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A longitudinal study on the effects of maternal smoking and secondhand smoke exposure during pregnancy on neonatal neurobehavior

Carmen Hernández-Martínez [a], Victoria Arija Val [b], Joaquín Escribano Subías [c], Josefa Canals Sans [a,*]

[a] Universitat Rovira i Virgili, Research Center for Behavioral Assessment (CRAMC), Department of Psychology, Ctra. Valls S/N, 43007, Tarragona, Spain
[b] Universitat Rovira i Virgili, Department of Preventive Medicine and Public Health, C/Sant Llorenç, 21, 43201, Reus, Spain
[c] Sant Joan University Hospital, Unit of Pediatrics, Av/ Josep Laporte, 1, 43204, Reus, Spain

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ABSTRACT

Maternal smoking during pregnancy is one of the most modifiable causes of morbidity and mortality for both pregnant women and their fetuses. The long-term effects of prenatal exposure to smoke on child behavior and development have been the subject of more extensive research than have the short-term effects. Therefore, the aim of this work is to examine the effects of smoke exposure during pregnancy on neonatal behavior, including in our study a group of mothers exposed to secondhand smoke. The behavior of 282 healthy full-term newborns was assessed using the Neonatal Behavior Assessment Scale (NBAS) at 48–72 h of life. Sixty-two mothers smoked during pregnancy (no mother smoked more than 15 cig/day) and 17 were exposed to secondhand smoke. After adjusting for socio-demographic and obstetric factors, both newborns whose mothers smoked and those whose mothers were exposed to secondhand smoke showed significantly lower scores in the habituation cluster than non-smoking mothers. Exposure to secondhand smoke was also related to lower motor system cluster scores as well as some supplementary items and the newborns of smoking mothers showed significantly lower scores in the state regulation cluster and in some items of the state organization cluster than the newborns of non-smoking mothers. We conclude that active and passive smoking during pregnancy affects several aspects of neurobehavioral development, regardless of socio-demographic, obstetric and pediatric factors.

1. Introduction

Tobacco use is a clearly toxic and teratogenic human phenomenon that causes detrimental effects on virtually every stage and facet of development and threatens the survival of the neonate [1]. For this reason, maternal smoking during pregnancy (MSDP) has been recognized as a highly important modifiable risk factor associated with adverse perinatal outcomes [2]. In spite of the well-established negative consequences, epidemiological studies have shown that between 11 and 30% of pregnant women smoke or are exposed to secondhand smoke (SHS), and this rate increases to 50% in high-risk samples, including young, poor and urban populations [3]. Even so, in many industrialized countries, the rates of women who actively smoke appear to have peaked and have now begun to decline [2]. In Spain, 43.5% of women between 25 and 44 years old smoke, but during pregnancy this percentage decreases to 26.6% [4]. This may be due to the pervasive medical recommendations and societal sanctions against maternal smoking during pregnancy. Although women tend to decrease their regular cigarette consumption when they become pregnant, it is important to study the effects of exposure to small amounts of cigarette smoke on fetal development, because when a pregnant woman smokes, the concentrations of nicotine on the fetal side of the placenta generally reach levels 15% higher than maternal levels. Therefore, even low levels of cigarette smoke may expose the fetus to harmful amounts of nicotine [5,6].

Compelling evidence has been published about the causal effects of pre-pregnancy and pregnancy tobacco exposure on various reproductive and obstetric conditions including delay in conception [7], ectopic pregnancy [8], stillbirth [9], placental pathologies [10], preterm and very preterm delivery [11], low birthweight [12] and Sudden Infant Death Syndrome (SIDS) [13]. Numerous studies have also shown that MSDP is related to cognitive, emotional, temperamental and behavioral problems throughout the life of the child. The problems most closely related to MSDP are negativity [14], difficult temperament [15], attention disorders, hyperactivity, and behavioral problems [16–18], although some evidence suggests an association with substance use problems as well [19]. During early infancy, the associations found between MSDP and behavioral disorders are more inconsistent. Some studies have revealed associations between MSDP and infant irritability, alterations in crying behavior and soothability, and increased muscle tone assessed by structured, examiner-administered neurobehavioral examinations [20–25], whereas others have not found any relationship [26,27]. Stroud

* Corresponding author. Tel.: +34 977 257 894; fax: +34 977 558 088.
E-mail address: josefa.canals@urv.cat (J. Canals Sans).

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et al. [20] studied a sample of 962 mother–newborn pairs of whom 61% smoked (46% smoked fewer than 20 cigarettes per day; 15% smoked more than 20 cigarettes per day) and assessed the neonatal behavior in the immediate postpartum period using the Graham–Rosenblith Behavioral Examination. These authors found that MSDP significantly influenced infant irritability and muscle tone. Specifically, neonates exposed to heavy maternal smoking showed greater irritability compared to neonates exposed to moderate maternal smoking or unexposed neonates. Moreover, neonates exposed to both heavy and moderate maternal smoking were also more hypertonic than unexposed neonates [20]. Five studies using a small sample have studied the relationship between MSDP and neonatal behavior assessed by the Neonatal Behavior Assessment Scale (NBAS) [26–30]. Some found that smoke-exposed infants scored lower on some orientation, soothability and autonomic nervous system (ANS) items [28–30]. Others found trends but not significant correlations, whereas the remaining studies did not find any effects of smoking on neonatal behavior [26,27]. These studies reveal that the effects of MSDP on neonatal behavior are still uncertain.

Although most attention has been focused on the effects of active smoking, exposure to SHS may affect more than 126 million non-smoking Americans, including adults and children [31]. In fact, according to the WHO, 40% of children, 33% of male non-smokers and 35% of female non-smokers were exposed to second-hand smoke [32]. Several studies have revealed a relationship between the exposure to SHS and reduced birthweight, preterm birth or SIDS as well as childhood cancer [31,33,34], and other studies have shown that infants exposed to environmental tobacco experience more behavioral problems [35]. Nevertheless, little evidence is available on the association between SHS exposure during pregnancy and child neurodevelopment, particularly at early stages of development. In fact, only the study published by Lee et al. [36] has investigated the effect of maternal SHS exposure on infant cognitive development. Those authors found that this prenatal condition was associated with a significant decrease in cognitive function in 6-month old infants. Other authors have suggested that more research into the effect of passive and active maternal smoking during pregnancy on neonatal behavior is needed [30].

In summary, although the effects of MSDP on obstetric and pediatric disorders are well-established, the effects on neonatal behavior are still poorly understood. Moreover, few studies have explored the effects of SHS exposure on neonatal behavior. Therefore, the aim of our study is to investigate the effects of active and passive maternal smoking during pregnancy on neonatal neurobehavior assessed using the NBAS in a homogeneous sample of healthy newborns to provide new data on the effects of MSDP and SHS exposure on infant behavior in a non-risk sample.

2. Methods

2.1. Sample

Participants were recruited between 2004 and 2009 by the gynecologists of the Obstetrics and Gynecology Unit of Sant Joan University Hospital in Reus (Spain). The initial eligibility criteria for participation in the study were that the women had to be pregnant, over 18 years of age and at no more than 11 weeks of gestation. During the five years of recruitment, all pregnant women who underwent gynecological examinations at Sant Joan University Hospital in Reus were evaluated as potential participants. Approximately 344 pregnant women met the initial eligibility criteria and were invited to participate in the study. Additional eligibility criteria included being healthy, with a singleton pregnancy, and having no chronic illness affecting nutritional status such as diabetes type I, Crohn's and celiac diseases. Of the 344 women that were invited to participate in the study, ten were excluded because they did not meet the additional eligibility criteria (four were diabetics, three had recently had major gastric surgery, and three more were pregnant with twins). Of the 334 remaining women, 15 refused to participate, 22 miscarried, five terminated their pregnancy due to major fetal malformations, four did not complete the study due to a change of residence and two gave birth at another hospital. Therefore, in the end a total of 282 (82% of those invited) mother–child dyads completed the study.

Of the 282 healthy full-term newborns, 139 were boys and 143 were girls. The mothers' mean age was 31.61 (SD = 4.29). The mean gestational age was 39.33 weeks (SD = 1.38), and the mean birthweight was 3237.79 g (SD = 406.37). 56.1% (n = 149) of the women were multiparous and none of the children had medical problems in the immediate postpartum period.

Of all the pregnant women studied, 6% (n = 17) were of low socioeconomic status, 55% (n = 155) were of middle socioeconomic status and 39% (n = 110) were of high socioeconomic status.

None of the pregnant women consumed alcohol or illicit drugs during pregnancy, a total of 72% (n = 203) of the mothers did not smoke during pregnancy. Of the exposed mothers, 6% (n = 17) were exposed to SHS and 22% (n = 62) smoked during pregnancy. Of the smoking mothers, 12.4% (n = 35) smoked between 1 and 5 cigarettes per day, 6.7% (n = 19) smoked between 6 and 10 cigarettes per day and 2.8% (n = 8) smoked 10 to 15 cigarettes per day. None of the mothers smoked more than 15 cigarettes per day.

2.2. Instruments

Neonatal behavior was assessed using the *Neonatal Behavior Assessment Scale* (NBAS) [37]. This scale allows the examiner to interact with the newborn and assess his or her behavior and responses. In this work, we used the NBAS clusters defined by the authors: the habituation cluster (the ability to respond to and inhibit discrete stimuli while asleep), the social-interactive (orientation) cluster (the ability to attend to visual and auditory stimuli and the quality of overall alertness), the motor system cluster (motor performance, quality of movement and muscular tone), the state organization cluster (arousal and state liability), the state regulation cluster (the ability of the newborn to regulate his or her state when faced with increasing levels of stimulation), and the autonomic system cluster (assessing signs of stress related to homeostatic adjustments in the central nervous system).

Data on prenatal toxic habits were collected during pregnancy by means of a survey specifically designed for this study. We asked the participants about their smoking habits as well as their consumption of alcohol and other drugs. Specifically, smoking habits were determined by asking the following questions: *Do you smoke?* If the response was negative, we included the pregnant woman in the *non-smoking* group. If the response was affirmative, we asked about the woman's current smoking habits and placed the participants in five categories based on the number of cigarettes smoked per day: 1–5, 6–10, 11–15, 15–20 and more than 20. SHS exposure was determined by asking the following questions: *Do you usually smell tobacco smoke at home? Do you usually smell tobacco smoke at your workplace?* Non-smoking pregnant women that responded affirmatively to either of these two questions were included in the *SHS exposure* group. We also recorded whether the mother had quit smoking when she got pregnant and 11 mothers informed that they quit smoking before 9 weeks of gestation.

The socio-demographic data of the sample was determined using the *Hollingshead index* (Hollingshead, 1975, unpubl. observ.). This index allows the social status of each individual to be determined by categorizing his or her occupation into one of nine categories (from unskilled work to highly skilled work) and his or her level of education into one of seven categories (from non-completed primary education to completed higher education). The status score is estimated by multiplying the occupation scale value by a weight of five and the education scale value by a weight of three and then combining the two scores. For this study, we determined family socioeconomic status by combining the data obtained from the father and the mother. The scores

range from 0 to 66, therefore, to obtain three categories (low, middle and high) we considered scores lower than 22 to be low socioeconomic status, scores between 23 and 44 to be middle, and over 44 as high.

Maternal anxiety was assessed by the *State-Trait Anxiety Inventory* (STAI) [38]. This self-questionnaire assesses anxiety and provides a State Anxiety score (the level of transient and situational anxiety) and a Trait Anxiety score (the level of dispositional and stable trait anxiety). In this study, we used the Trait Anxiety score because it represents a stable measure of anxiety.

2.3. Procedure

The study was approved by the Research and Ethics Committee of Sant Joan University Hospital in Reus (Spain) and informed consent was obtained from the participants.

The mothers were asked about their smoking habits, alcohol consumption and other toxic habits at three different times (in the second and third trimester and in the postpartum period) by members of the research team. Data confidentiality was ensured to encourage the participants to provide candid responses.

Neonatal behavior was assessed at 48–72 h after birth by two trained examiners (JC and CHM) in a hospital room with optimal physical conditions. All parents were present during the assessment. The examination was completed in 25–35 min and was performed midway between feedings. The inter-rater reliability (Kappa Index) was 0.94.

2.4. Statistical analysis

An analysis of variance was performed to study differences between non-smokers and women who quit smoking once pregnant (11 mothers) and revealed that the maternal, infant and socio-demographic characteristics of the mothers who had stopped smoking due to pregnancy and the outcome variable (neonatal behavior) of their neonates were comparable with the non-smoking group; therefore these mothers were included in the non-smoking group.

An analysis of variance and a Chi Square test were used to study the differences in maternal and infant characteristics between smoking, SHS exposed and non-smoking groups. A regression analysis was also conducted to adjust the NBAS scores for significant covariates. These covariates were selected from demographic (mother's age, socioeconomic status, infant gender), psychological (trait anxiety) and medical (birthweight, gestational age, APGAR scores, parity and mode of delivery) characteristics and were included if they differed significantly between smoking groups or were significantly correlated with the NBAS. On the basis of this criterion, the covariates included were socioeconomic status, birthweight, and gestational age. Based on these analyses, adjusted NBAS scores were obtained and the variance of the adjusted NBAS scores was analyzed between smoking groups using non-parametric methods due to the abnormal distribution of these scores. The Mann–Whitney method was used to obtain p values and the Bonferroni correction was applied to control the increase in type I error because of a multiple comparisons; so, the level of significance used has been 0.02. The scores that were not normally distributed are summarized by median and interquartile ranges.

The data were analyzed using the SPSS 17.0.

3. Results

3.1. Sample characteristics according to MSDP habits

The demographic and obstetric characteristics of the sample according to smoking group are shown in Table 1. In general, mothers exposed to SHS were found to have poorer obstetric characteristics than both non-smokers and smokers, but only birthweight was significantly lower. A significant correlation was found between smoking groups and socioeconomic status.

3.2. Relationship between MSDP and NBAS clusters and item scores

The multiple comparisons within smoking groups have shown that children of women who smoked during pregnancy or were exposed to SHS scored significantly lower in the habituation cluster ($p = 0.02$ and $p = 0.02$ respectively) than children of mothers in the non-smoking group. However, the children of women who were exposed to secondhand smoke during pregnancy scored significantly lower in the motor system cluster ($p = 0.01$) and in some supplementary items such as examiner facilitation ($p = 0.01$), robustness and endurance ($p = 0.01$) and state regulation ($p = 0.02$). Children of women who smoked during pregnancy achieved lower scores in the state regulation cluster ($p = 0.02$), in the inanimate visual item of the orientation cluster ($p = 0.01$), in some items of the state organization cluster such as peak of excitement ($p = 0.01$) and liability of state ($p = 0.01$) and in the examiner's emotional response ($p = 0.02$) supplementary item. These results are shown in Table 2.

4. Discussion

We assessed a non-risk sample of newborns of mostly non-smoking mothers and of mothers who smoked in small doses. We additionally considered a group of mothers who were exposed to secondhand smoke. Mainly, our results show that children prenatally exposed to tobacco smoke had poorer habituation, state organization and regulation capabilities, as well as poor motor maturity.

22% of the mothers in our sample smoked during their pregnancies, a ratio similar to the overall ratio in Spain as cited by Nerín and Jané [4], and in the United States of America [3]. However, in Spain smoking was allowed in closed public places such as restaurants and coffee shops until January of 2011 and, in fact, smoking was allowed in the workplace (both public and private), as well as on public transport and in cultural centers until 2007. Therefore, pregnant women would very likely have been involuntarily exposed to smoke, making it important to determine whether that type and level of exposure can affect fetal development and neurodevelopment. For this reason, we decided to study the group of SHS exposed mothers separately.

Our results show that, after adjusting for confounding variables, the newborns of smokers and SHS exposed mothers achieved lower scores in the NBAS habituation cluster, demonstrating difficulties in their ability to respond to and inhibit discrete stimuli while asleep. On the other hand, considering the smoking groups separately, newborns of SHS exposed mothers scored lower than children of non-smoking mothers in the motor system cluster and some supplementary items such as examiner facilitation, robustness and endurance and state, demonstrating difficulties in motor maturity and self-regulation behaviors. These results can be reinforced by the lower birthweight found in the children prenatally exposed to SHS. Previously, Rubin et al. [39] found a similar result, but with our data we cannot make conclusions about the lower birthweight due to the methodological limitations because the SHS exposed group is too small and we need to control more variables. On other hand, children of smoking mothers achieved lower scores in the state regulation cluster, in some items of the state organization cluster and in the examiner's emotional response supplementary item, showing more excitability and self-quieting difficulties than newborns of non-smoking mothers. In summary, we can conclude that the exposure to tobacco smoke during pregnancy is related to poorer neonatal behavioral outcomes. It is important to highlight these results because our society considers SHS exposure to be less dangerous than active smoking, but our results suggest that the two forms of exposure are harmful.

Most of these results coincide with those obtained by Mansi et al. [30] and Oyemade et al. [29], who used the NBAS to assess neonatal behavior and found differences in neonatal state organization and regulation capacities and in motor maturity. Other authors using other scales have also found that infants of smoking mothers are more excitable and hypertonic [20,22]. However, these studies did

Table 1
Sample characteristics according to smoking habits.

	Non-smoking (n = 203)	SHS exposure (n = 17)	Smoking (n = 62)	p value
	*Mean (SD) #Median (IQR)	*Mean (SD) #Median (IQR)	*Mean (SD) #Median (IQR)	
Mother's age*	31.77 (4.1)	29.94 (4.4)	31.56 (4.8)	0.24
Birthweight*	3279.34 (382.4)	3072.94 (372.1)	3146.94 (467.4)	**0.01**
Gestational age (weeks)*	39.43 (1.3)	38.91 (1.2)	39.15 (1.6)	0.16
Trait anxiety*	15.21 (8.4)	16.79 (7.7)	17.31 (8.2)	0.21
1-min APGAR score#	9.00 (0.0)	8.50 (1.0)	9.00 (0)	0.83
5-min APGAR score#	10.00 (0.0)	9.50 (1.0)	10.00 (0.0)	0.41
10-min APGAR score#	10.00 (0.0)	10 (0.0)	10.00 (0.0)	0.67
	% (n)	% (n)	% (n)	p value
Gender				
Boys	48.8 (99)	52.9 (9)	50.0 (31)	0.94
Girls	51.2 (104)	47.1 (8)	50.0 (31)	
Parity				
Primiparous	54.6 (111)	41.1 (7)	51.6 (32)	0.55
Multiparous	45.4 (92)	58.9 (10)	48.4 (30)	
Mode of delivery				
Normal[a]	61.1 (124)	70.5 (12)	62.9 (39)	0.73
Difficult[b]	38.9 (79)	29.5 (5)	37.1 (23)	
Socioeconomic status				
Low	20.3 (10)	0 (0)	11.3 (7)	0.02
Medium	51.2 (104)	64.7 (11)	64.5 (40)	
High	28.5 (89)	35.3 (6)	24.2 (15)	

IQR: Interquartile range
[a] Normal delivery: Vaginal delivery without medical problems.
[b] Difficult delivery: Instrumental delivery by forceps, vacuum or cesarean section.
Level of significance: 0.02.

not differentiate between mothers who actively smoked and those exposed to SHS.

There are three possibilities to explain the prenatal, perinatal and postnatal outcomes related to prenatal smoke exposure. Firstly, MSDP interferes with normal placental function such that the metabolites of cigarette smoke pass through the placenta and act as vasoconstrictors reducing uterine blood flow to the fetus by up to 38% [40,41]. Therefore, the fetus is deprived of nutrients and oxygen [42], causing interferences with the adequate development of the central nervous system (CNS) and fetal intrauterine growth. Secondly, nicotine is also a neuroteratogen that impacts the brain at critical developmental stages [43,44]. In utero, nicotine targets nicotinic acetylcholine receptors in the fetal brain to change the pattern of cell proliferation and differentiation so fetal nicotine exposure upregulates nicotinic cholinergic receptor binding sites causing abnormalities in the development of synaptic activity [45]. These mechanisms can explain the short- and long-term effect of MSDP on neonatal behavior and on both child cognitive and behavioral problems. However, several authors have hypothesized that the isolated symptoms (irritability and hypertonicity) observed in the newborns of mothers who smoke heavily can also be explained by the nicotine withdrawal syndrome as a result of chronic prenatal exposure to high levels of tobacco smoke [21,46,47]. To investigate this assertion, Stroud et al. [21] assessed the behavior of 56 infants at 10 and 27 days post-partum (past the half-life of nicotine) using the NICU Network Neurobehavioral Scale (NNNS), which was developed to assess the effects of prenatal drug exposure in infants, and found that infants of smoking mothers remained more irritable and had more self-regulation difficulties even when the withdrawal period had already passed, indicating that these persistent dysregulation symptoms can represent early vulnerability for later neurobehavioral deficits [21].

Our study has various strengths, but it also has some limitations. For example, our group of SHS exposed mothers is small, which may impede the extrapolation of our results. Although we assessed maternal smoking habits using self-report surveys, other studies have validated such surveys using saliva cotinine as a marker and their results suggest that self-reported smoking exposure during pregnancy is highly accurate [48–51]. Some of the strengths of our study include the analysis of a group of pregnant women exposed to SHS, something that few previous studies have taken into account, which may have affected those earlier results. Second, we used a follow-up method which entailed recruiting pregnant women before 13 weeks of gestation and assessing several aspects of their lifestyles (including their smoking habits) at three points during their pregnancies. That allowed us to corroborate the information provided by the mothers given that, in some cases, they might say that they smoke less than they really do. The third strength we think is important is the homogeneity of our sample. The smoking mothers were of comparable parity, age, mode of delivery and gestational age and the medical characteristics of the infants were similar to the other two groups. The differences between the groups were in the socioeconomic status and infant birthweight, but the NBAS scores were adjusted for these variables.

In summary, the infants of mothers exposed to SHS were found to have a lower habituation capacity and reduced motor maturity, were more excitable, irritable and had more difficulties with self-quieting. All these differences support the neurotoxic effects of prenatal tobacco exposure rather than the signs of nicotine withdrawal syndrome because the mothers were not heavy smokers. As Stroud et al. [21] conclude, these neonatal characteristics may represent the initial signs of later persistent behavioral dysregulation leading to long term impairments such as attention disorders, hyperactivity and behavioral problems, as seen in previous studies. In relation to long term effects, the NBAS has been described as a good tool by which detect infant emergent capacities and disabilities in the neonatal period [52], allowing infants at risk for later behavioral problems to be identified [53]. Our results are important because the NBAS scores of the infants in our study that are related to MSDP are consistent with the NBAS scores that other studies have related to later behavioral problems in high-risk and low-risk neonates throughout their childhood. Motor maturity, state regulation and neonatal habituation have been shown to be good predictors of an infant's fussy, difficult temperament at 4 months old [54] and of behavioral and psychological problems at 6 years old [53,55]. The combination of several prenatal risk factors including smoke exposure can result in an immature, less developed and excitable infant requiring more external regulation. Moreover, these risk factors will probably continue to be present during the postnatal period, affecting critical periods of infant development.

Table 2
Adjusted NBAS clusters and item scores according to smoking groups.

	Non-smoking[a]	SHS exposure[b]	Smoking[c]	p[a–b#]	p[a–c#]	p[b–c#]
	Median (IQR)	Median (IQR)	Median (IQR)			
Habituation cluster	7.61 (0.4)	7.42 (0.3)	7.46 (0.5)	0.02	0.02	0.51
Response decrement light	7.93 (0.2)	7.83 (0.3)	7.80 (0.1)	0.49	0.01	0.55
Response decrement rattle	7.85 (0.3)	7.87 (0.3)	7.95 (0.2)	0.78	0.04	0.42
Response decrement bell	8.32 (0.6)	7.80 (0.5)	7.92 (0.2)	0.10	0.01	0.33
Res. decre. tactile stimul. foot	6.42 (0.6)	6.05 (0.6)	6.23 (0.7)	0.06	0.12	0.39
Orientation cluster	5.47 (0.3)	5.45 (0.3)	5.45 (0.3)	0.38	0.92	0.50
Animate visual	5.72 (0.5)	5.48 (0.4)	5.58 (0.8)	0.03	0.24	0.39
Animate visual–auditory	6.45 (0.2)	6.34 (0.2)	6.40 (0.3)	0.03	0.26	0.26
Inanimate visual	4.65 (0.3)	4.50 (0.4)	4.50 (0.5)	0.03	0.01	0.86
Inanimate visual–auditory	5.77 (0.1)	5.76 (0.1)	5.76 (0.1)	0.20	0.94	0.46
Animate auditory	6.18 (0.4)	6.13 (0.6)	6.08 (0.4)	0.60	0.11	0.79
Inanimate auditory	5.96 (0.7)	5.89 (0.5)	6.02 (1.0)	0.83	0.53	0.63
Alertness	5.80 (0.5)	5.69 (0.7)	5.75 (0.5)	0.55	0.06	0.83
Motor system cluster	5.31 (0.2)	5.24 (0.2)	5.25 (0.3)	0.01	0.08	0.34
General tone	5.26 (0.2)	5.16 (0.3)	5.22 (0.3)	0.49	0.09	0.43
Motor maturity	6.08 (0.2)	5.93 (0.2)	6.04 (0.3)	0.01	0.18	0.19
Pull-to-sit	6.11 (0.4)	6.05 (0.5)	6.00 (0.5)	0.26	0.26	0.84
Defensive movements	5.35 (0.1)	5.35 (0.1)	5.32 (0.2)	0.67	0.51	0.97
Activity level	4.00 (0.1)	4.01 (0.1)	3.99 (0.8)	0.67	0.47	0.49
State organization cluster	3.72 (0.1)	3.76 (0.1)	3.73 (0.1)	0.14	0.24	0.56
Peak of excitement	3.08 (0.1)	3.13 (0.1)	3.14 (0.1)	0.09	0.01	0.45
Rapidity to build up	3.24 (0.3)	3.46 (0.4)	3.39 (0.5)	0.07	0.03	0.83
Irritability	5.20 (0.3)	5.27 (0.3)	5.18 (0.3)	0.22	0.90	0.31
Liability of state	3.73 (0.1)	3.70 (0.1)	3.67 (1.7)	0.18	0.01	0.36
State regulation cluster	5.61 (0.1)	5.59 (0.1)	5.58 (0.1)	0.09	0.02	0.99
Cuddliness	6.68 (0.1)	6.68 (0.1)	6.68 (0.1)	0.39	0.62	0.82
Consolability	5.86 (0.1)	5.81 (0.1)	5.82 (0.1)	0.37	0.41	0.64
Self-quieting	4.66 (0.1)	4.67 (0.1)	4.70 (0.1)	0.71	0.02	0.37
Hand-to-mouth	5.36 (0.1)	5.35 (0.1)	5.34 (0.1)	0.12	0.01	0.49
ANS cluster	7.19 (0.1)	7.15 (0.3)	7.26 (0.4)	0.10	0.85	0.20
Tremulousness	7.89 (0.3)	7.79 (0.3)	7.93 (0.5)	0.07	0.86	0.18
Starless	8.64 (0.1)	8.71 (0.1)	8.67 (0.1)	0.32	0.19	0.73
Labiality of skin color	5.39 (0.3)	5.32 (0.3)	5.44 (0.4)	0.11	0.72	0.25
Supplementary items						
Quality of alertness	5.08 (0.4)	4.89 (0.4)	4.99 (0.6)	0.31	0.15	0.40
Cost of attention	5.52 (0.2)	5.45 (0.1)	5.48 (0.1)	0.12	0.07	0.42
Examiner facilitation	5.25 (0.4)	5.07 (0.4)	5.19 (0.6)	0.01	0.30	0.18
General irritability	5.55 (0.2)	5.44 (0.2)	5.50 (0.4)	0.07	0.36	0.31
Robustness and endurance	5.46 (0.6)	5.12 (0.6)	5.30 (1.0)	0.01	0.06	0.21
State regulation	5.95 (0.3)	5.85 (0.3)	5.93 (0.5)	0.02	0.40	0.17
Examiner's emotional response	5.99 (0.5)	5.86 (0.5)	5.79 (0.5)	0.18	0.02	0.94

Scores adjusted by socioeconomic status and neonatal birthweight.
ANS: Autonomous Nervous System.
IQR: Interquartile range.
[#] Level of significance: 0.02.

In conclusion, low levels of maternal smoking during pregnancy and SHS exposure are related to neonatal behavioral impairments, which in turn are related (according to other studies) to later behavioral problems. Thus, primary care physicians, obstetricians, pediatricians and health professionals in general should encourage the mothers and their close relatives to cut back their smoking by including them in smoking cessation programs and informing them of the effects of involuntary smoke exposure to prevent direct damage to fetal and infant development.

Conflict of interest

We have no conflict of interest.

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