

The Role of Smoking in Allergy and Asthma: Lessons from the ECRHS

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Abstract The European Community Respiratory Health Survey is an international multicenter cohort study of asthma, allergy, and lung function that began in the early-1990s with recruitment of population-based samples of 20- to 44-year-old adults, mainly in Europe. The aims of the study are broad ranging but include assessment of the role of in utero exposure to tobacco smoke, exposure to environmental tobacco smoke, and active smoking on the incidence, prevalence, and prognosis of allergy and asthma. Cross-sectional and longitudinal analyses looking at these associations have been conducted, sometimes only using information collected in one country, and on other occasions using information collected in all the participating centers. This article summarizes the results from these various publications from this large epidemiologic study.

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Introduction

In the late-1980s and early-1990s, a group of interested epidemiologists, clinicians, and scientists led by Prof. Peter Burney (then of St Thomas' Hospital Medical School, now working at Imperial College London) developed and implemented a cross-sectional survey to assess the prevalence of and risk factors for allergy and asthma in young adults living in European nations. As the study progressed, other researchers, sometimes outside Europe, joined the initiative, and after several years, the European Community Respiratory Health Survey (ECRHS) [1] included information from more than 50 research centres in 25 countries (including information from countries outside Europe such as Australia, Canada, and the United States). In early-2000, some of these research groups (mainly European, but also including centers in Melbourne and Portland) agreed to follow-up participants in the first survey (ECRHS II) [2], and many are now (2011–2012) following these participants for a third time (ECRHS III) (<http://www.ecrhs.org>).

The ECRHS has collected a wealth of information on allergy and asthma symptoms, diagnoses and treatment, and information on lifestyles and environmental exposures. Each participant provided information on his or her personal smoking history, exposure to environmental tobacco smoke (ETS), and his or her parents' smoking. As in utero exposure to tobacco smoke, ETS, and active smoking have been

postulated to be important preventable causes of allergy and asthma and modifiers of the prognosis of disease, the ECRHS group has conducted several major analyses to explore these associations in the data collected. The purpose of this article is to summarize these findings.

The Overall Design of the ECRHS

ECRHS I

Between 1990 and 1992, in each participating center, a representative random sample of adults aged 20 to 44 years was identified from an appropriate population-based sampling frame and sent a short, nine-item postal questionnaire asking about symptoms suggestive of asthma [1]. This postal questionnaire did not include questions relating to smoking behavior because response rates are likely to be lower with longer questionnaires and with questionnaires that are “threatening” or “judgmental” (asking about smoking behavior in individuals who report respiratory symptoms could be perceived as such). In addition, the sample was relatively young and it was thought at the time that it was unlikely that the respiratory symptoms reported could be attributed to a long history of heavy smoking.

A random subsample of responders to the postal survey and an additional “enriched” sample of asthmatics (who had not been identified in the random sample) were then invited for an extended questionnaire, skin prick tests, blood tests for measurement of IgE, lung function testing (forced expiratory volume [FEV], forced vital capacity [FVC]), and testing of bronchial reactivity to methacholine. This longer administered questionnaire asked about the age at which the participant started smoking, the number of cigarettes smoked, the age of cutting down (and the amount of tobacco smoked following cutting down), and the age at which ex-smokers stopped smoking. Exposure to other people’s tobacco smoke was assessed, and participants were asked to recall whether their mother smoked while she was pregnant with them and/or during their early-childhood, and if their father smoked during their childhood. An overview of the main results of this survey up to 2000 is available [3].

ECRHS II

Between 2000 and 2002, all those who had completed the clinical assessment in ECRHS I were sent a postal questionnaire similar to that used in ECRHS I and then invited for further tests (just as in ECRHS I) [2].

ECRHS III

Between 2010 and 2012, participants in the clinical phase of ECRHS I are again being contacted by postal questionnaire and

being invited for further examination. The postal questionnaire on this occasion collects some basic information on smoking behavior.

In Utero Exposure to Smoking and Childhood Exposure to Environmental Tobacco Smoke

Among the almost 19,000 adults living in 37 ECRHS I-participating centers, more than half of the participants reported their father had smoked when they were a child (range, 57 % in Switzerland–79 % in The Netherlands), but smoking by mothers was less common and varied considerably among countries (range, 3 % in Spain–50 % in Ireland) [4]. Among those who reported that their mother had smoked when they were young, almost half reported they did not know if their mother had smoked while she was pregnant with them, but using information from those who did know, maternal smoking in pregnancy was relatively uncommon (range, 1 % in Spain–27 % in Ireland). Participants who reported that their mother smoked in pregnancy, their mother smoked during their childhood, or both parents smoked during their childhood were more likely to report wheeze in the past 12 months and three or more “asthma symptoms” (wheeze, wheeze with shortness of breath, wheeze without having a cold, waking with tightness in chest, waking with shortness of breath, waking with cough, asthma attacks, current use of medication for asthma), even after accounting for their own smoking behavior, exposure to ETS, and occupational exposures. They also had lower lung function (forced expiratory volume in 1 s [FEV₁]) and more airways obstruction (ratio of FEV₁ to FVC). However, bronchial reactivity and current adult-onset asthma were not associated with parental smoking.

These associations relied on recall by participants of their parents’ smoking behavior, a method of exposure assignment that could be criticized as being vulnerable to recall bias (the propensity of those with current symptoms to recall and report greater exposure to factors they perceive to have “harmed” them when compared with those who have no symptoms). We have no additional information to assess whether this is the case, but we observed some differential effects by gender in these associations that are less easy to attribute to recall bias. For example, maternal smoking in pregnancy was more strongly associated with current symptoms in women, although this difference between men and women in the effect of maternal smoking was not statistically significant ($P > 0.05$), and paternal smoking was more strongly associated with symptoms in men ($P = 0.003$ for the interaction of gender with paternal smoking for wheeze). All reported associations were seen consistently across the participating centers.

Taken as a whole, these data suggest that smoking by mothers and fathers has a detrimental effect on the respiratory

health of their offspring many years later. This manifests itself as symptoms that are suggestive of asthma and worse lung function. Within the ECRHS, the 24-mL decrement in FEV₁ seen with childhood exposure to smoking was equivalent to the additional loss in lung function over a 5-year period in active smokers (adult smokers showed an additional decline of ~5 mL/y compared with nonsmokers). In the absence of elevated bronchial hyperresponsiveness, the “asthma” symptoms may arise from an effect on lung growth rather than long-term “allergic” inflammation, and our findings are consistent with earlier meta-analyses of observational studies showing an effect of parental smoking on symptoms [5] and lung function [6], but not on sensitization in children [7]. The observed gender differences in these associations may reflect differences in the time window of susceptibility to environmental insults, which may reflect differences in pre- and postnatal lung growth in boys and girls [8]. It would have been useful to assess whether these effects were more marked in the offspring of mothers who smoked in pregnancy compared with those who only smoked after pregnancy, but as the vast majority of mothers who smoked in pregnancy also smoked after they gave birth, it was not possible to fully explore differences between these two time windows of exposure.

Active Smoking and Total IgE and Sensitization to Common Allergens

Prior to ECRHS I, there had been reports suggesting that smoking was associated with elevated total IgE [9, 10] and that active smoking may increase the risk of sensitization to workplace allergens [11, 12]. The association of smoking with sensitization to environmental allergen in the general population was not known. In a cross-sectional analysis of 13,000 participants in ECRHS I, we confirmed previous reports that total IgE levels were higher in smokers than nonsmokers, and higher in heavy smokers than light smokers, but we also found that smoking explained less than 1 % of the residual variation in total IgE levels (after adjustment for age and sex). Sensitization was assessed by the presence of serum-specific IgE, and smokers were more likely to be IgE sensitized to house dust mite and less likely to be IgE sensitized to grass and cat. These latter observations are hard to explain. Those who have asthma and allergies in childhood are less likely to take up smoking than their healthy peers (the “healthy smoker” effect), which might explain lower rates of sensitization in adult smokers compared with nonsmokers. However, when we excluded those who reported childhood-onset asthma, the associations remained. Furthermore, the healthy smoker bias cannot explain the positive association of smoking with sensitization to house dust mite.

Whatever difficulty we have interpreting these cross-sectional associations of smoking with sensitization, our data show that these associations are different for the different allergens. This has two important broader implications. First, it reflects an important underlying difference (which may be smoking itself or an important confounder of smoking) in the way sensitization to grass and cat occurs compared with house dust mite. Second, it shows that in epidemiologic studies, we should not automatically assume that the risk factors for sensitization to one allergen are the same for another. Identifying risk factors for “atopy” (that is, sensitization to any one of a number of tested allergens) may mask important differences between allergens in the associations being assessed.

Nine years later in ECRHS II, there had been relatively little change in sensitization status within the cohort overall, and the effect of smoking behavior in adults on changes in specific IgE could not be fully explored [13]. After 20 years of follow-up and using data from ECRHS III, we hope that we will be able to examine these relationships in more depth.

We have some information indicating that smoking may also influence IgG levels. At ECRHS II, measures of IgG and IgG₄ to house dust mite and to cat were made in a subsample of participants who also underwent a home visit [14]. In a cross-sectional analysis of this subsample of 2,780 participants (aged 27–54 years), there was a negative association of smoking with IgE to cat, and smokers had lower levels of cat-specific and house dust mite-specific IgG and IgG₄ than nonsmokers.

Active Smoking and Respiratory Symptoms

Smoking was common in all centers (range, 15.3 % in Portland, USA–57.5 % in Oviedo in Spain) in the early-1990s, but during the 9-year period of follow-up to ECRHS II, the proportion of the cohort who smoked had fallen by 5.9 % overall (from 33.9 % to 28.7 %) [15]. Several individual study groups within the ECRHS I examined the relationship of respiratory symptoms and active smoking in their local populations, and even in this young population, there was more wheeze and more cough in current smokers than in nonsmokers [16–19].

These symptoms may arise from a direct effect of smoking and may not reflect what most clinicians would consider to be “asthma.” The association between “asthma” and current smoking was less clear. In a nested case–control study based on the full international data set of the ECRHS I, the risk of reporting the “first asthma attack” had occurred within the past 3 years was 43 % lower in current smokers than in never smokers [20]. Björnsson et al. [17], on the other hand, found that the prevalence of reported “asthma

attacks in the last 12 months” and “use of asthma medication” in Sweden was similar in current smokers and non-smokers, while Abramson and coworkers [21] reported a higher risk of current asthma (defined as wheeze and bronchial reactivity to methacholine) in smokers than in non-smokers when analyzing information collected in Melbourne. These cross-sectional associations are difficult to assess, as the healthy smoker bias may be present. Longitudinal data such as those collected in the 3-year follow-up study of the Swedish participants in the ECRHS I may more accurately reflect the true associations. Using information collected by postal survey, they found that incident asthma (defined as having an asthma attack in the past 12 months or receiving treatment for asthma in those who reported neither at baseline) was more common in current smokers than nonsmokers [22], and although there was no statistically significant interaction ($P>0.05$), this association was stronger in nonatopics (OR, 5.7 [95 % CI, 1.7–19.2]) than atopics (OR, 1.8 [95 % CI, 0.8–4.2]). On the contrary, the 7-year follow-up of the Italian branch of the ECRHS I found that the incidence of asthma (defined as in the Swedish study) was lower in active smokers at baseline than in nonsmokers (incidence RR, 0.3 [95 % CI, 0.2–0.7]) [23]. In these two reports, the definition of incident asthma relied on a participant reporting that he or she had asthma and/or having treatment for asthma, both of which reflect local medical practice in the way that wheezing and asthma-like symptoms in smoking adults are diagnosed and labeled. Such practice may vary between the two regions, and this may explain the different findings in each study.

A comprehensive analysis of all factors associated with incident asthma in the full international cohort over the 9-year period of follow-up between ECRHS I and ECRHS II was published in 2010 [24•]. There were 179 new cases of asthma (reporting of “ever asthma” in adults who denied having asthma, wheeze in the absence of a cold, waking with shortness of breath 9 years earlier) among 4,588 participants who had taken part in the full clinical assessment at both surveys. Participants were considered atopic if they had specific IgE above 0.35 kU/L to any of the four allergens tested (house dust mite, cat, grass, *Cladosporium* spp), and the incidence of asthma was lower in smokers than in nonsmokers among the nonatopics, with the reverse being true for those who were atopic (P for interaction=0.01). However, there was a complex interplay between smoking and lung function decline and incident asthma, with a suggestion that these relationships were different in atopics and nonatopics. A definitive conclusion on the independent effect of smoking on incident asthma could not be reached.

Although there may be some doubt over the exact relationship of asthma symptoms and asthma diagnosis with smoking, the ECRHS shows more compelling evidence that smoking is associated with bronchial reactivity to

methacholine, a sensitive but not specific objective marker for asthma in young adults. In participants in the ECRHS I, being sensitized to environmental allergens was an important determinant of bronchial hyperresponsiveness [25], but even accounting for this, local analysis of the English subsample showed that older participants who smoked had greater bronchial hyperresponsiveness than the older participants who did not smoke [26]. In the Spanish subsample, smokers also had more bronchial hyperresponsiveness than non-smokers, but this was only seen in those who were nonatopic [27]. Using all data from all centers, there were 4,000 adults who had bronchial hyperresponsiveness tested at baseline and again after 9 years of follow-up. In this group, bronchial hyperresponsiveness was unchanged in lifetime nonsmokers but became worse in those who smoked throughout the period of follow-up and also became worse in the small number ($n=72$) of participants who commenced smoking [28]. These changes were independent of the greater decline in lung function in smokers that was seen over this period and independent of sensitization and change in sensitization.

Exposure to Environmental Tobacco Smoke and Asthma

In 12 of the 36 centers of the ECRHS I, more than half of lifetime nonsmokers reported they were regularly exposed to ETS [29]. Although these exposures may have occurred at home and in a variety of social settings, the workplace was also a common place for ETS exposure. There was considerable variation in workplace exposures across Europe (range, 2 % in Uppsala, Sweden–54 % in Galdakao, Spain). Reporting ETS exposure was significantly associated with reporting nocturnal respiratory symptoms, breathlessness after activity, and with bronchial responsiveness to methacholine. It was also significantly associated with “any respiratory symptom” and with current asthma (OR, 1.9 [95 % CI, 1.2–2.9]). Although smoking was associated with elevated total IgE, there was no evidence that ETS exposure had any effect on total IgE levels [29].

The prevalence of exposure to ETS in the workplace in Sweden at the time of ECRHS I was low compared with the rest of Europe, but there was evidence that this was associated with more symptomatic asthma [30]. Having to leave a job because of breathing problems was associated with having worked in a job with a high risk of exposure to “vapour gas dust and fumes” (prevalence ratio, 4.9 [95 % CI, 2.5–9.4]) but was also strongly associated with exposure to ETS in the workplace (prevalence ratio, 2.1 [95 % CI, 1.3–3.5]). A subsequent analysis of the complete international ECRHS data set confirmed a relationship between workplace ETS exposure and respiratory symptoms at work [31].

Taken together, our data indicate that decreasing involuntary exposure to tobacco smoke in the community, especially in the workplace, is likely to improve respiratory symptoms, including symptoms highly suggestive of asthma, in young adults. Fortunately, a comparison of the prevalence of exposure to ETS in the ECRHS I and II shows that such a reduction has taken place [15], although this was less marked in those in the lower socioeconomic groups. Over the 9-year follow-up period, the prevalence of ETS exposure among nonsmokers had decreased in most countries and fell from 41 % to 24 % in the entire cohort. Of further interest, there was evidence that within the ECRHS cohort, participants were more likely to give up smoking if they lived and worked in a smoke-free environment.

Active Smoking and Asthma Treatment and Asthma Prognosis

Smoking among those with asthma (defined as ever having physician-diagnosed asthma and having symptoms or treatment for asthma in the past 12 months) in the ECRHS was common (26.3 %), and there was little evidence that those with asthma gave up smoking more frequently than those without asthma over the period of follow-up [32].

To date, there has been relatively little and somewhat conflicting information on the long-term effects of cigarette smoking on health outcomes among population-based (rather than hospital-based) cohorts of asthmatic individuals. Some longitudinal surveys suggest that asthmatics who smoke have a more rapid loss of lung function than those who do not [33], but in contrast, three separate analyses of the international data within the ECRHS found that disease prognosis and decline in lung function in asthmatics who smoke were broadly similar to that seen in their nonsmoking peers. Smoking had no influence on the severity of disease at the end of the 9-year period of follow-up in the almost 900 adults with asthma who provided sufficient information for the severity of their asthma to be categorized according to the Global Initiative for Asthma guidelines of the period [34]. Furthermore, within this group and over the same period of follow-up, the predictors of a more rapid decline in lung function included male sex, older age, and less use of inhaled steroids, but no relationship with lifetime pack-years of smoking was observed [35, 36]. Indeed, the FEV₁ decline was similar ($P=0.13$) in lifetime nonsmokers with asthma (28.5 mL/y), asthmatics who reported smoking up to 12.5 pack-years (24.5 mL/y), and asthmatics who reported smoking more than 12.5 pack-years (33.3 mL/y). This lack of association was present before and after adjustment for a range of confounders and was similar in those with and without airway obstruction at baseline [36]. This is surprising because within the ECRHS, there was clear evidence

that giving up smoking was associated with a slower rate of decline in lung function (8 mL/y lower than in smokers) [37] in the general population (and this positive effect on lung function decline would have been even greater if those who gave up had maintained rather than increased their body weight). We did see that asthmatics that smoked throughout the period of follow-up reported more cough or phlegm than those who did not smoke [32].

We may have been unable to detect the detrimental effect of smoking on asthma prognosis because the sample of asthmatics was relatively small, they were relatively young at baseline (20–44 years of age), and they had been observed over a relatively short period. In this case, later follow-ups of the cohort may reveal harmful effects of smoking on the prognosis of asthma. However, our failure to observe the detrimental effects of smoking on asthma outcomes may have arisen because those with the most severe underlying disease are the least likely to smoke and the least likely to smoke heavily (the healthy smoker effect). In this case, follow-up over a longer period and to older ages may fail to show detrimental effects of smoking on asthma prognosis, even if they are present.

Smoking among asthmatics may have a more subtle detrimental effect on their health. There is evidence from clinical trials that active smoking impairs the beneficial response to inhaled steroids in those with asthma [38]. In addition, in ECRHS I, we showed that young adults with symptoms suggestive of asthma who smoke are less likely to be using appropriate asthma treatment than those with similar symptoms who do not smoke [39]. Over the period of follow-up to ECRHS II, smokers were less likely to start using inhaled corticosteroids [40], even though there was a substantial increase in the use of inhaled corticosteroids among asthmatics as a whole. It is possible that physicians, having elicited that their patients are smokers, are more likely to attribute the reporting of asthma symptoms to the effects of smoking and less likely to prescribe potentially effective medications for those who indeed have asthma.

Conclusions

Smoking remains one of the most common modifiable risk factors for chronic disease in adults, and the ECRHS provides some evidence that active smoking and exposure to environmental tobacco smoke in adult life are associated with symptoms suggestive of asthma and with bronchial reactivity. Although smoking is associated with elevated total IgE levels, its association with other serological markers of allergy is different for different allergens, with no clear reason why this should be so. Some of these unknown relationships may become more clear when the next phase of data collection has been completed, but even

so, the healthy smoker effect complicates interpretation of some analyses. In the meantime, the respiratory health benefits of not starting smoking and smoking cessation among those who do smoke are considerable, and further clarification of these relationships is unlikely to change the underlying public health message—do not smoke and avoid inhaling other people's tobacco smoke.

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