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Changes in smoking habits and risk of asthma: a longitudinal population based study

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ABSTRACT: A common statement from exsmokers is that symptoms of asthma develop shortly after smoking cessation. This study, therefore, investigated the relationship between smoking cessation and development of asthma in a large cohort from the Copenhagen City Heart Study (CCHS).

The CCHS is a longitudinal, epidemiological study of the general population from the capital of Denmark, conducted between 1976 and 1994. The study population involved the 10,200 subjects who provided information on self-reported asthma and smoking habits from the first two examinations (baseline and 5-yr follow-up), and the 6,814 subjects who also attended the third and last examination (10-yr follow-up). The point-prevalence of smoking cessation as well as the asthma incidence between examinations was estimated, and a multivariate logistic regression model was used to examine the relationship between changes in smoking habits and development of asthma.

During the study period, asthma incidence increased from 1.2–4.2%. Between examinations 1,316 subjects quit smoking. Smoking cessation between examinations was significantly related to reported asthma at follow-up. With never-smokers as the reference group and following adjustment for sex, age, chronic bronchitis, level of forced expiratory volume in one second and pack-yrs of smoking, the odds ratio (OR) for developing asthma when quitting smoking between examinations was 3.9 (95% confidence interval (CI) 1.8–8.2) from baseline to first follow-up and 3.1 (95% CI 1.9–5.1) from first to second follow-up. Continuing smoking also increased the risk of asthma significantly (OR 2.6 and 2.0, respectively).

The results indicate that exsmokers have a higher incidence of self-reported asthma than never-smokers. It is likely that subjects perceive chronic obstructive pulmonary disease as asthma, hence the relationship between smoking cessation and asthma might be due to misclassification rather than causality.

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Whether active smoking is an independent risk factor for developing adulthood asthma remains controversial. In a recent case-control study [1], adult onset of asthma was not associated with ever-smoking. However, current smoking was found to increase asthma severity, and furthermore, asthmatic cases were more likely to quit smoking than controls. These findings are in accordance with results from the Nurses Health Study [2], whereas the Lung Health Study [3] showed that increasing pulmonary symptoms were not related to smoking cessation. A Swedish case-control study [4] found that ever-smoking for $\geqslant 3$ yrs increased the risk of asthma two-fold, although this excess risk was seen exclusively among exsmokers. Other Scandinavian studies and an early report from the Tucson Study [5–9] found higher incidences of asthma in current and former smokers, compared with never-smokers. However, there were some differences regarding the strength of the association and outcome stratified by sex. A prospective study of asthma and smoking habits in a large cohort from Finland [10] could not identify smoking or smoking cessation as risk factors for asthma.

Most clinicians have at some point in time come across patients who complain of asthma-like symptoms, or if the disease is already present, of worsening of existing symptoms, in relation to smoking cessation. However, the present authors are familiar with only one study [11] that addressed the question directly. It showed that, of 59 asthmatics who stopped smoking, 18 reported worsening of their symptoms. It is possible that in some smokers, unrecognized asthma is revealed following smoking cessation when concomitant symptoms of smoking disappear. Other explanations, such as immunological mechanisms, misclassification of diagnosis, or a psychological element

must also be considered. As a consequence of this lack of information, the present study was undertaken in order to prospectively explore the possible relationship between smoking cessation and development of asthma. The analyses are based on the Copenhagen City Heart Study (CCHS), an ongoing epidemiological study of people who live in the city of Copenhagen, Denmark.

Methods

Study population

The CCHS, a prospective investigation of major diseases in a random sample of the general population, was initiated in 1976. The study has previously been described in detail [12]. Briefly, the study sample consisted of 19,698 persons selected from a population of ~90,000 residents of Copenhagen who were ⩾20-yrs-old at enrolment and who were listed in the Copenhagen Population Register. The first examination round took place from February 1976–March 1978, the second from 1981–1983 (including an additional 500 subjects 20–25 yrs of age) and the third (with an additional sample of 3,000 subjects 20–39 yrs of age) during 1991–1994. The response rates varied from 61–80%. Hence, a total of 14,223 subjects were examined in the first examination, 12,698 of the 18,089 subjects who were still alive participated in the second examination, and the third examination comprised 10,127 subjects. The survey consisted of a detailed health examination and a self-administered questionnaire concerning symptoms, diseases and lifestyle variables.

The present study comprises the 10,200 subjects who participated in the first and second examination (baseline and 5-yr follow-up) and the 6,814 who also participated in the third examination and provided adequate information on smoking habits and self-reported asthma. Approximately 3,500 subjects died during follow-up, 1,500 were lost to follow-up between baseline and the second examination and an equal number were lost between the second and third examinations. The nonresponders had the same distribution on age, sex, smoking habits and prevalence of asthma and chronic bronchitis as the active participants. Less than 1% of respondents had missing data on tobacco questions in any survey, 4.8% of the responders had missing data on self-reported asthma at baseline and 2.4 and 1.3% did not provide information on asthma at first and second follow-up, respectively. Only incident asthma cases were considered, hence the subjects with prevalent asthma at baseline were omitted from the study population.

Smoking habits, respiratory symptoms and lung function measurements

At all examinations, subjects described themselves as never-smokers, exsmokers or current smokers. For the statistical analysis, the subjects were divided into the following groups on the basis of changes in smoking habit either between baseline and second examination or between second and third examination: never-smokers at both examinations, exsmokers at both examinations (persistent quitters), smokers at both examinations, quitters between examinations (new quitters) and starters between examinations. Current smokers reported daily tobacco consumption, type of tobacco, duration of smoking and inhalation habits, and exsmokers were asked about duration of smoking and time since quitting (cut-off point at 5 yrs). Pack-yrs of smoking were calculated for all current smokers as the number of years of smoking× daily tobacco consumption (g) divided by 20. Presence of asthma was defined as an affirmative response to the question "Do you have asthma?" and was thus self-reported; this procedure does not differ from other epidemiological studies [13]. Chronic bronchitis was defined as bringing up phlegm during ⩾3 months·yr^{-1} for ⩾2 consecutive yrs. The measurement of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), and the calculation of FEV_1 as percentages of predicted values (% pred), which were used in the present study, are described for CCHS in detail elsewhere [14].

Statistical analysis

At each examination the point-prevalence of smoking cessation was estimated as well as the cumulative asthma incidence over 5 and 10 yrs, respectively. Differences in measures of prevalence and incidence between groups were tested with the Chi-squared test with two-tailed p-values. The relationship between smoking cessation and development of asthma was studied in a logistic regression model with self-reported asthma at first or second follow-up, respectively, as the dependent variable, and changes in smoking habits as the independent variable, with never-smokers as the reference group. Sex and age were adjusted for in the crude model and in the multivariate analysis, indicators of existing lung disease were further included: chronic bronchitis, pack-yrs (3 levels) and level of FEV_1 (3 levels). To determine whether the effects of changes in smoking patterns on asthma development were uniform in both males and females and across the age ranges, additional analysis was performed, including interaction terms between sex and smoking and between age and smoking. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) and STATA [15, 16].

Results

Subject characteristics, sex, age, smoking habits and chronic bronchitis at the first and second follow-up, stratified by presence or absence of asthma are presented in table 1. Between first and second and second and third examinations, 657 and 659 subjects stopped smoking, respectively. This corresponds to 10% of the current smokers quitting between baseline

Table 1. – Distribution of sex, age, smoking habits and presence of chronic bronchlitis on incident asthma eases and healthy subjects at 5- and 10-yr follow-up

	5-yr follow-up		10-yr follow-up	
	No asthma	Asthma	No asthma	Asthma
Patients n	10077	123	6525	289
Sex % male (n)	56.5 (5694)	39.0 (48)	43.5 (2838)	38.8 (112)
Age yrs	57±11.4	59±10.9	64±11.8	65±10.1
Never-smokers n (%)	2134 (21.2)	15 (12.3)	1644 (25.2)	34 (11 7)
Persistent quitters n (%)	1478 (15.5)	13 (10.5)	1249 (19.1)	36 (12.4)
New quitters n (%)	639 (6.3)	18 (14.6)	609 (93)	50 (17 5)
Continuous smokers n (%)	5477 (54.4)	75 (61.0)	2875 (44.1)	164 (56.7)
Starters n (%)	259 (2.6)	2 (1.6)	148 (2.3)	5 (1.7)
Chronic bronchitis n (%)	1067 (10.6)	60 (48 8)	781 (12.0)	130 (45.0)

The smoking categories refer to smoking status at follow-up. Numbers are not equal due to losses at follow-up (death and nonresponse).

and first follow-up, and 22% quitting between first and second follow-up. More subjects with asthma also reported chronic bronchitis.

Tables 2 and 3 show the asthma incidence, pack-yrs of smoking and lung function in the different smoking categories from the first and second follow-up, respectively. There were 123 new cases of asthma between baseline and first follow-up and 289 new cases between first and second follow-up. This corresponds to a 5-yr cumulative incidence (new cases/total population at risk) of 1.2% and a 10-yr cumulative incidence of 4.2% (data shown). The incidence of asthma was highest among new quitters and continuous smokers. Quitters (persistent and new) and continuous smokers also had the poorest lung function.

Table 4 shows the crude and adjusted ORs for developing asthma in the different smoking categories. In the new quitters, the main subjects of interest, the sex- and age-adjusted ORs were 4.8 (95% CI 2.3–10.0) and 4.2 (95% CI 2.6–6.7) for the first and second follow-up, respectively. When including chronic bronchitis, pack-yrs of smoking and level of FEV_1 in a multivariate model, ORs were 3.9 (95% CI 1.8–8.2) and 3.1 (95% CI 1.9–5.1), respectively. When splitting the analyses from the second part of the study (10-yr follow-up) in subjects who quit smoking >5 or <5 yrs prior to attending the examination (not shown), the estimates remained unchanged. Table 4 also shows that continuous smokers, when adjusting for the other covariates, had an increased risk of developing asthma between baseline and follow-up (OR 2.6 (95% CI

Table 2. – Asthma incidence after 5 yrs according to smoking habits at first follow-up

	Never-smokers	Persistent quitters	p-value¶	New quitters	p-value¶	Continuous smokers	p-value¶	Starters	p-value¶
Subjects n	2149	1581		657		5552		261	
Asthma incidence %	0.7	0.8	0.41	2.7	<0.001	1.4	0.007	0.8	0.73
Sex % male	23.6	54.2	<0.001	50.3	<0.001	48.3	<0.001	50.0	<0.001
Age yrs	52±12.6	55±11.0	NS	53±11.7	NS	51±11.5	NS	50±12.3	NS
Pack-yrs		#		21±19.2		25±17.9	<0.001§		
FEV_1 % pred	90.3±17.1	88.7±18.5	0.001	83.6±18.8	<0.001	83.5±16.8	<0.001	89.0±15.8	0.67

#: pack-yrs for subjects who were exsmokers at both examinations cannot be estimated; ¶: p-values are differences in asthma incidence, sex, age and mean forced expiratory volume in one second (FEV_1) compared to never-smokers; §: pack-yrs of smoking for continuous smokers compared to new quitters. NS: not significant.

Table 3. – Asthma incidence after 10 yrs according to smoking habits at second follow-up

	Never smokers	Persistent quitters	p-value¶	New quitters	p-value¶	Continuous smokers	p-value¶	Starters	p-value¶
Subjects n	1678	1285		659		3039		153	
Asthma incidence %	2.0	2.8	0.34	7.6	<0.001	5.4	<0.001	3.3	0.31
Sex % male	24.4	48.2	<0.001	54.0	<0.001	45.5	<0.001	48.8	<0.001
Age yrs	53±13.0	56±11.1	NS	53±12.4	NS	52±10.7	NS	53±13.0	NS
Pack-yrs		#		22±19.6		26±18.8	<0.001§		
FEV_1 % pred.	92.2±17.8	90.0±19.7	<0.001	84.8±20.5	<0.001	85.0±18.0	<0.001	92.0±19.5	0.69

#: pack-yrs for subjects who were exsmokers at both examinations cannot be estimated; ¶: p-values are differences in asthma incidence, sex, age and mean forced expiratory volume in one second (FEV_1) compared to never-smokers; §: pack-yrs of smoking for continuous smokers compared to new quitters. NS: not significant.

Table 4. – Odds Ratios (ORs) of developing asthma according to changes in smoking habits at second and third examination

Smoking categories at follow-up	5-yr follow-up			10-yr follow-up		
	Subjects n	OR (95% CI)		Subjects n	OR (95% CI)	
		Crude*	Adjusted**		Crude*	Adjusted**
Never-smokers	2149	1	1	1678	1	1
Persistent quitters	1581	1.5 (0.6–3.3)	1.2 (0.5–2.8)	1285	1.3 (0.8–2.1)	1.2 (0.8–2.0)
New quitters	657	4.8 (2.3–10.0)	3.9 (1.8–8.2)	659	4.2 (2.6–6.7)	3.1 (1.9–5.1)
Continuing smokers	5552	2.3 (1.2–4.3)	2.6 (1.2–5.5)	3039	2.8 (1.9–4.2)	2.0 (1.3–3.0)
Starters	261	2.1 (0.7–6.0)	2.0 (0.7–5.6)	153	1.7 (0.7–5.6)	1.7 (0.7–4.6)

*: adjusted for sex and age; **: fully adjusted regression model including sex, age, pack-yrs, chronic bronchitis and level of forced expiratory volume in one second. Numbers are not equal due to losses of follow-up (death and nonresponse). CI: confidence interval.

1.2–5.5) and 2.0 (95% CI 1.3–3.0)). The risk of asthma development was similar in persistent quitters and never-smokers. Starting smoking between examinations showed a positive trend but was not significantly associated with having asthma at follow-up (lack of power due to small numbers). After including interaction terms sex*smoking groups and age*smoking groups using a log likelihood ratio test (data not shown), it was found that there was no interaction present regarding development of asthma in the various smoking groups between the two sexes and the three age categories. In other words, the increased asthma risk seen in new quitters and continuous smokers was independent of age and sex.

Discussion

In this large population based study, subjects that gave up smoking in the interval between the first and second survey, or between the second and third survey, were more likely to report having asthma at the second or third examination than never-smokers and persistent quitters. It was also found that continuous smokers were at higher risk of developing asthma, although this association was somewhat weaker. The incidence study, which was not the main goal of the present paper, confirmed the findings of previously mentioned studies and recent reports from the European Community Respiratory Health Survey [17, 18] that asthma prevalence and incidence are increasing in the adult population. However, it has been demonstrated that a considerable amount of bias may be introduced when estimating these measures, since there is no simple relationship between the prevalence and incidence of asthma [19]. Furthermore, it was found that asthma incidence was highest among current and former smokers, which is controversial, as mentioned earlier.

Regarding the prospective analyses of smoking cessation and development of asthma, the present results are consistent with those of The Nurses Health Study and some of the Scandinavian studies. However, Troisi *et al.* [2] found that the higher risk of asthma in former smokers decreased within 5 yrs, whereas current smokers had a significantly lower risk of developing asthma compared to never-smokers. The implications of the findings concerning continuous smokers are generally attributed to the so-called "healthy smoker" effect, whereas the increased asthma risk in quitters is explained by the tendency to quit smoking in response to respiratory symptoms of any aetiology [2, 4]. Cross-sectional studies from Sweden and Norway [5, 8] found that the increased asthma risk in exsmokers was confined to males, and a longitudinal Swedish study [7] found that the strongest risk factors for asthma were family history of asthma and current or former smoking. Unfortunately, none of these studies discussed possible explanations of the relationship between smoking cessation and risk of asthma. Several studies have shown the beneficial effect of smoking cessation on pulmonary symptoms and signs [3, 20–22], and in the Lung Health Study (LHS), a decrease in the prevalence of chronic cough occurred within the first year of smoking cessation. The LHS also showed that sustained quitters had the lowest prevalence of pulmonary symptoms, whereas continuous smokers had the greatest symptom prevalence. Despite these findings, the same study demonstrated that subjects with chronic sputum/cough and dyspnoea at baseline were less likely to stop smoking. However, reports from the LHS differ at some points to those of other longitudinal studies, which might be due to the selection of subjects already diagnosed with chronic obstructive pulmonary disease (COPD).

The association of smoking, smoking cessation, and markers of airways inflammation, such as airway hyperresponsiveness (AHR), neutrophils, eosinophils and interleukins, is not easily understood and not many studies deal with this issue. One study of asthmatics [11], in which a substantial proportion of the subjects reported a worsening of symptoms following smoking cessation, suggested the finding could be explained by a state of transient immunological disequilibrium in the airways when tobacco smoke is no longer present. A recent population based study, the Vlagtwedde-Vlaardingen study [23], showed that cigarette smoking increased the risk of developing respiratory symptoms in a dose-dependent manner. The study also found that AHR, especially in connection with eosinophilia, increased this risk, whereas a positive skin test was negatively related to

respiratory symptoms. It must be noted that these results were independent in that there was no interaction between the effect of smoking and AHR and eosinophilia.

The present study was not able to draw any inferences with respect to the possible immunological mechanisms as an explanation of the findings. However, the authors are inclined to reflect upon the role of bias, especially misclassification of the diagnosis, which is suspected to be, at least in part, responsible for the findings. Smoking cessation in defined time intervals, as well as current smoking, were found to be risk factors for self-reported asthma, whereas sustained smoking cessation was not associated with asthma. In the multivariate regression analyses, the estimates were adjusted in as detailed a manner as possible in this cohort for pre-existing lung disease. Nevertheless, there is still a risk that some subjects suffer from COPD and not asthma. The difficulties in distinguishing adult onset of asthma from COPD in the past have been described previously [24] and there has been a discrepancy, especially when investigating end-points such as hospitalization due to these diseases. This study also found a strong correlation of self-reported chronic bronchitis with asthma, and a previous report from the CCHS has shown an association between mucus hypersecretion and a decline in FEV_1 in asthmatics [25]. Whereas the role of chronic mucus is well-established in COPD [26], it still remains unclear in connection with asthma and airway remodelling. It is highly plausible that the subjects in question gave up smoking due to recognition of respiratory symptoms and then reported the diagnosis of asthma at follow-up. The present findings were independent of age and sex, and therefore do not support the view that current and exsmoking males with respiratory symptoms are more likely to be diagnosed with COPD or emphysema than their female counterparts (who might be diagnosed with asthma).

Another selection bias that could influence the results of the present study concerns the possibility of nonresponse. Although the response rates in the CCHS as a whole were satisfying and the number of drop-outs in the present investigation was limited, a selection bias could occur if nonresponse was interdependently related to smoking/smoking cessation and asthma incidence, *i.e.* the risk of asthma among participating and nonparticipating smokers (including quitters) would somehow be different. In the present study, the proportion of nonresponders had the same distribution of demographics, smoking habits and asthma-prevalence as active participants and the authors do not believe this type of bias to be of major influence on the results. Since no exact dates for onset of asthma are available, the study was conducted using logistic regression instead of a survival analysis approach. This could lead to a biased result (underestimation of the true effect) of the relationship between smoking cessation and development of asthma if the outcome (asthma) occurred before the exposure (smoking cessation). Conversely, the relationship would be overestimated if all events took place at a later point in time among the quitters, compared to continuous smokers. As has been emphasized previously, the present study was not able to distinguish which of the features (smoking cessation or asthma) occurred first. To make this distinction, a much more detailed study design would be necessary. However, due to the nature of the follow-up study, the authors are convinced that the main results regarding the positive association between increased asthma incidence and former and current smoking are largely unbiased, although this does not *per se* imply involvement of causal mechanisms.

In conclusion, the present authors are not convinced that the positive association between recent smoking cessation and self-reported asthma is causal. It may well be that quitting smoking causes temporary asthma-like symptoms, but the overall health benefits of smoking cessation must not be discarded. However, it must be emphasized that adult-onset asthma is not entirely uncommon and to avoid underdiagnosis of this disease among new quitters, patients who present with respiratory symptoms following smoking cessation should be examined in line with everybody else having similar symptoms. To further clarify this issue, close follow-up and measurement of detailed respiratory parameters, for example, in cohorts from the various smoking cessation programmes, would be needed.

Members of The Copenhagen City Heart Study group: G. Jensen, P. Schnohr, P. Lange, M. Grønbæk, E. Prescott, B. Nordestgaard, J. S. Jensen and M. Appleyard.

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