria). Serum IL-6 concentrations were measured with enzyme-linked immunosorbent assays, using reagents obtained from IBL (Hamburg, Germany). The lower detection limit of the IL-6 assay was 0.074 ~~pg~~ng/~~m~~L. CRP concentrations were measured on a Kone 30 analyser using a commercially available latex-enhanced immunoturbidimetric assay from Roche Diagnostic Systems (Mannheim, Germany). The lower detection limit of the assay was 0.1 mg/L.

Definition of CAO

CAO was defined as post-bronchodilator FEV_1/FVC below lower limit of normal (LLN) using the reference values from the third United States National Health and Nutrition Examination Survey (NHANES III) for adult Caucasian men and women [12].

Smoking

The participants were divided into never, ex- and current smokers. Pack years were also calculated and the participants were categorized into those that had smoked 10 pack years or less or more than 10 pack years. Passive smoking was defined as answering 'yes' to the question: Has anyone living in your home (besides yourself) smoked a cigarette, pipe or cigar in your home during the past two weeks?

Diagnosed airway disease

Ever asthma was defined as answering yes to the questions: "Has a doctor or other health care provider ever told you that you have asthma, asthmatic bronchitis or allergic bronchitis?" Current asthma was defined as answering yes to the question above and also answering yes to the question: "Do you still have asthma, asthmatic bronchitis or allergic bronchitis?"

Diagnosed COPD was defined as reporting that a doctor or other health care provider had ever told the participant that he or she had chronic bronchitis, chronic obstructive pulmonary disease or emphysema,

Statistical analysis

The statistics were calculated using STATA software, version intercooled STATA 14.2 for Windows (Stata Corporation, Collage Station, Texas). The prevalence estimates for CAO were weighted to reflect the sampling site of each centre [7]. All other analyses used unweighted data. Chi^2 test and ANOVA in bivariable between-centre analyses and logistic regression were used when analysing the independent association between different variables towards CAO. The inflammatory variables were log transformed in the analyses and

expressed as geometric mean with a 95% confidence interval in the table. A $p<0.05$ denoted a statistically significant difference.

RESULTS

In total 1,037 men and 956 women from the different centres participated in the study. The characteristics of the studied population is presented in table 1. Of the participants 177 (9.2 %) had CAO. The prevalence of CAO was lowest in Tartu and highest in Reykjavik. Tartu also had the lowest prevalence of diagnosed asthma and use of medication against asthma or COPD, while no difference was found concerning diagnosed COPD.

Smoking and CAO in men and women

The prevalence of CAO was lower in women in Tartu compared to the other centres (4.9% vs. 13.4 and 8.7% in Reykjavik and Uppsala, respectively, $p=0.002$), while no difference was found for men (Table 2). A similar picture was seen for the proportion of participants that had smoked 10 pack years or more which was much lower in Tartu for women (13.2% vs. 33.7 and 29.2% in Reykjavik and Uppsala, respectively, $p<0.001$) (Table 2).

CAO in the different centres

Comparisons between participants with and without CAO in the three centre are presented in table 3. In all centres having CAO was related to higher age, smoking and lower educational level and asthma. In Reykjavik having CAO was associated with lower BMI and in Uppsala with higher CRP. Levels of IL6 was higher in Reykjavik than the other centres, but no association between IL6 and CAO was found. Of the participants with CAO the majority (57 to 67%) did not have a previous diagnosis of asthma or COPD (Figure 1). There were no significant differences in the characteristics of participants with CAO between the three centres.

Independent risk factors for CAO

In all the centres, older age, current smoking and ever having had asthma were independent risk factors for having CAO (Table 4). Having a low BMI was significantly associated with CAO in Tartu and Reykjavik while a high educational level decreased the risk of having CAO in Reykjavik.

Risk factors for CAO in men and women

Of the male participants with CAO altogether 25% had smoked less than 10 pack years and had never had asthma (Figure 2) with no significant difference between the centres. In women, the proportion with CAO that had smoked less than 10 pack years and had never had asthma was 56% in Tartu, which was significantly higher than in Reykjavik and Uppsala (23 and 18%, respectively) (p=0.04). Age was independently associated CAO in men and women in all centres (table 5). The only significant gender interaction was a stronger association between current smoking and CAO in men than women in Tartu (p=0.04).

DISCUSSION

In this study, we found that the prevalence of CAO in women was considerably lower in Tartu than in the other centres. This correlated to the low number of smokers among the women of Tartu. The study also shows that the majority of the subjects with CAO did not have a diagnosed lung disease. In men, the majority of those with CAO had smoked or had asthma whereas this was not the case in women from Tartu.

The most prominent finding of the study was the difference in prevalence of CAO in women, with Tartu having a much lower prevalence than the other centres. This was probably largely explained by the low frequency of smoking among the women in Tartu. The reason behind the difference in smoking habits among the women is probably multifactorial, including childhood risk factors, like respiratory infections and passive smoking that were not measured in the current study. Part of it could be explained by the model of the cigarette epidemic [13] where different countries are described to be in different stages at the same time. In the first stage smoking is introduced among men with higher socio-economic status while remaining

marginal among women. In the second stage smoking increases and reaches more than half of the male population in most societies, while smoking among women becomes a widespread middle class and later working class habit. In the third stage, smoking begins to decline, especially among men of higher socioeconomic status, but reaches a maximum among women. In the last stage, smoking prevalence decreases among both men and women. Western Europe is described as to be in stage four and a study of an Estonian population between 1990-2010 describes Estonia as to be in the middle of stage three.[14]. When looking at the smoking habits of the women of Tartu, with the lowest percentage of smokers in the oldest and the youngest group, it looks as though the women of Tartu have fast-forwarded through the middle phases and have now reached phase four. In another study, it would be interesting to investigate other sociological factors, such as gender equality and westernization and how it effects the smoking habits of a population.

Having CAO is the primary characteristic of COPD but is also relatively common in patients with chronic asthma [5, 15]. In the present study, however, the majority of the subjects with CAO did not report that they ever had been diagnosed with asthma, COPD, emphysema or chronic bronchitis. These results are in line with previous analyses of the BOLD study [8, 16] and underscore that underdiagnosis is a large problem in patients with airway obstruction. Interestingly there were no significant differences between the centres in the prevalence of underdiagnosed CAO.

As expected CAO was related to higher age, smoking [7], lower educational [8] level and asthma [5, 15]. The associations were similar in all three centres but in women there was a marked difference with a large proportion of women in Tartu that had neither smoked more than 10 pack years nor ever received a diagnosis of asthma.

Our data shows that having CAO is relatively common in never smokers. This is in accordance with results from the BOLD project in Austria [17] [18]. The never smokers with CAO in Austria were predominantly female and slightly older. The only risk factor that turned out significant was occupational exposure to organic dust, which was not a significant factor in our study. A female predominance of CAO in never smokers was also found in the BOLD

study in Poland [19]. In the NHANES study from 2005, 9 % of the never smokers had a non-reversible airflow obstruction. These obstructed never smokers represented 23 % of all people with such obstruction. In that study lower educational levels were related to CAO in never smoking subjects aged 60 years and older. [20] All together chronic airway obstruction among never smokers seems to be fairly prevalent, even though the prevalence is different over the world The causes are not fully known and only a limited number of studies have described this population in detail. [4, 20-22]. It should, however, be noted that the prevalence of CAO is related to how CAO is defined. Using LLN when defining CAO, as in the present study, means that the expected prevalence of CAO is 5% in a non-smoking population [23].

The rational for studying the prevalence and risk factors of CAO in Estonia, Sweden and Iceland was that we previously have found large differences in the prevalence of asthma, allergic sensitisation and infections between the three centres [9]. In accordance with this, ~~We~~ we found that the prevalence of diagnosed asthma and pharmacological treatment was lower in Tartu than in Reykjavik and Uppsala. A significant difference in the prevalence of CAO between the centres was, however, only found in women but not in men. ~~This is in accordance with the findings in a previous study from Iceland, Sweden and Estonia [9].~~ We did not find any significant association between markers of systemic inflammation (CRP and IL-6) and CAO and this is not unexpected as previous analyses have shown that systemic inflammation is more related to low FEV_1 and FVC than to the ratio between these lung function variables [24-27].

The advantages of the study were the internationally standardized protocol and the general population sample. A limitation is that the number of participants was limited which affected the power of the analyses especially when stratifying by gender. Another limitation is that the data on smoking and respiratory diseases were self-reported.

In conclusion, we find that the prevalence of having CAO defined as a post-bronchodilator FEV_1/FVC below LLN was lower among women in Tartu than in Reykjavik and Uppsala, whereas no such difference was found in men. A lower number of smokers among the women of Tartu is the most plausible reason for this difference. Our study also highlights that most

subjects with CAO do not have a diagnosed lung disease and that CAO is relatively common also among never-smokers.

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Table 1. Characteristics of the participants (% and mean±SD).

	Tartu (n=614)	**Reykjavik** (n=757)	**Uppsala** (n=547**)**	**p-value**
Women	49.3	46.8	48.0	0.65
Age (years)	61.0 ±11.9	56.4 ±11.9	58.8 ±11.2	<0.001
Body Mass Index kg/m2	28.7 ±7.8	27.9 ±4.9	27.0 ±4.3	<0.001
Smoking history				<0.001
Never smoked	52.5	39.1	44.0	
Ex smoker	29.8	42.6	42.0	
Current smoker	17.8	18.3	14.0	
Smoked 10 pack years or more	25.3	39.5	32.9	<0.001
Passive smoking	14.4	16.8	6.5	<0.001
Education				<0.001
Elementary school	12.5	25.1	24.7	
Highschool	51.7	46.6	47.0	
University	35.8	28.2	28.3	
Occupational expossure				
Dusty job for > 1year	35.8	31.9	31.6	0.20
Respiratory disease				
Ever diagnosed asthma	6.2	16.7	13.9	<0.001
Current asthma	3.7	8.0	9.2	<0.001
Ever diagnosed COPD**	6.2	8.2	5.6	0.14
Asthma/COPD medication	3.1	13.2	12.7	<0.001
Chronic Airflow Obstruction**	6.1	11.3	9.0	0.04

*Also including subjects with diagnosed chronic bronchitis and emphysema

** Defined as post bronchodilator FEV1/FVC below lower limit of normal

Table 2. A: Prevalence of chronic airflow obstruction* (%). B: Prevalence of having smoked 10 pack years or more

A

	Men				**Women**			
Age	**Tartu** (n=309)	**Reykjavik** (n=403)	**Uppsala** (n=283**)**	**p-value**	**Tartu** (n=305)	**Reykjavik** (n=354)	**Uppsala** (n=264**)**	**p-value**
40-49	2.7	2.7	6.2	0.40	0	10.4	3.4	0.009
50-59	7.8	7.3	4.1	0.52	4.4	8.1	5.6	0.59
60-69	10.4	12.5	11.3	0.92	6.4	20.3	11.0	0.04
70-96	13.9	22.6	26.0	0.22	8.8	19.4	15.9	0.15
40-96	7.8	9.2	10.5	0.79	4.9	13.5	8.7	0.002

** Defined as post bronchodilator FEV1/FVC below lower limit of normal

B

	Men				**Women**			
Age	**Tartu** (n=309)	**Reykjavik** (n=403)	**Uppsala** (n=283**)**	**p-value**	**Tartu** (n=305)	**Reykjavik** (n=354)	**Uppsala** (n=264**)**	**p-value**
40-49	52.6	41.2	25.0	0.003	10.1	31.0	22.6	0.004
50-59	36.1	53.3	36.2	0.01	21.4	42.9	34.1	0.02
60-69	41.1	33.3	44.9	0.34	17.3	28.1	30.3	0.13
70-96	42,3	50.8	45.5	0.60	6.1	30.9	26.9	<0.001
40-96	43.8	45.1	37.3	0.14	13.2	33.7	29.0	<0.001

Table 3. Characteristics in those with chronic airflow obstruction* (CAO) in the three centres (% and mean±SD).

	Tartu			Reykjavik			Uppsala		
	No CAO (n=571)	CAO (n=43)	p	No CAO (n=674)	CAO (n=83)	p	No CAO (n=496)	CAO (n=51)	p
Women	51	37	0.09	46	57	0.06	49	43	0.44
Age (years)	60±12	66±11	<0.001	56±11	62±13	<0.001	58±11	65±12	<0.001
BMI kg/m2	29±8	27±5	0.18	28±5	26±5	<0.001	27±4	27±4	0.66
Smoking history			0.005			0.04			0.03
Never smoked	54	30		40	28		44	27	
Ex-smoker	29	37		42	46		43	49	
Current smoker	17	33		17	27		13	24	
Smoked 10 pack years or more	26	56	<0.001	37	63	<0.001	32	63	<0.001
Passive smoking	14	19	0.41	16	22	0.22	5.4	11	0.07
Education			0.02			0.006			0.003
Elementary school	12	23		23	37		22	43	
Highschool	51	56		47	46		49	41	
University	38	21		30	17		29	16	
Dusty job	36	42.	0.41	32	34	0.70	31	41	0.14
Ever asthma	4.6	26	<0.001	15.1	29	0.001	12	29	0.001
Current asthma	2.6	19	<0.001	6.8	18.	<0.001	7.5	25	<0.001
Diagnosed COPD**	5.1	26	<0.001	5.3	31.	<0.001	3.8	24	<0.001
Asthma medication	1.9	21	<0.001	11	31	<0.001	11	33	<0.001
CRP mg/L**	1.7 (1.6-1.9)	1.5 (1.1-1.9)	0.38	1.4 (1.3-1.6)	1.2 (0.9-1.6)	0.14	1.5 (1.5-2.5)	1.9 (1.5-2.5)	0.048
IL-6 ng/L**	0.6 (0.5-0.8)	0.8 (0.4-1.6)	0.51	2.1 (1.8-2.4)	2.3 (1.6-3.4)	0.37	1.0 (0.8-1.2)	1.1 (0.5-2.3)	0.77

* Defined as post bronchodilator FEV1/FVC below lower limit of normal

**Also including subjects with diagnosed chronic bronchitis and emphysema

** Geometric mean (95% confidence interval)

Table 4. Independent variables associated with chronic airflow obstruction* in the three centres

	Tartu	**Reykjavik**	**Uppsala**
Men	0.82 (0.40-1.70)	1.09 (0.65-1.81)	0.71 (0.38-1.34)
Age per 10 year	1.76 (1.29-2.42)	1.54 (1.25-1.89)	1.93 (1.42-2.64)
BMI per 5 units	0.69 (0.49-0.99)	0.52 (0.38-0.70)	0.84 (0.57-1.22)
Smoke history			
Neversmoker	1	1	1
Exsmoker	2.73 (1.16-6.44)	1.73 (0.97-3.09)	1.63 (0.79-3.36)
Current smoker	5.22 (2.08-13.1)	2.64 (1.31-5.33)	4.32 (1.74-10.7)
Pack years 10 or more**	3.64 (1.75-7.59)	3.28 (1.97-5.47)	3.18 (1.67-6.06)
Education			
Elementary school	1	1	1
Highschool	0.89 (0.36-2.20)	0.65 (0.37-1.13)	0.76 (0.37-1.53)
University	0.43 (0.15-1.24)	0.48 (0.23-0.996)	0.59 (0.23-1.47)
Ever asthma	6.97 (2.88-16.9)	2.52 (1.43-4.43)	3.42 (1.67-6.99)

* Defined as post bronchodilator FEV1/FVC below lower limit of normal

**Entered separately and replacing smoke history in the model

Table 5. Independent variables associated with chronic airflow obstruction* in the three centres in men and women separately

	Tartu		**Reykjavik**		**Uppsala**	
	Men	Women	Men	Women	Men	Women
Age per 10 year	1.75 (1.16-2.63)	1.94 (1.12-3.36)	1.77 (1.30-2.41)	1.43 (1.08-1.90)	2.11 (1.39-3.19)	1.69 (1.04-2.75)
BMI per 5 units	0.91 (0.58-1.45)	0.48 (0.26-0.88)	0.55 (0.34-0.91)	0.48 (0.32-0.72)	1.02 (0.56-1.83)	0.64 (0.37-1.11)
Smoke history						
Neversmoker	1	1	1	1	1	1
Exsmoker	7.54 (1.59-35.7)	1.54 (0.35-6.80)	1.01 (0.44-2.36)	2.51 (1.12-5.64)	2.04 (0.74-5.57)	1.26 (0.40-3.92)
Current smoker	18.2 (3.58-92.5)	1.89 (0.33-10.5)	1.95 (0.66-0.58)	3.23 (1.27-8.20)	4.94 (1.21-20.2)	4.79 (1.36-16.8)
Pack years 10 or more**	5.60 (2.08-15.1)	1.58 (0.37-6.84)	2.12 (0.99-4.56)	4.33 (2.20-8.56)	3.44 (1.41-8.43)	3.57 (1.33-9.55)
Education						
Elementary school	1	1	1	1	1	1
Highschool	0.81 (0.24-2.71)	1.05 (0.24-4.65)	0.55 (0.24-1.29)	0.68 (0.32-1.44)	1.07 (0.39-2.90)	0.40 (0.14-1.16)
University	0.54 (0.14-2.12)	0.38 (0.06-2.25)	0.28 (0.08-0.92)	0.63 (0.24-1.62)	1.10 (0.36-3.39)	0.11 (0.01-0.98)
Ever asthma	5.17 (1.45-18.3)	13.4 (3.36-53.4)	1.72 (0.63-4.74)	3.13 (1.55-6.33)	3.38 (1.21-9.45)	3.87 (1.37-11.0)

* Defined as post bronchodilator FEV1/FVC below lower limit of normal

**Entered separately and replacing smoke history in the model

Figure 1 Diagnosed asthma or COPD* among participants with chronic airflow obstruction**.

*Also including subjects with diagnosed chronic bronchitis and emphysema

** Defined as post bronchodilator FEV1/FVC below lower limit of normal

Figure 2. Smoking* and asthma among participants with chronic airflow obstruction**.

*Defined as having smoked at least 10 pack year

** Defined as post bronchodilator FEV1/FVC below lower limit of normal

***Revision Notes**

Dear Professor Yawn

Thank you for you and your reviewer's comments on our manuscript: YRMED-D-18-00197
The prevalence of chronic airflow obstruction in three cities in the Nordic-Baltic region.

The following changes have been made in the manuscript

Editorial comments

Highlights consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). See the following website for more information http://www.elsevier.com/highlights

A: Highlights have now been provided

Reviewers' comments:

Reviewer #2: The manuscript " The prevalence of chronic airflow obstruction in three cities in the Nordic-Baltic region." By Broström E et. al. presents results of a branch of BOLD study. They focus on comparition of the prevalence of chronic airflow obstruction (CAO) and its' possible risk factors between Tartu in Estonia, Reykjavik in Iceland and Uppsala in Sweden. Base on the results from 1,037 men and 956 women authors conclude that the prevalence of CAO was lower in Estonian women than in women from Iceland and Sweden as well as that majority of those with CAO do not have a diagnosed lung disease. They also found that older age, current smoking and ever having had asthma were independent risk factors for having CAO.

As BOLD methodology as well its advantages and disadvantages are widely known and fully described there is no need to do any methodological remarks.

My biggest doubt is what does this work bring to science? The data describe epidemiological situation from 9-14 years ago (Reykjavik 2004-2005, Uppsala 2006-2007 and Tartu 2009), identified CAD risk factors are known from previous studies. The crucial would be information if this descriptive data were already publish in any form in one of BOLD papers or not?

This is a valid comments. This data has not been reported before and one of the reasons is that the data in Uppsala and Tartu was available only after the first major BOLD publication: Buist, A.S., et al., International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet, 2007. 370(9589): p. 741-50.

We have now described the rational for this particular analysis of the BOLD data in the third last paragraph of the discussion.

Minor remark: what for serum concentrations of interleukin 6 (IL-6) was measured if authors did not mention even one time about this factor in the results section. In the Table 3 values of IL-6 differ almost four times between groups (0.6 no CAO in Tartu vs 2.3 for CAO in Reykjavik) and there is no even one word about that differences. As a reader I also do not know I CRP and IL-6 values in the tables are crude values (what are the units) or OR with confidence intervals?

A: Thank you pointing this out. We now added a sentence on this in the result (third paragraph of the result section). We've also added the units for the inflammatory markers and added the information that CRP and IL6 are expressed as geometric mean (95% confidence interval). A sentence on this has also been added to the statistics section.

Thank you once again for these valuable comments and for the chance of improving our manuscript

Yours sincerely on behalf of all the authors

Christer Janson

Highlights

- The prevalence of having chronic airflow obstruction (CAO) defined as a post-bronchodilator FEV_1/FVC below LLN was lower among women in Tartu than in Reykjavik and Uppsala, whereas no such difference was found in men.
- A lower number of smokers among the women of Tartu is the most plausible reason for this difference.
- In men, the majority of those with CAO had smoked or had asthma whereas this was not the case in women from Tartu.
- Our study also highlights that most subjects with CAO do not have a diagnosed lung disease and that CAO is relatively common also among never-smokers.

Figure

Fig 1

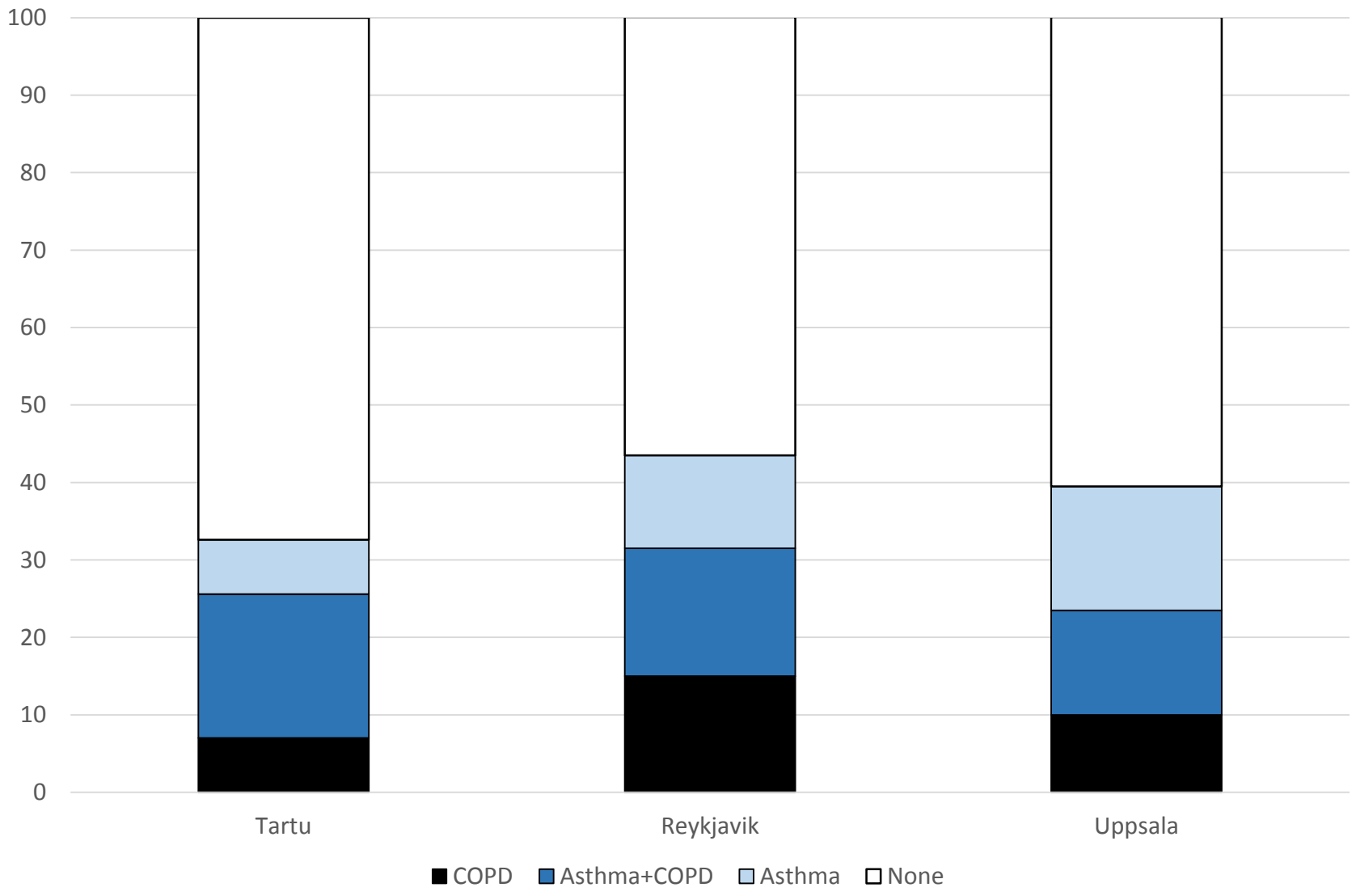
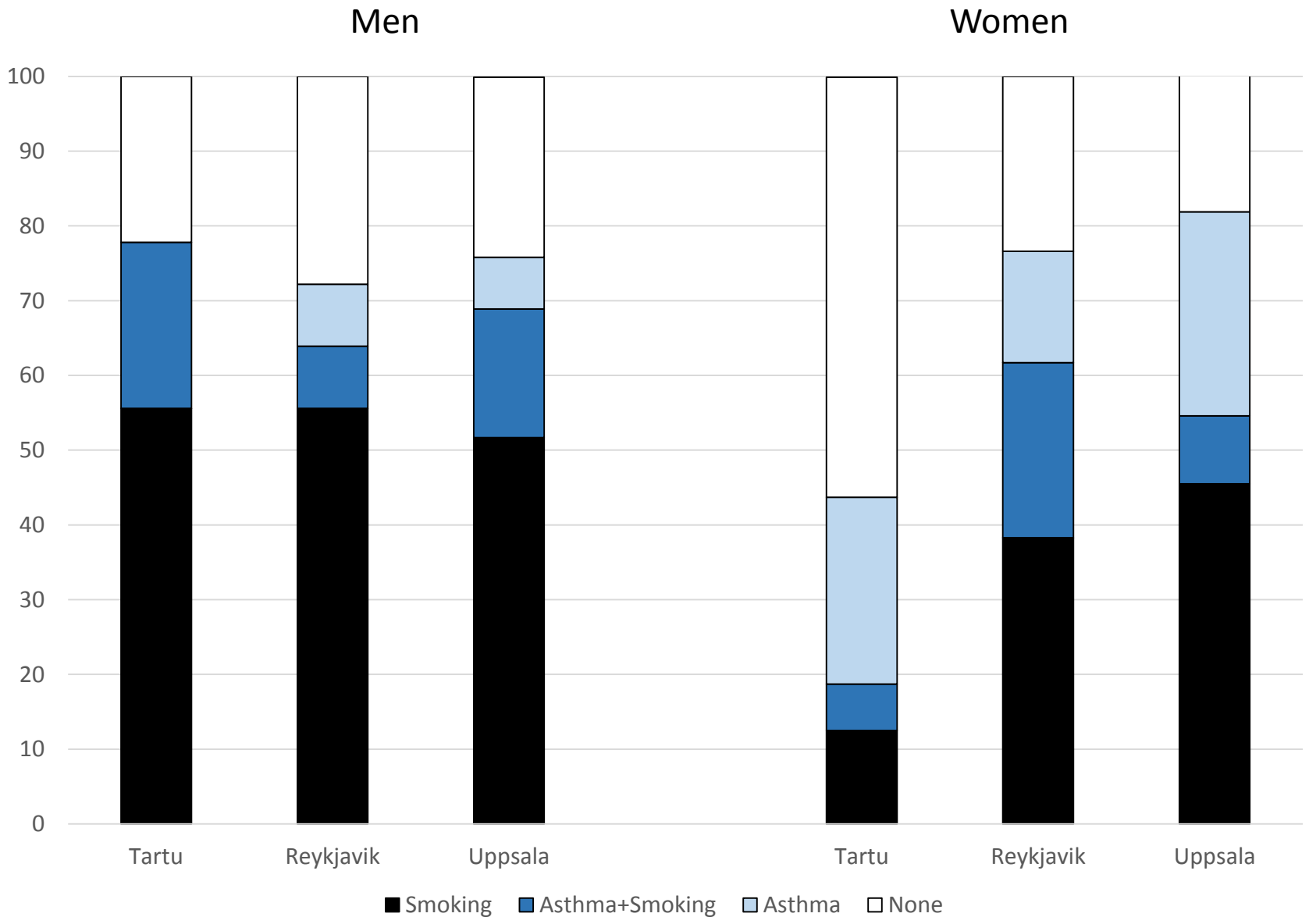

100
90
80
70
60
50
40
30
20
10
0
Tartu
Reykjavik
Uppsala
COPD
Asthma+COPD
Asthma
None

Fig 2


Men
Women
100
90
80
70
60
50
40
30
20
10
0
Tartu
Reykjavik
Uppsala
Tartu
Reykjavik
Uppsala
Smoking
Asthma+Smoking
Asthma
None