The Effect of Prenatal Smoke Exposure on Child Neuropsychological Function: a Prospective Mother-Child Cohort Study

Prenatal smoke exposure and child neurodevelopment

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This work was supported by the Comisión Interministerial de Ciencia y Tecnología, SAF2005-05096; Instituto de Salud Carlos III, Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica y el Instituto de Salud Carlos III – Fondo de Investigaciones Sanitarias (cofinanced by FEDER), 10/00035, 13/02500; 16/00506; IISPV 2010/21; Centros de Investigación Biomédica en Red CIBERobn; AGAUR SGR (2009-1237, 2014-332); Italfarmaco S.A. Spain.

The study is registered in clinicaltrials.gov: NCT01778205
https://clinicaltrials.gov/ct2/show/NCT01778205.

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Objective: To study prospectively the effect of prenatal smoke exposure (PSE) on child neuropsychological function and intelligence quotient (IQ) taking into account obstetric, neonatal and sociodemographic confounders.

Background: PSE has been associated with behavioural problems, higher risk of neurodevelopment disorders, impaired executive function, and lower IQ at the childhood. However, other studies did not found these associations, which disappear after adjustment for potential confounders.

Methods: A cohort of 248 mother-children was followed from the first trimester of pregnancy to when the children were 7.5 years old. PSE was recorded during pregnancy by questionnaire and plasma cotinine. The Wechsler Intelligence Scale for Children (WISC-IV), the Neuropsychological Assessment of Executive Functions for Children (ENFEN) and the School Neuropsychological Maturity Questionnaire (CUMANES) were administered at the age of 7.5 years. The effect of PSE on child IQ and neuropsychological function was assessed with ANCOVA, adjusting for several obstetric, neonatal and sociodemographic factors.

Results: Exposed children scored lower on interference compared to unexposed children ($F = 4.1$; $p = .008$). The results also suggest a possible detrimental effect on inhibitory control function assessed by colour making trail subtest of the ENFEN ($F = 2.2$; $p = .097$). Second-hand smoke (SHS) exposure or smoking only during first trimester did not differ of being unexposed.

Conclusion: PSE had little effect on child neuropsychological outcome and was limited to mental flexibility. Nevertheless, these findings support further efforts aimed at encouraging mothers to quit smoking in pregnancy.

Keywords: prenatal smoke exposure; second-hand smoke exposure; executive function; neuropsychological function; intelligence quotient

Introduction

Prenatal smoke exposure (PSE) has been associated with adverse effects on neonatal and infant behaviour (Hernández-martínez, Arija, Escribano, & Canals, 2012). Other studies have shown that the adverse effects of PSE persist throughout childhood. It has been associated with behavioural problems in the children such as high activity level, impulsivity and aggressiveness (Desrosiers et al., 2013), and increased risk of neurodevelopment disorders such as the Attention Deficit and Hyperactivity Disorder (Joelsson et al., 2016). It has also been associated with impaired executive function involving inhibitory control, ability on problem solving and mental flexibility (Boucher et al., 2014; Cornelius, Rayan, Day, Goldschmidt, & Willford, 2001; Julvez et al., 2007; Rose-jacobs et al., 2017); and lower Intelligence Quotient (IQ) scores (Holbrook, 2016; Rahu, Rahu, Pullmann, & Allik, 2010). Additionally, the effect on IQ, seems to persist to late adolescence (Rose-jacobs et al., 2017). Other studies suggest that rather than general IQ, PSE affects specific cognitive areas such as arithmetic and specific verbal abilities (Anthopolos, Edwards, & Miranda, 2013; Cho, Frijters, Zhang, Laura L. Miller, & Gruen, 2013).

Studies of the effects of prenatal exposure to second hand smoke (SHS) (in mothers that are passive smokers) on child neurodevelopment, suggest that it is as harmful as maternal active smoking (Mohamed, Loy, Lim, Al Mamun, & Jan Mohamed, 2018). Regarding the period of prenatal smoke exposure, (Gatzke-Koop & Beauchaine, 2007) have reported that the second and third trimester of pregnancy is the most vulnerable period for child neurodevelopment compared to early pregnancy.

Other studies, however, observed no effect of PSE on child IQ (Yang, Decker, & Kramer, 2013) and neuropsychological outcomes such as verbal abilities, visuo-spatial skills, verbal and visual memory, processing speed, resistance to interference and motor

dexterity (Kafouri et al., 2009). This lack of consensus may be explained by differences in the methodological approaches, neuropsychological assessment batteries used and confounders considered (Clifford, Lang, & Chen, 2012). Several studies have shown that the associations between PSE and neuropsychological function and IQ disappear after adjustment for potential confounders (Batty, Der, & Deary, 2006). Neuropsychological function and IQ may be affected by factors such as family sociodemographic level, maternal education and psychopathology, obstetrical conditions, postnatal smoke exposure and nutritional status during childhood, among others.

PSE affects Central Nervous System development by different mechanisms. It has been related to altered placental function in which increased uterine and umbilical artery resistance impairs blood flow from the mother to the foetus reducing oxygen and nutrient supply to the foetus (Albuquerque, Smith, Johnson, Chao, & Harding, 2004). As a result, foetal intrauterine growth and central nervous system development are impaired (Roos et al., 2015). Furthermore, nicotine is a neuroteratogenic substance, which activates cholinergic receptors and consequently alters cell proliferation, differentiation and myelination processes during early brain development (Dwyer, Broide, & Leslie, 2008).

The aim of the present study is to investigate the effect of PSE (including active and passive smoke exposure) on child neuropsychological function and IQ taking into account potential confounders. We hypothesized that, after adjustment for several obstetric, neonatal and sociodemographic covariates, children exposed prenatally to tobacco smoke would obtain lower scores in neuropsychological function and IQ tests than unexposed children. We expected to find a different effect depending on the

prenatal period affected by the exposure, with a greater effect on neuropsychological outcomes following active exposure throughout the entire pregnancy.

Method

Study design and sample

A prospective cohort study from before 12 weeks of pregnancy to 7.5 years of age in the children was carried out. It was approved by the Research and Ethics Committees of the participating hospitals and all participants provided their signed informed consent.

Pregnant women, aged 18 years and over, with a viable foetus confirmed by ultrasound scan and that provided a fasting blood sample before 12 gestational weeks were invited to participate in the study. The exclusion criteria were multiple pregnancy or chronic illness affecting maternal nutritional status during pregnancy. The final sample included 248 mothers and their offspring.

Variables and Instruments

Outcome variables: child neuropsychological function

Executive function was assessed using the *Neuropsychological Assessment of Executive Functions for Children* ('Evaluación Neuropsicológica de las Funciones Ejecutivas en Niños'; ENFEN) (Portellano, Martínez-Arias, & Zumárraga, 2009). ENFEN was designed to assess maturity and cognitive performance in activities related to different components of executive functions for children aged 6 to 12 and provided different scores on: *Verbal Fluency*, *Planning*; *Interference* and *Trail Making Test* (TMT). *Verbal Fluency* includes phonological and semantic, assessing expressive language, vocabulary span, verbal and semantic memory, working memory and crystallized intelligence. *Planning test* require the ability to identify and organize a sequence of events to achieve a specific goal, assessing mental flexibility, spatial orientation, motor

coordination, prospective and operative memory and sequencing ability. *Interference* (measured with Stroop Test) measuring selective and sustained attention, inhibition ability and mental flexibility. Finally, the *TMT* was composed by two forms: *grey TMT*, providing information regarding spatial perception, visual-motor coordination, perceptual speed, logical reasoning, ability to anticipate and planning; and the *Color TMT*, which is more complex than *Grey TMT*, additionally, assess mental flexibility, working memory, inhibition and attention problems.

The *School Neuropsychological Maturity Questionnaire* ('Cuestionario de Madurez Neuropsicológica Escolar'; CUMANES) (Portellano, Mateos, & Matrinez, 2012) has been developed to perform a neuropsychological evaluation of a broad repertoire of higher mental functions which influence the process of learning and behaviour in children aged 7 to 11. We administered the CUMANES to assess the children's *visual* and *auditory memory*.

The *Wechsler Intelligence Scale for Children* (WISC-IV) (Wechsler, 2005) was used to assess total IQ and several neuropsychological functions. The WISC-IV can be administered to children aged 6 to 16 years and provides 5 standardized composite scores (Mean=100; SD=15): *Verbal Comprehension,* assessing the child's verbal abilities and providing a valid measurement of verbal reasoning ability and acquired knowledge of their environment; *Reasoning Perceptive* assessing perceptual reasoning, spatial organization and integration of visual and motor ability that implies managing abstract concepts, rules, generalizations and logical relationships; *Working Memory* assessing attention span, concentration, the ability to retain certain information temporarily, work and operation to generate a result; *Processing Speed* assessing the child's ability to explore, sort or discriminate simple visual information quickly and

efficiently; and *Total IQ* representing total child intelligence. For this study, each subscale composite score was used.

Exposures: prenatal smoke exposure

Information regarding smoking exposure during pregnancy was collected from 3 sources. Firstly, participants were interviewed by a non-clinical member of the study team at 20 and 32 gestational weeks and smoking habits recorded by questionnaire. The number of cigarettes smoked per day during each trimester of pregnancy was recorded. The time of pregnancy that smoking was abandoned was recorded for participants that gave up during pregnancy. Participants were also asked whether they were habitually exposed to other people smoking at home or at work during pregnancy to classify for passive smoking exposure. Plasma cotinine concentration was determined during the 1st and 2nd trimesters and in umbilical cord plasma. Further information regarding active smoking during pregnancy was available from the prenatal clinical records.

Participants meeting the 3 conditions of reporting no smoking or exposure to passive smoking during pregnancy by questionnaire, plasma cotinine concentration <1 ng/ml at all time points and recorded as non-smoker in the prenatal clinical history were classified as non-smokers. Participants that declared exposure to passive smoking during pregnancy by questionnaire or had plasma cotinine concentration >1 ng/ml and <10 ng/ml at any of the time points, were classified as SHS exposure. Participants with self-reported smoking during the first trimester of pregnancy only and/or first trimester plasma cotinine concentration >10 ng/ml, followed by plasma cotinine concentration <1 ng/ml during the 2nd trimester and in the umbilical cord, were classified as first-trimester smokers. Self-reported smoking throughout pregnancy or plasma cotinine concentration >10 ng/ml (Florescu et al., 2009) during the 1st and 2nd trimesters and in

the cord, or smoking habit declared in the prenatal clinical records were classified as smokers throughout pregnancy.

Potential cofounders

Individual variables: Birth weight (gr; measured with a SECA electronic weighing scale with a precision of 10 grams), gestational age at birth (completed weeks), child sex and age (in months) at follow-up. Breastfeeding duration was collected retrospectively and corroborated with information recorded at routine paediatric check-ups during infancy. First trimester maternal plasma cobalamin concentration was determined by microbiological assay (*Lactobacillus leichmannii)* in Bevital AS, Norway (www.Bevital.no). Mothers with plasma vitamin B_{12} in the lowest tertile (≤ 319 pmol/L) were classified as having low plasma vitamin B_{12} status compared to mothers with plasma cobalamin > 319 pmol/L.

At the follow-up stage, Body Mass Index (BMI) and head circumference were measured by members of the study team trained in anthropometry and also used as covariates. Parents answered the Spanish version of the Child Behavior Checklist for ages 6 – 18 (CBCL/6-18) (Achenbach & Rescorla, 2001), that provides information regarding externalizing, internalizing and total psychological problems in the children.

Socio-familiar variables: Data regarding both paternal and maternal employment and education were collected when the children were 7.5 years of age. Employment was categorized based on (Alvarez-Dardet, Alonso, Domingo, & Regidor, 1995) criteria. Familial socioeconomic status (SES) was obtained using the Hollingshead Four Factor Index of Socioeconomic Status (Hollingshead, 2011). Postnatal smoke exposure was also obtained by a sociodemographic questionnaire completed by the children's parents.

Statistical analyses

ANOVA and Chi Square tests were used to analyse the differences between the four prenatal smoke exposure (PSE) groups in relation to neonatal characteristics and sociodemographic and descriptive data of the children.

To test our hypothesis, we performed a univariate analysis of covariance (ANCOVA) for each subscale of ENFEN, CUMANES and WISC-IV, adjusting for low vitamin B12 status during early pregnancy, sex of children, birth weight, gestational age, duration of breastfeeding, family SES level, postnatal tobacco smoke exposure, as well as psychological problems, age, BMI and head circumference in the children at follow up. Taking into account the high number of comparisons involved we use a α= .01 to control the increase of experimentalwise error rate. We performed the Tukey test for pairwise comparisons for the variables that reached significance using ANCOVA. Data were analysed using SPSS Statistics 25.0 (IBM, 2017).

Results

Characteristics of participants and differences between smoke exposure groups

56.5% (n = 140) of the pregnant women did not smoke during pregnancy, 15.3% (n = 38) were passively exposed to tobacco smoke, 12.5% (n = 31) quit smoking during pregnancy and 15.7% (n = 39) smoked throughout pregnancy. Of the smokers, 48.5% (n = 16) reported smoking 1-5 cigarettes/day, 42.4% (n = 14) reported smoking 6-10 cigarettes/day and 9.1% (n = 3) reported smoking more than 10 cigarettes/day.

Perinatal, sociodemographic and developmental data according to PSE group are reported in Table 1. Mean birth weight and gestational age were within the normal range. 50.8% of the offspring were boys (n = 122), 33.9% were born by eutocic delivery (n = 84) and the mean maternal age at birth was 32.02 years (SD = 4.07). No differences between PSE groups have been found for theses variables. The average

duration of breastfeeding was for 6.93 months (SD = 9.56). Breastfeeding duration in the offspring of mothers that smoked throughout pregnancy and only during the first trimester was shorter than in the offspring of non-smoking mothers.

BMI in the children was slightly above the 50th percentile according to the World Health Organization (WHO) tables. Anthropometrical measurements, psychological problems, prevalence of chronic illnesses in the children, and parental mental health at the follow-up stage did not differ between the PSE groups. Only 5.2% (n = 13) of the children were from families with low SES. Differences in SES were found between the PSE groups. The 40.7% (n = 101) of the offspring were exposed to tobacco smoke at the follow-up; predominantly in offspring who were prenatally exposed.

Effect of PSE on neuropsychological outcomes at the childhood

Table 2 shows the neuropsychological outcomes from the ENFEN, CUMANES and WISC-IV subscales according to PSE group using ANCOVA and adjusting for potential confounding variables. Mean scores of WISC-IV in the total sample for all subscales and for total intelligence were above the normal range (IQ score 90 – 109). Smoking throughout pregnancy was only associated with the Interference subscale of ENFEN ($p<.01$). The Tukey test showed that children of mothers that smoked throughout pregnancy scored lower on Interference compared to non-smokers ($p <.01$), smokers only during the first trimester ($p< .05$) and passive smokers ($p<.05$). A tendency for obtaining higher scores in inhibitory control (in Color TMT) was observed in unexposed children compared to others PSE groups.

Discussion

This prospective study assesses the effects of prenatal smoke exposure (PSE) on neuropsychological function and IQ in a psychosocially low-risk sample of children aged 7.5 years, after adjusting for potential confounding factors which may influence child neurodevelopment. We set out to examine the specific effects of different types of PSE: passive smokers, smoking only during the first trimester and smoking throughout pregnancy on IQ and other cognitive domains as well as on other measurements of executive functioning.

Unlike other studies which reported that PSE is a risk factor for low birth weight (Ko et al., 2014; Vivilaki et al., 2016), newborns of our study who were prenatally exposed to tobacco smoke did not weigh less than unexposed and were born at term. In contrast to some previous literature, neither prenatally exposed offspring did not differ in BMI either (Robinson et al., 2016), in psychological problems (Joelsson et al., 2016; Tiesler & Heinrich, 2014) and in chronic illness prevalence (Farber, Groner, Walley, & Nelson, 2015) from the unexposed children. This is possible because the heterogeneity in smoking exposure, even within the different PSE groups, weakened the association between smoking and birth weight in our study. We specifically looked at the beginning and the end of pregnancy, unlike other studies that classified smoking at any time of pregnancy as exposure to cigarette smoke. Almost half of the smokers in our study gave up during pregnancy and it is possible that the women that smoked throughout pregnancy, reduced the number of cigarettes that they smoked daily.

This study also differs from others that were carried out in offspring with higher exposure to tobacco smoke than ours. In the present study, only 9.1% of smoking mothers smoked more than 10 cigarettes per day, and this percentage was higher in the low socioeconomic level group as reported in other studies found (Smedberg et al.,

2014). Most of the participants in our study were from middle and high SES so the low prevalence of high cigarette consumption was expected.

We hypothesized that children who were prenatally exposed to tobacco smoke would score lower in neuropsychological function and IQ tests than unexposed children. Our results partially support our hypothesis. We found an adverse effect of PSE on a single limited executive function. Specifically, offspring who were prenatally exposed to tobacco smoke scored lower in Interference, than unexposed offspring. In the same way, the results suggest a possible adverse effect on Color Trail Making Test. These results are consistent with other studies, which reported lower scores for executive functions in children with PSE (Julvez et al., 2007; Rose-jacobs et al., 2017) showing that exposed children show inefficient activation of regions required for response inhibition. We also assessed child memory capability (auditory and visual), and contrary to other authors (Fried, Watkinson, & Gray, 2003) we did not observe a significant association between PSE and memory.

Regarding cognitive outcomes, we did not observe adverse effects on total IQ nor other cognitive domains, in line with reports by (Kafouri et al., 2009; Yang et al., 2013) and in contrast with (Anthopolos et al., 2013; Cho et al., 2013; Rahu et al., 2010). It has been proposed that although PSE may disrupt foetal brain structure and functions, these may not result in any measurable cognitive effects or changes in behavioural performance (Boucher et al., 2014). Finally, regarding specific prenatal exposure to SHS or smoking during the first trimester only, the offspring of the mothers in these groups did not differ to the unexposed offspring.

Data regarding PSE was rigorously and accurately and prospectively collected. We assured the participants regarding the confidentiality of the data to encourage them to provide candid responses. In many other studies PSE data was collect retrospectively.

Furthermore, we interrogated the participants on their smoking habits at two separate times of pregnancy and corroborated the data obtained in the questionnaires using plasma cotinine concentrations.

We carried out the study in a well-controlled birth cohort, and considered many potential cofounders which had been associated with child neuropsychological development, such as, SES level and child birth weight and growth. Controlling for relevant covariates is essential because some previous studies reported that the effect of PSE on child neuropsychological function was attenuated or completely disappeared when the potential confounders were taken into account (Batty et al., 2006).

The results suggest that some protective home environment factors may mitigate the adverse effects of PSE on child neuropsychological development in childhood. So earlier studies which did not control sufficiently for relevant confounding factors may overestimate the PSE effects or detect a positive finding that is influenced or driven by other factors. Other strengths of this study were that we examined the effect of SHS exposure, smoking only during the first trimester and smoking during throughout pregnancy separately and the broad scope of the child neuropsychological assessment, including both cognitive performance tests and other neuropsychological functions.

The study had some limitations. The total sample size was limited for subgroup analysis. As is common in longitudinal studies, this was compounded by the difficulty in maintaining the participation rate of offspring in the follow-up stage. Additionally, prenatal exposure to tobacco smoke was at low levels (in almost all cases below to 10 cigarettes per day) possibly due to awareness by the mothers of the harmful effects of smoking on the foetus, reinforced by repeated advice from the obstetricians to abandon the habit. This may also reduce the possible potential adverse effects of PSE on neuropsychological development.

We conclude that PSE adversely affected child executive functioning, precisely on mental flexibility performance and suggest a possible adverse effect on inhibitory control. However, PSE at the levels observed in this study did not adversely affect other cognitive scores in most of the tests performed. The findings support further efforts aimed at encouraging mothers to quit smoking in pregnancy.

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