



Critical age windows in the impact of lifetime smoking exposure on respiratory symptoms and disease among ever smokers

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ABSTRACT

Background: Despite extensive knowledge of smoking effects on respiratory disease, there is no study including all age windows of exposure among ever smokers. The objective of this study was to assess the effects from smoking exposure *in utero*, early childhood, adolescence and adulthood on respiratory health outcomes in adult male and female ever smokers.

Methods: Respiratory health outcomes were assessed in 10,610 participants of the European Community Respiratory Health Survey (ECRHS) I who reported a history of ever smoking by questionnaire. The associations of maternal smoking *in utero*, maternal smoking during childhood, age of smoking debut and pack-years of smoking with respiratory symptoms, obstructive diseases and bronchial hyperreactivity were analysed using generalized linear regression, non-linearity between age of smoking debut and outcomes were assessed by Generalized additive mixed models.

Results: Respiratory symptoms and asthma were more frequent in adults if their mother smoked during pregnancy, and, in men, also if mother smoked in childhood. Wheeze and ≥ 3 respiratory symptoms declined with later smoking debut among women [≤ 10 years: OR = 3.51, 95% CI 1.26, 9.73; 11–12 years: 1.57[1.01–2.44]; 13–15 years: 1.11[0.94–1.32] and ≤ 10 years: 3.74[1.56–8.83]; 11–12 years: 1.76[1.19–2.56]; 13–15 years: 1.12[0.94–1.35], respectively]. Effects of increasing number of packyears were pronounced in women (Chronic Obstructive Pulmonary Disease (COPD): OR/10 packyears women: 1.33 [1.18, 1.50], men: 1.14 [1.04, 1.26]

Abbreviations: BHR, Bronchial responsiveness to metacholine; COPD, Chronic obstructive pulmonary disease; ECRHS, European Community Respiratory Health Survey; FEV₁, Forced expiratory volume in 1 s; FVC, Forced vital capacity; LLN, Lower limit of normal; GAMMs, Generalized Additive Mixed Models

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$P_{\text{interaction}} = 0.01$).

Conclusions: Among ever smokers, smoking exposure in each stage of the lifespan show persistent harmful effects for adult respiratory health, while women appeared to be more vulnerable to an early age of smoking debut and amount of smoking in adulthood.

1. Introduction

Smoking is the best documented hazard to respiratory health. While smoking exposure and respiratory disease in adults have been studied extensively, there is increasing interest in how exposure during other critical age windows such as *in utero*, early childhood and adolescence impact subsequent respiratory health. Both animal and epidemiological studies suggest that exposure to smoking *in utero* or postnatally increases the incidence of respiratory disease and related symptoms in childhood (Martinez et al., 1992; Wu et al., 2012). There are less studies analyzing early life smoking exposure effects into adulthood; In a previous analysis of the European Community Respiratory Health Survey (ECRHS) cohort we found that *in utero* and post-natal smoking exposure was related to poorer adult respiratory health, while adjusting for adult smoking (Svanes et al., 2004). We have also in this cohort found that childhood disadvantage (including maternal smoking) was associated with lower lung function, accelerated lung function and Chronic Obstructive Pulmonary Disease (COPD), in models adjusting for current adult smoking (Svanes et al., 2004). However, tobacco smoking exposure in early life is related to subsequent smoking habits, and the influence of tobacco smoking on adult respiratory disease when concomitantly considering exposure through the life-span - *in utero*, in childhood, in adolescence and adult pack-years - has not been previously elucidated.

There is only limited information as to how age of onset of smoking influences subsequent respiratory health. Age of onset is relevant because exposure before the lungs are fully grown might have larger consequences than for the fully developed lungs. One study showed that early age smoking initiation was associated with a more rapid decline in forced expiratory volume in 1 s (FEV₁) (Apostol et al., 2002), and childhood smoking as defined by starting before age 16 years was shown to be a strong risk factor for asthma in adults (Patel et al., 2004). In these studies, non-smoking groups were used as reference category, and early life exposure was not accounted for.

There are important sex differences in lung development and airway behavior (Becklake and Kauffmann, 1999). Men have larger lungs in childhood and adolescents (Carey et al., 2007), as well as in adulthood, even when accounting for differences in age and height (Bellemare et al., 2003). Our previous results indicated that *in utero* exposure to tobacco smoking was more strongly associated with adult respiratory health in women while post-natal exposure had larger impact in men (Svanes et al., 2004). The respiratory health effects from adult smoking exposure also appear to be different in men and women. For example, the risk of COPD in one study was higher in women if they smoked before the age of 16 years (Patel et al., 2004). The number of pack-years is used as a measure of lifetime risk, with men smoking more and longer over their lifetime (Prescott et al., 1997). The effect of pack-years of smoking on respiratory symptoms appeared to be higher in women than men in two studies (Chinn et al., 2005; Langhammer et al., 2000), but was not significantly associated with lower FEV₁ in women with COPD in another study (Sorheim et al., 2010).

Thus, previous literature suggest that in addition to adult smoking, exposure to tobacco smoking *in utero* and post-natal as well as age of smoking debut in adolescence, are important for adult respiratory health. Further, gender differences in vulnerability to smoking are suggested both for early life and adult exposure. However, smoking exposure in these different time windows are inter-related, and effects of exposure in a specific age windows in previous studies may be confounded by smoking in age windows not accounted for. In this study

we therefore aimed to investigate, comprehensively and in the same models, the impact of tobacco smoking exposure *in utero*, postnatal, in adolescence and in adulthood, for adult respiratory health (respiratory symptoms, asthma, COPD and bronchial hyperresponsiveness) among ever-smokers enrolled in the ECRHS 1. Only ever smokers were included in order to promote the understanding of all vulnerable exposure windows from early life to adulthood in this risk group. Only ever smokers were included in this comprehensive analysis, in order to determine the relative importance of each of the vulnerable exposure windows from early life to adulthood, analysed in the same model and in this risk group. There is a plethora of evidence to suggest that smokers compared to non-smokers have a higher risk of asthma (Kumar and Ram, 2017). Non-smokers as the reference group are studied widely because the aim is to understand the role of “smoking” on respiratory disease among smokers compared to non-smokers. Similarly, evidence suggests that exposure to environmental tobacco smoke (ETS) (including maternal smoking and exposure to smoking inside the home) is associated with respiratory illness in children and adolescents (Vanker et al., 2017). Again, in these studies the comparison group are those not exposed to ETS. Therefore, we know that smoking is harmful for respiratory health when comparing with a reference group of non-smokers. However, the relative importance of early life smoking exposure, the age of starting smoking as well as total pack-years of smoking among ever-smokers is not known. In addition, we explored sex differences in vulnerability to tobacco smoking exposure in the different time windows.

2. Methods

2.1. Study participants

The study population was recruited from 29 study centres in 14 countries and comprised adults aged 20–44 years who participated in the European Community Respiratory Health Survey (ECRHS I), initiated in 1991–1994. The protocols have been fully described elsewhere and can be found at www.ecrhs.org. Briefly, the ECRHS I involved two stages. In the first stage, random general population samples were mailed a screening questionnaire, whereas in the second stage, both a random general population sample and a symptomatic sample were invited to participate in further clinical investigations, which included a detailed structured interview including socio-demographic factors, respiratory symptoms during the last 12 months as well as allergic symptoms. In addition, clinical assessment of spirometric lung indices was performed and anthropometric data were collected. The present study included 10,610 adults (5348 men and 5262 women) who reported to be current or former smokers in ECRHS I.

2.1.1. Definitions of outcome variables

2.1.1.1. Respiratory symptoms. Respiratory symptoms, current asthma or allergy were obtained from questionnaires available at www.ecrhs.org. “Wheeze” was defined as wheezing or a whistling sound in the chest in/during the last 12 months. The variable “≥3 respiratory symptoms” was defined as 3 or more of the following 8 symptoms in the past 12 months: wheeze, wheeze with symptoms of breathlessness, wheeze when not having a cold, waking up with tightness in chest, woken by an attack of shortness of breath, woken by an attack of cough, having had an attack of asthma or currently taking medicines for asthma. “Chronic cough and phlegm” was defined as cough or phlegm for three months each year.

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