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Pre- and postnatal exposure to tobacco smoke and respiratory outcomes during the first year

Abstract The different role of prenatal and postnatal exposure to tobacco smoke in respiratory outcomes in infants has not yet been clearly established. Our objective is to assess the effects of these exposures on the risk of respiratory outcomes during the first year of life of infants from a Spanish multicenter cohort study. A total of 2506 women were monitored until delivery. About 2039 infants made up the final population. The outcomes were caused by the occurrence of the following: otitis, cough persisting for more than 3 weeks, lower respiratory tract symptoms (wheezing or chestiness), and lower respiratory tract infections (bronchitis, bronchiolitis, or pneumonia). The relationship between prenatal and postnatal exposure and health outcomes was explored using logistic regression analysis. Maternal smoking during pregnancy increased the odds for wheezing (OR: 1.41, 95% CI: 0.99–2.01) and chestiness (OR: 1.46, 95% CI: 1.03–2.01). Postnatal exposure from fathers was associated with otitis (OR: 1.25, 95% CI: 1.01–1.54). Passive exposure at work of non-smoking mothers during pregnancy was related to cough (OR: 1.62, 95% CI: 1.05–2.51). Exposure to tobacco smoke was related to a higher risk of experiencing respiratory outcomes in young infants. Prenatal exposure was that most clearly associated with the respiratory outcomes analyzed.

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Practical Implications

Exposure to maternal smoking during pregnancy was related to a higher risk of having respiratory outcomes in young infants than those not exposed. Our study supports the evidence of the strongest effects of tobacco smoke when smoking takes place during pregnancy.

Introduction

Maternal tobacco smoke exposure has deleterious effects on the growing fetus, among which are those of a respiratory nature. It has been proved that infants of women smokers tend to have diminished lung function, that can lead to an increased respiratory morbidity after birth (Cheraghi and Salvi, 2009; Burke et al., 2012; Zlotkowska and Zejda, 2005; Moshammer et al., 2006). Moreover, postnatal infant exposure to second-hand smoke implies breathing in thousands of toxic chemicals; therefore, they have double the rate of respiratory disorders than infants living in a smoke-free environment (Braillon et al., 2010). Exposure at home from parents is probably the commonest source of environmental tobacco smoke (ETS) exposure to children (Cheraghi and Salvi, 2009).

Acute respiratory infections are the principal cause of infant morbidity (Kusel et al., 2006). Besides them, wheezing is the most common symptom in the lower respiratory tract during the first year of life (Shah and Sharieff, 2007). Although there is conclusive evidence about the association between tobacco smoke exposure and respiratory symptoms in children, particularly wheezing (Cook and Strachan, 1997), the different role of prenatal and postnatal exposure in respiratory outcomes during the first years of life has not yet been clearly established. Recent studies suggest an independent role of prenatal exposure in the development of lower respiratory tract infections(Friguls et al., 2009; Jaakkola et al., 2006).

INMA (Childhood and the Environment) is a multicenter prospective cohort study aimed at studying prenatal and postnatal environmental exposures and to establish any possible effects on children's development in seven areas of Spain (www.proyectoinma.org). The newest four cohorts within the project followed a common standardized protocol (Asturias, Gipuzkoa, Sabadell and Valencia; Guxens et al., 2012). The objective of this study is to assess the effects of prenatal and postnatal exposure to tobacco smoke on the risk of respiratory outcomes during the first year of life in infants from these four INMA cohorts.

Materials and methods

Study design and population

This study was approved by the hospital ethics committee, and all women gave their informed consent prior to their inclusion in the study. Pregnant women were recruited between 2003 and 2008. The inclusion criteria were at least 16 years of age, singleton pregnancy, enrolment at 10–13 weeks of gestation, no assisted conception, delivery scheduled at the reference hospital, and no communication handicap (Guxens et al., 2012). Of the 2644 women who agreed to participate (51%) in the study, after excluding those women who had a spontaneous abortion or fetal loss, those who withdrew, or were lost to follow-up, a sample of 2506 women was monitored until delivery. Of them, 2360 infants remained in the study after the first year of life. To avoid recall bias, we decided to remove from the analysis those children whose health questionnaires were completed after 30 months of age. Hence, 2039 infants constituted the final population for this study (Valencia $N = 705$, Sabadell = 549, Gipuzkoa $N = 541$, Asturias = 244).

Health outcomes

Information about respiratory health was obtained after the first year of life [mean: 14.8 months, standard deviation: 4.6 (range = 9–30)] through a structured questionnaire – adapted from the questionnaire used in the Asthma Multicenter Infants Cohorts Study (AMICS) – administered to the parents by trained pediatricians (Polk et al., 2004), (nurses in the cohort of Sabadell). Clinicians only collected health information and were not aware of environmental exposures. The outcomes were caused by the occurrence, during the first 12 months of life of the infant, of the following: otitis, cough persisting more than 3 weeks, lower respiratory tract symptoms (wheezing or chestiness), and lower respiratory tract infections (LRTI): bronchitis, bronchiolitis, or pneumonia. 'Wheezing' was defined as whistles coming from the chest, but not noisy respiration because of blocked nose; and 'chestiness' as the sensation of noise or mucosity in the chest. The infants were considered to have ever had lower respiratory tract infections if a doctor had ever diagnosed them with an episode of bronchiolitis, bronchitis or pneumonia, and the same proceeding was followed for identifying otitis. The respiratory outcomes were considered as dichotomous variables (ever had or not).

Exposure assessment

For exposure assessment, we divided the study into two periods: prenatal and postnatal. Smoking habits of the mothers and fathers, during pregnancy and during the first year of life, were compiled by structured questionnaires in the third trimester of pregnancy and at first year visit, respectively.

Infants were considered to be prenatally exposed if their mothers reported daily smoking up to the third trimester (from 635 mothers who smoked at the beginning of pregnancy, 329 continued smoking in the third trimester; 91.4% of women who quitted, did so during the first trimester of pregnancy $n = 280$). Mothers were also asked about exposure to ETS at home, work, restaurants, and leisure places during pregnancy. Exposure at home was considered if mothers reported that their partner, other cohabitants or frequent visitors (≥2

times per week) smoked at home. ETS at work was classified according to mothers' self-report as 'nothing,' 'little,' 'quite a bit,' and 'a lot'. Answers 'quite a bit' and 'a lot' were considered as exposed. Mothers exposed twice a week or more to ETS at restaurants and leisure areas were classified as exposed. The variable 'any ETS' exposure was created to measure if mothers were exposed to at least one of the ETS sources mentioned previously.

Collinearity between prenatal and postnatal tobacco consumption by the mothers and between consumption of both parents was explored.

Cotinine levels were measured in urine collected in the third trimester of pregnancy using the Cotinine 175 Micro-Plate EIA Kit (Ora Sure Technologies, Inc., Bethlehem, PA, USA). Validation of smoking information from the questionnaire throughout analysis of cotinine in urine samples has been explained elsewere (Aurrekoetxea et al., 2013; Iniguez et al., 2012).

Children were considered postnatally exposed if mothers and/or fathers did smoke during the first year of life of their infants. Mothers and fathers were defined as smokers if they smoked one or more cigarettes per day during the first year. Smoking habits of other cohabitants was also considered, but due to the scarce number of cases, this information was not included in the analysis. To explore the potential relationship between the number of postnatal smokers and respiratory effects, a variable considering if only one of the parents, both, or none of them smoked during the first year of life of their infants was created.

The potential effect of the number of cigarettes smoked by the mother per day was also explored, considering the number of cigarettes smoked in three categories (0, 1–10, more than 10).

Covariates and potential confounders

We collected information about potential confounders or effect modifiers by means of questionnaires and from medical records. Variables related to the infants were as follows: sex, preterm delivery (<37 weeks), small for gestational age (SGA) in weight (birth weight below the 10th percentile according to standard percentile charts; Aurrekoetxea et al., 2013), parity, season of birth, duration of breastfeeding, and day care attendance. Parent factors were the following: country of origin, educational level, social class, occupational status of the mother during pregnancy (employed vs. unemployed) and health history of the parents (asthma, rhinitis, atopic dermatitis). Data on indoor environment conditions were as follows: redecoration during pregnancy, age of the house, frequency of cleaning, ventilation, the presence of mold, carpets, cuddly toys, and furry pets during the first year of life. Levels of air pollution during pregnancy (NO_2) were also considered. For this exposure, individual estimates of exposure during pregnancy were obtained using Land Use Regression combining direct measurements and Geographical Information Systems in each cohort (Aguilera et al., 2013; Estarlich et al., 2011). Social class (SC) was classified according to a Spanish adaptation of the British Register General's Social Classification of Occupations (Domingo-Salvany et al., 2000). Class I + II included managerial and senior technical staff, intermediate occupations and commerce managers; class III comprised skilled nonmanual workers; class IV + V included skilled and partly-skilled manual workers and unskilled manual workers.

Statistical methods

Logistic regression analyses were used to estimate odds ratios for the relationship between prenatal and postnatal exposure to tobacco smoke and respiratory outcomes. Multivariate models were built following a two-step procedure. Cohort and child's age at the time of completing the questionnaire were included in all models regardless of their statistical significance. In the first step, a core model was built using all the covariates related to the outcome [likelihood ratio (LR) test P-value <0.20 in the univariate models]. Following a backward procedure, the covariates were excluded if they were not related to the outcome at a P-value of <0.10 based on the LR test. Then, we introduced the exposure variables. Additional confounders were included if they changed the magnitude of the main effects by more than 10% and when they had been previously excluded from the model.

Final models were stratified by cohort for testing the existence of heterogeneity. Meta-analysis techniques were used to obtain combined estimates, and the heterogeneity was quantified by means of the I-squared statistic (I^2; Higgins et al., 2003). The random-effect model was applied if an I^2 above 50% was obtained.

A sensitivity analysis was completed excluding different subgroups of the population: children SGA, preterm, and women that reported not having smoked during pregnancy with cotinine levels >100 ng/ml; for all subjects with full information (i.e., without excluding those who were 30 months) Effect modification by potential protective factors, such as breastfeeding, and potential risk factors, such as levels of air pollution (NO_2), was conducted by means of interactions analysis and stratified analysis when interaction was detected.

Results

Study population characteristics and health outcomes

Study population characteristics according to variables related to smoking status are shown in Tables S1 and S2. Women who remained in the study compared with

those who did not belonged to a higher social class, were more likely to be Spanish, worked during pregnancy in a higher proportion, had a higher prevalence of allergic problems and were more likely to have breastfeed for more than 24 weeks ($P < 0.05$).

Around 36.8% of the children experienced almost one episode of LRTI, 34.7% wheezing or 31.7% otitis. Chestiness was the most frequent health outcome affecting 47.5% of infants, and infants with an episode of cough reached 15.6% (Table 1).

Exposure to tobacco smoke

Maternal smoking up to the third trimester of pregnancy was about 16.4%, reaching 26.3% during the first year. Around 39.0% of partners reported that they smoked during pregnancy and the first year. Mothers of lower SC showed higher risk of smoking in both periods (OR for SC III 2.43, 95% CI 1.37–4.31) and (OR for SC IV+V 3.35, 95% CI 2.00–5.60).Valencia presented the highest rates of smokers for the whole of the study period (Table 1).

Any ETS was reported by 63.1% of non-smoking women, of these 11.6% reported ETS in their places of work. ETS at restoration and leisure places was the most common ETS (44.2%), with least frequency in Asturias (24.1%). Home exposure during pregnancy was 32.7% (Table 1).

Multivariate analyses

Being a boy, having brothers, the absence of breastfeeding or being breastfed for less than 2 weeks, parental history of allergies, not having pets, lower social classes (IV and V vs. I to III), and day care attendance were related to a higher risk of having an episode of some of the respiratory outcomes with a significance level of $P < 0.05$ (data not shown).

Regarding the association between tobacco exposure and infant respiratory outcomes, for most of the studied relations heterogeneity among cohorts was low, so a fixed effects model was used, except for the case of LRTI and prenatal exposure from the mother ($I^2 = 55.8$), and for cough and prenatal and postnatal exposure from the mother (I^2 prenatal = 68.3; and I^2 postnatal = 56.7), where a random effects models was used.

After adjustment, maternal active smoking during pregnancy increased the odds for LRTI (OR 1.40, 95% CI 0.99–1.98), wheezing (OR 1.41, 95% CI 0.99–2.01), and chestiness (OR 1.46, 95% CI 1.03–2.01; Table 2).

Postnatal exposure from fathers increased the odds of otitis (OR 1.25, 95% CI 1.01–1.54) and exposure from the mother was marginally associated with chestiness (OR 1.32, 95% CI 0.98–1.77; Table 2). The exposure to parental smoking reflecting if one, both or neither parent smoked at home during the first year of life, in comparison with the sole consideration of smoking habits of either parent, did not show additional statistically significant differences for the health outcomes analyzed (data not shown). No colineality between prenatal and postnatal consumption of the mother or between parents was found (in all the models VIF -variance inflation factor- was <3).

In the multivariate analysis, ETS at work of non-smoking mothers during pregnancy was related to a

Table 1 Frequency of respiratory outcomes and exposure to tobacco smoke in the study population

	Cohort									
	All		Asturias		Gipuzkoa		Sabadell		Valencia	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
LRTI	749	36.79	114	46.91	212	39.19	219	40.04	204	28.94
Wheezing	708	34.74	135	55.33	194	35.86	198	36.13	181	25.67
Otitis	646	31.74	95	38.93	193	35.81	186	34.00	172	24.40
Cough	310	15.63	41	18.06	123	22.95	91	17.60	55	7.81
Chestiness	957	47.47	160	68.97	177	32.96	323	59.27	297	42.31
Smoking pregnancy (mother)[a]	329	16.43	42	18.42	62	11.76	70	12.89	155	21.99
Smoking first year (mother)	528	26.27	64	27.83	104	19.37	143	26.05	217	31.27
Smoking pregnancy (father)	780	38.94	78	34.21	155	29.41	205	37.75	342	48.51
Smoking first year (father)	781	39.01	78	34.06	167	31.16	218	40.00	318	45.95
Home ETS exposure in pregnancy[b]	653	32.67	73	32.02	76	14.42	181	33.39	323	46.01
Work ETS exposure in pregnancy[b]	233	11.64	15	6.58	37	7.02	60	11.05	121	17.19
ETS exposure in restaurants and leisure places [b]	883	44.22	55	24.12	272	51.61	213	39.30	343	49.00
Any ETS in pregnancy[b,c]	1256	63.05	111	48.68	304	57.69	332	61.37	509	73.13
ETS exposure during first year of life										
One parent	629	31.43	62	27.07	156	29.10	171	31.38	240	34.73
Both parents	336	16.79	40	17.47	57	10.63	93	17.06	146	21.13

LRTI, Lower Respiratory Tract Infection; ETS, Exposure to Environmental Tobacco Smoke.

[a]Continued smoking up to the third trimester of pregnancy.

[b]Mothers that did not smoke.

[c]Mothers exposed to at least one: home, work, and/or restaurants and leisure places.

Table 2 Association between prenatal and postnatal tobacco smoke exposure and respiratory outcomes (n = 1934)

	Tobacco smoke exposure from active smoker parent											
	Mother								Father			
	Pregnancy				Postnatal				Postnatal			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
LRTI	1.37	1.07, 1.75	1.40	0.99, 1.98	1.16	0.95, 1.43	0.98	0.73, 1.32	1.02	0.85, 1.24	1.01	0.82, 1.25
Wheezing	1.65	1.29, 2.12	1.41	0.99, 2.01	1.52	1.23, 1.88	1.23	0.91, 1.67	1.19	0.98, 1.44	1.10	0.88, 1.37
Cough	0.90	0.63, 1.29	0.82	0.51, 1.33	1.07	0.80, 1.42	1.08	0.73, 1.60	0.96	0.74, 1.24	0.97	0.73, 1.29
Otitis	1.07	0.82, 1.38	0.87	0.61, 1.24	1.20	0.97, 1.49	1.17	0.87, 1.57	1.26	1.03, 1.53	1.25	1.01, 1.54
Chestiness	1.67	1.31, 2.14	1.46	1.03, 2.01	1.66	1.34, 2.04	1.32	0.98, 1.77	1.16	0.96, 1.39	1.04	0.85, 1.29

[a]Adjusted for: LRTI (Lower Respiratory Tract Infection): sex of the infant, gestational age, day care attendance at age 1 year, country of origin, maternal education, parity, season of delivery, parental allergy history, pets; Wheezing: sex of the infant, gestational age, day care attendance at age 1 year, maternal education, social class, parity, parental allergy history, any breastfeeding, pets, house cleaning frequency; Cough: sex of the infant, gestational age, day care attendance at age 1 year, social class; Otitis: sex of the infant, gestational age, day care attendance at age 1 year, maternal education, parental allergy history, pets; Chestiness: sex of the infant, gestational age, day care attendance at age 1 year, maternal age, maternal education, parity, pets, damp.

All the models adjusted by cohort, age at completion of the questionnaire, maternal smoking during the first year, paternal smoking during the first year, and maternal smoking during pregnancy (up to the third trimester).

greater odds for cough (OR: 1.62, 95% CI 1.05–2.51). Exposure at home was marginally associated with chestiness: OR 1.28 (95% CI 0.95–1.72; Table 3).

The trend analysis for the amount of cigarettes smoked by mothers per day during pregnancy was marginally related to LRTI and wheezing episodes during the first year (Table 4).

We found a significant interaction in the risk for otitis between having been breastfed and postnatal exposure from the father during the first year (p interaction = 0.03), with an association observed in nonbreastfed infants alone (OR 1.98, 95% CI 1.28–3.06 vs. OR 1.09, 95% CI 0.85–1.40). Another significant interaction in the risk for otitis between having been exposed to high NO_2 levels (more than 27.6 $\mu g/m^3$) and postnatal exposure from the mother during the first year was found (p interaction = 0.04), but the OR was not significant (OR 0.90, 95% CI 0.56–1.50). We also found a modification effect in the risk of wheezing between prenatal exposure to maternal active smoking and social class group (OR for group III, skilled nonmanual workers: 2.16, 95% CI 1.01–4.62). No other significant interaction was found. Dose-response effect during the first year could not be studied because of the differences between the questions about tobacco consumption among cohorts.

Sensitivity analysis showed significant changes in the basal models (>10%) with a change in the direction of the association for cough: for prenatal exposure from the mother and for postnatal exposure from the mother (Figure 1).

Discussion

Exposure to maternal smoking during pregnancy was related to a higher risk of having LRTI, wheezing and

Table 3 Adjusted[a] association between environmental tobacco smoke (ETS) during pregnancy and respiratory outcomes (restricted to non-smoking women during pregnancy) (n = 1617)

	Home		Work		Restaurants and Leisure Places		Any ETS	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
LRTI	1.09	0.80, 1.48	1.15	0.81, 1.64	1.01	0.81, 1.26	1.10	0.87, 1.39
Wheezing	1.17	0.85, 1.60	1.10	0.76, 1.58	1.15	0.91, 1.44	1.16	0.91, 1.47
Cough	0.76	0.50, 1.16	1.62	1.05, 2.51	0.78	0.58, 1.04	0.78	0.58, 1.06
Otitis	1.13	0.84, 1.54	0.93	0.65, 1.33	1.07	0.86, 1.33	1.08	0.86, 1.37
Chestiness	1.28	0.95, 1.72	1.08	0.77, 1.53	1.13	0.91, 1.41	1.17	0.93, 1.48

LRTI, Lower Respiratory Tract Infection; any ETS, any exposure to tobacco smoke.

[a]Adjusted for: LRTI (Lower Respiratory Tract Infection): sex of the infant, gestational age, day care attendance at age 1 year, country of origin, maternal education, parity, season of delivery, parental allergy history, pets; Wheezing: sex of the infant, gestational age, day care attendance at age 1 year, maternal education, social class, parity, parental allergy history, any breastfeeding, pets, house cleaning frequency; Cough: sex of the infant, gestational age, day care attendance at age 1 year, social class; Otitis: sex of the infant, gestational age, day care attendance at age 1 year, maternal education, parental allergy history, pets; Chestiness: sex of the infant, gestational age, day care attendance at age 1 year, maternal age, maternal education, parity, pets, damp.

All the models adjusted by cohort, age at completion of the questionnaire, maternal smoking during the first year, and for paternal smoking during the first year.

Table 4 Association between the amount of cigarettes smoked per day by the mother during pregnancy[a] and respiratory outcomes (n = 1934)

	Number of cigarettes smoked per day	OR	95% CI	
LRTI	0	1		
	1–10	1.38	0.95	2.01
	>10	1.45	0.84	2.50
Wheezing	0	1		
	1–10	1.40	0.96	2.04
	>10	1.44	0.83	2.51
Cough	0	1		
	1–10	0.82	0.49	1.37
	>10	0.83	0.38	1.85
Otitis	0	1		
	1–10	0.954	0.66	1.39
	>10	0.63	0.35	1.14
Chestiness	0	1		
	1–10	1.60	1.10	2.33
	>10	1.07	0.62	1.87

[a]Tobacco consumption reported during the third trimester; LRTI (Lower Respiratory Tract Infection).

Adjusted for: LRTI (Lower Respiratory Tract Infection): sex of the infant, gestational age, day care attendance at age 1 year, country of origin, maternal education, parity, season of delivery, parental allergy history, pets; Wheezing: sex of the infant, gestational age, day care attendance at age 1 year, maternal education, social class, parity, parental allergy history, any breastfeeding, pets, house cleaning frequency; Cough: sex of the infant, gestational age, day care attendance at age 1 year, social class; Otitis: sex of the infant, gestational age, day care attendance at age 1 year, maternal education, parental allergy history, pets; Chestiness: sex of the infant, gestational age, day care attendance at age 1 year, maternal age, maternal education, parity, pets, damp.

All the models adjusted by cohort, age at completion of the questionnaire, maternal smoking during the first year, and for paternal smoking during the first year.

chestiness episodes in the first year of life. ETS at work of non-smoking pregnant women was related to a greater risk of cough. After adjusting by prenatal exposure, postnatal exposure showed results in the same direction but did not achieve statistical significance except for otitis, related to postnatal paternal exposure.

Only a few studies have distinguished between prenatal and postnatal tobacco smoke exposure and their consequences on respiratory outcomes in early life (Burke et al., 2012; Haberg et al., 2007; Latzin et al., 2007; Neuman et al., 2012; Pattenden et al., 2006). Some of them, such as the one conducted by Jaakkola et al., (2006), agree that the adverse effects of tobacco smoke on the lower respiratory tract are strongest when smoking takes place during pregnancy. Wheezing is the commonest respiratory outcome studied in the scientific literature. Our results coincide with Jaakkola's study. Our results for wheezing and prenatal exposure are consistent with those of the meta-analysis obtained by Burke (Burke et al., 2012), in which the result of the pooled analysis was similar to ours (OR 1.41, 95% CI 1.20–1.67 vs. 1.41, 95% CI 0.99–2.01). In Neuman's paper (Neuman et al., 2012), the pooled result in preschool aged children (with ages from 4 to 6) was also similar to ours (OR 1.39, 95% CI 1.08–1.77). For postnatal exposure of the infant from the mother smoking, our results for wheezing differed from those of Neuman, probably due to the effect of the adjustment by prenatal smoking of the mother in our work.

The significant result for chestiness and prenatal exposure is in line with other works (Dong et al., 2007; Stathis et al., 1999). In the study of Dong et al., (2007), authors considered prenatal exposure to be passive exposure and/or active smoking of the mother, but we considered both exposures separately; moreover, Dong et al., did not adjust by postnatal exposure. Despite this, the OR obtained (1.55, 95% CI 1.05–2.29) was similar to ours.

Our results on postnatal smoking from fathers during the first year and the higher risk of otitis agree with other works, so there is likely to be a causal relationship in very young children (Adair-Bischoff and Sauve,

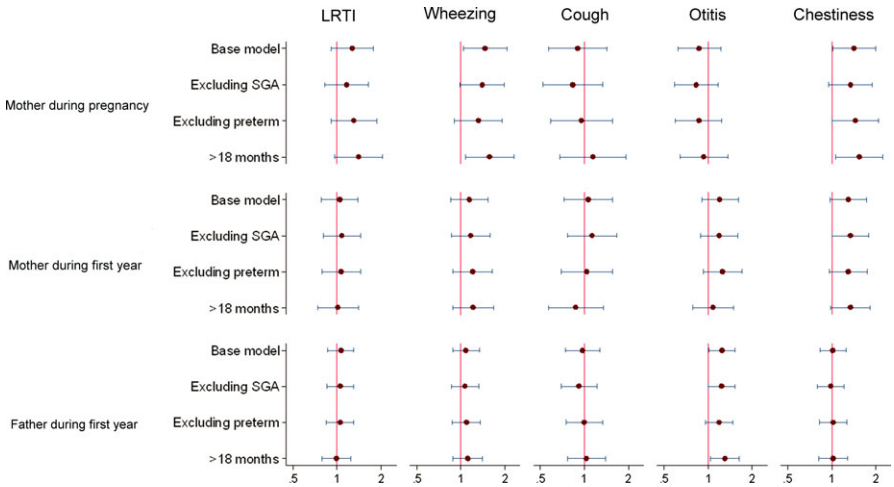

Fig. 1 Sensitivity analysis for the risk of having respiratory outcomes during the first year and tobacco smoke exposure, excluding different subgroups of the population. LRTI, Lower Respiratory Tract Infection; SGA, Small for Gestational Age. All the models adjusted by cohort, age at completion of the questionnaire, maternal smoking during the first year, paternal smoking during the first year, and maternal smoking during pregnancy (up to the third trimester)

1998; Strachan and Cook, 1997). Potential confounding derived from fathers' social class identified in the ALSPAC cohort (Blair et al., 2004) was explored, but this effect was not found. This relationship, if causal, could be related to intensive ETS, despite the intermittent exposure from fathers, whose median of consumption (14 cig. per day) was higher than that of mothers (9 cig. per day). Other studies have suggested a greater importance of prenatal exposure for acute ear infections in children, especially for heavy smokers during pregnancy (more than 20 cig. per day; Stathis et al., 1999).

The increased risk in relationship with levels of air pollution from NO_2 has also been reported, although more studies are needed to analyze interactions between air pollution and tobacco smoke exposure (Heinrich and Raghuyamshi, 2004; Zemek et al., 2010).

Environmental tobacco smoke (ETS) during pregnancy at work was related to a greater risk of cough. Several works make reference to the link between high ETS during pregnancy and asthmatic symptoms during early childhood (Stein et al., 1999). No statistically significant effect for cough was observed for the other prenatal or postnatal passive exposures. In case of parents with allergic antecedents, mothers tended to report more ETS at work (2% more), contrary to the other ETS considered during pregnancy (Table S2). An explanation could be that these mothers generally avoided ETS during pregnancy and when exposure was unavoidable – as could have been in the workplace – got more sensitive to report cough. For the postnatal period, this fact may be due to the fact that exposure to passive smoking in children is one of the factors related to undiagnosed asthma, with cough being the major symptom of those underdiagnosed (Siersted et al., 1998) and that a trend has been identified of under-reporting cough among parental smokers (Dales et al., 1997). In our study, the effect of ETS during pregnancy was explored among non-smoking women.

In prenatally exposed children (from the mother), postnatal exposure from either parent did not significantly increase the occurrence of the respiratory health outcomes analyzed. This result is in accordance with other work (Haberg et al., 2007). The only exception was otitis, as explained previously.

We considered the children to be prenatally exposed if the mother had smoked during pregnancy until the third trimester. By the third trimester, the pulmonary system reaches its full development and deleterious influences could play a major role at this time. Mechanisms of uteroplacental insufficiency have been reported as an explanation for the deleterious effects of smoking upon the fetal/maternal unit during this period (Dempsey and Benowitz, 2001). Also, infants of women smokers are more likely to have diminished lung function soon after birth, which could contribute to the development of acute respiratory outcomes such as infections as its concomitant symptoms (Gilliland et al., 2001). As most of the mothers quitted smoking during the first trimester (91.4%), we conducted the analysis considering exposure up to the first trimester; afterwards, we explored whether there were differences with respect to those who quitted smoking during the first trimester. A reduction in risk was observed for LRTI and chestiness, with a reduction percentages of 32% and 45%, respectively.

Postnatal exposure may contribute to respiratory outcomes during childhood due to allergic inflammatory mechanisms by enhancing Th2 activity. These defence mechanisms could increase mucus secretion and thereby promote chestiness symptomatology; the increase in the production of immunoglobulin E and other cellular, molecular and genetic mechanisms (GSTM1 null genotype; Cheraghi and Salvi, 2009; Panasevich et al., 2010) on how ETS is harmful for the respiratory function have been described. Besides, compared with adults, children inhale much greater volumes of air per kilogram body weight than adults, meaning that they inhale greater amounts of air pollutants (Cheraghi et al., 2009). Furthermore, a recent systematic review affirms with ample evidence that the risk of being infected by the Respiratory Sincytial Virus (RSV), a common cause of acute respiratory outcomes in infants, can be enhanced by ETS exposure, also increasing the severity among hospitalized children (Difranza et al., 2012).

Breastfeeding provides developmental, nutritional, and immunological benefits to the infant. A recent study suggests that the effect is not mediated via avoidance of early infections or atopy but rather through a direct effect on lung growth (Dogaru et al., 2012). In our study, we found a protective effect of having been breastfed and the risk of otitis episodes related to postnatal exposure from father's smoking. The protective effect found in otitis episodes of being breastfed is in accordance with other works (Duncan et al., 1993; Hakansson and Carlsson, 1992). A longer follow-up of the children could clarify if this protective effect remains over time. The modification effect pattern found for social class in the risk of wheezing for prenatal exposure was unclear; that is, the bigger effects were observed among infants from intermediate social class compared with those from upper and lower classes.

This study could have been affected by some limitations such as differences in diagnostic criteria that could have contributed to a misclassification error. However, questionnaire data were collected by trained pediatricians with the same criteria for data collection as studies performed by the AMICS cohort. Dose-response effect for the amount of cigarettes smoked by parents during the first year could not be studied because of the differences between the questions about

tobacco consumption among cohorts. During pregnancy, dose-response effect was explored and did not provide additional information.

This study with a cohort design strengthens the evidence of the role of tobacco smoke exposure in respiratory outcomes in infants. Our results contribute to the growing evidence on the major role of prenatal exposure to tobacco smoke in the respiratory health of children and the relationship between ETS from the father and the increased risk of otitis episodes. Quitting smoking during the first trimester showed a risk reduction of between 30 and 45% for some of the respiratory outcomes studied. These facts should be taken into account for preventive actions as when drafting health programs to encourage the absence of tobacco consumption and passive exposure during pregnancy, even during the earliest stages, and subsequently.

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Conflict of interest

The authors declare that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Study population characteristics according to variables related to smoking status or smoking exposure during pregnancy.

Table S2. Study population characteristics according to variables related to smoking status or smoking exposure during the first year of life.

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