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Maternal smoking during pregnancy and asthma during the first year of life: a comparative study between smokers and nonsmoker mothers

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Abstract

Background: We investigated the relationship between maternal smoking in pregnancy and health care problems in the offspring during the first year of life, particularly asthma.

Material and Methods: A cohort of 648 consecutive infants born at term and alive at Hospital de Sagunto (Valencia, Spain) over one year period was followed for 12 months. Clinical data of the infants were prospectively collected from the database of ambulatory medical records (ABUCASIS) of the Valencia health system.

Results: Smoking during pregnancy was recorded in 164 (25.3%) mothers. During the first year of life, asthma was diagnosed in 101 infants, with an incidence of 15.7%. The diagnoses of asthma (25.6% vs. 12.3%; $P < 0.0001$) and bronchiolitis (44.5% vs. 28.6%; $P = 0.0002$) during the first year of life were more common among infants in the smoking group. The probability of developing asthma during the first year of life was two-fold higher for the male gender and 2.5 times higher when mothers smoked while pregnant. Up to 52% of asthma cases could have been avoided in infants born to smoking mothers if they did not smoke during pregnancy. Infants in the smoking group showed a lower weight and length at birth than infants in the nonsmoking group differences almost disappeared at 6 months and 12 months.

Conclusion: Asthma during the first year of life showed a clear relationship with maternal smoking in pregnancy. Pregnant women should be advised of the significant perinatal risk for respiratory diseases associated with tobacco use.

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Introduction

Smoking during pregnancy has been largely recognized as one of the most important preventable risk factors for adverse fetal and birth outcomes including miscarriage, preterm delivery, low birth weight, poor intrauterine growth, and sudden infant death.^{1,3} In addition to its direct effect on perinatal outcomes, smoking during pregnancy also predisposes the offspring to neurodevelopment deficits, such as behavioral and cognitive disorders, obesity and related comorbidities, impaired cardiovascular health, reduced lung function, and respiratory diseases.^{4,9} Although there is robust evidence of the link between smoking during pregnancy and numerous adverse events, a systematic review and meta-analysis of 259 studies with statistical modeling for 131 countries showed a global prevalence of smoking during pregnancy in the general population of 1.7%, varying from 8.1% in the European region to 0.8% in the African.¹⁰ Moreover, 72.5% of pregnant women who smoked were daily smokers, of which 13.5% were heavy smokers.¹⁰ Data from 1999 to 2006 National Health and Nutrition Examination Survey revealed that 13% of infants in the United States were exposed to maternal smoking,¹¹ and 7.2% of women who gave birth in 2016 smoked cigarettes during pregnancy.¹² Despite public health advice and multiple approaches to smoking cessation, the prevalence of smoking during pregnancy remains high. In developed countries, up to 25% of pregnant women smoke, and 4% or lesser stopped smoking during pregnancy.¹³

The primary effects of maternal smoking on offspring lung function are reduction in forced expiratory flows, decreased passive respiratory compliance, increased hospitalization for respiratory infections, and an increased prevalence of childhood wheeze and asthma.¹⁴ It is well documented that asthma incidence is increased by maternal smoking in pregnancy.^{15,16} A meta-analysis of 79 prospective studies showed that exposure to pre- or postnatal passive smoking increased the incidence of wheeze and asthma in children and young people by at least 20%.¹⁷ A recent observational study showed that maternal smoking during pregnancy was associated with a cumulative incidence of adult-onset asthma (31-46 years) of 5.1% and 8.8% among men and women, respectively.¹⁸ In addition, a pooled analysis of eight European birth cohorts with data of more than 21,000 children showed that maternal smoking during pregnancy was associated with wheeze and asthma in preschool children.¹⁹ In younger children, a meta-analysis of 14 studies showed an increased risk for asthma in children aged ≤ 2 years (odds ratio [OR], 1.85; 95% confidence interval [CI], 1.35-2.53) in association with prenatal tobacco exposure.²⁰

However, only a few studies have recorded the impact of maternal smoking during pregnancy on the development of asthma in offspring during the first year of life. So, this study aimed to compare the incidence of asthma during the first year of life in a cohort of infants born to mothers who actively smoked during pregnancy versus those who did not.

Materials and Methods

Study design and population

This research was a noninterventive observational study of a cohort of consecutive babies born at term and alive

in the Hospital de Sagunto, Valencia, Spain, between September 1, 2017 and September 1, 2018. The primary objective of the study was to compare the incidence of asthma diagnosed in infants of this cohort during the first year of life according to the smoking status of their mothers during pregnancy (smokers vs. nonsmokers). The secondary objectives were to assess the distribution of infants diagnosed with otitis media, atopic dermatitis, pneumonia, bronchiolitis, and food allergy during the first year of life in the groups of smoker and nonsmoker mothers. Because all data analyzed were collected as part of routine diagnostic procedures and stored in clinical databases, approval by the Institutional Review Board was waived for this study.

Data collection

Data of the mothers and neonates at the time of delivery were retrospectively collected from the hospital database, and clinical data of the infants during the first year of life were prospectively collected from the database of ambulatory medical records (ABUCASIS)²¹ of the Valencia Health System, implemented in 2006, as the electronic medical record for primary and specialized outpatient activity.

ABUCASIS comprises of two main modules: the ambulatory information system (SIA) and the pharmaceutical module including pediatric and adult primary care, mental health care, prenatal care, and specialist outpatient services, as well as providing information about dates, visits, procedures, laboratory test results, diagnoses, clinical, and lifestyle information. The SIA module uses the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) for coding diagnoses, and the clinical risk groups (CRG) system to stratify the morbidity of the entire population.

The health program of the autonomous community of Valencia includes scheduled visits during the first and second weeks of life and at 1, 2, 4, 6, and 12 months after birth. The data was collected using the ABUCASIS registry between September 1, 2018 and October 1, 2019.

Study variables

Neonatal and maternal variables included: sex, date of birth, gestational age, type of birth (spontaneous or cesarean section), birth weight, length at birth, birth weight, length at birth percentiles using the 2010 Spanish reference population,²² mother's date of birth; active smoking during pregnancy (yes/no), number of cigarettes/day, type of lactation at the time of hospital discharge (breastfeeding only, mixed feeding, or artificial feeding), maternal work status (paid/unpaid), mother's nationality (Spanish/foreign), and family history of atopy (yes/no).

Variables recorded during the first year of life were as follows: diagnosis of asthma (yes/no) that included ICD-9 code 493 (asthma, bronchospasm, bronchoconstriction crisis, bronchitis, and acute bronchitis), date of the first diagnosis of ICD-9 code 493; number of episodes diagnosed with ICD-9 code 493, diagnosis of atopic dermatitis (yes/no), diagnosis of any food allergy (yes/no), diagnosis of

otitis media (yes/no) and number of events, diagnosis of bronchiolitis (yes/no), date of the first diagnosis of bronchiolitis and number of episodes, diagnosis of pneumonia/bronchopneumonia (yes/no), date of the first diagnosis of pneumonia and number of incidences, diagnosis of a life-threatening episode (yes/no), and weight and length at 6 and 12 months of life.

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables as mean and standard deviation ($\pm$ SD) or median and interquartile range (IQR; 25th to 75th percentile). The distribution of variables in the mothers who smoked or did not smoke during pregnancy was compared with the Mann-Whitney U test for categorical data with two categories or the Kruskal-Wallis test for continuous data with three or more categories.

Logistic regression models with a forward selection strategy were used to assess the relationship between the appearance of a health problem during the first year of life (independent variable) and the presence of maternal and neonatal factors (dependent variables), which included sex, gestational age, type of delivery, birth weight, smoking during pregnancy, number of cigarettes smoked per day, type of lactation, age of the mother, and mother's nationality.

Linear regression analysis assessed the number of incidences of asthma, otitis media, bronchiolitis, and pneumonia during the first year of life according to maternal and neonatal factors. The course of weight and length of infants during the first year of life according to the mother's smoking status in pregnancy was analyzed using linear mixed-effects models, with weight and length as the response variables, and time of measurement (birth, 6 and 12 months) and smoking during pregnancy as explanatory variables. Statistical significance was set at $P < 0.05$. The R statistical package (version 4.0.2; <https://www.R-project.org/>) was used for statistical analysis.

Results

The study cohort included 648 infants (352 males, 296 females), with a mean birth weight of 3276 ± 479 g and length of 47.1 ± 27.9 cm. Smoking during pregnancy was recorded in 164 (25.3%) mothers, with a mean number of 1.7 ± 3.7 cigarettes/day. During the first year of life, asthma was diagnosed in 101 infants, with an incidence of 15.6%. Other diagnoses in infants were bronchiolitis (32.7%), otitis media (14.3%), atopic dermatitis (18.3%), food allergy (4.1%), and pneumonia (1.9%). Table 1 shows the distribution of study variables in the overall study population and according to the mother's smoking status. Infants born to smoking mothers showed a significantly lower birth weight and length at birth versus nonsmoker mothers and received more mixed or artificial feeding frequently. Also, the diagnoses of asthma (25.6% vs. 12.3%; $P < 0.0001$) and bronchiolitis (44.5% vs. 28.6%; $P = 0.0002$) during the first year of life were more common among infants in the smoking group (Table 1). Between-group differences in the occurrence of

pneumonia, atopic dermatitis, food allergy, and changes of anthropometric parameters during the first year of life were not found.

Table 2 shows the distribution of variables in the group of 101 infants diagnosed with asthma versus those without asthma. The group of infants with asthma showed a higher percentage of males, maternal smoking during pregnancy, bronchiolitis, atopic dermatitis, food allergy, and higher weight at 6 and 12 months.

In the multivariable analysis (Table 3), the probability of developing asthma during the first year of life was two-fold higher for males and 2.5 times higher when mothers smoked while pregnant, and the probability of developing otitis media was 1.8 times higher in infants with a family history of atopy. Concerning bronchiolitis, the probability was 2.1 times higher when mothers smoked during pregnancy; it also augmented as birth weight increases and increased as gestation age decreases. The probability of atopic dermatitis was 1.9 times higher in infants with a family history of atopy, and the probability of food allergy was almost three times higher in male versus female infants. Table 4 shows the risk for asthma and bronchiolitis associated with maternal smoking in pregnancy. For every 100 infants exposed to maternal smoking during pregnancy, 13 of them developed asthma, and 16 developed bronchiolitis during the first year of life. About 52% of asthma cases could have been avoided in infants born to smoking mothers if smoking refrained during pregnancy and 22% veif exposure to maternal smoking was eliminated. The corresponding percentages for bronchiolitis were 36% and 12%, respectively. A significantly increased risk for other health problems during the first year of life was not found.

The effect of smoking during pregnancy on anthropometric parameters at birth and 6 and 12 months is shown in Table 5. Although infants in the smoking group showed a lower weight and length at birth than infants in the nonsmoking group, differences almost disappeared at 6 and 12 months (Figure 1). In the mixed-effects models, the birth weight of infants born to smoking mothers was 0.2 kg lower than that of those born to nonsmoking mothers, but this difference was 0.1 kg at 6 months and disappeared at 12 months. Differences in length were 1 cm, 0.4 cm, and 0.2 cm at birth, 6 months, and 12 months, respectively.

Discussion

This study shows that asthma during the first year of life occurred in 25.6% versus 12.3% of infants born to mothers who smoked versus nonsmokers during pregnancy. This difference was statistically significant. Maternal smoking during pregnancy appears to increase the risk for wheeze and asthma even among children who were not exposed to maternal smoking after birth.¹⁹ Our results showing an increased risk for asthma in infants whose mothers smoked during pregnancy agreed with earlier findings of other studies.^{2,7,8,14,19} In a birth cohort of 4089 newborn infants followed for 2 years, when the mother had smoked during pregnancy and stopped after that, an increased risk for recurrent wheezing for up to 2 years of age was recorded (adjusted OR, 2.2; 95% CI, 1.3-3.6); maternal

Table 1 Distribution of study variables in the overall population and according to the mother's smoking status during pregnancy.^a

Variables	All infants (n=648)	Smoking status during pregnancy		P value
		Nonsmokers (n=484)	Smokers (n=164)	
Neonatal and maternal factors				
Gender				
Male	352 (54.3)	266 (55.0)	86 (52.4)	0.587
Female	296 (45.7)	118 (45.0)	78 (47.6)	
Gestational age, months, median (IQR)	39 (38–40)	39 (38–40)	39 (38–40)	0.154
Type of delivery				
Normal	516 (79.6)	381 (78.7)	135 (82.3)	0.369
Cesarean section	132 (20.4)	103 (21.3)	29 (17.7)	
Birth weight, g, mean±SD	3276.1 (479.0)	3329.2 (477.6)	3119.3 (449.1)	<0.0001
Birth weight percentile, median (IQR)	49 (24.5–76.0)	56 (28–79)	34.5 (17.0–63.2)	<0.0001
Length at birth, cm, mean±SD	49.6 (2.1)	49.9 (2.0)	48.9 (2.1)	<0.0001
Length at birth percentile, median (IQR)	47 (23–69)	50 (28–72)	35.5 (11.7–57.3)	<0.0001
Maternal age, years, mean±SD	32.4 (5.8)	32.6 (5.9)	31.9 (5.4)	0.085
Mother's nationality				
Spanish	489 (75.5)	343 (70.9)	146 (89.0)	<0.0001
Foreign	159 (24.5)	141 (29.1)	11 (11.0)	
Mother's work status				
Unpaid	230 (35.5)	180 (37.2)	50 (30.7)	0.155
Paid	417 (64.4)	304 (62.8)	113 (69.3)	
Type of lactation				
Breastfeeding	405 (62.6)	319 (66.1)	86 (52.4)	0.006
Mixed feeding	59 (9.1)	42 (8.7)	17 (10.4)	
Artificial feeding	183 (28.3)	122 (25.3)	61 (37.2)	
Family history of atopy	159 (24.6)	120 (12.3)	39 (23.9)	0.834
Diagnosis during the first year				
Asthma	101 (15.7)	59 (12.3)	42 (25.6)	<0.0001
Episodes, number, mean ±SD	0.4 (1.14)	0.28 (0.93)	0.76 (1.55)	<0.0001
Otitis media	92 (14.3)	66 (13.7)	26 (15.9)	0.517
Bronchiolitis	211 (32.7)	138 (28.6)	73 (44.5)	0.0002
Pneumonia	12 (1.9)	7 (1.5)	5 (3.1)	0.192
Atopic dermatitis	118 (18.3)	91 (19.0)	27 (16.5)	0.559
Food allergy	26 (4.1)	21 (4.4)	5 (3.1)	0.646
Anthropometric data during the first year				
At 6 months				
Weight, g, mean±SD	7713.3 (958.1)	7734.6 (958.2)	7653.7 (958.4)	0.544
Weight percentile, median (IQR)	42 (22–64)	41 (23.0–64.7)	43.5 (20–64)	0.480
Length, cm, mean±SD	67.0 (2.6)	67.1 (2.5)	66.9 (2.7)	0.170
Length percentile, median (IQR)	50 (28.72)	50 (30–73)	45 (25.0–67.7)	0.186
At 12 months				
Weight, g, mean±SD	9715.1 (1174)	9717.3 (1165.3)	9708.7 (1204.7)	0.865
Weight percentile, median (IQR)	34 (14–58)	34 (15–58)	33.5 (14.0–57.5)	0.942
Length, cm, mean±SD	75.6 (3.1)	75.6 (2.8)	75.4 (3.6)	0.449
Length percentile, median (IQR)	50 (24–75)	50 (25–77)	48 (21–74)	0.487

^aData as frequencies and percentages in parenthesis unless otherwise stated. IQR, interquartile range.

smoking during pregnancy but no exposure to environmental tobacco smoke also increased the risk for doctor's diagnosed asthma up to 2 years of age (adjusted OR, 2.1; 95% CI, 1.2–3.7).²³ In a longitudinal study of lung function data from 5933 participants in the Children's Health Study, in utero exposure to maternal smoking and early asthma diagnosis was associated with higher decreases of pulmonary function parameters.²⁴ In fact, pregnancy represents

a unique opportunity for smoking cessation and showed that up to 45% of women quit before their antenatal visit or during pregnancy, but based on nicotine biomarker data, about 25% of women report their smoking status at prenatal visits.²⁵ In our study, there was also a disparity between the percentage of smoking mothers (25.3%) and the few numbers of cigarettes that they reported to smoke on daily basis (mean, 1.7 ± 3.7 cigarettes/day). Smoking during

Table 2 Distribution of variables in infants with and without a diagnosis of asthma during the first year of life. ^a

Variables	Diagnosis of asthma		P value
	No (n=543)	Yes (n=101)	
Gender			
Male	281 (51.7)	69 (68.3)	0.002
Female	262 (48.3)	32 (31.7)	
Smoking during pregnancy			
No	421 (77.5)	59 (58.4)	0.0001
Yes	122 (22.5)	42 (41.6)	
Cigarettes per day, mean $\pm$ SD	1.39 (3.5)	2.61 (4.6)	0.0014
Episodes of asthma, mean $\pm$ SD	0	2.71 (1.6)	<0.0001
Bronchiolitis	116 (21.4)	94 (93.1)	<0.0001
Episodes of bronchiolitis, number, mean $\pm$ SD	0.21 (0.42)	1.02 (0.4)	<0.0001
Atopic dermatitis	90 (16.6)	28 (27.7)	0.001
Food allergy	18 (3.3)	8 (7.9)	0.049
Weight at 6 months, g, mean $\pm$ SD	7665.3 (944.4)	7945.7 (993.6)	0.006
Weight at 12 months, g, mean $\pm$ SD	9650.6 (1154.0)	10054.6 (1231.8)	0.005
Weight percentile at 12 months, median (IQR)	33 (14–55)	38 (19.0–68.5)	0.03

^aOnly variables with statistical significance are shown; data as frequencies and percentages in parenthesis unless otherwise stated. IQR, interquartile range.

Table 3 Results of multiple regression models.

Variables	Coefficient (β)	Standard error	P value	Odds ratio (95% CI)
Model 1. Asthma during the first year of life ^a				
Female gender	−0.738	0.233	0.0002	0.48 (0.29–0.75)
Smoking during pregnancy	0.934	0.229	<0.0001	2.54 (1.61–3.98)
Model 2. Otitis media during the first year of life ^b				
Family history of atopy	0.586	0.244	0.01	1.79 (1.10–2.89)
Model 3. Bronchiolitis during the first year of life ^c				
Smoking during pregnancy	0.756	0.199	0.0001	2.13 (1.44–3.15)
Birth weight	0.0008	0.0002	0.0001	1.00 (1.00–1.00)
Gestational age	−0.177	0.067	0.008	0.83 (0.73–0.95)
Model 4. Atopic dermatitis during the first year of life ^d				
Family history of atopy	0.635	0.220	0.004	1.88 (1.21–2.89)
Model 5. Food allergy during the first year of life ^e				
Females	−1.071	0.473	0.023	0.34 (0.12–0.81)

^aOptimal cutoff, 0.119; sensitivity, 0.85; specificity, 0.37; area under the ROC curve, 0.651.

^bOptimal cutoff, 0.121; sensitivity, 0.79; specificity, 0.42; area under the ROC curve, 0.639.

Model 3: ^cOptimal cutoff, 0.267; sensitivity, 0.82; specificity, 0.42; area under the ROC curve, 0.657.

Model 4: ^dOptimal cutoff, 0.171; sensitivity, 0.54; specificity, 0.61; area under the ROC curve, 0.590.

^eOptimal cutoff, 0.048; sensitivity, 0.69; specificity, 0.60; area under the ROC curve, 0.666.

CI, confidence interval; ROC, receiver operating characteristic curve.

pregnancy is a particularly stigmatized activity, which may lead to hidden smoking and a barrier to obtaining actual data on questioning for smoking habits.²⁶

In the logistic regression analysis, we found that the probability of developing asthma during the first year of life was 2.5 times higher in women who smoked while pregnant. Concerning the attributable risk for exposure to maternal smoking, 52% of cases of asthma in infants could have been avoided if mothers did not smoke during pregnancy, a clinically relevant finding of the study supports the need to carry out actions to help women stop smoking during pregnancy.

The diagnosis of bronchiolitis was also significantly more common in infants born to smoking mothers (44.5%) than in nonsmokers (28.6%). Moreover, bronchiolitis was diagnosed in 93.1% versus 21.4% of infants with or without asthma. Smoking during pregnancy was a variable independently associated with bronchiolitis in the logistic regression analysis. Here, 36% of cases of bronchiolitis could have been avoided in the absence of exposure to maternal smoking during pregnancy. These results are consistent with other studies showing that prenatal smoking increases the risk for severe bronchiolitis in children.^{27,29}

Table 4 Risk for asthma and bronchiolitis during the first year of life associated with maternal smoking during pregnancy.

Risk measure (95% CI)	Asthma	Bronchiolitis
Attributable risk ^a	13.32 (6.02–20.62)	15.88 (7.27–24.49)
Attributable risk in the population ^a	3.39 (0.00–7.46)	4.03 (0.00–9.45)
Attributable risk fraction in exposed infants	52 (31.63–66.30)	35.68 (19.73–48.46)
Attributable risk fraction in the population	21.63 (8.95–32.53)	12.34 (5.20–18.95)

^aPer 100 population units.
CI: confidence interval.

Atopic dermatitis and food allergy were also significantly more common in infants diagnosed with asthma. Although, both conditions were unrelated to the smoking status of mothers during pregnancy. The interrelationship of atopic disorders has been extensively investigated. Numerous studies have provided evidence of the strong associations between atopic dermatitis, allergic rhinitis, and asthma (the so-called “atopic march”).^{30–32}

Statistically significant differences in anthropometric variables, with lower birth weight and length in infants born to smoking mothers, were observed in this study with solid evidence of reduced fetal measurements (reduced head size and femur length)³³ and low birth weight provided by multiple studies including systematic reviews and meta-analysis. These effects may be attenuated if mothers quit or reduce cigarette consumption during pregnancy. In a meta-analysis of 30 studies, active maternal smoking was associated with low birth weight (OR, 2.00; 95% CI, 1.77–2.26).³⁴ In a cross-sectional study of full-term infants, birth weight decreased with increased daily number of cigarettes. Compared with infants born to non-smoking mothers, mean birth weight was 320g lower in infants whose mothers smoked 6 to 10 cigarettes per day and 435g lower in infants whose

mothers smoked 11 to 40 cigarettes per day during pregnancy.³⁵ However, present study did not examine the relationship between cigarettes smoked per day and reduced birth weight.

Our study has some limitations. First is the difficulty to make an asthma diagnosis in the first years of life. Even though using the expression asthma is controversial in this age, it is widely accepted that asthma is a heterogeneous syndrome that can be clinically diagnosed in preschool children.³⁶ Second, all the diagnoses recorded in the database were made by a pediatrician and codified with code 493 of ICD-9. The possibility of the inaccuracy of the diagnosis could be equally distributed between smokers and non-smoker's mothers.

Unfortunately, the number of cigarettes smoked per day was inaccurate in this study because the data was self-reported. Hence, we were not able to examine a dose-response effect.³⁷ Future studies should also include the paternal smoking status in the maternity reports. Exposure to paternal smoking is independent of maternal smoking during pregnancy and is linked to an increased risk of wheezing in children.^{38,39}

The precise effect of pre- and postnatal exposure to smoking habit on the offspring is difficult to identify as women who smoke during pregnancy continue smoking after delivery. Hence, this information was uncollected.

Conclusion

Although our findings are limited by a single-center design and retrospective maternal and neonatal data collection based on a hospital database, asthma, and bronchiolitis during the first year of life showed a clear relationship with maternal smoking in pregnancy. About 52% of cases of asthma could have been avoided in the absence of fetal exposure to maternal smoking. Pregnant women need to be informed of the significant perinatal risk for respiratory diseases associated with tobacco use. Clinicians should individualize care by offering cessation-aid services and resources and provide all support necessary for smoking cessation success.

Table 5 Changes in birth weight and length during the first year of life according to the smoking status of the mother during pregnancy.

Parameters	Smoking during pregnancy		Median difference
	No (n=484) median (IQR)	Yes (n=164) median (IQR)	
Weight, g			
At birth	3310 (3020–3650)	3125 (2798–3362)	185
At 6 months	7645 (7.132–8.299)	7635 (6898–8268)	10
At 12 months	9670 (8900–10390)	9650 (8950–10450)	20
Length, cm			
At birth	50 (49–51)	49.0 (47.4–50.1)	1
At 6 months	67.0 (65.6–69.0)	66.5 (65.0–68.5)	0.5
At 12 months	75.5 (73.5–77.8)	75 (73–78)	0.5

IQR, interquartile range (25th–75th percentile).

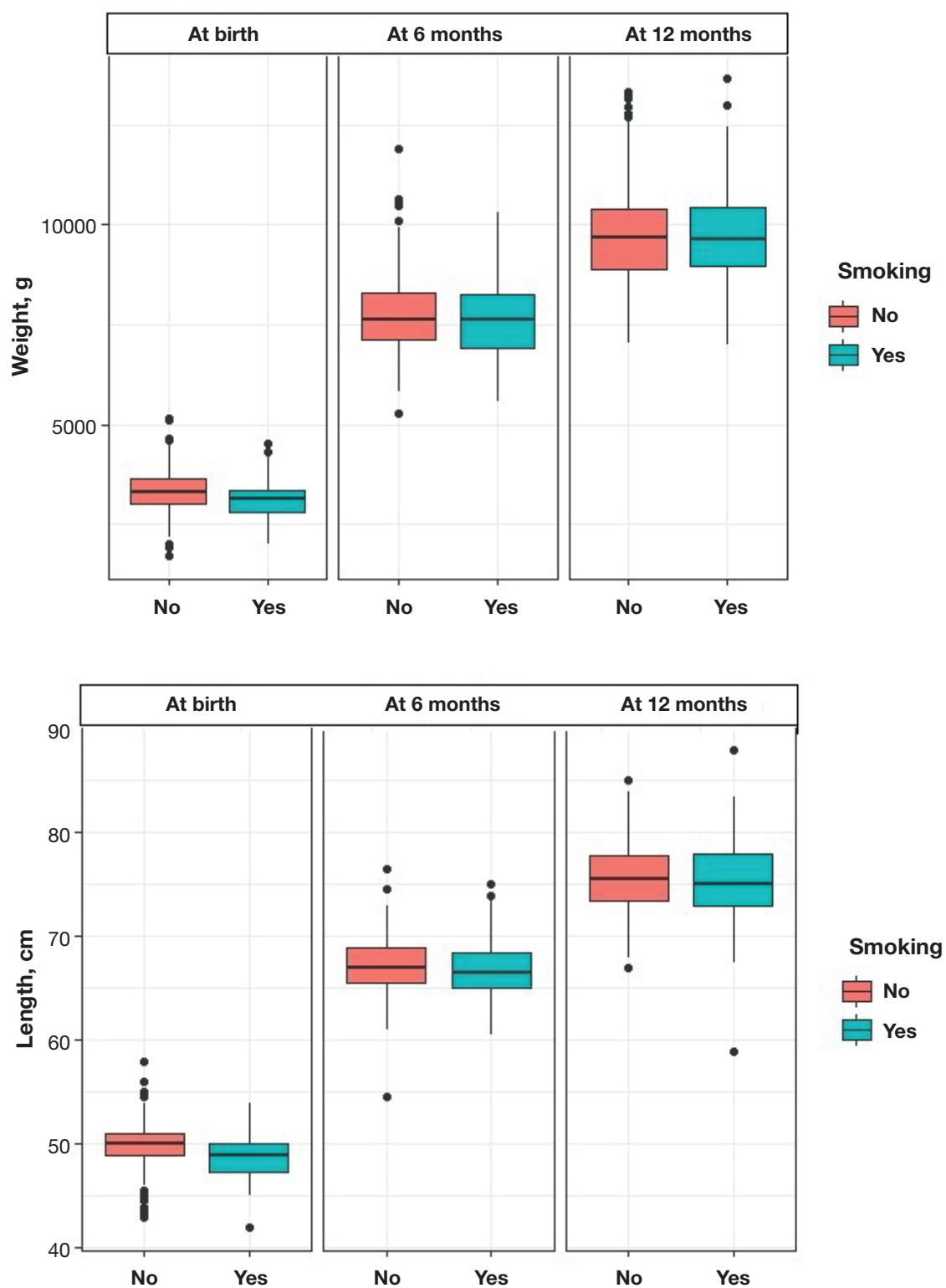


Figure 1 Changes of infants' weight (upper panel) and length (lower panel) during the first year of life according to the smoking status of the mother during pregnancy.

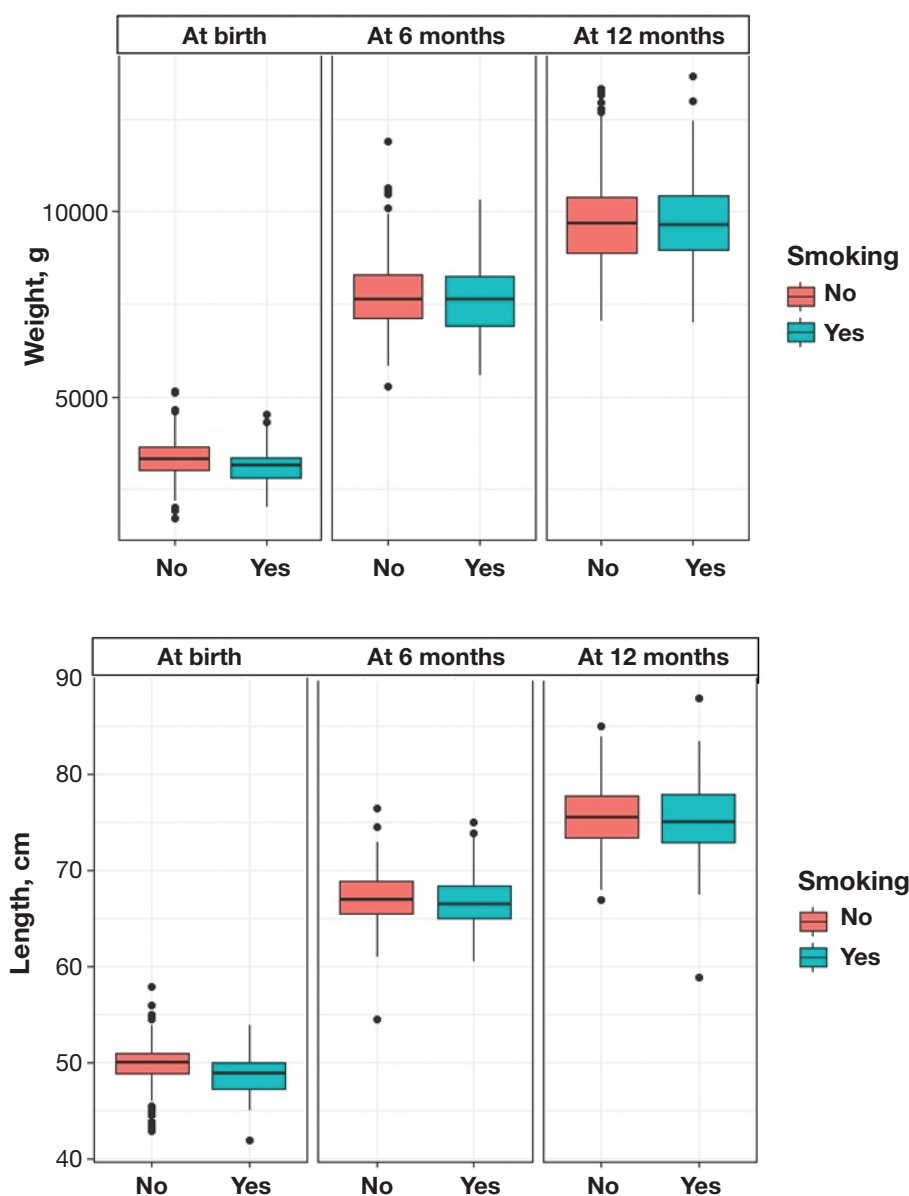


Figure 1 (Continued)

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Conflicts of Interest

No potential conflict of interest was reported by the authors.

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