Risk factors for incident asthma and COPD in a cohort of young adults

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Abstract

Introduction: The aim of the study was to describe potential shared risk factors for incident asthma and COPD in a population-based, 9-year follow-up study.

Methods: From a cohort of 1191 individuals, aged 20-44, who participated in baseline survey including spirometry, bronchial challenge, and skin prick test (SPT) 742 subjects (62%) were reexamined at follow-up in 2012-2014.

Results: A total of 27 incident cases of asthma and 22 cases of COPD were identified at follow-up corresponding to an incidence rate of 5.8 (95% CI 3.9-8.4) and 3.5 (2.2-5.3) per 1000 person years, respectively. Among the identified COPD cases a total of 12 were Asthma-COPD Overlap Syndrome (ACOS). Atopy defined by positive SPT was a risk factor for asthma in males (OR 7.54; 95% CI 1.24-45.90), whereas risk factors in females were nasal allergy (3.81; 1.20-12.11), FEV1 < 100% predicted (3.96; 1.07-14.62) and parental asthma (3.06; 1.00-9.40). Risk factors for COPD in males were bronchial hyperresponsiveness (23.13; 1.41-380.50) and FEV1 < 100% predicted (3.96; 1.07-14.62) and parental asthma (3.06; 1.00-9.40). Risk factors for COPD in males were bronchial hyperresponsiveness (23.13; 1.41-380.50) and FEV1 < 100% predicted (all male cases had FEV1 < 100% predicted) and in females current smoking (3.34; 1.16-9.59) and asthma at baseline (5.21; 1.48-18.34).

Conclusions: No shared risk factors for incident asthma and COPD were found. Despite low power when stratifying by sex risk factors for incident asthma and COPD emphasize considerable gender differences.

KEYWORDS
adult, asthma, cohort study, COPD, epidemiology, risk factor
1 | INTRODUCTION

Asthma and COPD are frequent inflammatory obstructive lung diseases with immense impact on individual health and public resources.

The prevalence of adult asthma in Denmark is estimated to 6%-8%. In the RHINE study the crude incidence rate of asthma was 2.2 per 1000 person years with higher incidence in females than males.

Incidence and prevalence of COPD vary widely depending on definitions and methods used, diagnostic criteria and populations studied. The prevalence of COPD in Denmark is estimated to 8% and 15% in persons older than 40 years.

Asthma and COPD have a considerable functional and pathological overlap and share symptoms and features including airway inflammation, airway obstruction, and bronchial hyperresponsiveness (BHR). More than 20% actually show components of both diseases having asthma-COPD overlap syndrome (ACOS). The overlap syndrome is supported by the Dutch Hypothesis, which states that asthma and COPD are different expressions of a single airway disease. In contrast the British Hypothesis holds that asthma and COPD are distinct diseases that develop by unique mechanisms.

Numerous risk factors are described for adult-onset asthma such as prior respiratory infections, occupational exposures, hormonal factors, smoking, Atopy, BMI, and exposure to mould. Several studies have shown gender differences in incidence, prevalence, diagnosis and severity of asthma, and also differences in perception and behavior are described. The main risk factor for COPD is tobacco smoking, while age, genes, early respiratory infections, and previous asthma also contribute. In the European Community Respiratory Health Survey (ECRHS) examining young adults, tobacco smoking was still the main risk factor, while BHR, a family history of asthma, and respiratory infections in childhood were other important determinants. Among environmental determinants occupational exposures to dust and smoke are well-known risk factors.

The aim of this study was to describe risk factors for incident asthma and COPD to elucidate shared determinants for the two diseases in line with the Dutch Hypothesis.

2 | METHODS

This multicentre study was a 9-year follow-up study of 742 individuals and based on the protocol of ECRHS II. The baseline study population was a random sample of 10 000 individuals, aged 20-44 years and standardized by sex and age. The baseline study consisted of a screening questionnaire (Phase 1), which was answered by a total of 7271 individuals (73%) plus interview and clinical examination (Phase 2) of a random sample corresponding to 20% of the study population, a complementary symptom group of individuals reporting respiratory symptoms in the screening questionnaire and a subsample of non-symptomatic individuals comprising a case-enriched population of 1191 subjects.

A total of 449 individuals were lost prior to the final analyses (Figure 1).

The follow-up survey consisted of an interview questionnaire and clinical examination (2012-2014).

The study was approved by The Regional Scientific Ethical Committees for Southern Denmark and written informed consent was obtained from all participants.

2.1 | Interview

The interview at baseline and follow-up was a slightly modified ECRHS II main questionnaire.

2.2 | Clinical examination

The clinical examination at baseline has been reported elsewhere. In brief, the examination included spirometry followed by methacholine challenge test alternatively bronchodilation (if FEV₁ was <70% of predicted or <1.5 L), and skin prick test (SPT). The SPT comprised a panel of 13...
commercially available inhalation allergens from ALK-Abelló, Gentofte, Denmark.

In the follow-up examination lung function testing by spirometry and bronchodilation by inhalation of SABA (Salbutamol, 200 µg) from spacer (AeroChamber Plus Flow-Vu), was carried out using an EasyOne Spirometer (ndd Medical Technologies, Andover, Massachusetts).

2.3 | Definitions

Asthma at baseline was defined by an affirmative answer to the question “Have you ever had asthma?” combined with reporting asthma-like symptoms, use of medication or airflow obstruction at baseline according to a modified definition used by de Marco et al. in a recent study19 (Supporting Information Table S1). Obstruction was defined according to the lower limit of normal (LLN) i.e. the 5th percentile of FEV1/FVC distribution corresponding to a z-score < −1.64. At baseline the maximum values of FEV1 and FVC were applied as methacholine challenge test was performed, whereas at follow-up the maximum value was the best of either the pre- or post-bronchodilator value. COPD was defined according to criteria of LLN combined with symptoms consistent with COPD, modified from de Marco et al.19 (Supporting Information Table S1). Transient airflow obstruction was defined by obstruction at baseline but no obstruction at follow-up, while fixed obstruction was defined by having post-bronchodilator obstruction at follow-up. Incident cases of asthma and COPD during the follow-up-period were identified by applying definitions used at baseline, although slightly modified since BHR was not measured at follow-up (Supporting Information Table S1). ACOS was defined when criteria for both asthma and for COPD were met.

BHR at baseline was defined as a drop of 20% or more in FEV1 associated with a dose of methacholine of 1 mg or less. The bronchodilation was positive with an increase in FEV1 of ≥12% and ≥200 ml. Atopy was defined by one or more positive SPT (mean wheal diameter ≥3 mm). FEV1 as a potential risk factor was defined by a FEV1 less than 100% of the predicted corresponding to a z-score <0.20 Current smokers were defined as individuals, who reported smoking for at least 1 year and were still smoking.

Occupation at baseline, reported as the last held job, was coded according to ISCO88. Each code was categorized in occupations potentially having high or low risk of asthma and COPD, respectively, using job grouping tools formerly applied in the ECRHS.21

2.4 | Statistical analyses

Univariate analyses were conducted for each potential risk factor with the outcome incident asthma, alternatively COPD calculating odds ratios. Next, data were analyzed by logistic regression mutually adjusting for the major factors associated with the outcomes. Results were considered significant using a five percent level of significance.

Analyses were carried out using Stata, version 13.1 (StataCorp, College Station, Texas).

3 | RESULTS

Among the 742 individuals, participating in both the baseline and follow-up survey, individuals with asthma (n = 239) and COPD (n = 55) at baseline were excluded, leaving a population at risk of asthma comprising 503 individuals and a population at risk of COPD of 687 individuals.

Withdrawal analyses of the 449 non-responders showed that the proportion of cases of asthma and COPD at baseline did not differ between participants and non-responders (asthma: 32.2% vs. 27.8%, P = .120; COPD: 7.4% vs. 6.5%, P = .561). Compared with non-responders a larger proportion of the participants were older than 35 years old (53.6% vs. 41.4%; P = .000) and reported nasal allergy (42.1% vs. 32.3%; P = .01) whereas a smaller proportion were female (53.6% vs. 60.6%; P = .022) and current smoker (27.0% vs. 33.0%; P = .120). Participants and non-responders did not differ significantly concerning the other variables analyzed.

A total of 27 incident cases of asthma and 22 cases of COPD were identified at follow-up corresponding to a cumulative incidence proportion of 5.4% (95% confidence interval (CI) 3.4-7.4%) and 3.2% (1.9-4.5%), respectively. Median length of follow-up was 9.2 years (range 7.0-10.8). The incidence rates were 5.8 per 1000 person years (95% CI 3.9-8.4) for asthma and 3.5 per 1000 person years (2.2-5.3) for COPD. A total of 29 cases of ACOS were identified at follow-up: 16 had already ACOS at baseline and of the remaining 13 incident cases 12 had asthma and one had COPD at baseline leaving no incident cases of ACOS without a diagnosis of respiratory disease at baseline.

Characteristics of the population at risk by diagnosis at follow-up are shown in Table 1 and univariate OR for risk factors are shown in Figure 2. Nasal allergy constituted a risk factor for incident asthma (Figure 2; Supporting Information Table S1). BHR, FEV1 <100% predicted and having asthma at baseline were all risk factors for COPD.

The final multivariate model for incident asthma showed nasal allergy to be an overall risk factor (Table 2). When stratified by sex Atopy was a risk factor in males and nasal allergy, FEV1 <100% predicted, and parental asthma were all risk factors in females.

The final multivariate model for incident COPD (Table 3) showed that current smoking, asthma at baseline and FEV1 <100% predicted were all risk factors. Stratified by sex
### TABLE 1  Characteristics of the population at risk and associations between determinants at baseline and incident asthma and COPD

<table>
<thead>
<tr>
<th></th>
<th>Population at risk, asthma n = 503 (%)</th>
<th>Incident asthma n =27 (%)</th>
<th>P, Fisher’s exact</th>
<th>Population at risk, COPD n = 687 (%)</th>
<th>Incident COPD n =22 (%)</th>
<th>P, Fisher’s exact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female</td>
<td>248 (49.3)</td>
<td>17 (63.0)</td>
<td>.168</td>
<td>371 (54.0)</td>
<td>16 (72.7)</td>
<td>.084</td>
</tr>
<tr>
<td>Age ≥35 y</td>
<td>276 (54.9)</td>
<td>12 (44.4)</td>
<td>.321</td>
<td>370 (53.9)</td>
<td>15 (68.2)</td>
<td>.197</td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness</td>
<td>16 (3.2)</td>
<td>2 (7.4)</td>
<td>.210</td>
<td>87 (12.7)</td>
<td>10 (45.5)</td>
<td>.000</td>
</tr>
<tr>
<td>Atopy</td>
<td>141 (28.0)</td>
<td>12 (44.4)</td>
<td>.075</td>
<td>262 (38.1)</td>
<td>11 (50.0)</td>
<td>.269</td>
</tr>
<tr>
<td>FEV$_1$&lt;100% predicted</td>
<td>310 (61.6)</td>
<td>19 (70.4)</td>
<td>.418</td>
<td>448 (65.2)</td>
<td>21 (95.5)</td>
<td>.001</td>
</tr>
<tr>
<td>BMI &gt;30 kg*m$^{-2}$</td>
<td>64 (12.7)</td>
<td>4 (14.8)</td>
<td>.765</td>
<td>105 (15.3)</td>
<td>1 (4.6)</td>
<td>.229</td>
</tr>
<tr>
<td>Nasal allergy</td>
<td>144 (28.6)</td>
<td>15 (55.6)</td>
<td>.003</td>
<td>274 (39.9)</td>
<td>13 (59.1)</td>
<td>.076</td>
</tr>
<tr>
<td>Parental asthma</td>
<td>74 (14.7)</td>
<td>7 (25.9)</td>
<td>.097</td>
<td>148 (21.5)</td>
<td>8 (36.4)</td>
<td>.110</td>
</tr>
<tr>
<td>Current smoking</td>
<td>132 (26.2)</td>
<td>7 (25.9)</td>
<td>1.000</td>
<td>175 (25.5)</td>
<td>12 (54.6)</td>
<td>.004</td>
</tr>
<tr>
<td>High-risk occupation (asthma)$^a$</td>
<td>268 (53.8)</td>
<td>12 (44.4)</td>
<td>.329</td>
<td>363 (53.3)</td>
<td>13 (59.1)</td>
<td>.667</td>
</tr>
<tr>
<td>High-risk occupation (COPD)$^b$</td>
<td>281 (56.4)</td>
<td>14 (51.9)</td>
<td>.692</td>
<td>383 (56.2)</td>
<td>14 (63.6)</td>
<td>.520</td>
</tr>
<tr>
<td>Respiratory infection &lt;5 y of age</td>
<td>28 (5.6)</td>
<td>0 (0.0)</td>
<td>.388</td>
<td>48 (7.0)</td>
<td>2 (9.1)</td>
<td>.662</td>
</tr>
<tr>
<td>Mould inside the home</td>
<td>119 (23.7)</td>
<td>5 (18.5)</td>
<td>.645</td>
<td>181 (26.4)</td>
<td>7 (31.8)</td>
<td>.623</td>
</tr>
<tr>
<td>Asthma baseline</td>
<td>193 (28.1)</td>
<td>16 (72.7)</td>
<td>.000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$N = 498 (asthma); 5 participants had missing in variable “high risk occupation.”

$^b$N = 681 (COPD); 6 participants had missing in variable “high risk occupation.”

Bold values denote significant associations (P < .05).

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**FIGURE 2**  Risk factors for incident asthma and COPD during follow-up by univariate analyses. The figure shows odds ratios (OR) with 95% confidence intervals (95% CI)
BHR and FEV<sub>1</sub>&lt;100% predicted showed significance in males, whereas current smoking and asthma at baseline were risk factors in females. In males the OR of current smoking was high as in females but not significant due to the low number of male cases.

Stratification by Atopy showed that the proportion of females in non-atopics was higher than in atopics (86.7% vs. 33.3%; \( P < .007 \)). Risk factors for non-atopic asthma were female sex (OR 6.33; 95% CI 1.33-30.08), FEV<sub>1</sub>&lt;100% predicted (12.00; 1.49-96.98), nasal allergy (3.88; 1.17-12.91), and parental asthma (5.07; 1.60-16.06), while none of the risk factors in the final analysis showed significant association with incident atopic asthma.

Analyses of COPD stratified by Atopy revealed current smoking to be a risk factor in non-atopic participants (OR 6.16; 95% CI 1.51-25.11) whereas asthma at baseline (9.22; 1.05-81.22) and FEV<sub>1</sub>&lt;100% predicted (OR not applicable as all 11 cases with Atopy had FEV<sub>1</sub>&lt;100% predicted) were risk factors in COPD for atopic participants. Female sex was correlated to COPD in non-atopics (6.24; 95% CI 0.76-51.41).

Analysis of incident asthma by smoking status showed similar pattern for risk factors in both groups except BHR since none of the incident cases of asthma who were current smokers (\( n = 7 \)) had BHR at baseline.

The proportion of current smokers was higher among incident cases of COPD compared with the population at risk (54.6% vs. 24.5%; \( P = .004 \)) but 10 of the 22 incident cases (45%) were not current smokers and 7 of the 10 being never-smokers. Analyses of COPD by smoking status showed that considering the remaining risk factors only having asthma at baseline stood out since all non-smokers had asthma at baseline (100% vs. 50%; \( P = .015 \)). Former smokers had no increased risk of COPD compared with non-smokers.

The majority of non-smoking COPD incident cases were actually ACOS at follow-up (i.e. asthma at baseline and ACOS at follow-up) according to the diagnostic criterion of ACOS in this study having diagnosis of both asthma and COPD, whereas the minor part of smokers were ACOS (66.7% vs. 33.3%; \( P = .043 \)).

Initial analyses of the 13 incident cases of ACOS showed no significant association with selected risk factors (data not shown) and no further analyses were performed due to the few cases. Sensitivity analyses defining asthma solely by an affirmative answer of the participant to the question “Have

### TABLE 2  Risk factors for incident asthma by multivariate analyses; all variables mutually adjusted

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 27/503)</th>
<th>Male (n = 10/255)</th>
<th>Female (n = 17/248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female</td>
<td>1.82 (0.79-4.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness</td>
<td>2.02 (0.40-10.17)</td>
<td>4.93 (0.40-60.87)</td>
<td>1.32 (0.15-11.92)</td>
</tr>
<tr>
<td>Atopy</td>
<td>1.31 (0.50-3.47)</td>
<td><strong>7.54 (1.24-45.90)</strong></td>
<td>0.53 (0.13-2.09)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;&lt;100% predicted</td>
<td>1.55 (0.65-3.71)</td>
<td>0.40 (0.10-1.53)</td>
<td><strong>3.96 (1.07-14.62)</strong></td>
</tr>
<tr>
<td>Nasal allergy</td>
<td><strong>2.84 (1.11-7.27)</strong></td>
<td>1.52 (0.34-6.93)</td>
<td><strong>3.81 (1.20-12.11)</strong></td>
</tr>
<tr>
<td>Parental asthma</td>
<td>2.13 (0.84-5.41)</td>
<td>0.92 (0.11-8.01)</td>
<td><strong>3.06 (1.00-9.40)</strong></td>
</tr>
</tbody>
</table>

The table shows odds ratios (OR) with 95% confidence intervals (95% CI). Bold values denote significant associations (\( P < .05 \)).

### TABLE 3  Risk factors for incident COPD by multivariate analyses; all variables mutually adjusted

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 22/687)</th>
<th>Male (n = 6/316)</th>
<th>Female (n = 16/371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female</td>
<td>1.80 (0.66-4.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness</td>
<td>2.10 (0.77-5.74)</td>
<td><strong>23.13 (1.41-380.50)</strong></td>
<td>1.18 (0.37-3.77)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;&lt;100% predicted</td>
<td><strong>9.32 (1.22-71.35)</strong></td>
<td>NA</td>
<td>7.11 (0.91-55.63)</td>
</tr>
<tr>
<td>Current smoking</td>
<td><strong>3.83 (1.56-9.42)</strong></td>
<td>5.86 (0.90-38.30)</td>
<td><strong>3.34 (1.16-9.59)</strong></td>
</tr>
<tr>
<td>Asthma baseline</td>
<td><strong>4.44 (1.50-13.13)</strong></td>
<td>0.95 (0.06-15.82)</td>
<td><strong>5.21 (1.48-18.34)</strong></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
The table shows odds ratios (OR) with 95% confidence intervals (95% CI). All male cases had FEV<sub>1</sub> less than 100% predicted. Bold values denote significant associations (\( P < .05 \)).
you ever had asthma” and COPD solely by airway obstruction resulted in a slight increase in the number of incident cases. However, it did not alter the pattern of risk factors when stratifying by sex (Supporting Information Tables S3 and S4).

4 | DISCUSSION

This study showed that reported nasal allergy at baseline was a risk factor for incident asthma and current smoking, asthma at baseline and FEV$_1$<100% predicted were risk factors for COPD. When stratified by sex the results showed gender differences as well as analyses by Atopy differentiated results. We identified 27 cases of incident asthma and 22 cases of COPD corresponding to incidence rates of 5.8 and 3.5 per 1000 person-years, respectively, implying that the onset of both diseases in young adults is quite common.

Incidence rates for asthma in this study were comparable with the ECRHS (4.5)$^9$ but higher than in the RHINE-study (2.2)$^3$ with reservations for modified diagnostic criteria.

Regarding COPD our incidence rate of 3.5 was higher than in ECRHS (1.9) when using comparable criteria.$^{14}$ This may be due to the fact that most of the incident cases of COPD in our study in fact were ACOS i.e. they had asthma at baseline and met the criteria for both asthma and COPD at follow-up. Thus, the higher incidence rate of COPD in this study compared with ECRHS may in addition to the identified risk factors represent cases of severe asthma classified as COPD as well due to shared symptoms and incomplete reversibility.

In this study females had a higher risk than males of both asthma and COPD. Even though stratification decreased the power it affected the outcome of the other determinants significantly. Previous studies have found increased risk of asthma in females,$^{9,22}$ especially non-allergic asthma,$^{23}$ and that sex hormones may play a major role in the difference between males and females, but the mechanism is unclear.$^{24,25}$

Self-reported nasal allergy was an overall risk factor for incident asthma. When stratified by sex, however, only in females. In males, but not females, Atopy was a risk factor, although these results must be interpreted with caution due to the few incident cases. Previous studies have shown that risk factors for adult-onset asthma include female sex, Atopy and nasal allergy, despite that the majority of incident cases are seen in non-sensitized individuals.$^9$ Leynaert et al. showed a higher incidence of asthma in females than in males and that more females than males with incident asthma were non-atopic.$^{23}$ A recent study supported that the female predominance is more pronounced in non-sensitized individuals.$^{12}$ This is consistent with our findings, where males with asthma were sensitized to a greater extent than females. In contrast, in females nasal allergy was a risk factor, which may be due to a gender difference in experiencing and reporting symptoms, or that symptoms of nasal allergy are a precursor of sensitization. For COPD neither Atopy nor nasal allergy was a risk factor.

Further analysis of incident asthma by atopic status revealed distinct differences showing that in non-atopic individuals the determinants female sex, FEV$_1$<100% predicted, nasal allergy and parental asthma had elevated OR, which was not the case in atopic individuals implying that Atopy plays a minor role in the development of incident asthma in young adults or that other determinants play a role in atopics. Concerning COPD the pattern of risk factors were overall less affected by atopic status except regarding female sex which also in this group is associated with non-atopic individuals.

It is suggested from previous studies that reduced lung function in childhood or adolescence is associated with an increased risk of asthma in adulthood.$^{26,27}$ In this study FEV$_1$ less than 100% of predicted at baseline was a risk factor for asthma in females, but not in males. This could be a consequence of gender differences in the dimensions of airways. FEV$_1$<100% predicted was a risk factor for COPD both in males and females showing an impact of even a slightly impaired lung function. A recent study using FEV$_1$<80% predicted as cut off suggested that low FEV$_1$ in early adulthood is important in the genesis of COPD.$^{28}$ For COPD “childhood disadvantage factors” have been shown to be associated with FEV$_1$ lower than predicted and an increased risk of COPD$^{29}$ being in agreement with this study.

In accordance with previous studies BHR in this study was positively associated with incident asthma as well as COPD—significantly for males—in accordance with the results of ECRHS$^{14}$ emphasising the impact of BHR in both diseases.

Parental asthma was associated with incident asthma, but in the stratified analysis in females only. Previous studies have shown that a family history of asthma is associated with a higher risk of incident asthma.$^9,12$

The role of smoking in the development of asthma remains controversial. In the final model smoking did not have any association with incident asthma, whereas current smoking was a risk factor for COPD as expected. Analyses regarding smoking were reported for current smoking instead of ever smoking since preceding analyses of both determinants showed that current smoking had a higher impact on the risk of COPD. Including both current and ever smoking in the model confirmed these observations. Due to low number of cases no further analyses of intensity of smoking were conducted. In non-smokers asthma at baseline was the only determinant for COPD. A majority of the incident cases of
COPD in non-smokers had actually ACOS at follow-up i.e. COPD in addition to a preceding asthma, opposed to the smokers where the majority had exclusively COPD. This could lead to considerations if ACOS in line with the observations of de Marco et al.\textsuperscript{19} represents a severe form of asthma, since 92\% of incident ACOS in this study have asthma at baseline and emphasizes the need of consensus regarding diagnostic criteria for ACOS.

In this study high risk occupation did not show significant association with neither asthma nor COPD. The association between certain occupational exposures and asthma is well established\textsuperscript{21} as well as the association between occupational exposures and COPD.\textsuperscript{15} A recent Danish study has shown occupational exposure to be an essential risk factor for COPD in never-smokers.\textsuperscript{30} The negative findings in this study may be due to the relatively few cases of incident asthma and COPD resulting in low power or due to a relatively short period of exposure. Alternatively it could express a healthy worker effect.

4.1 | Strengths and limitations

The present population-based study allows us to describe risk factors of both asthma and COPD in the same population of healthy young adults within an age range where debut of childhood asthma is a closed chapter and the individuals are not yet as prone to be affected by comorbid factors as an older population. In addition, the follow-up study design eliminates recall bias when using self-reported risk factors at baseline for analyzing risk factors for the diseases.

However, the relatively low response rate at follow-up (62\%) and the limited number of incident cases of asthma and COPD leading to low power of the analyses are limitations of the study.

Furthermore, misclassification may occur due to the choice of diagnostic criteria including the use of self-reported information e.g. the question of ever asthma and applying the LLN i.e. the 5th percentile of FEV\textsubscript{1}/FVC corresponding to \textit{z-score} \textless; 1.64 in this healthy study population. The applied criteria for asthma and COPD are in line with recent research.\textsuperscript{19} However, using ever asthma plus asthma-like symptoms identifies only individuals with current asthma which implies a risk of including cases with relapse of asthma at follow-up but free of symptoms at baseline. Sensitivity analysis applying only the question of ever asthma did not alter the pattern of risk factors. The application of exclusively ever asthma as a diagnostic criterion in turn has a risk of recall bias and all in all this highlights the challenges with diagnostic criteria. Sensitivity analyses of COPD by only applying airway obstruction as diagnostic criterion resulted in an increased number of incident cases which partially could be due to an additional inclusion of non-symptomatic individuals with airway obstruction.

5 | CONCLUSIONS

In this study no shared risk factors for incident asthma and COPD were found, which is in favor of the British Hypothesis. However, asthma at baseline was a determinant for COPD at follow-up supporting the Dutch Hypothesis of fluent development from asthma to COPD. Despite the fact that individuals with ACOS constitute a subgroup in the analyses of both asthma and COPD, no shared risk factors were found when analyzing asthma and COPD separately. Risk factors for both asthma and COPD were gender specific. Altogether stratification of determinants by sex, Atopy and smoking status shows that risk factors for each individual are highly interdependent and thus the sum of risk factors is prone to a high individual diversity.

Although our results were only applicable on the young adults investigated, the results emphasized the need for early identification of young adults at risk for the obstructive lung diseases, ACOS included. Furthermore, additional investigations are needed to shed light on gender differences in the obstructive lung diseases.

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CONFLICT OF INTEREST

None of the authors has declared any conflict of interest related to the work presented.

AUTHOR CONTRIBUTIONS

\textit{Study design:} JB, GT, TT, DS, TS, ØO, TM and LRS  
\textit{Acquisition of data:} LKT, JB, GT, TT, DS, TS, ØO, TM and LRS  
\textit{Analyses and interpretation of data:} All authors  
\textit{First drafting of the manuscript:} LKT  
\textit{Critical revision of the manuscript:} All authors

ETHICS

The study was approved by The Regional Scientific Ethical Committees for Southern Denmark and written informed consent was obtained from all participants.
REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1: Diagnostic criteria at baseline and follow-up:

Table S2: The table shows odds ratios (OR) with 95% confidence intervals (95% CI).
Table S3: Mutually adjusted risk factors (OR; 95%CI) for incident asthma by multivariate analyses. Sensitivity analysis based on alternative definition of incident asthma (i.e. no affirmative answer to ‘Have you ever had asthma’ at baseline and affirmative answer at follow-up).

Table S4: Mutually adjusted risk factors (OR; 95%CI) for incident COPD by multivariate analyses. Sensitivity analysis based on alternative definition of incident COPD (i.e. no obstruction according to LLN at baseline and fixed obstruction at follow-up).

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