

Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life

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Summary

Background Prenatal maternal smoking has been associated with adverse respiratory effects in childhood such as lung deficits and wheezing, but results concerning asthma, hayfever, and atopic eczema are inconsistent.

Objective In the present study, we investigate the effects of maternal smoking in pregnancy on asthma, hayfever, atopic eczema, and wheezing in the offspring up to the age of 14–18.

Methods The study was based on a cohort of mothers enrolled during midwife visits around the 36th week of gestation in Odense and Aalborg, Denmark, 1984–1987. Singleton, live born children ($n = 11\,144$) were followed-up in 2002 to obtain a childhood history of atopic diseases, by means of questionnaires to the parents. Multivariate logistic regression analyses for medical diagnoses of asthma, hayfever, atopic eczema, and symptoms of wheezing before the age of 3, were carried out on 7844 children.

Results After adjustment for confounders, late prenatal smoke exposure was associated with wheezing, with an odds ratio (OR) of 1.2, and a 95% confidence interval (CI) of 1.1–1.5. Furthermore, slightly reduced estimates for hayfever (OR 0.8, CI 0.7–1.0) and atopic eczema (OR 0.8, CI 0.7–0.9) were obtained for children exposed in late pregnancy compared with non-exposed.

Conclusion Late gestational smoke exposure was associated with wheezing but not with asthma, while null or even protective estimates were indicated for hayfever and atopic eczema. However, lack of control options for hereditary factors may have affected the results.

Keywords atopic diseases, prenatal, smoke exposure, tobacco, wheezing

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Introduction

Studies indicate an increased prevalence of atopic or allergic diseases such as asthma, rhinitis, and atopic eczema in many countries during the last decades [1–4]. These diseases cause significant problems for the affected individuals, parents, as well as society [5, 6]. Tobacco smoke, one of the most important toxic exposures *in utero* and in early childhood, has been implicated in the aetiology of asthma and allergies. Exposure to tobacco smoke postnatally has been considered consistently associated with detrimental effects on lung function, respiratory symptoms, and asthma [7–9], but no consistent associations with IgE levels, skin prick positivity, allergic rhinitis (AR) or eczema in children were found in a study by Strachan and Cook [10]. There are also strong indications of a reduced lung function in children exposed to tobacco in fetal life [11–16]. Increased risks for wheezing and asthma in connection with maternal smoking in pregnancy have been suggested [17] and a study by Schafer et al. [18] reported a significant association between maternal smoking during pregnancy and/or lactation and atopic eczema.

However, whether '*in utero* smoke exposure' is causally linked to atopic disease or not is an unsettled matter, and published studies have shown conflicting results. As women who smoke during pregnancy usually continue smoking after delivery, the sample sizes of children who were only prenatally exposed to tobacco smoke have often been small. Animal studies have suggested nicotine as the key constituent causing alterations in e.g. pulmonary function [19, 20], possibly through binding nicotinic acetylcholine receptors and subsequent hyperplasia of the pulmonary neuroendocrine cells [21], but potential causes remain unclear. The aim of the present study was to investigate the risk of atopic eczema, hayfever, asthma, and wheezing in childhood after prenatal exposure to maternal smoking, also by taking the nicotine content of the cigarettes into consideration.

Material and methods

Study population

All pregnant women in the two Danish cities, Odense and Aalborg, were invited to participate in a health campaign entitled 'Healthy habits for two' during April 1984–April 1987 [22]. At midwife visits, at approximately 36th week of gestation, women were given a self-administrated question-

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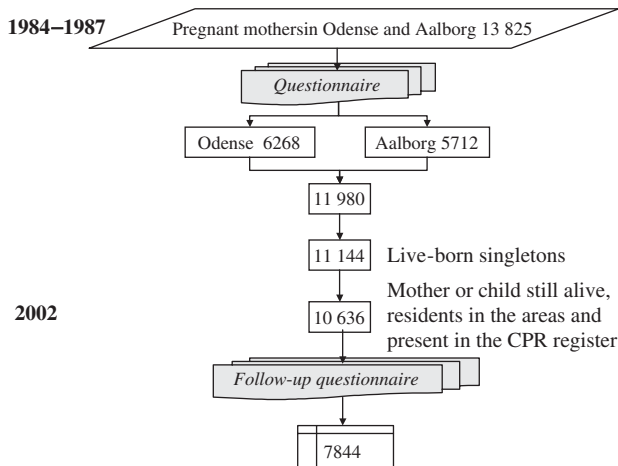


Fig. 1. The cohort and data collection procedure.

naire about life-style and other social conditions with particular focus on risk behaviours such as smoking, eating, and drinking. About 87% ($N = 11\,980$) of the pregnant women in the region participated (Fig. 1) and obstetric information was extracted from medical records. Out of singletons born alive ($n = 11\,144$), 10 636 children and their mothers were still alive, residents in the county, and could be traced by means of the Civil Registration System in 2002. A follow-up questionnaire was sent to the parents of these children in order to retrieve information about health parameters such as atopic diseases during the childhood period [23]. The parents, usually the mother, of 74% of the children responded to the questionnaires. The study population thus consisted of 7844 children of whom 51.6% ($n = 4045$) were boys and 48.4% were girls ($n = 3798$).

Exposure data

Mothers were asked about their smoking habits before being pregnant, in early pregnancy, as well as at the time of filling out the questionnaire in their late pregnancy period (around week 36). If the mother reported smoking in early (before week 36), late pregnancy (based on information obtained during week 36) or both in early and late gestation, the child was considered exposed to tobacco smoke *in utero*. Mothers who smoked late in pregnancy were further asked about the average number of cigarettes per day and which type and brand of tobacco they smoked. This information was used to classify the nicotine content of the cigarettes based upon reports from the tobacco companies. Smoke exposure late in pregnancy was categorized accordingly in '1-9', '10-19' and '20 or more' cigarettes per day and the level of nicotine as low (< 1.5 mg/cigarette), moderate (1.5-1.9 mg/cigarette) or high (≥ 2.0 mg/cigarette). Moreover, information about parental smoking anytime after birth was collected in the follow-up questionnaire. If either the mother or father had smoked in this period, postnatal environmental tobacco smoke (ETS) exposure was considered present, provided that the father was recorded as cohabitating with the mother at the time of birth. Based on this information, children were also classified according to tobacco exposure: (a) in pregnancy only (maternal smoking in late gestation); (b) in the postnatal

period only (either parent); (c) in both periods; or (d) remained unexposed both pre- and postnatally.

Outcomes

Responses from the mailed questionnaires were used to categorize children with regard to a history of wheezing, asthma, hayfever and atopic eczema. Questions concerning atopic diseases were primarily derived from a Danish questionnaire (questions 1-7) developed from the UK Party's questionnaire for atopic dermatitis [24, 25]. Children were classified as having asthma or hayfever, when parents responded positively to the questions: 'Have you ever been informed by a doctor that your child has asthma?' and 'Have you ever been informed by a doctor that your child has hayfever?' respectively, at any point in time during childhood. Additionally, the occurrence of a doctor's diagnosis of atopic eczema was assessed with the question 'Have you ever been informed by a doctor that your child has eczema?' Questions on wheezing were also included, which were originally developed for the International study of asthma and allergies (ISAAC) questionnaire (questions 1-5 and 7, 8 from the core questionnaire wheezing module for 13-14-year olds) [26]. Question number 1 was, however, used with the modification 'Have your child *before 3 years of age* ever had wheezing or whistling in the chest?' Children with a positive answer to this question were classified with 'wheezing', if they had never been diagnosed with asthma during their childhood. Data on hospitalization in atopic diseases up to 1996 was also retrieved by linkage to the Danish National Hospital Discharge Registry (NHDR), which contains information about hospital admissions from 1977 [27].

Covariates

Socio-economic grouping were based on job titles, description of working processes, and industrial codes at the time of pregnancy, forming a classification similar to the International Standard Classification of Occupations (ISCO-68). The child was assigned to a socio-economic group based on the highest parental ranking, where group 1 represents parents with academic background or with executive jobs; group 2, parents with lower levels of management tasks or an intermediate vocational training; group 3, parents with lower levels of management tasks or with a shorter education; group 4, parents who were skilled workers; group 5, parents being unskilled or semiskilled; group 6, parents who were students; and group 7, parents who were unemployed [28]. Information about maternal occupation in pregnancy was classified as 'no occupation', or else according to the major groups in the Danish classification Fagkode [29]. Moreover, maternal data on educational level (-9 , 10, 11+ years), age (15-19, 20-24, 25-29, 30-34, ≥ 35), parity (0, 1, 2, 3+), consumption of alcohol (0, <1 , 1-4, 5-9, 10+ drinks/week, coffee (0-3, 4-7, 8+ cups/day), tea (0-3, 4-7, 8+ cups/day), fish, vitamins, and folic acid during pregnancy as well as body mass index (BMI) (<20 , 20-24, 25-29, 30+) derived from the pregnancy questionnaire were taken into consideration. Furthermore, birth weight (<2500 , 2500-3999, ≥ 4000 g), gestational age, and caesarean section from medical records, as well as on breastfeeding (no breastfeeding, exclusive less

Table 1. Maternal prenatal smoking habits according to mother's age, socio-economic group, and atopic diseases in childhood

	N	Maternal age: mean	Socio-economic group: % with academic/managerial occupation*	Wheezing		Asthma diagnosis		Hayfever diagnosis		Atopic eczema diagnosis	
				n	%	n	%	n	%	n	%
No smoking	4559	27.8	51.5	634	15.0	488	10.8	658	14.6	780	17.3
Any smoking	3252	26.8	37.5	594	20.1	394	12.2	416	12.9	461	14.3
1–9 cigarettes†	1411	26.7	39.0	242	18.8	168	12.0	189	13.5	195	14.0
10–19 cigarettes†	1309	26.7	32.7	263	22.1	160	12.3	153	11.8	169	13.1
20+ cigarettes†	95	27.4	28.0	22	26.5	12	12.8	6	6.5	17	18.3

*Socio-economic groups 1–3 were regarded as academic or managerial occupations, and socio-economic groups 4–7 as non-academics. †Late in pregnancy (~ week 36).

than 4 months, exclusive more than 4 months), day-care attendance, number of children in household (1, 2, 3, 4 or more), and animal contact in the first year of life, as reported in the follow-up questionnaire, were treated as potential confounders in the analyses.

Statistical analyses

We estimated the risk of the different outcomes by using multivariate logistic regression analysis, calculating odds ratios (ORs) and 95% confidence intervals (CIs). The *in utero* smoke exposure was analysed both according to number of cigarettes and level of nicotine, adjusted for postnatal ETS exposure. Potential confounders were included in the multivariate models if they changed the estimates for smoke exposure more than 5% when dropped from the full model. The results were stratified for birth weight and gestational age, as these covariates are potential intermediate factors (on the causal pathway between smoking and atopic diseases) [9]. Potential interactions between maternal smoking and gender, socio-economic group, and parity were also tested. No notable differences in effect measures were found when stratifying for gender, but this variable was included in all models based on *a priori* criteria [30]. A trend test between number of cigarettes smoked in pregnancy and the end-points was performed by including smoking as a continuous variable in the logistic regression model. The same procedure was carried out for nicotine level after stratification by number of cigarettes smoked. For validation, the association between prenatal smoking and atopic diseases were also estimated based on the data from hospital records. Data analyses were performed with Stata Statistical Software [31].

Results

The response proportion was 74%, corresponding to 7844 of the 10 636 children from the present cohort who were possible to trace for follow-up at age 14–18. Boys constituted 51.6% of the study population, and girls 48.4%, respectively. The number of children for whom asthma had been diagnosed by a physician was 888 (11.4%) according to the parental reports; additionally, 1232 (17.1%) of the children with no asthma diagnosis ($n = 7205$) had wheezing before 3 years of age, and 1083 (13.9%) children had been diagnosed with hayfever. These conditions were more frequent in boys;

12.2%, 17.9%, and 15.3% (vs. 10.6, 16.3, and 12.4% in girls), respectively. The prevalence of atopic eczema, on the other hand, was slightly higher in girls (17.1% compared with 15.1% in boys), with a total proportion of 16.1% ($n = 1248$).

The number of women who reported smoking 'anytime in gestation', according to the questionnaire data from late pregnancy (36th week), was 3252 (41.5%) (Table 1), while 33 mothers reported no data. Moreover, 417 reported smoking only early in gestation, 12 only late in gestation, and 2813 smoked throughout pregnancy. Smoking in pregnancy was slightly more common among younger mothers as well as in women from lower socio-economic groups, as shown in Table 1. No crude association was found between any prenatal smoke exposure and asthma, nor when adjusting for socio-economic group, maternal occupation, age, coffee consumption in pregnancy, parity, gender, breastfeeding, and postnatal smoke exposure (OR 1.0, CI 0.8–1.2). The corresponding analysis for wheezing gave an OR of 1.2 (CI 1.0–1.4). This slightly elevated risk estimate was only seen for smoking in late gestation (OR 1.2, CI 1.1–1.5). In contrast, the risk estimates for hayfever and atopic eczema relative to any *in utero* smoke exposure were 0.9 (CI 0.7–1.0) and 0.8 (CI 0.7–1.0). These borderline negative associations were also seen for prenatal smoke exposure late in pregnancy exclusively (OR 0.8, CI 0.7–1.0 and 0.8, CI 0.7–0.9). For wheezing, there was a dose-response pattern in relation to the number of cigarettes the mother smoked per day in late pregnancy (P -value <0.01) (Fig. 2). The analysis of hayfever and atopic eczema also showed decreased risk estimates in a dose-response pattern with number of cigarettes per day; the P -values for trend were <0.01 and <0.01 , respectively. The corresponding P -value for asthma was 0.70. No clear trends for any of the outcome variables were observed according to nicotine exposure, after adjustment for the number of cigarettes smoked (Table 2). The adjusted ORs with nicotine level as continuous variable were 1.1 (CI 0.9–1.3) for wheezing, 1.0 (CI 0.8–1.2) for asthma, 1.0 (CI 0.8–1.2) for hayfever, and 1.1 (CI 0.9–1.3) for atopic eczema.

The number of women reporting smoking only in gestation was 95, and 35 of these had smoked in the late part of pregnancy. The number of children with only postnatal ETS was 1904, while 2775 were both pre- and postnatally exposed. Although there was a limited possibility to stratify for the two time periods of exposure (Table 3), the results point towards a possible stronger association with wheezing for

prenatal smoke exposure (OR 1.6, CI 0.7–3.7), compared with parental smoking in the postnatal period only (OR 1.2, CI 1.0–1.4).

Maternal alcohol, tea, fish, vitamins, and folic acid intake in pregnancy, BMI, caesarean section, head circumference, early animal contact, day-care attendance, and number of children in household did not affect the associations of interest; neither did birth weight and gestational age. These variables were therefore not included in the final models. However, when stratifying for gestational age and birth

weight the effect measures differed somewhat for birth weight. In children with a birth weight of 2500 g or more, late pregnancy smoke exposure was associated with ORs of 1.3 (CI 1.1–1.5) for wheezing, 1.0 (CI 0.9–1.2) for asthma, 0.8 (CI 0.7–1.0) for hayfever, and 0.8 (CI 0.6–0.9) for atopic eczema, when adjusted for postnatal parental smoking, maternal age, parity, gender, gestational age, and breastfeeding. The corresponding estimates were 0.8 (CI 0.3–2.1) for wheezing ($n = 21$), 1.0 (CI 0.3–3.2) for asthma ($n = 20$), 0.7 (CI 0.2–2.8) for hayfever ($n = 13$), and 0.9 (CI 0.3–2.6) for atopic eczema ($n = 18$), in children with low birth weight. None of the tested covariates showed an interaction with maternal smoking in pregnancy in the logistic regression models.

Only a few of the cases were hospitalized in bronchitis, asthma, AR or atopic eczema. The precision for validation analyses regarding pre- vs. postnatal exposure, number of cigarettes, and nicotine content were therefore low. However, when we based our analyses on the hospitalization data only, i.e. the more severe cases, risk estimates for late gestational smoke exposure were not considerably different (Table 4).

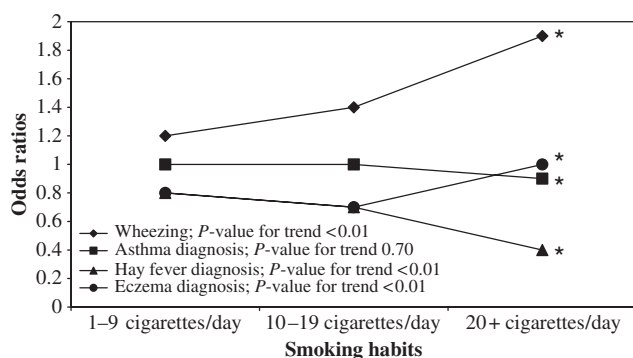


Fig. 2. Adjusted odds ratios for wheezing, asthma, hayfever, and atopic eczema, according to maternal smoking habits in late pregnancy. *The number of exposed cases with wheezing, asthma, hayfever, and atopic eczema were 22, 12, 6 and 17, respectively.

Discussion

We found maternal smoking at the 36th week of gestation to be associated with wheezing in children who were not diagnosed with asthma later in childhood. Hayfever and

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for atopic diseases up to 14–18 years of age, according to maternal smoking in late pregnancy and nicotine content of the cigarettes

	Nicotine content*	Wheezing			Asthma diagnosis			Hayfever diagnosis			Atopic eczema diagnosis		
		<i>n</i>	OR	OR (CI)†	<i>n</i>	OR	OR (CI)†	<i>n</i>	OR	OR (CI)†	<i>n</i>	OR	OR (CI)†
No smoking		634	1.0	1.0	488	1.0	1.0	658	1.0	1.0	780	1.0	1.0
1–9 cigarettes	Low	35	1.0	0.9 (0.6–1.3)	31	1.1	1.0 (0.7–1.5)	42	1.1	1.0 (0.7–1.5)	40	0.9	0.9 (0.6–1.2)
	Medium	91	1.2	1.1 (0.9–1.5)	71	1.2	1.1 (0.8–1.5)	78	1.0	0.9 (0.7–1.2)	70	0.7	0.7 (0.6–1.0)
	High	90	1.6	1.4 (1.0–1.8)	51	1.1	0.8 (0.6–1.1)	55	0.8	0.7 (0.5–1.0)	67	0.8	0.8 (0.6–1.1)
10–19 cigarettes	Low	26	1.5	1.5 (0.9–2.4)	20	1.4	1.3 (0.8–2.1)	13	0.6	0.6 (0.3–1.0)	18	0.7	0.8 (0.5–1.3)
	Medium	120	1.8	1.6 (1.2–2.0)	50	0.8	0.7 (0.5–1.0)	62	0.8	0.7 (0.5–1.0)	59	0.6	0.6 (0.4–0.8)
	High	88	1.5	1.3 (1.0–1.8)	72	1.5	1.1 (0.8–1.6)	60	0.9	0.8 (0.6–1.1)	66	0.8	0.8 (0.6–1.1)
20+ cigarettes	Low	2	1.4	1.6 (0.3–7.5)	1	0.8	0.6 (0.1–4.8)	1	0.7	0.6 (0.1–5.2)	1	0.5	0.5 (0.1–3.9)
	Medium	4	1.3	1.2 (0.4–3.7)	3	1.1	1.0 (0.3–3.4)	2	0.5	0.5 (0.1–2.2)	3	0.7	0.7 (0.2–2.4)
	High	11	2.7	2.3 (1.1–4.8)	8	2.0	1.3 (0.6–3.0)	2	0.3	0.3 (0.1–1.3)	10	1.6	1.5 (0.7–3.1)

*Test for trend; wheezing $P = 0.33$, asthma $P = 0.89$, hayfever $P = 0.53$, and atopic eczema $P = 0.45$.

†Adjusted for socio-economic group, maternal occupation, maternal age in pregnancy, coffee consumption in pregnancy, parity, breastfeeding, gender, and parental postnatal smoking.

Table 3. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for atopic diseases up to the age of 14–18 according to prenatal smoke exposure only, postnatal only, or both

	Wheezing			Asthma diagnosis			Hayfever diagnosis			Atopic eczema diagnosis		
	<i>n</i>	OR	OR (CI)*	<i>n</i>	OR	OR (CI)*	<i>n</i>	OR	OR (CI)*	<i>n</i>	OR	OR (CI)*
No smoke exposure	314	1.0	1.0	238	1.0	1.0	325	1.0	1.0	408	1.0	1.0
Prenatal smoke exposure only†	7	1.6	1.6 (0.7–3.7)	3	0.8	0.8 (0.2–2.6)	5	1.1	1.1 (0.4–2.9)	6	1.0	1.0 (0.4–2.4)
Postnatal ETS exposure only	288	1.2	1.2 (1.0–1.4)	221	1.2	1.1 (0.9–1.4)	291	1.1	1.1 (1.0–1.4)	322	1.0	1.0 (0.8–1.1)
Both pre- and postnatal exposure†	518	1.6	1.5 (1.3–1.8)	341	1.3	1.1 (0.9–1.4)	345	0.9	0.9 (0.7–1.1)	379	0.8	0.7 (0.6–0.9)

*Adjusted for socio-economic group, maternal occupation, maternal age in pregnancy, coffee consumption in pregnancy, parity, breastfeeding, and gender.

†Maternal smoking in late pregnancy only.

Table 4. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for hospitalization with atopic diseases according maternal smoking in pregnancy

	Bronchitis			Asthma			Allergic rhinitis			Atopic eczema		
	<i>n</i>	OR	CI	<i>n</i>	OR	CI	<i>n</i>	OR	CI	<i>n</i>	OR	CI
No smoking	27	1.0		204	1.0		8	1.0		105	1.0	
Any smoking	23	1.2	0.7–2.1	144	1.0	0.8–1.2	3	0.5	0.1–2.0	53	0.7	0.5–1.0
1–9 cigarettes*	13	1.6	0.8–3.0	65	1.0	0.8–1.4	1	0.4	0.1–3.2	23	0.7	0.4–1.1
10–19 cigarettes*	9	1.2	0.5–2.5	50	0.8	0.6–1.2	1	0.4	0.1–3.5	16	0.5	0.3–0.9
20+ cigarettes*	0	–		7	1.7	0.8–3.7	0	–		4	1.9	0.7–5.2

*Prenatal smoke exposure in late pregnancy only

atopic eczema diagnoses were associated with ORs slightly below unity.

The results for wheezing in our study are consistent with several previous reports [32–37]. A dose–response association with number of cigarettes per day, as found in our cohort, was also observed by Lewis et al. [33] and Neuspiel et al. [32], but not by Lux et al. [36]. Some studies have observed a greater impact of prenatal smoking on asthma or wheezing than postnatal smoking [35, 38–41]. Other studies have observed independent contributions by both time periods of exposure [36, 37, 42]. Although our possibility to separate the effect of prenatal smoking alone was limited, smoke exposure both *in utero* and postnatally showed a stronger association with wheezing than ETS exposure alone. The effect of smoking on hayfever, atopic eczema, and atopy has been more sparsely investigated. A negative association, similar to our findings, between maternal smoking in pregnancy and atopy [43, 44], skin sensitivity [45], atopic eczema [44, 46] or hayfever in relation to maternal smoking of more than 15 cigarettes/day [47], have previously been reported. On the other hand, *in utero* and/or postnatal smoke exposures have been associated with a higher risk of sensitization [48, 49], or no apparent effect on sensitization [50] or atopic eczema [51]. Presence of IgE antibodies in cord blood have also been related to maternal smoking in pregnancy by some authors [52, 53], but not by others [54, 55] or only in infants with a family history of allergy [56].

Our study has the advantage of being based on prospective data and the follow-up period is long, including the entire childhood. The study was also conducted in a time period when smoking during pregnancy was frequent and accepted in Denmark. We therefore believe that under-reporting constitutes a minor problem and that the data we obtained on maternal smoking in pregnancy might be at least as valid a data that could have been obtained from biomarkers that only provide snapshot information [37].

Our study also has limitations. The data on postnatal smoking are rather crude, and the timing of exposure is unknown. The exposure could therefore have occurred after the sensitive periods of lung or immune system development, possibly explaining the low OR obtained for postnatal smoke exposure alone. A certain degree of misclassification of outcome data may also be expected as parents do not always correctly recall medical diagnoses or if the diagnoses, often given by the family physician, were incorrect. Smoking in pregnancy was slightly more common among mothers who did not respond to the follow-up questionnaire. A higher proportion of children in the non-response group also had mothers who smoked more than 10 cigarettes/day late in

pregnancy. However, end-point measures, based upon hospitalization data that were available for all, did not indicate a bias because of differential response to the follow-up questionnaire or loss to follow-up. As we only have data on two time-points, our possibilities to adjust for confounding are limited. The same is also true for genetic factors, as we did not have information about family history of atopy/allergy. Several studies have found estimates for prenatal smoke exposure that differ by family history of atopic/allergic disease [40, 57], although family history had little effect in other studies [39, 47]. A lower impact of heredity on transient wheezing compared with persistent and late onset wheezing has been observed [58]. Nevertheless, we cannot exclude potential confounding by family history, which may be associated with smoking habits. Parental smoking also seems to have a stronger effect on non-atopic wheezy bronchitis than allergic asthma [8]. No information about the date of diagnosis was available in our data, but wheezing before 3 years of age without an asthma diagnosis during childhood is likely to mainly represent children with transient wheezing that is characterized by impaired lung function and lack of atopic markers [59].

Smoking is a well-established determinant of low birth weight and there is also some support for an association between high exposure and pre-term birth [60]. As low and high-birth weight and pre- and post-term birth have also been associated with wheezing, asthma, hayfever and/or atopic eczema [9, 35, 47, 51, 61–63], we stratified for these covariates. However, our results do not suggest that birth weight and/or gestational age are intermediate factors in this cohort.

There was no apparent indication of an effect of maternal smoking on the children's developing immune system that could lead to an increased risk for atopic diseases. On the contrary, the data showed a tendency towards a protective effect of smoking on hayfever, and eczema. One possible explanation for these results could be a bias caused by the lack of control for family heredity, although potential mechanisms for a protective effect, such as alterations in the T lymphocyte system or in the respiratory tract, has been discussed [64]. Concerning wheezing, it seems likely that prenatal smoke exposure may affect lung function negatively and give rise to an increased susceptibility towards factors that may provoke wheezing symptoms, such as viral infections or ETS [21, 36, 65]. It has been suggested that decrements in lung growth and/or development following exposure to maternal smoking may be caused by toxins like nicotine and carbon monoxide [7, 17], and animal studies have implicated nicotine as a key constituent [19, 20]. Our data did not support these findings, but we have limited

power to test the nicotine effect because of small (and perhaps even non-existing) nicotine exposure contrast. Other authors have, however, speculated that it is probably the combination of effects of various toxins that is responsible for reproductive toxicity of cigarette smoke, and not nicotine *per se* [66].

In summary, the dose-response relationship between prenatal maternal smoking and wheezing is consistent with previous literature. No association between asthma and *in utero* smoke exposure was observed, while slightly decreased effect measures for hayfever and atopic eczema were obtained. However, lack of control options for hereditary factors may have affected the results.

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