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Long-Term Outcome of Childhood Asthma: Characterizing COPD-A and COPD-C Subtypes in Adulthood

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Background and Aim: Asthma in early life has been linked to subsequent development of COPD and according to GOLD 2023 COPD may be divided into distinct subtypes. We aimed to investigate factors associated with the GOLD classification COPD-A (asthma in childhood) and COPD-C (tobacco exposure) in a cohort of adults with a history of severe childhood asthma.

Patients and Methods: In a cohort of Danish adults with a history of severe childhood asthma and a previous 4-month stay during childhood at the asthma care facility in Kongsberg, Norway, we divided participants in a long-term follow-up examination into COPD-A and COPD-C, defined as post-bronchodilator $FEV_1/FVC < 0.7$, and never-smoker or ever-smoker, respectively, and no airflow limitation. Characteristics between groups were analysed.

Results: The study cohort comprised 232 adults with a history of severe childhood asthma, of whom 30 (13%) and 23 (10%), respectively, were classified as COPD-A and COPD-C. Compared to those with no airflow limitation, individuals with COPD-A and COPD-C more often had had at least one exacerbation (filled prescription of oral corticosteroid) in the past 12 months (risk ratio [RR] 1.83 and 2.65, respectively). The COPD-C group had a significantly higher Medical Research Council dyspnoea score ($p<0.01$) and significantly higher blood eosinophil count ($p<0.01$) than those with no airflow limitation. Compared to the COPD-C group, the COPD-A group had higher fractional exhaled nitric oxide (mean 29 [SD 28]) and FEV_1%pred (mean 75 [SD 20]). Finally, when comparing participants with COPD-A to both COPD-C and participants without airflow limitation, the proportion of participants with osteoporosis (17%) and depression (10%) was more than twice as high.

Conclusion: Our study revealed a high prevalence and unique features of the two COPD subtypes COPD-A and COPD-C in a cohort of adults with a history of severe childhood asthma.

Keywords: early life, asthma, etiotypes, adult, Kongsberg cohort

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic respiratory diseases worldwide.[1,2] The main risk factor for COPD is tobacco smoking.[3] However, non-tobacco-related risk factors for COPD, including childhood asthma, have increasingly been acknowledged.[4–6] Persistent asthma with onset in early childhood has been associated with the presence of COPD in adulthood.[7–9]

Previous studies suggest that reduced growth of FEV_1 during adolescence and early adulthood due to severe asthma may potentially lead to airflow limitation later in adulthood.[9–13] In the Tasmanian Longitudinal Health Study, spirometry data were gathered at four time points spanning from childhood to 53 years of age in a cohort of 8,583 individuals. The study revealed a strong correlation between childhood asthma and presence of COPD in adulthood.[14] The Melbourne Study of Childhood Asthma reported a lung function trajectory from early adulthood into later adulthood that did not differ between individuals with severe asthma and those with less severe asthma during childhood.[8] However, severe

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childhood asthma was the strongest predictor of the presence of COPD at the age of 50 years (OR 37).[8] Furthermore, a prospective cohort study comprising 2,511 children aged 10–15 years (the WHEASE cohort, Aberdeen, UK) investigated the associations between childhood asthma, wheezing bronchitis, and subsequent development of COPD.[15] At the age of 61, 338 (13%) individuals were followed up, including 38 and 53, respectively, with childhood asthma and childhood wheezing bronchitis, together with 239 controls. Childhood asthma was found to be associated with a higher risk of COPD (defined as post-bronchodilator $FEV_1/FVC < 0.7$) at the time of follow-up (at the age of 60 to 65 years).[15]

Increasing awareness of non-tobacco-related risk factors for the development of COPD have facilitated the proposal of subtypes or etiotypes of the disease. A classification has, therefore, been proposed to classify individuals with COPD and a history of childhood asthma as COPD-A, in contrast to those with tobacco exposure denoted as COPD-C.[3,7,16]

In a cohort of elderly adults with a history of severe asthma in childhood, we hypothesised that individuals with COPD-A (that is asthma in childhood and no tobacco exposure) would differ in clinical characteristics compared to those with COPD-C (tobacco exposure), and that both groups would differ from those without airflow limitation, that is non-COPD.

Materials and Methods

Study Cohort

The study cohort comprised Danish individuals with a history of severe childhood asthma and at least one 4-month stay during childhood (3 to 13 years) at the asthma care facility in Kongsberg, Norway, between 1950 and 1979 (referred to as the Kongsberg cohort). The Kongsberg cohort comprised approximately 5000 children managed for their asthma at Queen Louise's Children's Hospital in Copenhagen, Denmark, and from there referred to Kongsberg.[17] The Danish Red Cross was running the asthma care facility and coordinated the stays in Kongsberg. It was assumed that a stay in the Norwegian mountain air would be beneficial for the children's asthma control.

The Kongsberg cohort was invited to a follow-up examination at the Respiratory Research Unit, Copenhagen University Hospital - Hvidovre, Denmark. Eligible individuals were invited by advertisements on social media groups for adults with a previous stay at the Kongsberg asthma care facility and personal invitation letters. All individuals in the cohort who were alive at the time of follow-up received a personal invitation letter. The selection process for the participants in the present study is illustrated in Figure 1.

Participants underwent an examination program consisting of questionnaires, spirometry, mannitol bronchial challenge test, bronchodilator reversibility tests, and measurement of the diffusing capacity for carbon monoxide (DLCO). The examination program also comprised type 2 (T2) biomarker measurements, including fractional exhaled nitric oxide (FeNO), blood eosinophil count (BEC) and total immunoglobulin E (IgE). Further details have previously been published.[18]

Definitions

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023, COPD-A is characterised by post-bronchodilator (post-BD) airflow limitation, defined as $FEV_1/FVC < 0.7$, alongside a history of childhood asthma. Conversely, COPD-C, as outlined by GOLD 2023, is defined by post-BD airflow limitation ($FEV_1/FVC < 0.7$) in combination with a history of tobacco exposure (ever smokers). No airflow limitation was defined as a post-BD $FEV_1/FVC > 0.7$ and a history of childhood asthma.

Exacerbations were defined as the redemption of a prescription for oral corticosteroids (daily dose $\geq$ 25 mg/day for a minimum of five consecutive days), visits to the emergency room, and/or hospitalization due to an acute worsening of respiratory symptoms.[19]

The severity of dyspnoea was assessed using the Medical Research Council (MRC) scale.[20]

Statistical Analysis

Data was reported as mean ± standard deviation (SD) or median ± interquartile range (IQR). Categorical variables were presented as numbers and percentages. Clinical variables and characteristics of participants with COPD, that is either

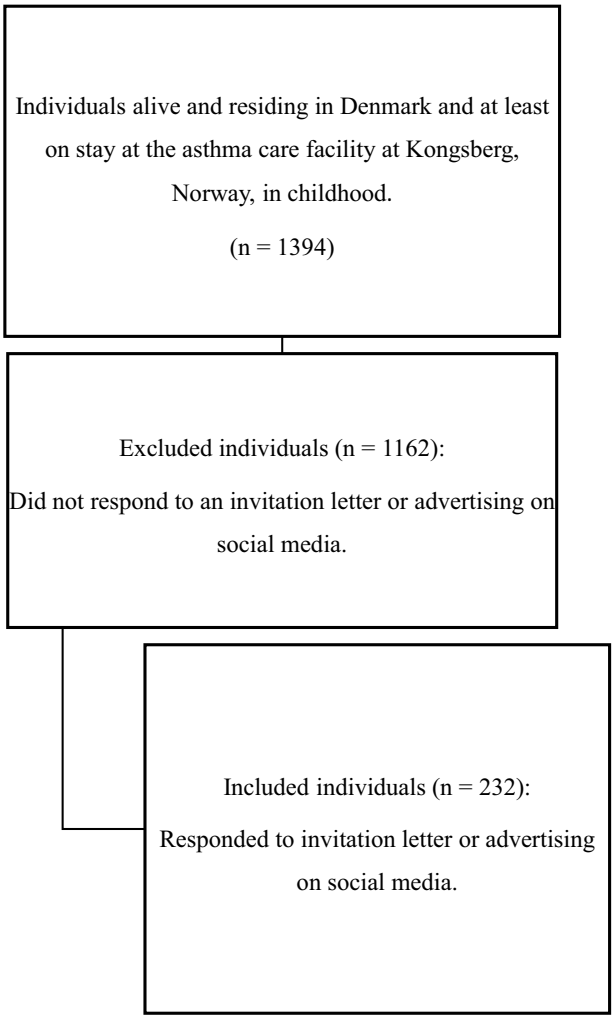

Figure 1 Flowchart of the selection process in the study. Included adult participants (n = 232) with a previous stay at the asthma care facility in childhood in Kongsberg, Norway, and a history of severe childhood asthma divided according to whether participants had COPD-A (n=30), COPD-C (n=23), or none of the two classifications (n=179) at follow-up.

COPD-A or COPD-C, in adulthood were compared to participants without airflow limitation using an independent sample *t*-test for continuous variables and a chi-square test or Fisher's exact test for categorical variables. Mann–Whitney *U*-test was used for non-normally distributed variables. Statistical significance was set at $p < 0.05$. Data were analysed using the statistical program R Statistics 3.61 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1,394 individuals with a history of severe childhood asthma were identified and eligible for participation in the present study. Of the eligible individuals, 232 (16.6%, mean age 66 [SD 7.2] years) participated in the follow-up examination. Of the participants, 30 (13%) and 23 (10%) were classified as having COPD-A (mean age 66.7 [SD 8.2] years) and COPD-C (mean age 66.1 [SD 7.8] years), respectively. For further details, see Table 1.

Characteristics of COPD-A, COPD-C and Participants Without Airflow Limitation

COPD-A

Patients with COPD-A had significantly lower DLCO%pred than participants with no airflow limitation (81.7 [SD 16.3] and 89.2 [SD 15.3], respectively, (p=0.01), although mean values were within the reference range. In addition,

Table 1 Characteristics of Enrolled Adult Participants with a Previous Stay at the Asthma Care Facility in Childhood in Kongsberg, Norway, and a History of Severe Childhood Asthma Divided According to Whether Participants Had COPD-A (n=30), COPD-C (n=23), or No Airflow Limitation (n=179) at Follow-Up

	No Airflow Limitation (n=179)	**COPD-A (n=30)**	**COPD-A versus No Airflow Limitation**	**COPD-C (n=23)**	**COPD-C versus No Airflow Limitation**	**COPD-A versus COPD-C**
			P-value		**P-value**	**P-value**
Sex, females, no. (%)	90 (50.28)	15 (50)	NS	9 (39.13)	NS	NS
Age (years)	66.02 (7.2)	66.7 (8.2)	NS	66.09 (7.77)	NS	NS
BMI (kg/m^2)	29.67 (22.83)	24.45 (6.13)	0.22	27.3 (6.78)	0.63	0.11
Pack Years	6.47 (12.45)	-	-	16.61 (15.35)	*<0.01*	-
Smoking status, no. (%)						
- Never-smoker	89 (52.66)	30 (100)		-		
- Ex-smoker	74 (43.79)	-		21 (91.30)		
- Current smoker	6 (3.55)	-	-	2 (8.70)	-	-
MRC	1.48 (0.69)	1.57 (0.63)	0.53	1.91 (0.95)	*<0.01*	0.11
Spirometry						
- FEV_1 (%pred)	93.01 (17.35)	74.67 (20.12)	-	63.78 (22.67)	-	0.07
- FEV_1/FVC	0.71 (0.08)	0.61 (0.07)	-	0.57 (0.12)	-	0.13
Diffusion Capacity (DLCO) (%)	89.19 (15.32)	81.73 (16.31)	*0.01*	80.32 (23.95)	*0.02*	0.79
P-IgE (10^3 IU/L)	295.95 (622.77)	425.10 (562.67)	0.29	536.65 (889.62)	0.09	0.58
BEC (10^9/L), median (IQR)	0.18 (0.14)	0.18 (0.17)	0.50	0.24 (0.16)	*<0.01*	*0.04*
FeNO (ppb)	25.48 (20.23)	28.91 (27.50)	0.42	26.63 (21.39)	0.80	0.75

Notes: Mean (standard deviation) values except otherwise indicated. COPD-A: Irreversible airflow limitation and no smoking history. COPD-C: Irreversible airflow limitation and either current smoker or ex-smoker. P-values less than 0.05 are considered statistically significant (displayed in italic text) and calculated for the difference between subgroups with no airflow limitation versus COPD-A, no airflow limitation versus COPD-C, and COPD-A versus COPD-C. **Abbreviations**: BMI, body mass index; MRC, Medical Research Council; DLCO, Diffusion Capacity for Carbon monoxide; BEC, blood eosinophil count; P-IgE, plasma immunoglobulin E; FeNO, fractional exhaled nitric oxide; IQR, interquartile range; NS, non-significant.

a numerical higher FeNO was found in those with COPD-A (28.9 [SD 27.5]) compared to those with no airflow limitation (25.5 [SD 20.2]). Further details are given in Table 1.

COPD-C

Participants with COPD-C had significantly higher MRC-scores (1.91 [SD 0.95]) than those with no airflow limitation (1.48 [SD 0.7]) ($p<0.01$) and, although not statistically significant, also compared to those with COPD-A ($p=0.11$).

Participants with COPD-C had significantly lower DLCO%pred (80.32 [SD 23.95]) than participants with no airflow limitation (89.19 [SD 15.32]) ($p=0.02$), although, also here, the mean values were within the reference range.

Furthermore, participants with COPD-C had significantly higher BEC (median 0.24 [IQR 0.16]) than both those with COPD-A (0.18 [IQR 0.17]) ($p=0.04$) and those with no airflow limitation (median 0.18 [IQR 0.14]) ($p<0.01$). Further details are provided in Table 1.

Exacerbations

COPD-C patients had had significantly more exacerbations in the past 12 months compared to participants with no airflow limitation (RR 2.65 (95% CI 1.20–5.82), $p=0.01$), and, likewise, a higher exacerbation rate was observed in those with COPD-A compared to those with no airflow limitation (RR 1.83 (95% CI 0.93–3.59), $p=0.08$). Additionally, COPD-C had the highest proportion of hospitalizations due to exacerbation (13.0%) compared to COPD-A (6.7%) and individuals without airflow limitation (7.2%). Further details are provided in Table 2.

Comorbidities

The prevalence of hypertension was highest in the COPD-A group (33.3%), followed by those with COPD-C (26.1%) and no airflow limitation (18.4%) ($p=0.15$).

Furthermore, COPD-A also had the highest prevalence of osteoporosis (16.7%) compared to both those with COPD-C (0%) and no airflow limitation (6.7%) ($p=0.06$). Similarly, the prevalence of self-reported depression was higher in participants with COPD-A (10%) than in those with COPD-C (4.3%) and no airflow limitation (3.4%) ($p=0.25$).

The prevalence of diabetes was numerical higher in COPD-C patients (8.7%) than among COPD-A (3.3%) and those with no airflow limitation (5.0%) ($p=0.67$).

Additional details of the comorbidities are presented in Figure 2.

Discussion

The present study showed that, in adults with a history of severe childhood asthma, one out of four had non-reversible airflow limitation that could be classified as either COPD-A or COPD-C. In the two groups of patients with COPD, COPD-C had the highest proportion of hospitalizations due to exacerbation, more dyspnoea, and significantly higher BEC.

Association Between Childhood Asthma and COPD-A

Approximately one-tenth of our study population met the criteria for COPD-A, indicating that meeting the spirometric criteria for COPD in individuals with no smoking history may at least partly result from severe asthma earlier in life. While our study highlights an association between childhood asthma and COPD in adulthood, diagnostic ambiguity between COPD and asthma-related traits complicates the interpretation. Both COPD and severe asthma may present with similar response to treatment and symptoms that are not specific to either condition, making it challenging to differentiate between them based solely on clinical presentation and examination.[21] In addition, COPD and asthma may have variable disease progression trajectories. Some individuals with asthma may develop irreversible airway obstruction over time, resembling COPD, while others may maintain variable and reversible airflow limitation characteristic of asthma.[22] The fluctuation in symptoms and disease progression may obscure the differentiation between these two conditions, particularly in longitudinal research or when evaluating elderly individuals with a history of early life asthma. Furthermore, being exposed to environmental pollution may be a contributing factor to the development of both asthma and COPD.[23]

Table 2 Exacerbation and Treatment with Corticosteroids and/or Antibiotics in Enrolled Adult Participants with a Previous Stay at the Asthma Care Facility in Childhood in Kongsberg, Norway, and a History of Severe Childhood Asthma Divided According to Whether Participants Had COPD-A (n=30), COPD-C (n=23), or None of the Two Classifications at Follow-Up

	No Airflow Limitation (n=179)	COPD-A (n=30)	COPD-A versus No Airflow Limitation		COPD-C (n=23)	COPD-C versus No Airflow Limitation		COPD-A versus COPD-C	
			RR (95% CI)	P-value		RR (95% CI)	P-value	RR (95% CI)	P-value
Exacerbations	36 (22.6)	11 (37.9)	1.83 (0.93–3.59)	0.08	10 (47.6)	2.65 (1.20–5.82)	*0.01*	0.84 (0.51–1.39)	0.49
Hospitalization due to exacerbation	12 (7.2)	2 (6.7)	1.01 (0.81–1.26)	0.92	3 (13.0)	1.75 (0.59–5.22)	0.32	0.69 (0.23–2.06)	0.43
Lower airway infection treated with antibiotics	36 (22.0)	5 (17.2)	0.77 (0.31–1.89)	0.59	6 (27.3)	1.29 (0.54–3.08)	0.58	0.76 (0.39–1.52)	0.39

Notes: All variables include number of participants (percentage of total for each group) and are based on the past 12 months. 'Exacerbations' include at least one exacerbation. COPD-A: Irreversible airflow limitation and no smoking history. COPD-C: Irreversible airflow limitation and either current smoker or ex-smoker. P-values less than 0.05 are considered statistically significant (displayed in italic text) and calculated for the difference between subgroups with no airflow limitation versus COPD-A, no airflow limitation versus COPD-C, and COPD-A versus COPD-C.

Abbreviations: RR: risk ratio; CI: confidence interval.

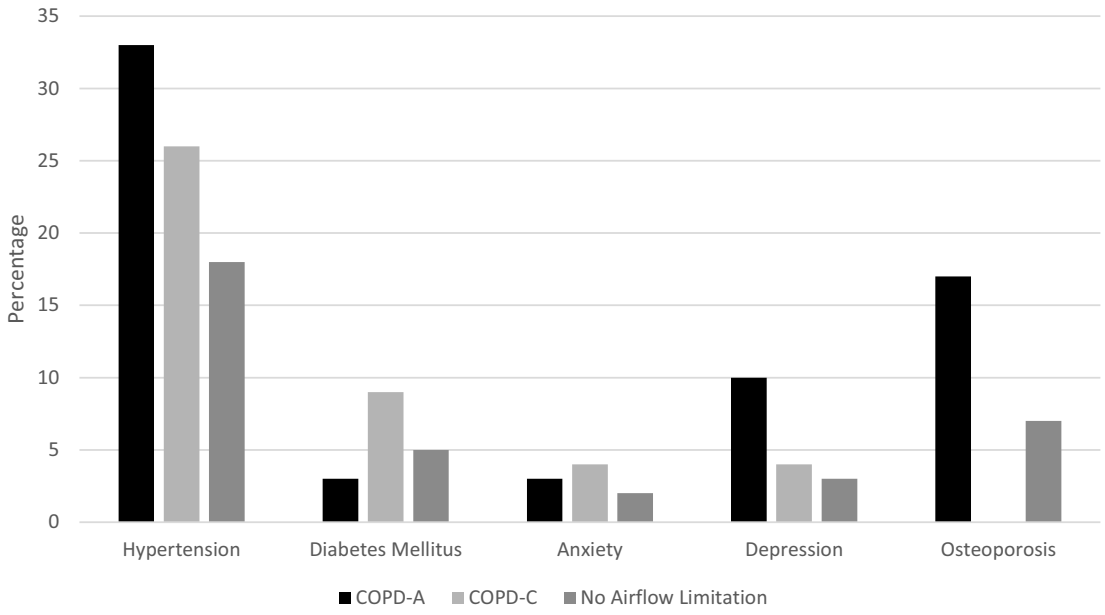

Figure 2 Distribution of comorbidities (%) divided according to whether enrolled adult participants with a history of severe childhood asthma had COPD-A (n=30), COPD-C (n=23), or no airflow limitation (n=179). No significant differences in comorbidities were found between those with COPD-A versus no airflow limitation, COPD-C versus no airflow limitation, or COPD-A versus COPD-C.

COPD-C - Exploring the Interaction Between Smoking and Asthma

Our study revealed that approximately one out of 10 participants met the criteria for COPD-C, possibly resulting from the interaction between smoking and asthma over time. Moreover, tobacco exposure is known to have negative impact on the effect of inhaled corticosteroids (ICS) on disease control in patients with asthma,[24] which adds to the complexity of the interaction. Individuals with COPD-C in our study had significantly higher BEC compared to both participants without airflow limitation and those with COPD-A. One interpretation might be that COPD-C represents eosinophilic asthma with fixed airflow limitation, not least because individuals categorized as COPD-C in our study had relatively limited life-time tobacco exposure. However, attributing COPD-C solely to eosinophilic asthma with fixed airflow limitation might be oversimplifying the complex interplay of factors involved. The clinical presentation and disease course of COPD-C may vary widely between individuals, making it challenging to classify all cases under a single pathophysiological umbrella. Factors such as response to treatment may differ between patients with COPD-C, suggesting underlying heterogeneity in disease mechanisms. Furthermore, the relatively low life-time tobacco exposure among the participants with COPD-C does clearly not exclude a diagnosis of smoking-related COPD, as the range of tobacco exposure varies substantially among patients with COPD.[25] Increased levels of blood eosinophils seem to indicate the potential response of individuals with COPD to ICS.[26] Studies have proposed elevated blood eosinophil count as a biomarker for predicting the effectiveness of ICS therapy.[27,28] A recent pooled data analysis of clinical trials found no significant clinical correlation between blood eosinophil count and rate of exacerbations.[29] However, according to the strategy paper of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), it is suggested to use a blood eosinophil threshold of >300 cells/μL to guide the likely benefit from ICS.[2] Furthermore, in the process of making treatment decisions, GOLD advises considering the individual benefits and risks of ICS.

Our study findings on exacerbation rate in individuals with a smoking history was similar to findings in a recent study based on the nationwide Danish COPD registry by Nielsen et al, who reported that individuals with no previous smoking history had a significantly lower risk of exacerbation compared to patients with a smoking history.[30] Similarly, we found that COPD-C patients had the highest exacerbation and hospitalization rates, with a notable 13% experiencing hospitalizations due to exacerbations compared to 6.7% in the COPD-A group. These observations are likely to reflect smoking as an important risk factor for exacerbation, including more severe

exacerbations leading to hospitalization.[31] In addition, studies have previously shown that smoking is associated with an increase in dyspnoea severity.[32] Our study also found that COPD-C (current and ex-smokers) patients had higher MRC dyspnea scores (mean 1.91 [SD 0.95]) compared to both COPD-A (although not statistically significant, p=0.11) and those without airflow limitation, indicating more severe symptom burden in COPD-C.

Overall, in our view, our study provides valuable insights into the relationship between T2 biomarkers, including BEC, and the presence of COPD in elderly adults with a history of severe asthma in childhood. However, categorizing participants into COPD-A and COPD-C based on exposure history presents challenges in differentiating COPD from features associated with long-standing asthma. The elevated BEC in COPD-C compared to COPD-A might suggest an association between increased blood eosinophils, persistent airway inflammation and irreversible airflow limitation.[33,34] Nonetheless, the complex pathways leading to the development of airflow limitation must be explored further in future studies.

Strengths and Limitations

Our study has strengths worth mentioning. First, no studies have, to our knowledge, so far examined characteristics using the classification of COPD-A or COPD-C in a cohort of individuals with a history of severe asthma in childhood.[3,16]

Our study has several limitations. Being observational in nature, our study design limits the ability to draw conclusions with regard to causality. Additionally, our study design may not permit a definite distinguishing between COPD and asthma-related irreversible airflow limitation. Furthermore, all comorbidities, MRC scores, and acute exacerbations were self-reported with the risk of misclassification due to misunderstanding or inaccurate responses. However, redemption of prescriptions was confirmed through the nationwide digital system on filled prescriptions (the "Common Medication Card"). Limited statistical power might have resulted in nonsignificant p-values, particularly noticeable in the analysis of exacerbation rates across subgroups. Therefore, caution is warranted when interpreting the findings due to the relatively small sample size of the subgroups.

Conclusion

Based on the proposed COPD classification in the GOLD 2023 strategy document, our study assessed characteristics of distinct COPD subtypes (COPD-A and COPD-C) within a cohort of adults with a history of severe childhood asthma. Individuals with COPD-C, characterized by tobacco exposure, had significantly higher dyspnoea scores and blood eosinophil counts compared to those with COPD-A, that is airflow limitation and no tobacco exposure, while COPD-A individuals showed higher levels of FeNO and FEV_1%pred, and a higher prevalence of osteoporosis and depression compared to COPD-C and participants without airflow limitation.

Data Sharing Statement

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request if in accordance with Danish legislation.

Ethics Approval and Consent for Participation

The present study is a non-drug, non-interventional study. All methods were carried out in accordance with relevant guidelines and regulations, including The Code of Ethics of the World Medication Association (Declaration of Helsinki). Informed consent was obtained from all subjects and/or their legal guardian(s). All relevant study information was given to the scientific ethics committees and the study was accordingly approved (H-20071320) by The Regional Scientific Ethics Committees (in Danish "De Videnskabsetiske Komiteer (VEK)") in the Capital Region of Denmark (Full name: Center for Regional Development, Health Research and Innovation, The Regional Scientific Ethics Committees, Capital Region of Denmark).

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, and took part in drafting, revising and critically reviewing this article. Furthermore, all authors gave final approval of the version to be submitted for publication and agree to be accountable for all aspects of the work.

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Disclosure

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