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TITLE PAGE

Assessment of chronic bronchitis and risk factors in young adults: Results from BAMSE

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Author's contributions

Authors J.H., A.L., and E.M. designed the study and outlined the contents of the manuscript. G.W. was responsible for the practical conduct of the study, including the planning, coordination and analyzes of the data, and the writing the manuscript under the supervision by E.M. J.H. had overall responsibility for the fractional exhaled nitric oxide and the lung function measurements at 24 years of age. G.P. and O. G. had overall responsibility for the air pollution data. P.U.B., C.J., M.v.H., A.G., A.B. and I.K. revised the work critically for the content. All authors contributed to the interpretation of the data and approved the final manuscript prior to its submission.

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Take home message

Chronic bronchitis in young adults is strongly associated with recurrent respiratory infections. Besides smoking, our results support role of early life air pollution and breast-feeding for respiratory health in this age group.

Abbreviation list

BAMSE	: Swedish abbreviation for Barn/Children, Allergy, Milieu, Stockholm, Epidemiology
BC	: black carbon
BMI	: body mass index
CB	: chronic bronchitis
COPD	: chronic obstructive pulmonary disease
CI	: confidence interval
FEV ₁	: forced expiratory volume in 1 second
FeNO	: fractional exhaled nitric oxide
FVC	: forced vital capacity
GLI	: the Global Lung Function Initiative
IQR	: interquartile range
LLN	: the lower limit of normal
NO _x	: nitrogen oxides
OR	: odds ratio
ppb	: parts per billion
SD	: standard deviation

ABSTRACT

Background: Chronic bronchitis is associated with substantial morbidity among elderly adults, but little is known about its prevalence and risk factors in young adults. Our aim was to assess the prevalence and early life risk factors for chronic bronchitis in young adults.

Methods: Questionnaire data and clinical measures from the 24-year follow-up of the Swedish BAMSE cohort were used. We assessed chronic bronchitis (CB) as the combination of cough and mucus production in the morning during winter. Environmental and clinical data from birth and onwards were used for analyses of risk factors.

Results: At the 24-year follow-up, 75% (n=3,064) participants completed the questionnaire and 2,030 performed spirometry. The overall prevalence of CB was 5.5% (n=158) with similar estimates in males and females. Forty-nine percent of CB cases experienced more than 3 self-reported respiratory infections in the last year compared to 18% in non-CB subjects ($p<0.001$), and 37% of cases were current smokers (vs. 19%). Statistically significant lower post-FEV₁/FVC were observed in CB compared to non-CB subjects (mean z-score -0.06 vs. 0.13, $p=0.027$). Daily smoking (adjusted Odds Ratio, aOR = 3.85, $p<0.001$), air pollution exposure (black carbon during ages 1-4 years old, aOR = 1.71 per 1 $\mu\text{g}/\text{m}^3$ increase, $p=0.009$) and exclusive breast-feeding during four months or more (aOR = 0.66, $p=0.044$) were associated with CB.

Conclusion: Chronic bronchitis in young adults is associated with recurrent respiratory infections. Besides smoking, our results support role of early life exposures, such as air pollution and exclusive breast-feeding, for respiratory health later in life.

Key Words:

Air pollution; Breast-feeding, Chronic bronchitis, Lung function, Smoking

Introduction

Chronic bronchitis is characterized by cough and hypersecretion of mucus and associated with chronic inflammation in the airways [1]. Chronic bronchitis is also associated with acute respiratory health events including exacerbations [2, 3] and hospitalizations [4] as well as airflow obstruction [5], progressive lung function decline [6], and eventually higher all-cause mortality [5].

Chronic bronchitis is common in the general adult population and the prevalence ranges from 3.6% to 22% worldwide [7], and from 5.5% to 7.2% in Sweden [8, 9]. Moreover, the prevalence is even higher in smokers with chronic obstructive pulmonary disease (COPD), ranging from 19% up to 74% [10-12]. Due to the enhanced prevalence in elderly and patients with COPD [9, 13], few studies on chronic bronchitis have focused on young adults. Most of these studies include subjects 18-40 years of age, and report prevalence ranging from 1% to 10% [9, 13-15]. However, little is known about the prevalence and early life risk factors for chronic bronchitis in the specific age group of young adults in their early 20s.

Ongoing exposure to cigarette smoke is known as a primary risk factor for chronic bronchitis, whereas other risk factors, such as ambient air pollutants, may also play a role [14]. Although the relationship between air pollution exposure in adulthood and chronic bronchitis has been well studied [13, 16], no studies have evaluated associations between early-life exposure and later disease. Our previous studies found impaired development of lung function, as well as asthma during childhood and adolescence, to be linked to traffic-related air pollution exposure in infancy [17-19]. Given these facts, we hypothesized that childhood air pollution exposure and other environmental exposures may also influence the risk of chronic bronchitis in young adults. Thus, the aim of this study was to assess the prevalence of chronic bronchitis in young adults in a Swedish population-based birth cohort and to identify early life risk factors, including environmental exposures, for disease development.

Methods

Subjects

In this project, data from the follow-up of the Swedish population-based birth cohort BAMSE (Swedish abbreviation for Child (Barn), Allergy, Milieu, Stockholm, Epidemiological) were used [20-22]. Between February 1994 and November 1996, 4089 infants from inner-city, urban and suburban districts of Stockholm were included in the cohort. Data on background characteristics, respiratory health, and exposure factors were obtained from parental questionnaires administered at age of 2 months. Follow-up questionnaires were repeatedly answered by parents at age of 1, 2, 4, 8, 12, and 16 years. The response rates were 96%, 94%, 91%, 84%, 82% and 78%, respectively. At the 24-year follow-up, questionnaires focusing on respiratory symptoms and key exposures such as smoking habits were answered by the participants themselves. Details about the definitions of health outcomes and covariates are provided in the online supplement.

The study was approved by the Ethics Committee of Karolinska Institutet (Ref 2016/1380-31/2), Stockholm, Sweden, and all participants gave their oral and written informed consent, in accordance with the Helsinki Declaration.

Measurements and definitions of outcomes

We assessed chronic bronchitis as the combination of the symptoms of cough and mucus production in the morning during winter (defined as “CB”), which required positive answers to the following two binary-choice questions: 1) “In the winter, do you usually cough as soon as you wake up in the morning?” and 2) “In the winter, do you usually bring up mucus as soon as you wake up in the morning?” [23].

Childhood asthma at ages 1-16 years of age was defined if at least two of the following three criteria were fulfilled: doctor's diagnosis of asthma ever; wheezing in the last 12 months; and/or use of asthma medication during the last 12 months [24].

Current asthma was defined as a positive answer to doctor diagnosis of asthma, and at least one of the following: wheezing in the last 12 months; or use of asthma medication during the last 12 months.

Lung function was tested according to ATS/ERS spirometry criteria [25] using the Jaeger MasterScreen-IOS system (Carefusion Technologies™, San Diego, CA) and post-bronchodilator lung function was tested 15 minutes after the administration of 400 µg salbutamol. The highest values of pre- and post-forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were recorded [19, 20]. Predicted values and z-scores of FEV₁, FVC and FEV₁/FVC ratios were calculated for each patient using equations from the Global Lung Function Initiative (GLI) [26] according to age, sex, height, and ethnicity. The lower limit of normal (LLN) was defined as the bottom fifth percentile of the predicted value and calculated by GLI equations for every participant.

Fractional exhaled nitric oxide (FeNO) was measured with a chemiluminescence analyzer (EcoMedics Exhalyzer®, Duernten, Switzerland) according to the ATS/ERS guidelines [27].

Definition of air pollution exposure

Details of air pollution exposure concentrations have been described previously [28]. Briefly, historical emission databases and Gaussian air dispersion models were used to calculate the time-weighted average outdoor concentration of two representative traffic-related air pollutants (nitrogen oxides (NO_x) and black carbon (BC)) for different time windows, namely during the first year of life (i.e. 0-1 years), as well as average exposures since the date of the previous follow-up (i.e. 1-4, 4-8, 8-12 and 12-16 years), according to geocoded lifetime residential, day-care, and school addresses. All air pollution concentrations were estimated and presented as continuous variables (µg/m³).

Statistical analysis

The prevalence of CB in BAMSE was expressed as the percentage of the total number of participants who completed the 24-year questionnaire. Comparisons between participants with and without CB were performed using ANOVA, Kruskal-Wallis rank, Chi-squared tests and Fisher's exact test as appropriate. Odds ratios (ORs) and 95% confidence interval (95% CI) of potential risk factors in relation to CB were estimated based on multivariable logistic regression. As concurrent asthma may be associated with cough and mucus production, we performed a sensitivity analysis where participants with current asthma were excluded. P-values of <0.05 were considered statistically significant. Analyses were performed using the R software (version 4.0.2).

Results

Baseline characteristics

Among the 4,089 children in the original BAMSE cohort, 3,064 (75%) participants completed the questionnaire at the 24-year follow-up. Of these respondents, 2,890 provided valid information on morning cough and mucus production, and 2,030

performed lung function measurements. The overall prevalence of cough only was 3.3% (n=95, 95% CI 2.6% to 3.9%), mucus production only 9.6% (n=276, 95% CI 8.5% to 10.6%), and both cough and mucus production, thus CB, 5.5% (n=158, 95% CI 4.6% to 6.3%). There was no difference of CB prevalence between males (n=73; 5.5%) and females (n=85; 5.5%). Table 1 shows that, compared with non-CB subjects (without cough and mucus production), CB cases had higher body mass index (BMI), smoked more often (former and current smoking and electronic cigarette smoking) and smoked more cigarettes (cigarette consumption per day). No statistically significant differences were found in relation to age, sex, or education.

Table 1. Characteristics of cohort participants with and without chronic bronchitis (CB)

	CB (N=158)	No CB (N=2,361)	p value
Age, y, mean (SD)	22.4 (0.5)	22.4 (0.5)	0.361
Sex, Female, n (%)	85 (53.8%)	1,278 (54.1%)	0.935
BMI, kg/m ² , mean (SD)	24.03 (4.4)	23.15 (3.8)	0.005
Education, n (%)			0.544
Secondary school	106 (67.1%)	1,503 (63.8%)	
High school	34 (21.5%)	514 (21.8%)	
University	18 (11.4%)	340 (14.4%)	
Smoking status, n (%)			< 0.001
Never	72 (45.6%)	1628 (69.1%)	
Former smoker	27 (17.1%)	289 (12.3%)	
Current smoker, sometimes	27 (17.1%)	297 (12.6%)	
Current smoker, every day	32 (20.3%)	142 (6.0%)	
Cigarette consumption per day *, median (IQR)	4.3 (1.1, 10.0)	1.4 (0.4, 5.0)	< 0.001
Electronic cigarette smoking, Yes, n (%)	11 (7.0%)	82 (3.5%)	0.025

SD: standard deviation; IQR: interquartile range; BMI: body mass index.

* Based on current smokers.

Respiratory health events and lung function

Self-reported respiratory symptoms and lung function data for each group are presented in Table 2. In the group of CB cases, 62% reported any respiratory symptoms in the last 12 months compared to 19% in the non-CB group, and the proportion of subjects with emergency department visits due to respiratory symptoms was 6 times higher among those with CB. Self-reported pneumonia in the last 12 months was more common in the group of CB cases (8.3% vs. 2.1%) as well as self-reported recurrent (>3) respiratory infections (49% vs. 18%) compared to the non-CB group. Thirty-two of the CB cases had concurrent current asthma at 24 years, respectively, compared to 8.6% in subjects without CB. Besides, more subjects in the group of CB cases were using inhaled steroids (18.5% vs. 4.7%) and sensitized to common food allergens at 24-years compared to the non-case group (16.5% vs. 7.6%). However, no statistically significant differences were observed for sensitization to airborne allergens. Compared to subjects without CB, pre- and post-FEV₁/FVC ratios were lower in the group of CB cases (mean pre- and post-z-score -0.59 and -0.06, respectively, vs. -0.33, and 0.13 in the non-CB group; P=0.003 and P=0.027), and greater change in FEV₁ after reversibility test was also found (4.0% FEV₁ change compared to baseline value vs 3.0%, respectively, P=0.005). No pronounced differences were detected for pre- and post-FEV₁, pre- and post-FVC or FeNO between subjects with or without CB. Sensitivity analyses that excluded current asthma subjects showed overall similar results, with the addition that more cases with CB had pre- and post-FEV₁ below LLN compared to the non-case group (9.9% and 6.3%, respectively, vs. 4.3% and 1.8%, P=0.027 and P=0.011, Table E1).

Table 2. Respiratory health events and lung function in participants with and without chronic bronchitis (CB)

	CB (N=158)	No CB (N=2,361)	p value
Self-reported respiratory symptoms *, Any, n (%)	98 (62.0%)	451 (19.1%)	< 0.001
Emergency department visits, Yes, n (%)	14 (8.9%)	33 (1.4%)	< 0.001
Self-reported respiratory infections, n (%)			< 0.001
Never	6 (3.8%)	339 (14.4%)	
1-3 times	75 (47.5%)	1,591 (67.4%)	
More than 3 times	77 (48.7%)	431 (18.3%)	
Self-reported pneumonia, Yes, n (%)	13 (8.3%)	50 (2.1%)	< 0.001
Current asthma, Yes, n (%)	50 (31.6%)	203 (8.6%)	< 0.001
Sensitization to airborne allergens ‡, Yes, n (%)	60 (49.6%)	746 (41.6%)	0.083
Sensitization to food allergens §, Yes, n (%)	20 (16.5%)	137 (7.6%)	< 0.001
FeNO, ppb, median (IQR)	11 (9, 19)	12 (8, 19)	0.987
% predicted † pre-FEV ₁ , mean (SD)	95.7 (10.1)	97.1 (10.1)	0.184
Pre-FEV ₁ lower than LLN †, Yes, n (%)	8 (7.7%)	74 (4.5%)	0.140
Pre-FEV ₁ z-score †, mean (SD)	-0.37 (0.9)	-0.25 (0.9)	0.178
% predicted † pre-FVC, mean (SD)	100.0 (9.7)	99.4 (10.3)	0.561
Pre-FVC z-score †, mean (SD)	-0.01 (0.8)	-0.06 (0.9)	0.557
Pre-FEV ₁ /FVC, %, mean (SD)	81.8 (6.3)	83.5 (6.1)	0.005
Pre-FEV ₁ /FVC z-score †, mean (SD)	-0.59 (0.9)	-0.33 (0.9)	0.003
Reversibility test			
Change in FEV ₁ , ml, median (IQR)	139 (80, 220)	115 (54, 195)	0.011

Change in FEV ₁ % baseline value, %, median (IQR)	4.0 (2.1, 5.7)	3.0 (1.3, 4.9)	0.005
% predicted † post-FEV ₁ , mean (SD)	99.2 (9.8)	100.1 (9.9)	0.372
Post-FEV ₁ lower than LLN †, Yes, n (%)	4 (4.2%)	29 (1.9%)	0.117 ll
Post-FEV ₁ z-score †, mean (SD)	-0.07 (0.8)	0.02 (0.9)	0.360
% predicted † post-FVC, mean (SD)	99.3 (9.8)	98.9 (10.4)	0.723
Post-FVC z-score †, mean (SD)	-0.07 (0.8)	-0.10 (0.9)	0.731
Post-FEV ₁ /FVC, %, mean (SD)	85.4 (5.6)	86.6 (5.3)	0.035
Post-FEV ₁ /FVC z-score †, mean (SD)	-0.06 (0.8)	0.13 (0.8)	0.027

SD: standard deviation; IQR: interquartile range; FeNO: fractional exhaled nitric oxide; ppb: parts per billion; FEV₁: forced expiratory volume in 1 second; LLN: lower limit of normal; FVC: forced vital capacity.

* Self-reported respiratory symptoms were assessed as any troublesome breathing, chest tightness or wheezing during the last 12 months.

† Based on the reference equation from the Global Lung Initiative 2012 [26].

‡ Sensitization was assessed to a mix of common airborne allergens with Phadiatop® (ImmunoCAP System; ThermoFisher, Uppsala, Sweden, and a positive test was defined as specific IgE ≥ 0.35 kU_A/L).

§ Sensitization was assessed to a mix of common food allergens with fx5® (ImmunoCAP System; ThermoFisher, Uppsala, Sweden, and a positive test was defined as specific IgE ≥ 0.35 kU_A/L).

ll Based on Fisher's exact test.

Risk factors for CB in young adults

In regression models adjusted for age, sex and BMI (Table 3), childhood asthma was a strong risk factor related to CB in young adults (OR = 3.08, 95% CI 2.17 to 4.35). In mutually adjusted models exploring the role of environmental exposures, we found that smoking status (former smoker, aOR = 1.90, 95% CI 1.16 to 3.14; current smoking, sometimes, aOR = 1.99, 95% CI 1.22 to 3.26; current smoking, daily, aOR = 3.85, 95% CI 2.32 to 6.39, Figure 1), and exposure to air pollution (BC concentration during age 1-4 years old, aOR = 1.71, 95% CI 1.14 to 2.57 per 1 $\mu\text{g}/\text{m}^3$ increase, Figure 1; NO_x concentration during 1-4 years old; aOR = 1.01, 95% CI 1.00 to 1.03 per 1 $\mu\text{g}/\text{m}^3$ increase, Figure E1) were independent risk factors for CB. Besides, exclusive breast-feeding during 4 months or more was found to be a protective factor (aOR = 0.66, 95% CI 0.44 to 0.99). Subgroup analyses of smoking history showed that the risk of CB was particularly increased for a combination of parental smoking during childhood and ever smoking, defined as former or current smoking (aOR = 3.63, 95% CI 2.33 to 5.64 compared to non-exposed, non-smokers; supplement Table E2), while a smaller risk increase was observed for ever smokers who were not exposed to parental smoking during childhood (aOR = 1.58, 95% CI 0.98 to 2.50 with significant OR for interaction = 2.79, 95% CI 1.31 to 6.17). There was no clear association between parental smoking and CB in never smokers. In addition, electronic smoking (e-smoking) trended to be associated with and increased risk of CB (OR = 1.92, 95% CI 0.99 to 3.72, Table 3), but no clear association were observed between other potential risk factors (i.e. parental occupation, parental asthma, maternal smoking during pregnancy, premature birth, low birth weight, bronchitis during infancy, respiratory syncytial virus infection /pneumonia during early childhood and air pollution during other time windows) and CB.

Sensitivity analyses that excluded subjects with current asthma showed overall similar results with significant associations for smoking status and air pollution exposure, although estimates for exclusive breast-feeding during 4 months or more became non-significant (aOR = 0.77, 95% CI 0.46 to 1.27, supplement Figure E2).

Table 3. Distribution of potential risk factors for chronic bronchitis (CB) among young adults from the BAMSE birth cohort.

	CB (N=158)	No CB (N=2,361)	Logistic regression model *		
			OR	95% CI	P value
Electronic cigarette smoking, Yes	11 (7.0%)	82 (3.5%)	1.916	0.937 to 3.573	0.055
Parental occupation, n (%)					
Unemployed/blue collar	18 (12.9%)	212 (10.1%)	Ref	-	-
Low white collar	60 (43.2%)	843 (40.0%)	0.874	0.489 to 1.467	0.555
High white collar	61 (43.9%)	1,050 (49.9%)	0.705	0.408 to 1.219	0.211
Parental education, n (%)					
University	71 (44.9%)	1,365 (57.9%)	Ref	-	-
Primary school/High school	87 (55.1%)	993 (42.1%)	1.618	1.167 to 2.249	0.004
Parental asthma, Yes, n (%)	33 (21.6%)	444 (18.9%)	1.174	0.776 to 1.730	0.432
Exclusive breast-feeding during 4 months or more, Yes, n (%)	115 (75.7%)	1,857 (80.8%)	0.743	0.510 to 1.107	0.132

Maternal smoking during pregnancy, Yes, n (%)	21 (13.3%)	253 (10.7%)	1.249	0.752 to 1.979	0.365
Parental smoking during childhood, Yes, n (%)	65 (41.4%)	644 (27.3%)	1.822	1.301 to 2.563	< 0.001
Premature birth, Yes, n (%)	9 (5.7%)	129 (5.5%)	1.026	0.475 to 1.957	0.942
Low birth weight, Yes, n (%)	4 (2.5%)	84 (3.6%)	0.728	0.220 to 1.781	0.541
Respiratory syncytial virus infection / Pneumonia during infancy, Yes, n (%)	14 (9.2%)	164 (7.1%)	1.282	0.691 to 2.205	0.399
Bronchitis during infancy, Yes, n (%)	12 (7.8%)	178 (7.8%)	0.975	0.503 to 1.728	0.937
Pneumonia during age 0-4 years old, Any, n (%)	16 (10.3%)	249 (10.7%)	0.950	0.536 to 1.576	0.851
Childhood asthma during age 1 to 4 years old, Yes, n (%)	31 (19.9%)	228 (9.8%)	2.129	1.367 to 3.225	0.001
Childhood asthma during age 1 to 8 years old, Yes, n (%)	42 (26.9%)	275 (11.7%)	2.629	1.773 to 3.831	< 0.001
Childhood asthma during age 1 to 16 years old, Yes, n (%)	59 (37.6%)	367 (15.6%)	3.082	2.166 to 4.351	< 0.001
Nitrogen oxides, $\mu\text{g}/\text{m}^3$, median (IQR)					
Age 0-1 years old	29.12 (20.3, 45.0)	29.3 (18.3, 42.5)	1.006	0.997 to 1.014	0.195
Age 1-4 years old	25.8 (16.9, 37.7)	24.2 (15.3, 33.6)	1.011	1.000 to 1.022	0.038
Age 4-8 years old	20.5 (13.1, 29.8)	18.2 (12.1, 27.1)	1.010	0.994 to 1.025	0.192

Age 8-12 years old	14.2 (10.0, 22.9)	13.8 (10.1, 22.2)	1.002	0.983 to 1.020	0.837
Age 12-16 years old	11.7 (7.9, 17.1)	11.3 (8.3, 18.1)	0.997	0.970 to 1.022	0.811
Black carbon, $\mu\text{g}/\text{m}^3$, median (IQR)					
Age 0-1 years old	0.97 (0.8, 1.4)	0.97 (0.7, 1.3)	1.278	0.905 to 1.764	0.149
Age 1-4 years old	0.96 (0.7, 1.3)	0.89 (0.7, 1.2)	1.575	1.060 to 2.289	0.020
Age 4-8 years old	0.87 (0.7, 1.2)	0.81 (0.6, 1.1)	1.388	0.849 to 2.205	0.177
Age 8-12 years old	0.71 (0.6, 1.0)	0.70 (0.6, 0.9)	1.070	0.585 to 1.876	0.820
Age 12-16 years old	0.66 (0.6, 0.8)	0.65 (0.5, 0.8)	0.916	0.350 to 2.249	0.853

IQR: interquartile range.

* Results after adjustment for age, sex and body mass index.

Discussion

In the present study on data from a population-based birth cohort, the overall prevalence of chronic bronchitis (CB) in young adults was 5.5% with similar estimates in males and females. The group of cases with CB had more self-reported respiratory infections and emergency department visits in the last 12 months compared to the group of subjects without CB. Furthermore, using the longitudinal data in our BAMSE birth cohort, we found that previous or current smoking and early life air pollution exposure were risk factors for CB while exclusive breast-feeding during 4 months or more was a protective factor. These findings were robust after adjustment for several potential confounders, and support the role of early life events for later respiratory health [29].

Smoking as risk factor for chronic bronchitis

In Sweden, the prevalence of chronic bronchitis in adults below the age of 45 has decreased from around 12% in the 1990s [30] to around 4% after the 2000s [9, 13, 14]. The decrease in prevalence is believed to be mostly due to decreased smoking in the general population during the same periods [9, 31]. In the 1990s, more than 30% of young adults in their 20s in Stockholm were current smokers [32], while the prevalence of current smoking (sometimes or daily) was found to be 20.8% in our BAMSE study. As expected, cigarette smoking strongly increased the risk of CB (almost 4-fold increased risk for current daily smoking) in our study. In addition, the risk increase for smoking was found to be particularly high in study participants who were also exposed to parental smoking during childhood (with significant interaction effect); a finding that underlines the combined effects as earlier suggested [33]. Thus, our results confirm that even a short duration of smoking, and in particular, the combination of smoking and parental smoking exposure, may lead to chronic bronchitis in young adults. As persistent CB symptoms have been found to accelerate the decline in FEV₁ and CB symptoms prevalence following smoking cessation returned to levels in never-smokers [34], decreasing cigarette smoke exposure would be an essential way to improve CB-related symptoms as well as long-term health effects.

The use of electronic cigarettes has increased rapidly among young adults in the United States and increases the risk of CB [35]. In our study, e-smoking tended to increase the risk of CB (two-fold), but this association did not reach statistical significance, partly because of the relatively low prevalence of e-smoking in our study, reflecting the situation in Sweden [36].

Early life environmental risk factors

To our knowledge, ours is the first study to investigate the association between early life air pollution exposure and chronic bronchitis in truly young adults. The long-term effects of exposure to air pollution on chronic bronchitis in middle-aged adults and elderly have been investigated previously [16]. In children, short-term exposure to air pollution is well-known to be associated with exacerbations of respiratory infections [37], and long-term exposure with decreased lung function development [18, 19] and wheezing/asthma [38]. In particular, early life BC exposure has been related to wheezing, cough and respiratory infections in pre-school and school children [38, 39]. In our current study, we explored the relationship between early life BC and NO_x exposure and CB in young adults and found that BC and NO_x concentration during age 1-4 years old was an independent risk factor. This relationship was robust to adjustment for several potential confounders, and after the exclusion of participants with current asthma. The levels of BC and NO_x in Stockholm mainly reflect local emissions from road traffic [40], which implies that this intervenable exposure may play an important role in the etiology of chronic bronchitis in young adults, particularly as air pollution in Stockholm are lower than in most other cities. Another early-life exposure, exclusive breast-feeding, was found to be an independent protective factor for CB. In our previous study, exclusive breast-feeding during 4 months or more reduced the risk of asthma up to 8 years [21]. In other studies, exclusive breast-feeding has been associated with reduced risk of childhood respiratory infections [41], which in the long-run might help to protect from chronic bronchitis. Childhood asthma *per se* was associated with CB in our study, and the associations between exclusive breast-feeding and CB were also

somewhat attenuated after the exclusion of participants with current asthma (OR decreased from 0.66 to 0.77). Notably, the relationship between breast-feeding, childhood asthma and subsequent chronic bronchitis will require additional studies for validation. Since current asthma also leads to cough and mucus production, it is difficult to say whether asthma is a mediator or confounder in relation to analyses of environmental factors and chronic bronchitis, even if asthma and chronic bronchitis may display different pathology [42].

Clinical respiratory events and airway obstruction

Mucus hypersecretion and decreased mucociliary clearance are considered as basic pathologic features of chronic bronchitis [1, 3], and accumulated mucus that cannot be expectorated typically triggers respiratory symptoms and intermittent infections [43]. Our study showed that almost half of the cases in the group of CB had experienced more than three episodes of respiratory infections per year, which is more than 2.5-fold higher than the group of subjects without CB. Moreover, emergency department visits and history of pneumonia were reported around 6 and 4 times higher in the CB group, respectively. The incidence and severity of acute exacerbations in patients with chronic bronchitis may accelerate the progression of disease severity, including loss of lung function [3]. Chronic bronchitis may exist with or without airway obstruction [2, 11]. In our study, we found that pre- and post-FEV₁/FVC z-scores were significantly lower in subjects with CB. Although absolute differences were small, our results suggest early signs of airway obstruction in this group of cases who also presented with higher FEV₁ change from baseline in the reversibility test. Furthermore, a sensitivity analysis excluding current asthma patients confirmed lower FEV₁/FVC z-scores in the group of cases with CB, and also a larger proportion of subjects with pre- and post-FEV₁ below the LLN compared to the group of subjects without CB. As recently reported by Breyer-Kohansal and colleagues [44], CB relates to not only pre-BD FEV₁/FVC lower than LLN, but also pre-BD FEV₁ lower than LLN in adults. These results imply that chronic bronchitis in this age group is associated with airflow limitation, albeit with limited clinical importance at this stage. However, long-term effects of chronic bronchitis on

the risk for COPD have been reported [5]. No association with FeNO levels was observed, but interestingly, we found increased sensitization to food allergens in the group of cases with CB compared to the group of subjects without CB, also after the exclusion of patients with asthma. To the best of our knowledge, no study has previously explored the relationship between food sensitization and chronic bronchitis and it is known that IgE sensitization to food allergens may cause respiratory symptoms and/or inflammation through systemic inflammation [45]. Besides, food allergy in children typically leads to food avoidance [46], and possibly to insufficient intake of dietary antioxidant as well. We have previously shown that low dietary intake of antioxidants in school age is associated with worsen lung function development among school children with asthma [47]. Thus, it is tempting to speculate that specific food intake may influence the development of CB through altered intake of antioxidants and related mechanisms. Whether systemic inflammation or such dietary factors relate to food sensitization may lead to chronic bronchitis needs to be explored in more detail.

Strengths and Limitations

Our study has the strength of using data from a large population-based birth cohort with a high response rate, i.e. 75% from baseline at the 24-year follow-up. We used several objectively measured data sets for clinical characterization: e.g. spirometry, reversibility test, IgE data, as well as for risk factor analyses: e.g. air pollution data. Besides, the precision of the air pollution exposure assessment in the children was enhanced by not only considering residential addresses but also addresses of day care and schools. The use of the longitudinal data in BAMSE allowed us to explore early life risk factors for later chronic bronchitis, with relatively little risk of bias and problems with selection, which is crucial for improving the understanding the origin of the disease.

Our study has some limitations. Firstly, our definition of chronic bronchitis is based on questionnaire data on cough and mucus symptoms during winter without any time period specified, which differs from the classic definition that requires two consecutive years [23]. Therefore, we have chosen to describe our outcomes as “assessment of

chronic bronchitis” (CB) rather than “chronic bronchitis”. In this context, it is important to consider that, in the literature, the definition of chronic bronchitis varies, in particular in epidemiological studies [7]. Secondly, although we explored well-known risk factors for respiratory disease, our analyses should be considered exploratory for this age group, and as such, we didn’t correct for multiple tests. However, our findings were robust after adjustment for several potential confounders. Besides, we also aware that misclassification of asthma as chronic bronchitis cannot be excluded, but importantly, our sensitivity analysis in participants without current asthma showed congruent results. Thirdly, the self-report of respiratory health events by participants is a potential limitation of this study, as well as a lack of laboratory workup for the detection of virus or bacteria in conjunction with reported respiratory tract infection. In addition, critically ill new-borns were not included in the BAMSE study, which limits our possibility to assess the influence of extreme prematurity and very low birth weight.

Conclusions

The overall prevalence of chronic bronchitis in our population-based birth cohort BAMSE is 5.5% at 24 years of age. Recurrent respiratory infections may be as common in young adult patients with chronic bronchitis as in elderly patients. We identified current and former smoking as well as early life air pollution exposures and childhood asthma as potential risk factors, and exclusive breast-feeding as a protective factor for chronic bronchitis, which underline the importance of early life events for maintaining lung health during the course of life.

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Figure legends

Figure 1: Mutually adjusted logistic regression analyses for chronic bronchitis (CB) among young adults from the BAMSE birth cohort. The model included age, sex, body mass index (BMI), smoking, parental education, parental smoking during childhood, air pollution during age 1-4 years old (black carbon, BC) and exclusive breast-feeding during 4 months or more as covariates.