Environmental Research 164 (2018) 241–247

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

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

Bircan Erbas[a,*], Toril Mørkve Knudsen[b], Christer Janson[c], Roy M. Nilsen[d], Simone Accordini[e], Bryndis Benediktdottir[f], Julia Dratva[g,q], Joachim Heinrich[h,r], Debbie Jarvis[i], Benedcite Leynaert[j], Melanie C. Matheson[k], Dan Norbäck[l], Francisco G. Real[b,s], Chantal Raherison-Semjen[m], Simona Villani[n], S.C. Dharmage[k,1], C. Svanes[o,p,1]

[a] Department of Public Health, La Trobe University, Melbourne, Australia
[b] Department of Clinical Sciences, University of Bergen, Norway
[c] Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Sweden
[d] Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway
[e] Unit of Epidemiology & Medical Statistics, Dept. of Public Health & Community Medicine, University of Verona, Verona, Italy
[f] Faculty of Medicine, University of Iceland. Department of Respiratory Medicine and Sleep, Landspitali University Hospital, Reykjavik, Iceland
[g] Department of Public Health and Epidemiology, Swiss Tropical and Public Health Institute, Basel, Switzerland
[h] Institute of Epidemiology I, Helmholtz Zentrum, Munich, Germany
[i] Department of Respiratory Epidemiology, Occupational Medicine and Public Health, National Heart and Lung Institute, Imperial College, London, United Kingdom
[j] Inserm UMR1152 Team of Epidemiology, Paris, France
[k] Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, Australia
[l] Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[m] INSERM U897, Institute of Public health and Epidemiology, Bordeaux University, Bordeaux, France
[n] Department of Public Health, Experimental and Forensic Medicine, Unit of Biostatistics and Clinical Epidemiology, University of Pavia, Italy
[o] Centre for International Health, University of Bergen, Norway
[p] Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway
[q] University of Basel, Basel, Switzerland
[r] Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Inner City Clinic, University Hospital Munich, Ludwig-Maximilians-Universität of Munich, Munich, Germany
[s] Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway

ARTICLE INFO

Keywords:
Cigarette smoking
Lung function
Asthma
Respiratory symptoms
ECRHS

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; FEV_1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; LLN, Lower limit of normal; GAMMs, Generalized Additive Mixed Models

* Correspondence to: School of Pyschology and Public Health, La Trobe University, Room 520, Health Sciences 2, Bundoora 3086, Victoria, Australia.
E-mail address: b.erbas@latrobe.edu.au (B. Erbas).

[1] Equal senior authors.

https://doi.org/10.1016/j.envres.2018.02.028
Received 11 December 2017; Received in revised form 8 February 2018; Accepted 20 February 2018
Available online 06 March 2018
0013-9351/

$p_{interaction}$ = 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 (FEV_1) (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 FEV_1 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 adult hood 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.

2.1.1.2. Asthma, COPD and bronchial hyperresponsiveness (BHR). "Current asthma" was defined as an attack of asthma or use of asthma medication in/during the last 12 months. "BHR", a term confirming bronchial responsiveness to metacholine, was defined as presence of a 20% fall in forced expiratory volume. COPD was defined as a pre-bronchodilator forced expiratory volume in one second (FEV_1) divided by forced vital capacity (FVC) less than the lower limit of normal (LLN). FEV_1 and FVC were measured, and the best pulmonary function curve was selected based on up to five technically acceptable manoeuvres.

2.1.1.3. Atopy. Atopy was defined as specific IgE against the following allergens; house dust mites (*Dermatophagoides pteronyssinus*), cat dander, timothy grass, and/or *Cladosporium herbarum*.

2.2. Smoking exposure variables

Smoking habits were recorded in the ECRHS I main questionnaire and subjects were categorised as either ex-smokers (yes to question - "Have you ever smoked for as long as year?") or current smokers (yes, to question – "Do you now smoke, as for one month ago?").

Childhood and intrauterine exposure to smoking was defined as a positive response to the question, "Did your mother ever smoke regularly during your childhood, or before you were born?" Intrauterine exposure was defined as a positive response to the additional questions "When your mother was pregnant, in particular with you, did she smoke as usual during pregnancy?" and "Did she cut down or stop during pregnancy?"

Age at smoking debut was determined based on the question "how old were you when you started smoking?" It was coded both as a continuous variable (age in years, in GAMM analyses), and categorised in the following categories; ≤10, 11–12, 13–15, 16–18 and 19 years or more (logistic regression analyses). Pack-years smoked was constructed based on questions regarding ever or current smoking, age at smoking initiation, ever cutting down or stopped smoking and amount of smoking at present or in the past.

2.3. Other variables

Paternal smoking exposure during childhood was based on the question "Did your father ever smoke regularly during your childhood?". Educational level was coded as a dichotomous variable defined as completion of full-time education. Exposure to passive smoking was based on the question "*Have you been exposed regularly to tobacco smoke in the last 12 months?*". Anthropometric data was obtained during clinical assessment.

2.3.1. Statistical methods

Separate generalized linear (logit link) regression models for men and women were fitted to all outcomes with a random effect for centre (Long and Freese, 2006). Age of smoking initiation were categorized as ≤10 years, 11–12 years, 13–15 years, 19 plus years with 16–18 years as the reference age group. Maternal smoking in utero and postnatal and pack-years of smoking were mutually adjusted in all models. All regression models were adjusted for age, education level (Pekkanen et al., 2005; Vittinghoff et al., 2007), paternal smoking and passive exposure to smoking. These variables were retained in the models if they were significant at the 5% level of significance or they changed the estimated effects by more than 10%.

Interactions between sex and smoking exposures were tested and p value < 0.1 considered statistically significant to avoid missing any important interactions. Data were further stratified by ex/current smokers and interactions tested. Additional sensitivity analysis (where required) were conducted by adjusting for current smoking. All results in the logistic regression analyses tables are presented as odds ratios (OR) and 95% confidence intervals (CIs). These analyses were performed using Stata release 12.1 (College Station, Texas).

To explore whether associations between age of smoking debut (as a continuous variable) and respiratory outcomes were nonlinear we fitted generalized additive mixed models to account for the study centre (GAMM) (Altman, 1990; Hastie and Tibshirani, 1986) separately for males and females using the the MGCV 1.8–3 package (Wood, 2013) in R (Version 3.1.0) (R Core Team, 2015). A similar approach to the Generalized Linear modelling was adopted for the GAMMS. We fitted GAMMS to all outcomes to examine any non-linear associations with age of smoking debut. If non-linearity was present we fitted sex and age of smoking debut interaction terms and present results separately by men and women if these interaction terms were significant at $p < 0.1$.

The non-linear associations between age of smoking debut and outcomes by men and women are presented in graphical format. The x-axis is defined as age of smoking debut (continuous) with cubic spline curves fitted versus age of smoking debut. The 95% CI are also shown. A probability density graph for the age of smoking debut is also plotted on each graph.

3. Results

Table 1 shows selected characteristics of the ECRHS study participants by gender. Men generally started smoking at a younger age (mean age of smoking debut 16.6 years, standard deviation (SD) = 3.3) than women (17.2 years, SD = 3.3) $p < 0.001$, and had smoked a larger number of pack-years than women (mean = 16.2, SD = 14.4, and mean = 11.2, SD = 10.6 respectively), $p < 0.001$. Prevalence of respiratory symptoms and outcomes by age of smoking debut for men and women are displayed in the online supplement (Supplementary Table 1).

In women, exposure to maternal smoking *in utero* was associated with a greater risk of wheeze, wheeze without a cold, chest tightness, nocturnal cough, more than three respiratory symptoms and current asthma (Table 2A). Associations with postnatal maternal smoke

Table 1
Selected characteristics of the study population.

	Overall N = 10,553[a]	Men N = 5348 = (50.41)	Women N = 5262 (49.59)
Ex smokers	3.730 (35.35)	1796 (33.77)	1934 (36.95)
Age of exsmokers, mean (SD)	36 (6.54)	36.60 (6.52)	35.44 (6.51)
Current smokers	6823 (64.65)	3523 (66.23)	3300 (63.05)
Age of current smokers, mean (SD)	33.57 (7.01)	33.77 (7.09)	33.35 (6.92)
Morther smoked in childhood	1778 (17.23)	907 (17.47)	871 (16.98)
Father smoked in childhood	7076 (70.75)	3599 (71.20)	3477 (70.30)
Maternal smoke *in utero*	1029 (9.97)	401 (7.72)	628 (12.24)
Age of smoking debut mean (SD)	16.9 (3.3)	16.6 (3.3)	17.2 (3.3)
Pack years median (25th%, 75th%)	10 (4.5, 19)	12.5 (6, 22.5)	8.2 (3.5, 15.75)
Did not complete full time education	1383 (13.03)	737 (13.78)	646 (12.28)

Data presented as number (%).
[a] Total of Ex and current smokers.

Table 2A
Respiratory symptoms and health outcomes in women as related to time windows of smoking exposure through the lifespan.

Respiratory outcomes	Age started smoking OR 95% CI							
	Maternal smoking In utero OR 95% CI	Maternal smoking Postnatally OR 95% CI	≤ 10	11–12	13–15	16–18	19 +	Pack years per year OR 95% CI
Wheeze	1.51 1.24, 1.86***	1.14 0.97, 1.32	3.51 1.26, 9.73*	1.57 1.01, 2.44*	1.11 0.94, 1.32	Ref	1.04 0.89, 1.22	1.04 1.07, 1.92*
Wheeze with symptoms of breathlessness	1.25 0.94, 1.66	1.14 0.91, 1.45	3.84 1.38, 10.64**	1.82 1.19, 2.76**	1.21 1.02, 1.43*	Ref	1.01 0.85, 1.19	1.02 1.01, 1.04***
Wheeze without having a cold	1.46 1.21, 1.79**	1.16 0.96, 1.41	1.88 0.64, 5.55	1.47 0.94, 2.23	1.10 0.91, 1.34	Ref	1.06 0.92, 1.22	1.04 1.02, 1.045***
Chest tightness	1.31 1.01, 1.69*	1.001 0.82, 1.23	2.59 1.11, 6.07*	1.32 0.88, 1.97	1.14 0.94, 1.37	Ref	1.18 1.02, 1.39*	1.02 1.01, 1.03***
Nocturnal breathlessness	0.99 0.72, 1.32	0.98 0.72, 1.32	2.38 0.82, 6.96	1.15 0.61, 2.18	0.95 0.76, 1.23	Ref	1.32 1.11, 1.59**	1.02 1.01, 1.03**
Nocturnal cough	1.35 1.11, 1.63**	1.11 0.95, 1.31	2.76 0.94,8.13	0.93 0.69, 1.24	0.93 0.81, 1.07	Ref	1.15 0.99, 1.34	1.02 1.01, 1.03***
Morning cough	1.15 0.91, 1.417	0.98 0.77, 1.24	1.37 0.62, 3.01	0.73 0.46, 1.14	0.96 0.79, 1.15	Ref	1.25 0.99, 1.57	1.06 1.04, 1.07***
≥3 respiratory symptoms	1.51 1.21, 1.89***	1.14 0.95, 1.36	3.74 1.56, 8.83**	1.76 1.19, 2.56**	1.12 0.94, 1.35	Ref	1.13 0.94, 1.37	1.03 1.02, 1.04***
Atopy	1.07 0.82, 1.42	1.18 0.94, 1.47	3.76 1.18, 11.97*	0.97 0.65, 1.44	0.94 0.77, 1.13	Ref	0.86 0.72, 1.02	0.99 0.98, 1.01
BHR	1.18 0.86, 1.61	1.25 0.98, 1.57	1.22 0.31, 4.71	1.01 0.52, 1.92	0.99 0.77, 1.26	Ref	1.15 0.98, 1.36	1.02 1.01, 1.03***
Current asthma	1.4 1.14, 1.75**	1.48 1.06, 2.06**	4.32 1.87, 9.96**	1.85 0.97, 3.56	1.07 0.81, 1.39	Ref	0.87 0.62, 1.21	0.99 0.98, 1.01
COPD	1.01 0.55, 1.82	1.21 0.87, 1.67	1.06 0.28, 3.95	1.18 0.56, 2.53	1.13 0.76, 1.65	Ref	1.28 0.89, 1.86	1.03 1.02, 1.05***

All models adjusted for age, pack-years, maternal and paternal smoking, educational level and centre.
* Significant at 0.05 level.
** Significant at 0.01 level.
*** Significant < 0.001.

exposure were significant only for current asthma. Associations of early life exposure and COPD did not reach statistical significance. Compared to age of smoking debut at 16 years of age, early age of smoking debut was associated with wheeze and wheeze with symptoms of breathlessness but not BHR alone. Smoking debut less than 10 years of age alone was associated with higher odds of chest tightness, atopy and current asthma. Pack-years of smoking were significantly associated with all respiratory outcomes, but not with current asthma.

Among men, exposure both to maternal smoking *in utero* and postnatal were strongly associated with increased risk of respiratory symptoms and asthma but not COPD (Table 2B). Compared to women, the early life impact seemed more consistent for men, in particular the impact of postnatal exposure. Onset of smoking at ages 11–12 in men was associated with wheeze, wheeze without a cold, chest tightness, nocturnal breathlessness, but not asthma and COPD than age of smoking debut at age 16–18 years (Table 2B). Similar to women, age of smoking debut wasn't associated with current asthma or COPD. Further adjustment of all regression models by exposure to passive environmental tobacco smoke and current adult smoking did not change the observed effects by more than 10% or were not significant when entered into the models.

Interaction terms between sex and smoking exposures were fitted using the Generalized Linear Models (Supplementary Table 2). In this table we present regression models for men and women combined and present the p value for the interaction term between sex and the smoking exposure in parentheses for each outcome analysis. The effects of maternal smoking *in utero* appeared to be slightly stronger among men (wheeze with symptoms of breathlessness: $p_{interaction} = 0.07$ term). The effects of earlier age of smoking debut were significantly stronger among women than among men for most outcomes (Supplementary Table 2 p values for interactions in parentheses).

Considering interaction by sex for age of smoking debut as a continuous variable, the non-linear associations between age of smoking debut and wheeze and more than three symptoms were significantly different for men and women, women being more vulnerable to early smoking debut ($p_{interaction} = 0.002$ and 0.02 respectively). Figs. 1 and 2 shows the GAMMS fit for age of smoking debut as a continuous variable, for wheeze and for ≥3 symptoms, separately for men and women. For all other outcomes, non-linear associations were not observed and hence GAMMs were not presented as the effects from the Generalized Linear Models sufficed.

As a sensitivity analysis, we stratified the data by ex-smoker and current smokers separately for men and women. Among women (Supplementary Table 3a and 3b) the effects of maternal smoking *in utero* and postnatal seem to be consistent between ex and current smokers. The observed effect of age of smoking debut, more than three symptoms, atopy and current asthma were only significant in current smokers. In men (Supplementary Table 3c and 3d) the effects of maternal smoking maternal smoking *in utero* and postnatal seem to be consistent between ex and current smokers, although for some outcome variables the estimated effects failed to reach statistical significance among ex-smokers. The observed effects for age of smoking debut when stratified by ex and current smokers were generally similar. Other observed effects were generally similar as in the combined group (Table 2A and 2B) but failed to reach statistical significance in smaller subgroups (Supplementary Table 3c and 3d).

4. Discussion

Our comprehensive analysis of ever smokers, incorporating smoking

Table 2B
Respiratory symptoms and health outcomes in men as related to time windows of smoking exposure through the lifespan.

Respiratory outcomes	Age started smoking OR 95% CI							
	Maternal smoking In utero OR 95% CI	Maternal smoking Postnatally OR 95% CI	≤10	11–12	13–15	16–18	19 +	Pack years per year OR 95% CI
Wheeze	1.52	1.18	0.88	1.38	1.11	Ref	1.14	1.02
	1.16, 1.99**	0.97, 1.42	0.64, 1.22	1.03, 1.84*	0.94, 1.31		0.94, 1.39	1.01, 1.03***
Wheeze with symptoms of breathlessness	1.83	1.32	0.99	1.35	1.11	Ref	1.01	1.01
	1.44, 2.31***	1.03, 1.68*	0.65, 1.52	0.96, 1.89	0.89, 1.40		0.79, 1.29	0.99, 1.02
Wheeze without having a cold	1.41	1.21	1.13	1.38	1.08	Ref	1.09	1.02
	1.11, 1.79**	1.02, 1.42*	0.72, 1.76	1.06, 1.79*	0.87, 1.34		0.87, 1.38	1.01, 1.03***
Chest tightness	1.4	1.04	1.61	1.33	1.14	Ref	1.08	1.01
	1.03, 1.89*	0.86, 1.26	1.09, 2.36*	1.03, 1.73*	0.93, 1.42		0.83, 1.40	1.002, 1.02***
Nocturnal breathlessness	0.94	0.72	1.66	1.67	1.28	Ref	1.64	1.003
	0.56, 1.55	0.51, 1.03	1.16, 2.39**	1.27, 2.21***	1.03, 1.59*		1.27, 2.13***	0.99, 1.011
Nocturnal cough	1.19	0.99	1.03	0.97	0.89	Ref	1.05	1.02
	0.94, 1.51	0.82, 1.19	0.62, 1.71	0.68, 1.39	0.75, 1.07		0.89, 1.26	1.01, 1.03***
Morning cough	0.96	0.86	0.69	1.27	0.98	Ref	1.05	1.04
	0.71, 1.31	0.71, 1.07	0.39, 1.22	0.88, 1.81	0.83, 1.18		0.85, 1.31	1.03, 1.05***
≥3 respiratory symptoms	1.53	1.24	1.17	1.30	1.14	Ref	1.16	1.02
	1.19, 1.96**	1.01, 1.52*	0.82, 1.67	1.02, 1.66*	0.92, 1.42		0.92, 1.46	1.008, 1.03***
Atopy	1.09	1.16	0.62	1.10	0.82	Ref	0.86	0.99
	0.83, 1.44	0.97, 1.38	0.4, 0.95*	0.79, 1.54	0.71, 0.94**		0.74, 1.00	0.98, 0.999**
BHR	1.25	1.01	0.84	1.31	1.22	Ref	0.86	1.006
	0.82, 1.92	0.78, 1.29	0.48, 1.49	0.81, 2.13	1.01, 1.46*		0.66, 1.14	0.99, 1.02
Current asthma	1.76	1.62	1.001	1.22	1.12	Ref	1.002	0.97, 0.95, 0.98***
	1.04, 2.95*	1.26, 2.09**	0.46, 2.15	0.62, 2.46	0.77, 1.62		0.72, 1.43	
COPD	1.06	1.51	0.45	1.14	1.28	Ref	0.68	1.011
	0.59, 1.87	0.96, 2.34	0.17, 1.21	0.59, 2.22	0.81, 2.04		0.45, 1.03	1.001, 1.03*

All models adjusted for age, pack-years, maternal and paternal smoking, educational level and centre.
* Significant at 0.05 level.
** Significant at 0.01 level.
*** Significant < 0.001.

exposure in early life, adolescence and adulthood in the same models, shows important impacts of exposure in each time window for respiratory symptoms and asthma, in both men and women. With regard to COPD, amount of adult exposure in terms of pack-years of smoking picked up the major part of the effects. There appeared to be differences between men and women in response to exposure at the different time windows: Generally, the effects of early life exposure on respiratory symptoms seemed slightly more consistent in men while the effects of early smoking debut and per pack-year were significantly stronger among women.

To our knowledge, there are not previous studies concomitantly accounting for exposure in utero, post-natal, adolescence and adulthood. It is well understood that smoking during the adult lifespan is a key contributor to respiratory disease. Although extensively studied in children, data on maternal smoking *in utero* and respiratory disease in adults are limited. Our findings are similar to a study by Skorge et al. (Skorge et al., 2005) reporting significant associations between maternal smoking *in utero* and incidence of asthma and respiratory symptoms in adults from a community based cohort aged between 15 and 70 years. They also reported increased odds of wheeze with both pre- and postnatal exposure combined. An earlier cohort study of early life risk factors, asthma and wheezing in adults followed until age 33

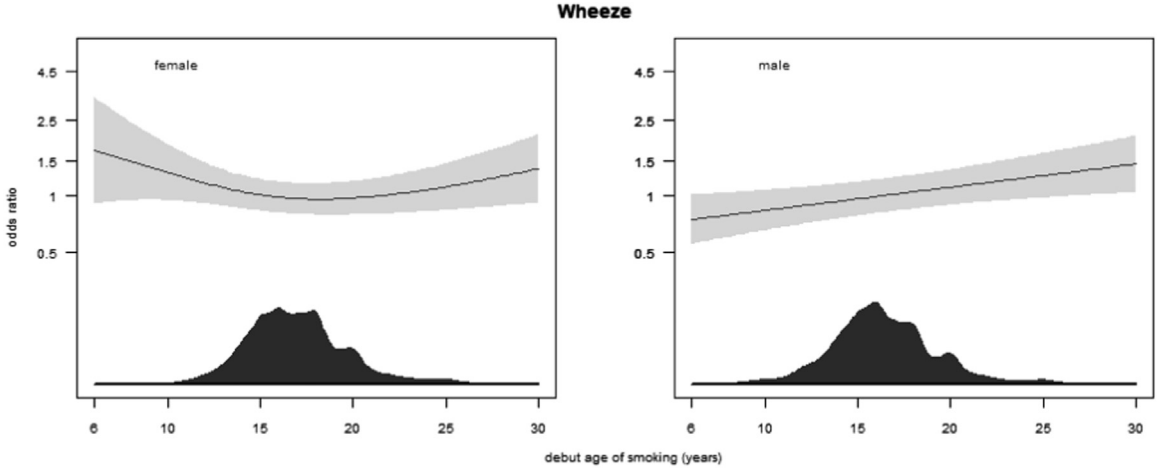

Fig. 1. Nonlinear effects of age of smoking debut as a continuous variable and wheeze separately by men and women.

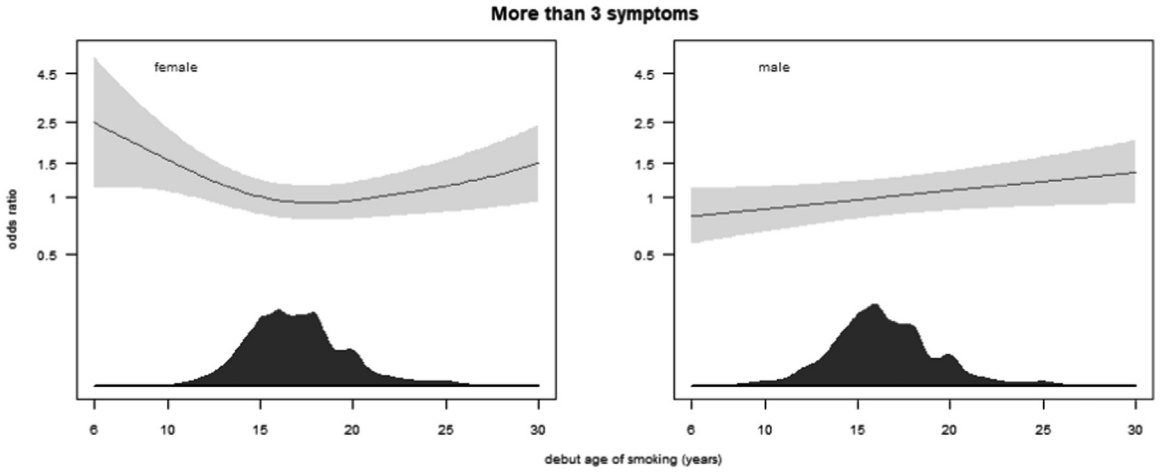

Fig. 2. Nonlinear effects of age of smoking debut as a continuous variable and more than 3 symptoms separately by men and women.

years, found that both smoking during pregnancy and starting smoking at 16 years of age was a strong predictor of wheeze in adults (Strachan et al., 1996). This study did not examine differences between men and women nor assessed effects concomitantly.

Studies focusing on age of smoking debut and respiratory disease in adults are rare. In our study mean age of onset of smoking in men and women are similar to other studies (Clennell et al., 2008; Patel et al., 2004; Vianna et al., 2008). Patel and colleagues (Patel et al., 2004) reported increased odds of asthma in women who started smoking in childhood defined as less than 16 years of age but not in men. Although we find similar results for women too, our findings are not directly comparable as they fitted separate models for current and ex-smokers while we combined current/ex smokers in all our analysis. Besides, the study by Vianna and colleagues (Vianna et al., 2008) did not report findings by age of onset of smoking and respiratory outcomes although they used the Brazil sample from ECRHS. Moreover, neither of these studies examined the association between age of smoking onset and respiratory outcomes whilst mutually adjusting for early life exposure to smoking and pack-years separately by men and women. In our study, women were more vulnerable to early age of smoking debut than men, in models accounting for gender differences in all exposure periods.

Our findings of increasing risk for respiratory symptoms with higher tobacco exposure (in our study measured as number of pack-years), are consistent with a large Norwegian population based study (Langhammer et al., 2000). In this study the odds of current asthma and wheeze in adults increased with the number of daily cigarettes, and in agreement with our results, the risk related to increasing exposure was greater in women than in men. Also a study of young adults in Brazil reported increase in odds of respiratory symptoms with increasing numbers of cigarettes smoked per day (Oliveira et al., 2008). The inverse association observed for pack-years and asthma and only slightly lower odds for men is intriguing. Smoking may be a determinant for diagnosing respiratory symptoms as asthma or not, thus, the finding is likely to be explained by diagnostic bias. The results on symptoms are more reliable in this context.

Although other studies using ECRHS data have examined various smoking exposure windows and respiratory outcomes (Milenkovic et al., 2011; Urrutia et al., 2005), no previous analysis has examined comprehensively respiratory health effects of tobacco exposure over the life course, including all exposure windows in the same models. This might explain why a previous analysis suggested that *in utero* exposure had stronger effects in women while the current analysis indicates slightly more convincing early life effects on respiratory health among men (Svanes et al., 2004). Previous analyses of early life exposure have not accounted for potential gender-specific confounding i.e. by adolescent smoking. The discrepancy might possibly also be related to the fact that the current analysis only included ever-smokers; i.e. if *in utero* exposure was particularly harmful in never-smoking women. The current results are, however, in agreement with the previous analysis (Svanes et al., 2004) concerning effects of post-natal smoking being more convincing among men.

We included education level as *a priori* in all models as this variable has been shown to be a major confounder in smoking exposure associations. This variable is a good marker of socio-economic status and to some extent also reflects air pollution (as lower SES are often located in high pollution/less green space areas). We do not have birth weight data for the full cohort, and it has been shown that *in utero* smoking exposure effects were independent of birth weight on the development of the respiratory system (Hoo et al., 1998). Additional variables would contribute to over adjustment of models.

This study has a number of strengths. Although the design was cross-sectional, the large ECRHS I cohort design enabled analysis of differences by men and women with sufficient power to detect associations between exposures and outcomes. The participants included in this study are a large subsample of the full cohort in ECRHS in Phase I. ECRHS is an international cohort with each included centre a representative sample of the general population within that region and although there may be heterogeneity between regions, we used appropriate statistical methodology to accommodate for these possible differences. Self-reported symptoms are collected through a validated international questionnaire and although there was some variation of prevalence of reported respiratory symptoms between countries, a validation study showed good internal consistency suggesting that country specific characteristics are unlikely to impact on self reporting of respiratory symptoms (Janson et al., 2001). Because we have combined current smokers and ex-smokers we have confidence in our calculation of pack-years, because recall bias may be an issue when estimating smoking, especially among ex-smokers (Vold et al., 2014).

A number of limitations do need to be acknowledged when interpreting our findings. Only prebronchodilator spirometry was measured and as such should be considered as a limitation when assessing exposure outcome associations for COPD. By restricting our study base to ever-smokers we do not understand these associations for the group who were only exposed to maternal smoking during pregnancy or postnatal, but were never smoking themselves and therefore strictly do not cover all aspects of lifetime exposure to tobacco smoke. Healthy smoking bias is also a possibility. Smokers without symptoms may continue to smoke and those that quit early possibly because they experience respiratory symptoms and then subsequent asthma diagnosis (ex-smokers). The pool of current smokers over time may include those who have had few respiratory symptoms and so the current smokers are “healthier” and less likely to develop asthma and mask the true

association between smoking exposures and respiratory outcomes.

Most epidemiological studies use self report data on smoking and recall bias can be an issue. Women who are current smokers are less likely to report smoking (Shipton et al., 2009). However, a study of the agreement between nicotine levels and self report smokers reported 93% agreement for women and 92% agreement for men in an adult population in the United States (Caraballo et al., 2001). Although maternal smoking questions were not validated in ECRHS, recall bias may be limited as Svanes et al. (2004) showed that there were little difference in how symptomatic and non-symptomatic participants responded to questions regarding parental smoking. Nevertheless, self-reported data on smoking may not be completely accurate and therefore may lead to conservative estimates of the effects of smoking. Self report childhood exposure to environmental smoking in adults may also be susceptible to differential bias. Our data on adult smoking and pack-years is much better than the data on early life exposure as the latter are crude and do not include information about the amount of exposure. By including them all in one model it is possible that we are underestimating the early life effects. However, investigating all exposures concurrently is important and a major strength of this study.

In summary, smoking exposure in each stage of the lifespan showed persistent harmful effects with regard to adult respiratory health. The impact of early life exposure appeared to be somewhat more consistent in men than in women, while women appeared to be more vulnerable to an early age of smoking debut and a large amount of adult exposure. Our findings reinforce the notion that there are several critical windows of exposure that are all of importance, even in mutually adjusted analytical models. Basic research should explore the mechanisms for gender differences in effects of tobacco smoke exposure during different critical age windows.

Author contributions

CJ, JH, DJ, BL, DN, CS designed the ECRHS study and obtained project funding. All authors contributed with developing the design of this analysis. CJ, JD, JH, DJ, BL, CRS, SV, SD, CS were responsible for data collection. BE, TMK, RN analysed data. BE, SD, CS drafted the manuscript. TK, CJ, RN, SA, BB, JD, JH, DJ, BL, MM, DN, FGR, CRS and SV commented on the manuscript. All authors read and approved the final manuscript before submission.

Financial/nonfinancial disclosures

All other authors have no conflicts of interest to declare.

Other contributions

The authors would like to acknowledge the contributions of the late Professor Roberto de Marco, who played a substantial part in the ECRHS study.

Conflict of interest

Dr. Jarvis reports grants from European Commission during the conduct of the study. All other authors have no conflicts of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2018.02.028.

References

Altman, D.G., 1990. Practical Statistics for Medical Research. Taylor & Francis.
Apostol, G.G., et al., 2002. Early life factors contribute to the decrease in lung function between ages 18 and 40: the Coronary Artery Risk Development in Young Adults study. Am. J. Respir. Crit. Care Med. 166, 166–172.
Becklake, M.R., Kauffmann, F., 1999. Gender differences in airway behaviour over the human life span. Thorax 54, 1119–1138.
Bellemare, F., et al., 2003. Sex differences in thoracic dimensions and configuration. Am. J. Respir. Crit. Care Med. 168, 305–312.
Caraballo, R.S., et al., 2001. Factors associated with discrepancies between self-reports on cigarette smoking and measured serum cotinine levels among persons aged 17 years or older: third National Health and Nutrition Examination Survey, 1988–1994. Am. J. Epidemiol. 153, 807–814.
Carey, M.A., et al., 2007. It's all about sex: gender, lung development and lung disease. Trends Endocrinol. Metab. 18, 308–313.
Chinn, S., et al., 2005. Smoking cessation, lung function, and weight gain: a follow-up study. Lancet 365, 1629–1635 (discussion 1600-1601).
Clennell, S., et al., 2008. Characterisation of smoking behaviour across the life course and its impact on decline in lung function and all-cause mortality: evidence from a British birth cohort. J. Epidemiol. Community Health 62, 1051–1056.
Hastie, T., Tibshirani, R., 1986. Generalized additive models. Stat. Sci. 297–310.
Hoo, A.F., et al., 1998. Respiratory function among preterm infants whose mothers smoked during pregnancy. Am. J. Respir. Crit. Care Med. 158, 700–705.
Janson, C., et al., 2001. Determinants of cough in young adults participating in the European Community Respiratory Health Survey. Eur. Respir. J. 18, 647–654.
Kumar, P., Ram, U., 2017. Patterns, factors associated and morbidity burden of asthma in India. PLoS One 12, e0185938.
Langhammer, A., et al., 2000. Cigarette smoking gives more respiratory symptoms among women than among men. The Nord-Trondelag Health Study (HUNT). J. Epidemiol. Community Health 54, 917–922.
Long, J.S., Freese, J., 2006. Regression Models for Categorical Dependent Variables Using Stata, Second edition. Stata Press.
Martinez, F.D., et al., 1992. Increased incidence of asthma in children of smoking mothers. Pediatrics 89, 21–26.
Milenkovic, B., et al., 2011. Asthma and chronic bronchitis symptoms among adult population of Belgrade. Srp. Arh. Celok. Lek. 139, 149–154.
Oliveira, A.F., et al., 2008. The disease burden attributable to smoking in the state of Rio de Janeiro, Brazil in 2000. Clinics 63, 215–222.
Patel, B.D., et al., 2004. Childhood smoking is an independent risk factor for obstructive airways disease in women. Thorax 59, 682–686.
Pekkanen, J., et al., 2005. Operational definitions of asthma in studies on its aetiology. Eur. Respir. J. 26, 28–35.
Prescott, E., et al., 1997. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. Eur. Respir. J. 10, 822–827.
R Core Team, 2015. R A Language and Environment for Statistical Computing 2015.
Shipton, D., et al., 2009. Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. Bmj 339, b4347.
Skorge, T.D., et al., 2005. The adult incidence of asthma and respiratory symptoms by passive smoking in uterus or in childhood. Am. J. Respir. Crit. Care Med. 172, 61–66.
Sorheim, I.C., et al., 2010. Gender differences in COPD: are women more susceptible to smoking effects than men? Thorax 65, 480–485.
Strachan, D.P., et al., 1996. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 312, 1195–1199.
Svanes, C., et al., 2004. Parental smoking in childhood and adult obstructive lung disease: results from the European Community Respiratory Health Survey. Thorax 59, 295–302.
Urrutia, I., et al., 2005. Smoking habit, respiratory symptoms and lung function in young adults. Eur. J. Public Health 15, 160–165.
Vanker, A., et al., 2017. The association between environmental tobacco smoke exposure and childhood respiratory disease: a review. Expert Rev. Respir. Med. 11, 661–673.
Vianna, E.O., et al., 2008. Respiratory effects of tobacco smoking among young adults. Am. J. Med. Sci. 336, 44–49.
Vittinghoff, E., et al., 2007. 5 Linear and non-linear regression methods in epidemiology and biostatistics. In: Rao, J.P.M.C.R., Rao, D.C. (Eds.), Handbook of Statistics. Elsevier, pp. 148–186.
Vold, M.L., et al., 2014. Low FEV1, smoking history, and obesity are factors associated with oxygen saturation decrease in an adult population cohort. Int. J. Chron. Obstruct Pulmon Dis. 9, 1225–1233.
Wood, S., 2013. Mixed GAM Computation Vehicle with GCV/AIC/REML smoothness estimation and GAMMs by REML/PQL 2013 [updated R Documentation for package 'mgcv' version 1.7-22].
Wu, Z.X., et al., 2012. Early postnatal exposure of mice to side-steam tobacco smoke increases neuropeptide Y in lung. Am. J. Physiol. Lung Cell Mol. Physiol. 302, L152–L159.