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Original Research

Association between abdominal and general obesity and respiratory symptoms, asthma and COPD. Results from the RHINE study

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ABSTRACT

Introduction: Previous studies on the association between abdominal and general obesity and respiratory disease have provided conflicting results.
Aims and objectives: We aimed to explore the associations of abdominal obesity with respiratory symptoms, asthma, and chronic obstructive pulmonary disease independently from general obesity in women and men.
Methods: This cross-sectional study was based on the Respiratory Health in Northern Europe (RHINE) III questionnaire (n = 12 290) conducted in 2010–2012. Abdominal obesity was self-measured waist circumference using a sex-specific standard cut-off point: ≥102 cm in males and ≥88 cm in females. General obesity was defined as self-reported BMI ≥30.0 kg/m^2.
Results: There were 4261 subjects (63% women) with abdominal obesity and 1837 subjects (50% women) with general obesity. Both abdominal and general obesity was independent of each other and associated with respiratory symptoms (odds ratio (OR) from 1.25 to 2.00)). Asthma was significantly associated with abdominal and general obesity in women, OR (95% CI) 1.56 (1.30–1.87) and 1.95 (1.56–2.43), respectively, but not in men, OR 1.22 (0.97–3.17) and 1.28 (0.97–1.68) respectively. A similar sex difference was found for self-reported chronic obstructive pulmonary disease.
Conclusions: General and abdominal obesity were independent factors associated with respiratory symptoms in adults. Asthma and chronic obstructive pulmonary disease were independently linked to abdominal and general obesity in women but not men.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are among the leading causes of morbidity worldwide [1,2]. Obesity is one of the risk factors for these chronic respiratory diseases [3], particularly asthma [4]. High body mass index (BMI) is correlated with a greater incidence of asthma, a higher prevalence of respiratory symptoms, lung function decline, poor disease control and a reduced response to asthma treatment [5–8]. Some epidemiological studies report that the prevalence of obesity has increased in COPD patients [9–11]. On the other hand, obese people with COPD demonstrate higher survival than those with normal weight [12].

BMI is used as a comprehensive measure of obesity, and a BMI equal to or higher than 30 kg/m^2 is referred to as general obesity [13]. Regarding abdominal obesity measuring waist circumference (WC) is an anthropometric indicator of abdominal obesity, one of the most

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important components of the metabolic syndrome [14,15]. Measuring WC is a convenient, inexpensive method that, unfortunately, is not used to a large extent in clinical practice [16].

A meta-analysis from 2019 found that the association between abdominal obesity and asthma was similar in both sexes [17]. In contrast, a previous meta-analysis (2007) indicated that this association was more pronounced in women than men [18]. However, there has been a limited number of studies investigating the association between abdominal obesity and asthma independently from general obesity and vice versa [17]. Existing studies report inconsistent results due to differences in the evaluated study population, such as different ages, genders, disease phenotypes and methodology. The knowledge of the link between general and abdominal obesity and COPD remains even more limited [19]. A recent study on COPD suggested that abdominal obesity but not BMI was associated with more comorbidities and poorer COPD-related outcomes [20].

The aim of the study was to explore whether abdominal obesity measured by self-reported waist circumference and general obesity measured by BMI was independently associated with respiratory symptoms, asthma, COPD, chronic bronchitis and allergic rhinitis. We also focused on differences between asthma phenotypes, including early- and late-onset asthma and differences between genders.

2. Methods

2.1. Study population and questionnaire

This cross-sectional investigation is based on a large population-based study Respiratory Health in Northern Europe (RHINE) III, described previously [21,22]. RHINE III is the second follow-up survey of the European Community Respiratory Health Survey (ECRHS). ECRHS I was conducted on randomly selected young adults in 1990–1994 to evaluate asthma and allergy prevalence and risk factors [23]. Further, the participants from seven Northers European centres, including Umea, Uppsala, Gothenburg (Sweden), Bergen (Norway), Aarhus (Denmark), Reykjavik (Iceland) and Tartu (Estonia), were followed up with questionnaires after ten (RHINE II) and twenty (RHINE III) years. In RHINE III, conducted from 2010 to 2012, the participants responded to similar questions as in RHINE II. They were also asked to measure WC with a measuring tape attached to the questionnaire. Of 13 463 (53% response frequency) individuals who responded to RHINE III [21], all subjects that reported weight, height, and WC were included in this study (n = 12 290).

2.2. Definitions of outcome and exposure variables

Consistent with the previous RHINE analyses [22], current asthma was defined as answering 'yes' to at least one of the following questions.

- *Have you had an asthma attack during the last* 12 months*?*
- *Are you currently taking any medications (spray, inhalers or tablets) for asthma?*

The age of asthma onset was determined in the subjects with asthma by the question. *How old were you when the first symptoms of asthma appeared?* Early-onset asthma was defined as a disease onset of <18 years, while late-onset asthma was defined as a disease onset of≥ 18 years of age [24,25].

The following respiratory symptoms were assessed: wheeze, wheeze in combination with breathlessness, wheeze when not having a cold, nocturnal chest tightness, nocturnal attacks of dyspnea and nocturnal attacks of cough. The recall period was 12 months.

Allergic rhinitis was defined as an affirmative answer to the question: *"Do you have any nasal allergies, including hay fever?"*

Chronic bronchitis was defined as a positive answer to both following questions.

- *Do you usually cough up mucus or have mucus in the chest that is hard to get out?*
- *Does this occur almost every day for at least three months for at least two years in a row?*

COPD was defined as a positive answer to the question: *Has a doctor diagnosed you with COPD?*

BMI in kg/m^2 was based on self-reported weight and height. General obesity was defined as BMI ≥30 kg/m^2.

WC was obtained by asking the participant to measure WC at the level of the belly button with a non-elastic flexible tape that was attached to the questionnaire. Abdominal obesity was defined as WC ≥ 102 cm for men and WC ≥ 88 cm for women [26].

2.3. Confounders

Smoking status was categorized as a current smoker (applies even if you smoke any cigarette/cigar or pipe every week), former smoker (no smoking for at least one month) and never smoker [27].

Physical activity was grouped as never/less than once a week, once a week, 2–3 times a week and almost every day.

The highest obtained educational level included elementary school (at least nine years of elementary school), gymnasium (at least nine years of elementary school and three years of gymnasium) and high school/university (at least nine years of elementary school, three years of gymnasium and three years of high school/university).

The study was approved by The Regional Committees for Medical and Health Research Ethics West in Norway, the National Bioethics Committee in Iceland, the Research Ethics Committee of the University of Tartu in Estonia, The Regional Ethical Review Board in Uppsala, Sweden and the Scientific Committee for Central Denmark.

2.4. Statistical analysis

The statistical analysis was conducted in STATA IC (version 15), College, Texas, USA. The categorical variables were presented in percentages and continuous as mean with standard deviation (SD). Chi-squared test (for categorical variables) and *t*-test (for continuous variables) were used to evaluate differences between subjects with and without general and abdominal obesity. A Pearson correlation coefficient (r) was calculated to determine the strength of the linear association between WC and BMI. Association between abdominal and general obesity, WC or BMI per SD increase, respiratory symptoms, asthma and COPD were analyzed with multivariable logistic regression presented as odds ratio (OR) with 95% confidence intervals (CI). The first model (partially adjusted) abdominal or general obesity was adjusted for age as a continuous variable, sex, educational level, level of physical activity, smoking status and centre. In the second model (fully adjusted), abdominal or general obesity was additionally adjusted for general and abdominal obesity, respectively, or BMI and WC, respectively. Associations between abdominal and general obesity and respiratory symptoms and disease were also analyzed, stratified by sex. Interaction analyses using multiple logistic regression were performed to assess whether there were any differences in associations above between women and men. A p-value of <0.05 was considered statistical significance. There was a low number of missing variables (Supplementary Table 1), managed by deletion.

3. Results

3.1. Characteristics of the study population

In total, there were 12290 subjects, 4261 (34.7%) subjects with abdominal obesity, and 1837 (6.7%) subjects with general obesity, Table 1. There were 1669 (13.6%) subjects with both types of obesity, Fig. 1. The characteristics of the participants with and without

Table 1
The characteristic of the study population divided into those with and without abdominal and general obesity presented as mean with standard deviation (SD) or prevalence (%).

	Abdominal obesity			General obesity		
	No (n = 8029)	Yes (n = 4261)	P-value	No (n = 10 453)	Yes n = 1837)	P-value
Age, mean with SD	50.7 ± 7.2	52.4 ± 7.2	<0.001	51.1 ± 7.2	52.1 ± 7.1	<0.001
Sex (female)	47.9	62.7	<0.001	53.6	50.1	0.005
Smoking status			<0.001			<0.001
Never	49.5	42.8		48.1	41.7	
Former	33.0	39.6		34.4	40.8	
Current	17.5	17.5		17.5	17.5	
Level of physical activity			<0.001			<0.001
<1 times per week	18.1	29.4		19.7	35.0	
1 time per week	17.1	20.1		17.9	19.3	
2–3 times per week	40.3	33.2		39.1	30.7	
Almost every day	24.5	17.3		23.2	14.9	
Educational level			<0.001			<0.001
Elementary school	8.6	15.1		9.8	16.7	
Gymnasium	40.1	44.4		40.7	46.7	
High school/ university	51.3	40.4		49.4	36.6	

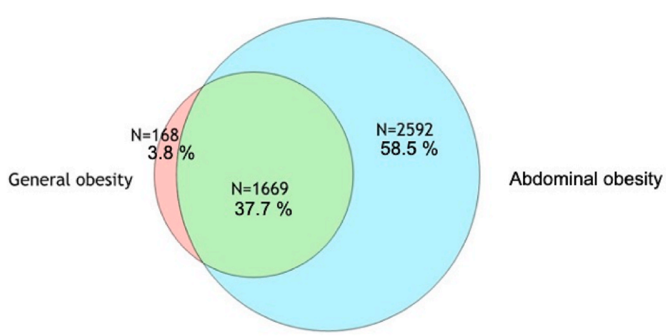

Fig. 1. The study population with abdominal obesity (waist circumference ♂ ≥ 102 cm, ♀ ≥ 88 cm) and general obesity (BMI ≥30 kg/m2), and both.

abdominal and general obesity are presented in Table 1. Significantly more women than men were in the group with abdominal obesity than in the group without it, while the opposite was found for general obesity. Subjects with abdominal and general obesity were older, more often former smokers, had lower levels of education, and reported a lower level of physical activity compared to the group without abdominal or general obesity.

3.2. Respiratory symptoms, asthma, COPD in abdominal and general obesity

A significantly higher proportion of subjects with abdominal and general obesity had respiratory symptoms such as wheeze, wheeze when not having a cold, wheeze and breathlessness, nocturnal chest tightness and nocturnal attacks of breathlessness, Table 2. Asthma, adult-onset asthma, chronic bronchitis and COPD were more prevalent among subjects with abdominal and general obesity, while allergic rhinitis was less prevalent in people with abdominal obesity than those without, Table 2.

Table 2
The percentage (%) of subjects with/without abdominal or general obesity among those with asthma, late/early-onset asthma, respiratory symptoms such as wheeze and chronic bronchitis and COPD (%).

	Abdominal obesity			General obesity		
	No (n = 8029)	Yes (n = 4261)	P-value	No (n = 10 453)	Yes (n = 1837)	P-value
Wheeze	15.4	25.2	<0.001	16.5	32.3	<0.001
Wheeze when not having a cold	10.0	16.1	<0.001	10.4	21.7	<0.001
Wheeze and breathlessness	8.1	14.3	<0.001	8.7	19.1	<0.001
Nocturnal chest tightness	8.9	13.7	<0.001	9.3	17.4	<0.001
Nocturnal attack of breathlessness	4.4	7.4	<0.001	4.8	8.8	<0.001
Nocturnal attack of cough	24.0	33.0	<0.001	25.5	36.2	<0.001
Allergic rhinitis	25.0	23.4	0.049	24.7	22.9	0.091
Asthma	7.1	10.5	<0.001	7.6	12.1	<0.001
Late-onset asthma	3.0	5.6	<0.001	3.4	6.7	<0.001
Early onset asthma	2.0	2.0	0.864	2.0	2.3	0.399
Chronic bronchitis	4.9	7.4	<0.001	5.3	8.5	<0.001
COPD	2.1	3.8	<0.001	2.2	5.8	<0.001

Abdominal obesity (with or without general obesity) was independently associated with respiratory symptoms, asthma, late-onset asthma and chronic bronchitis after adjustment for age, sex, smoking status, educational level, physical activity, centre and general obesity, Table 3.

Table 3
Association between abdominal and general obesity and respiratory symptoms and disorders presented as odds ratio (OR) with 95% confidence intervals (95% CI). In the partially adjusted model, abdominal or general obesity was adjusted for age, sex, smoking status, educational level, physical activity and centre. In the fully adjusted model, abdominal or general obesity was additionally adjusted for general or abdominal obesity, respectively.

	Partly adjusted		Fully adjusted	
	Abdominal obesity	General obesity	Abdominal obesity	General obesity
Wheeze	1.84 (1.66–2.04)	2.41 (2.13–2.73)	1.40 (1.24–1.58)	1.96 (1.70–2.27)
Wheeze when not having a cold	1.73 (1.52–1.96)	2.28 (1.98–2.63)	1.31 (1.13–1.52)	1.93 (1.64–2.28)
Wheeze and breathlessness	1.77 (1.55–2.01)	2.39 (2.06–2.77)	1.32 (1.13–1.53)	2.03 (1.70–2.41)
Nocturnal chest tightness	1.54 (1.35–1.75)	1.84 (1.59–2.14)	1.27 (1.09–1.47)	1.60 (1.34–1.90)
Nocturnal attack of breathlessness	1.57 (1.32–1.88)	1.65 (1.34–2.03)	1.39 (1.13–1.71)	1.35 (1.06–1.71)
Nocturnal attack of cough	1.35 (1.24–1.49)	1.56 (1.39–1.75)	1.20 (1.08–1.33)	1.40 (1.22–1.60)
Allergic rhinitis	0.96 (0.87–1.06)	0.95 (0.84–1.09)	0.97 (0.878–1.08)	0.98 (0.84–1.13)
Asthma	1.41 (1.22–1.62)	1.62 (1.37–1.93)	1.23 (1.05–1.45)	1.43 (1.18–175)
Late-onset asthma	1.59 (1.30–1.94)	1.953 (1.55–2.45)	1.30 (1.03–1.64)	1.67 (1.28–2.18)
Early onset asthma	1.14 (0.85–1.53)	1.31 (0.91–1.89)	1.04 (0.74–1.46)	1.28 (0.84–1.96)
Chronic bronchitis	1.36 (1.16–1.61)	1.43 (1.17–1.76)	1.23 (1.01–1.50	1.26 (1.00–1.60)
COPD	1.31 (1.02–1.69)	2.04 (1.55–2.69)	0.92 (0.68–1.26)	2.14 (1.54–2.99)

However, abdominal obesity (with or without general obesity) was not associated with COPD when adjusted for general obesity. Abdominal obesity (without general obesity) was still significantly associated with respiratory symptoms, asthma, adult-onset asthma and chronic bronchitis,Supplementary table 2. General obesity was significantly associated with COPD and respiratory symptoms, asthma and adult-onset asthma after adjustment for abdominal obesity, Table 3. Early-onset asthma and allergic rhinitis were not associated with abdominal or general obesity either in the partially or fully adjusted model, Table 3.

3.3. Sex differences in the association between obesity and respiratory disorders

An association between both abdominal and general obesity and respiratory symptoms was found in both women and men, Table 4. Asthma and COPD were, however, significantly associated with abdominal and general obesity only in women, Fig. 3 and Table 4. Abdominal obesity (without general obesity) was significantly associated with asthma only in women but a significant association to most respiratory symptoms was found in both genders, Supplementary Table 2.

3.4. Body mass index and waist circumference

BMI and WC were highly correlated when analyzed in the simple linear regression, Fig. 2. WC and BMI were associated with respiratory symptoms, asthma, late and early-onset asthma, chronic bronchitis and COPD in the partially adjusted model, Supplementary Table 3. In the fully adjusted model where WC was adjusted for BMI and vice verse, BMI but not WC was independently associated with nocturnal cough, late-onset asthma and COPD. In contrast, WC but not BMI was associated with nocturnal chest tightness, nocturnal cough, nocturnal breathlessness and chronic bronchitis. Early-onset asthma and allergic rhinitis were not associated with either WC or BMI in either the partially or fully adjusted model, Supplementary Table 3.

4. Discussion

The main result of this study was that both general and abdominal obesity were independently associated with respiratory symptoms in adults. However, asthma and COPD were significantly associated with abdominal and general obesity in women only.

There are few previous studies on the independent association between general or abdominal obesity and the risk of respiratory symptoms and asthma. Our result that abdominal obesity was positively associated with asthma independently of general obesity is in line with the cross-sectional analysis of Leone et al. [28]. We also showed that general obesity was associated with asthma independently of abdominal obesity. This is different from the results of the previously cited study [28]. However, that study included only subjects over 65 years, whereas our study also included younger participants. The importance of measuring WC was also confirmed in the study with lung function, which reported that the decline of lung function was more affected by WC than BMI [29].

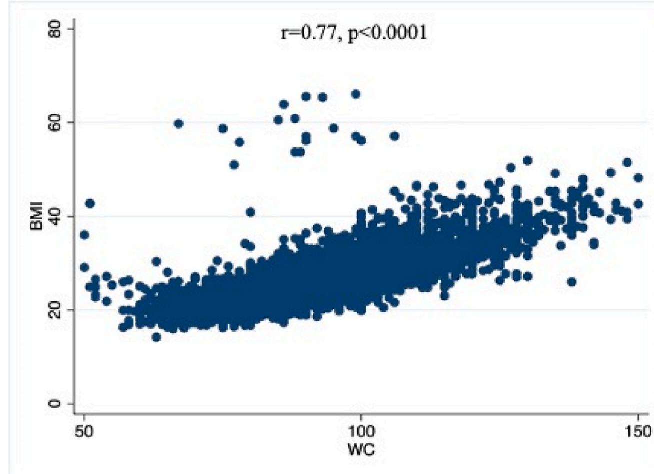

Fig. 2. The association between waist circumference (WC) and body mass index (BMI) was determined by Pearson correlation coefficient (r), and the p-value was calculated.

The pathophysiological explanation of the link between abdominal obesity and asthma could be that fat disposition in the abdominal region leads to restricted diaphragm movement and increased pulmonary blood volume that causes an alteration in the dynamic of the respiratory system [30]. This may lead to increased constriction tendency of the smooth muscles in the airways and increased airway responsiveness and functional respiratory decline [31,32]. In addition, an excess of adipose tissue also leads to chronic systemic inflammation with increased levels of factors such as leptin and adiponectin [33].

When studying gender differences, we found that both abdominal and general obesity was much stronger associated with asthma in women than in men. In line with our result, Brumpton et al. demonstrated that abdominal obesity in the middle age population was associated with a higher incidence of asthma independent of BMI in women but not men [34]. A different result was found in a study in an elderly French population showing that abdominal obesity was strongly associated with asthma in both women and men [28,35]. The different findings might be attributed to the changes in BMI and abdominal fat distribution with age. In younger men, BMI might be higher due to a high muscle mass compared to younger women [36], whereas ageing

Table 4
Association between abdominal or general obesity and respiratory symptoms in both sexes presented as odds ratio (OR) with 95% confidence intervals (95% CI), adjusted for age, sex, smoking status, educational level, physical activity and centre. P presented an interaction analysis between the sexes.

	Abdominal obesity			General obesity		
	Men	Women	$p_{interaction}$	Men	Women	$p_{interaction}$
Wheeze	1.85 (1.58–2.16)	1.82 (1.59–2.11)	0.71	2.13 (1.78–2.54)	2.70 (2.27–3.21)	0.046
Wheeze when not having a cold	1.62 (1.36–1.94)	1.86 (1.56–2.21)	0.17	1.91 (1.56–2.34)	2.72 (2.23–3.32)	0.008
Wheeze and breathlessness	1.78 (1.46–2.16)	1.77 (1.48–2.11)	0.89	2.13 (1.71–2.65)	2.66 (2.17–3.26)	0.10
Nocturnal chest tightness	1.69 (1.40–2.05)	1.42 (1.19–1.69)	0.232	1.95 (1.57–2.41)	1.74 (1.41–2.16)	0.393
Nocturnal attack of breathlessness	1.74 (1.34–2.25)	1.50 (1.18–1.91)	0.36	1.71 (1.30–2.34)	1.61 (1.20–2.15)	0.80
Nocturnal attack of cough	1.38 (1.19–1.60)	1.34 (1.20–1.51)	0.75	1.49 (1.25–1.77)	1.63 (1.39–1.91)	0.48
Allergic rhinitis	0.99 (0.84–1.15)	0.95 (0.83–1.08)	0.52	0.90 (0.75–1.09)	1.03 (0.87–1.23)	0.04
Asthma	1.22 (0.97–3.17)	1.56 (1.30–1.87)	0.052	1.28 (0.97–1.68)	1.95 (1.56–2.43)	0.006
Late-onset asthma	1.66 (1.16–2.38)	1.57 (1.23–1.99)	0.98	1.80 (1.20–2.69)	2.05 (1.55–2.72)	0.45
Early onset asthma	0.92 (0.60–1.41)	1.44 (0.95–2.19)	0.13	0.92 (0.53–1.59)	1.93 (1.17–3.18)	0.02
Chronic bronchitis	1.28 (1.01–1.63)	1.43 (1.12–1.84)	0.42	1.35 (1.02–1.78)	1.54 (1.14–2.07)	0.45
COPD	1.02 (0.68–1.54)	1.62 (1.15–2.28)	0.02	1.29 (0.83–2.02)	2.87 (2.00–4.10)	0.001

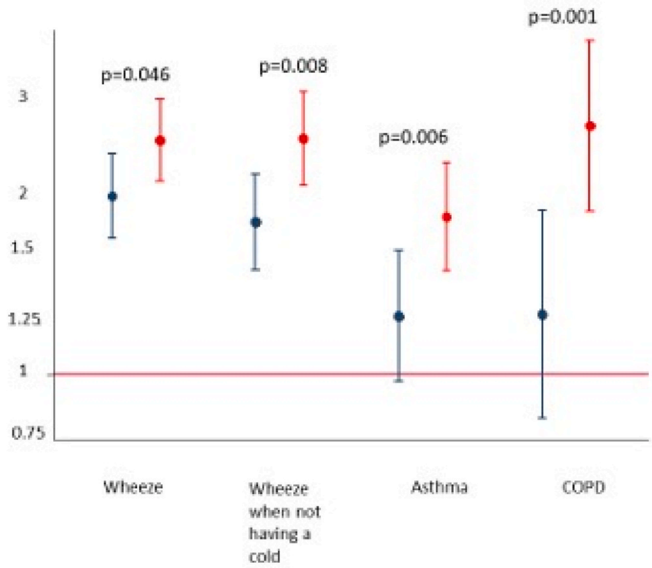

Fig. 3. Association between general obesity and wheeze, asthma and COPD in men (blue) and women (red) presented as odds ratio (OR) with 95% confidence intervals (95% CI), adjusted for age, sex, smoking status, educational level, physical activity, and centre. P-value <0.05 denotes if significant interaction with gender was found on the association between general obesity and wheeze, asthma and COPD interaction analysis between sexes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

men have a more increased accumulation of central fat than women [37].

In addition, we found that late-onset asthma was independently associated with abdominal and general obesity. This is in line with previous studies where increasing WC independently from BMI was linked to the risk for late-onset asthma [28,38]. On the other hand, we observed no association between early-onset asthma and allergic rhinitis and general or abdominal obesity, which was also consistent with previous studies [28,39]. Previous studies have shown that obesity in children increases the risk of early allergic asthma and allergic status, particularly in girls [40,41].

The results of previous studies on the association between general and abdominal obesity and COPD are inconsistent. In our study, general but not abdominal obesity was associated with chronic bronchitis and COPD. In addition, COPD was associated with BMI but not WC, whereas chronic bronchitis was linked to increasing WC but not BMI. When analyzing gender-stratified data, the association between abdominal and general obesity and COPD was stronger in women than in men. Similar to us, a cross-sectional study from Morocco showed that high WC was not linked to COPD. However, contrary to us, that study did not show a significant link between BMI and COPD in women or men [42]. Also, in contrast to our study, a study using the UK Biobank database showed that a high waist-to-hip ratio but not high BMI gave a higher risk for COPD, which was higher in men than in women [43]. These differences across the studies might result from different methodologies and, in particular, different methods to measure abdominal obesity. In addition, the study population might differ in genetics, diet, smoking and physical activity [44,45].

A strength of our study is that it was based on a large sample size, and participants were randomly selected from five countries in Northern Europe. Thus, we were able to adjust for many potential confounders simultaneously. We believe that our study can be generalized, reproduced, and applied to other populations. There were also several limitations. The study is based on the questionnaire and self-reported information on respiratory symptoms and doctors diagnosed asthma and COPD. In the follow-up, a little more than half of those selected 20 years earlier participated. From a previous analysis, we know that the participants were more likely to be women and have a slightly lower respiratory symptom prevalence than the non-participants, whereas most exposure variables are similar [21]. We don't think this will have affected our results significantly. In addition, we did not have data on the severity of the obstructive respiratory disease. For example, previous studies suggested that different severity of COPD and also COPD phenotypes may play a role in BMI-related mortality [46]. Also, we measured BMI based on self-reported weight and height. WC was measured by the participants themselves and not by trained staff. The accuracy of WC measurements may depend on the correct positioning and the tightness of the measuring tape, the posture and the phase of respiration during the measurement [47].

The clinical relevance of this study is that measuring WC in addition to height and weight can be important when seeing patients with respiratory symptoms. We conclude that both general and abdominal obesity was independent of each other associated with respiratory symptoms in adults. However, for self-reported asthma and COPD, a significant association with abdominal and general obesity was found in women but not men.

CRediT authorship contribution statement

Marta A. Kisiel: Conceptualization, Formal analysis, Writing – original draft, the conception and design of the study, data analysis and interpretation, drafting the article and submission. **Oscar Arnfelt:** Conceptualization, Formal analysis, Writing – original draft, the conception and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted. **Eva Lindberg:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Oscar Jogi:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Andrei Malinovschi:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Ane Johannessen:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Bryndis Benediktsdottir:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Karl Franklin:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Mathias Holm:** interpretation of data, discussion, final approval of the version to be submitted. **Francisco Gomez Real:** interpretation of data, discussion, final approval of the version to be submitted. **Torben Sigsgaard:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Thorarinn Gislason:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Lars Modig:** Conceptualization, the conception of the study, interpretation of data, discussion, final approval of the version to be submitted. **Christer Janson:** Conceptualization, Formal analysis, Writing – original draft, the conception and design of the study, data analysis and interpretation, drafting the article and final approval of the version to be submitted.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107213.

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