Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort

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Background Active maternal smoking during pregnancy has been associated with a higher risk of behavioural disorders in children, but a few cohort studies measuring smoking data prospectively have studied its specific effects on the cognitive abilities of pre-schoolers.

Method A birth cohort was set up in Menorca Island in 1997 within the Asthma Multicenter Infants Cohort Study. A total of 420 (87% of those eligible) children had complete data for final analyses at age 4 years. Interviewer-administered questionnaires were completed by mothers during the third trimester of pregnancy and then every year up to age 4 years of their child. A standardized version of the McCarthy Scales of Children's Abilities (MCSA) was used to evaluate the child’s motor and cognitive capabilities. Multivariable regressions were used with MCSA’s assessed outcomes adjusting for: home location, maternal alcohol consumption, mother's social class and level of education during pregnancy, parity, marital status, father’s education level, child’s gender, birth weight and height, breastfeeding duration, passive smoking, school season, age during test administration and evaluator (psychologist).

Results A high global consistency in maternal smoking habits was found (total agreement = 88.7%). Maternal social class and education level were inversely associated with maternal smoking behaviour. Maternal smoking during pregnancy (in cig./day) was associated with a decrease (in points) of children’s global cognitive score \( \beta = -0.59, (95\% \text{ CI: } -0.11; -0.09) \); as well as global cognitive sub-areas like verbal score \( \beta = -0.59, (95\% \text{ CI: } -1.11; -0.07) \); quantitative score \( \beta = -0.57, (95\% \text{ CI: } -1.08; -0.06) \); executive function score \( \beta = -0.71, (95\% \text{ CI: } -1.23; -0.20) \); and working memory score \( \beta = -0.46, (95\% \text{ CI: } -0.92; -0.01) \).

Conclusion Our findings suggest an association with maternal smoking during pregnancy and lowered cognitive development in children at age 4 years.

Keywords Maternal smoking habits, smoking during pregnancy, Paternal smoking habits, Cognitive development, Neurocognitive functions, Pre-school children, Population based study, Birth cohort

Introduction

Active maternal smoking during pregnancy has been associated with a higher risk of behavioural disorders in children. These disorders range from personality temperament, neuropsychiatric outcomes like attention disorders (ADHD) or conduct disorder (CD), to lowered cognitive abilities.1-3 However, the tracking between pre-natal and post-natal smoking behaviour makes it difficult to disentangle the role of active smoking during the post-natal period.2-6 Various biological pathways for tobacco...
neurotoxicity have been specifically identified during pregnancy, and it has been suggested that this is a particularly vulnerable period for the developing fetus.\(^1\)\(^,\)\(^7\)\(^,\)\(^8\)

Other mechanisms relating to psychosocial characteristics such as parental education level, intelligence and mental health may also be involved in the inter-relationship between smoking and neurodevelopment.\(^9\)\(^-\)\(^13\) Some authors have suggested that people who smoke tend to be more depressed, have a lower level of education and have lower IQ scores than non-smokers.\(^1\)

Such parental characteristics may explain part of the variance of the association between smoking and child neurobehaviour found in previous studies.\(^12\)

Additionally, most of the studies have been performed retrospectively; thus even if they had longitudinal designs, in which the children were followed-up for many years, the pre-natal exposure measure was assessed after birth.\(^2\)\(^,\)\(^3\)\(^,\)\(^12\) In contrast, the exposure measures in the present study have been conducted prospectively on maternal and paternal smoking reported yearly since pregnancy. There are other three cohort studies among pre-schoolers starting at pregnancy.\(^14\)\(^-\)\(^16\) However, their findings were not consistent. One of them showed a negative association with pregnancy exposure,\(^14\) another with post-natal exposure\(^15\) and in the third, no association was observed.\(^16\)

In this study, we report the effects of pre- and post-natal maternal smoking habits on 4-year-old children’s cognitive development in a community-based-birth-cohort in Spain which has moderate to light tobacco consumption. We assessed global cognitive outcome, and its specific sub-areas to gain a better understanding of the underlying pathways relating to smoking neurotoxicity.

**Methods**

**Participants**

This study is based on a birth-cohort from Menorca, one of the Balearic Islands of the northeast coast of Spain. The Menorca cohort was established within the Asthma Multicenter Infants Cohort Study\(^17\) and recruited all women presenting for antenatal care over a 12-month period starting in mid-1997 who were then followed-up until their child was 4 years of age. A total of 482 children (94% of those eligible) were enrolled with 422 (87.5%) providing data up to the fourth year visit. Of these, 420 (87%) subjects had complete data for final analyses. Participants (\(n = 420\); never actively smoked = 72.2%) did not differ from non-participants (\(n = 54\); never actively smoked = 66.4%) in any of the categories of parental smoking habits (\(P > 0.85\)). Written informed consent was obtained following an explanation and information sheet about the study being given to parents.

**Outcome variables**

A standardized version of the McCarthy Scales of Children’s Abilities (MC SA) adapted to the Spanish population by TEA (editorial company in psychometric tests for Spain)\(^18\) was used to evaluate motor and cognitive capabilities. The MC SA includes five conventional sub-area scores: verbal which refers to those cognitive tasks related to any kind of verbal information processing; quantitative which takes into account the numerical abilities; memory which includes short-time retention of information (verbal, perceptive or numerical); perceptive-performance which refers to those cognitive tasks related to any kind of perceptive information processing, including manual performance; and motor abilities which include fine (i.e. drawing) and gross (i.e. playing with a ball) ability types. Two neuropsychologists were trained to administer and interpret the MC SA. A strict protocol was applied to avoid inter-observer variability, including inter-observer trainings and three sets of quality controls (inter-observer-reliability-tests) undertaken during the fieldwork. The inter-observer variability was <5%. MC SA’s subtests were reorganized into new outcome sub-area scores according to those tasks highly associated with specific neurocognitive function (i.e. the underlying construct between the relation of a brain function to a specific behaviour).\(^17\)\(^-\)\(^19\)\(^-\)\(^21\) We created these new outcomes instead of using separated subtest scores\(^22\) with the intention of minimizing the difficulty associated with a low level of score reliability that, in turn, could affect the power of the analyses (type II error).\(^12\) The new outcome sub-areas were: working memory (5 and 14\(_1\)) which refers to those cognitive tasks related to temporarily storing and managing the information required to carry out other cognitive tasks such as learning, reasoning and comprehension; memory span (6, 7\(_p\), 14\(_p\)) which refers to those cognitive tasks related to short-term memory, which is the number of items, usually words or numbers, that a person can retain and recall; executive function (2, 5, 6, 14\(_b\), 15, 17 and 18) which refers to those cognitive tasks critical to non-routine, goal-oriented situations that are performed by the pre-frontal cortex;\(^23\)\(^-\)\(^24\) and cognitive functions of posterior cortex (1, 3, 4, 7\(_p\), 7\(_b\), 12, 13 and 16) referring to those cognitive tasks predominantly performed by the posterior cortex (parietal, temporal and occipital lobes). We analysed the internal construct validity of executive function sub-area using Confirmatory Factor Analyses; which showed an acceptable goodness of fit (\(\chi^2/df = 21.4743/14 = 1.53\); Bentler’s Comparative Fit Index ‘CFI’ = 0.9464; Bentler and Bonett’s Non-Normed Fit Index ‘NNFI’ = 0.9495; Standardized Root-Mean Square Residual ‘SRMR’ = 0.0448).\(^25\) Additionally, we analysed the Cronbach’s Alpha Coefficient for internal consistency of executive function and cognitive functions of posterior cortex sub-areas which were 0.68 and 0.69, respectively.

**Smoking variables**

Interviewer-administered questionnaires were used with mothers to obtain information relating to their own smoking habits (including daily frequency of cigarettes and passive exposure to environmental tobacco smoke during pregnancy) and those of their partner during the third trimester of pregnancy and then yearly up to age 4 years of their child. Mothers were divided into the following exclusive categories: (0) Mothers reporting never smoking in any of the surveys; (i) Mothers reporting smoking at least 1 cig./day during pregnancy irrespective of whether they smoked in post-natal period; (ii) Mothers reporting smoking (>1 cig./day) at least once in a post-natal survey, but not during pregnancy. The two smoking categories were also converted into two different continuous variables using the number of cigarettes per day in
order to study dose-response. For the category of mothers smoking (≥1 cig./day) at least once in a post-natal survey, the average number of cigarettes per day over all four post-natal surveys was calculated. Fathers were also divided into two groups: (0) Fathers reporting never smoking in any survey; (i) Fathers reporting at least 1 cig./day in any of the surveys. A continuous smoking variable for fathers was created in the same way as that described earlier for mothers.

Covariates
Information on maternal and paternal education, maternal and paternal social class (using The UK Registrar General’s 1990 classification according to parental occupation by ISCO88 code) and socio-demographic data was collected. Additionally, information relating to maternal health and obstetric history, fetal exposure to alcohol (ever exposure during pregnancy), type and duration of breastfeeding, child’s age when attending kindergarten and his dietary fish intake was obtained after delivery and at 4 years post-partum. Information relating to the child’s gestational age, Apgar test scores and anthropometric measures at birth were obtained from the clinical records and anthropometric measures on the 4-year-old child were collected using standard devices and methods by the same field worker.

Statistics
Continuous outcomes were standardized to a mean of 100 points with a 15 SD to homogenize all the scales and linear regressions were used for the statistical analyses. These typifying parameters are conventionally used in psychometrics for assessing IQs. Final multivariable models were adjusted for maternal social class (collapsed into two categories), paternal alcohol consumption during pregnancy, mother’s parity, marital status and home location, child’s gender, birth weight and height, child’s duration of breastfeeding, child’s exposure to passive smoking (which included paternal smoking data from pregnancy to 4th-year survey), the child’s age and school season during test administration and evaluator ‘neuropsychologist’.

The variables child’s gestational age, cranial perimeter and Apgar test scores, child’s age at start of kindergarten attendance, child’s weight and height at age 4 years, child’s dietary fish intake, child’s having older siblings at age 4 years, mother’s type of delivery, mother’s age and height after delivery, maternal weight, father’s age and alcohol consumption after delivery, number of rooms in the home were not retained because their inclusion one by one in a model with

maternal smoking did not change the coefficient of the latter by >5%.

Because the two maternal continuous smoking variables are mutually exclusive, there is no problem of colinearity. Dose (in cig./day) for only post-natal smoking is zero for mothers smoking during pregnancy.

Adjusted General Additive Models (GAM) were used to evaluate the linearity of the relation between continuous smoking variables and MCSA’s global cognitive outcome through non-parametric depiction of the predictor on the outcome, over the range of the predictor when the effects of the other variables had been taken into account. We reported the statistic GAIN, which is the difference in normalized deviance between the GAM and a model with a linear term for that predictor. A large gain indicates a lot of non-linearity, at least as regards statistical significance. The associated $P$-value is based on a chi-square approximation to the distribution of the gain if the true marginal relationship was linear.

We used a Wald test ($f$ statistic) to formally compare the coefficients of maternal smoking during pregnancy and paternal (any report) smoking associations for the final multivariable models, which included both smoking variables as well as other confounders. A further refinement of this approach was to examine the role of non-paternity in generating and comparing associations between maternal smoking during pregnancy and offspring cognitive development and paternal smoking and offspring cognitive development, given the non-biological relationship between some fathers and their apparent offspring. We conducted sensitivity analyses modelling the effects of non-paternity rates of 1–15%, using the equation given in the Appendix of Lawlor et al. article.

Results
Table 1 describes the consistency of maternal smoking habits for the period under study. There was a high global consistency of smoking habits overall with a lower frequency of active smoking reported at the third trimester survey. Eighty-seven per cent of those mothers reporting smoking at the third trimester also reported smoking at the 4th-year survey. There was an increase in active smoking following delivery (at 1st-year survey) with levels comparable with the 2nd-, 3rd- and 4th-year surveys. The intensity of active smoking between the third trimester and the four post-natal surveys was different (median = 5 cig./day and mean of medians = 13 cig./day, respectively). Seventeen per cent of those

<table>
<thead>
<tr>
<th>Smoking through the years (%)</th>
<th>Smoking at 4th-year-survey (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
</tr>
<tr>
<td>3rd-trimester-survey</td>
<td>421</td>
</tr>
<tr>
<td>1st-year-survey</td>
<td>424</td>
</tr>
<tr>
<td>2nd-year-survey</td>
<td>417</td>
</tr>
<tr>
<td>3rd-year-survey</td>
<td>424</td>
</tr>
</tbody>
</table>

*Never* refers to reporting ‘no smoking’ in both comparative surveys, the first ‘No’ refers to the respective 3rd-trimester–3rd-year surveys (row) and the second ‘No’ to the 4th-year survey (column); ‘Ever’ refers to reporting actively smoking in both surveys; ‘Start’ refers to only reporting actively smoking in the 4th-year survey; ‘Quit’ refers to only reporting actively smoking in the any of the respective 3rd-trimester–3rd-year surveys.
mothers who were exposed to environmental tobacco smoke during pregnancy were active smokers at the time of the 4th-year survey. Almost 80% of those mothers who did not smoke during pregnancy and were not exposed to environmental tobacco smoke were still non-smokers at the 4th-year survey. Overall, 253 mothers never smoked, 90 mothers smoked during pregnancy and in the post-natal period and 77 mothers smoked only after delivery. There were no mothers who smoked during pregnancy period but not following delivery.

Table 2 presents the percentages of parental smoking habits according to social class and education level. Maternal indicators were associated with smoking, however, social class level showed a stronger inverse association with smoking behaviour than education level. The results were unchanged when social class and level of education were treated as individual (non-collapsed) categories.

Table 3 presents the results for the crude and fully adjusted analyses between parental tobacco habits (treated as categorical and continuous variables) during the 4-year period of follow-up and the child’s global cognitive outcome at age 4 years. We tested the linearity between the outcome and smoking dose (cig/day) using GAM adjusted for the same variables as the final regression model (Table 3). We found a GAIN ($P$-value = 0.05) for linearity (null hypothesis) of 0.936 (0.33), 0.322 (0.57) and 3.166 (0.08) for maternal smoking during pregnancy, maternal smoking only in the post-natal period and paternal smoking, respectively, indicating a linear relationship with the global cognitive outcome at age 4 years and maternal smoking during and after pregnancy.

There was an overall reduction in the strength of the association seen after the inclusion of child and parental covariates; however, smoking (in cig./day) during pregnancy was only moderately reduced. It has been suggested that maternal socio-educational background may be more important than tobacco neurotoxicity in determining the children’s cognitive development. However, we found no interactions with maternal smoking categories and mother’s social class or education level on the global outcome.

When we transformed the continuous paternal smoking variable to one treated in quartiles, because cigarettes per day showed only a marginal linear relationship using GAM; and we included it in the final model instead of the continuous variable, the results were unchanged.

We analysed whether the maternal (during pregnancy) and paternal smoking (any time) coefficients for the continuous variables of the final model (Table 3) were different. We obtained an $F (1, 356) = 4.33, P$-value = 0.038, which suggested that when studying a dose-response (in cig./day) pattern, the effect of maternal smoking during pregnancy was different from paternal one. In addition, we performed a sensitivity analysis using plausible levels of non-paternity up to 15% and the $P$-value for difference between the coefficient of maternal smoking and the coefficient of paternal smoking was always below $P$-values of 0.038. However, we did not find these differences between maternal and paternal smoking habits when smoking variables were treated as dichotomous variables (never/ever) ($P$-values >0.1).

Table 4 describes the association of parental smoking habits (in cig./day) with specific sub-areas derived from MCSA’s global cognitive outcome. There was an association seen with a decrease (in points) of $\beta = -0.59 (-1.11; -0.07)$ of verbal, $\beta = -0.57 (-1.08; -0.06)$ of quantitative and $\beta = -0.71 (-1.23; -0.20)$ of executive function scores with maternal smoking (in cig./day) during pregnancy. There was no association seen with global memory score, however, when we divided global memory into specific categories of working memory and visual and verbal span, a negative association was seen with working memory score $[\beta = -0.46 (-0.92; -0.01)]$. Perceptive-performance and motor sub-area scores were not associated with any of the smoking variables (data not shown).

**Discussion**

Active maternal tobacco smoking was highly consistent throughout the 4 years of follow-up in the current study, with a small reduction in smoking consumption seen during...
MATERNAL SMOKING HABITS AND COGNITIVE DEVELOPMENT OF CHILDREN

Table 3  Sensitivity analysis of the association [coefficient and (95% confidence interval)] between global cognitive (MCSA) outcome scores and maternal and paternal smoking habits during 4 years of follow-up

<table>
<thead>
<tr>
<th>Parental smoking habits</th>
<th>Global cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes, during pregnancy (Mother)</td>
</tr>
<tr>
<td>n (420)</td>
<td>90</td>
</tr>
<tr>
<td>Crude</td>
<td>–4.5 (–8.1; –0.9)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusteda</td>
<td>–3.3 (–6.9; 0.2)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.07</td>
</tr>
<tr>
<td>Adjusted + mutual adjustmentb</td>
<td>–2.5 (–6.3; 1.2)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.18</td>
</tr>
</tbody>
</table>

The MCSA range score for the reference category is around 102 points. The comparison group is no smoking.

aAdjusted for: Home location, maternal alcohol consumption during pregnancy, child’s gender, child’s birth weight and height, child’s breastfeeding duration, child’s school season and age during test administration, evaluator (psychologist), mother’s social class in two categories and level of education in two categories during pregnancy, mother’s parity, mother’s marital status at child’s age of 4 years, father’s education level in two categories.

bAdjusted for the same covariates as full adjustment models of Table 3, including all smoking determinants in the same model per each outcome variable.

The MCSA range score for the reference category is around 103 points. The comparison group is no smoking.

Smoking variables treated as continuous (cig/day)

<table>
<thead>
<tr>
<th>Parental smoking habits</th>
<th>Global cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During pregnancy (Mother)</td>
</tr>
<tr>
<td>n (420)</td>
<td>90</td>
</tr>
<tr>
<td>Crude</td>
<td>–0.75 (–1.20; –0.30)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.00</td>
</tr>
<tr>
<td>Adjusteda</td>
<td>–0.51 (–0.99; –0.04)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted + mutual adjustmentb</td>
<td>–0.60 (–1.10; –0.09)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.02</td>
</tr>
</tbody>
</table>

The MCSA range score for the reference category is around 100 points. The comparison group is no smoking.

aAdjusted for: Home location, maternal alcohol consumption during pregnancy, child’s gender, child’s birth weight and height, child’s breastfeeding duration, child’s school season and age during test administration, evaluator (psychologist), mother’s social class in two categories and level of education in two categories during pregnancy, mother’s parity, mother’s marital status at child’s age of 4 years, father’s education level in two categories.

bAdjusted for the same covariates as full adjustment models of Table 3, including all smoking determinants in the same model per each outcome variable.

Table 4  Association [coefficient and (95% confidence interval)] between the sub-areas of the global cognitive (MCSA) outcome scores and parental smoking habits during 4 years of follow-up

<table>
<thead>
<tr>
<th>Sub-areas of the global cognitiveb</th>
<th>Parental smoking habitsa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During pregnancy (Mother)</td>
</tr>
<tr>
<td>n (420)</td>
<td>90</td>
</tr>
<tr>
<td>Verbal</td>
<td>–0.59 (–1.11; –0.07)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.03</td>
</tr>
<tr>
<td>Quantitative</td>
<td>–0.57 (–1.08; –0.06)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.03</td>
</tr>
<tr>
<td>Memory</td>
<td>–0.10 (–0.63; 0.43)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.71</td>
</tr>
<tr>
<td>Visual and verbal span</td>
<td>–0.26 (–0.80; 0.28)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.34</td>
</tr>
<tr>
<td>Working memory</td>
<td>–0.46 (–0.92; –0.01)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.04</td>
</tr>
<tr>
<td>Executive functions, frontal cortex predominance</td>
<td>–0.71 (–1.23; –0.20)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.01</td>
</tr>
<tr>
<td>Cognitive functions, posterior cortex predominance</td>
<td>–0.32 (–0.83; 0.18)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.21</td>
</tr>
</tbody>
</table>

The MCSA range score for the reference category is around 108 points. The comparison group is no smoking.

aSmoking variables are treated as continuous in number of cig/day.

bAdjusted for the same covariates as full adjustment models of Table 3, including all smoking determinants in the same model per each outcome variable.

the pregnancy period. We found lower McCarthy’s global cognitive scores in the 4-year-old offspring of mothers who reported smoking at least one cigarette per day during pregnancy adjusted for a range of confounders, which was not seen in mothers who smoked only in the post-partum period. Some cognitive sub-areas, specifically verbal, quantitative, executive and working memory scores, showed a higher negative association.
Our results for smoking behaviour are consistent with those reported in previous studies. Smoking tobacco has been shown to be very addictive and less episodic than other toxic behaviours, and while there may be considerable energy devoted to quitting or moderating tobacco consumption during pregnancy due to high social pressure, it is difficult to maintain this without continued support in the post-natal period.

Experiments in animals and epidemiological studies have reported that exposure to tobacco smoke during the intrauterine and early life period disrupts neurodevelopment, but few studies have focused on this in relation to cognitive functioning of children (aged 3–7 years). Many biological mechanisms have been proposed to better understand the neurotoxic effects of tobacco and the increased potential for damage to result during pregnancy. The vulnerability of the nervous system to injury extends from the fetal to neonatal period and through to infancy thus covering all aspects of nervous system development. Nicotine levels in the fetus have been found to be 15% higher than maternal levels and normal fetal development of the brain may be affected by exposure to cigarette smoke by, for example, reducing uterine blood flow to the placenta resulting in chronic deprivation of nutrients and oxygen; or by acting as a neurotoxin affecting the frontal cortex, hippocampus and cerebellum where there is a high density of these receptors present during pregnancy. Other effects due to nicotine such as increased oxidative stress and hypoactivity of the noradrenergic and dopaminergic systems have also been documented. Nicotine exposure in the post-natal period appears to be less influential on brain development in infants although there may be some residual effects from the intra-partum period on the nervous system. One of the alternative biological pathways recently suggested for environmental exposure to tobacco is through breast milk.

Results from cohort studies regarding the post-natal effects of tobacco smoke on neurodevelopment are not conclusive. Methodologically, it is difficult to separate pre-natal and post-natal exposure, and a large population sample would be needed to obtain a sufficient number of mothers who smoked only in the post-natal period. The fact that we observed no consistent association with smoking during the post-natal period suggests that exposure to environmental tobacco smoke after birth is less relevant than exposure during pregnancy.

For those mothers who reported smoking during pregnancy we found a consistent effect in their children for specific cognitive areas negatively associated with smoking including verbal and numerical abilities, executive function and working memory. Executive, quantitative and memory functions require the well functioning of frontal, temporal and hippocampus structures, and during the fetal development stage there is a high density of nAChRs. Other observational studies about cognitive affection have also described delays in verbal development. Additionally, an association has also been documented in prospective and retrospective studies between maternal smoking during pregnancy and offspring’s attention behaviour and hyperactivity disorder, the alteration of these behaviours appearing to be specifically associated with lower scores in cognition related with executive function and working memory.

In order to control for the possible effect of socio-demographic factors, we added a number of psychosocial variables including paternal factors, although we may have over-adjusted for the association with smoking. Adjustment for education in other studies has explained as much as 50% of maternal IQ variance, however, we observed a reduction of only 29% of the association in the current study. In addition, the association of maternal smoking (during pregnancy) with child’s cognitive development was different than that for paternal smoking (any time). These findings suggest that smoking during pregnancy is not only a marker of social disadvantages but may also have an intrinsic biological effect. Moreover, the fact that specific cognitive areas were negatively dose-response associated with active smoking during pregnancy which is in concordance with other animal and epidemiological studies, reduces the probability of residual confounding fully explaining the association.

However, several limitations in this study do not permit us to infer that the findings with regards to the neurotoxic processes of tobacco smoke are causally based. Although we included a large number of covariates, we were unable to control for parental IQ, mental health, problematic family functioning or genetic background which have all been linked to tobacco addictive behaviours. Inclusion of psychosocial covariates such as mother’s age, marital and social status, duration of exclusive breastfeeding and alcohol consumption and, father’s alcohol and smoking behaviour and social status may have reduced part of the residual confounding. All these covariates are documented predictors of psychopathology, low IQ or genetic background related to addictive behaviours. The fact that neither smoking or alcohol behaviour in fathers has not been found to be associated with their children’s cognitive development suggests that autosomally linked genetic background arguments are less likely to explain the causal link, but paternal associations could be attenuated because of not controlling for biological paternity. Also, we found that the beneficial breastfeeding effects in this cohort were specifically related to different cognitive sub-areas (those related with perceptive-performance MCSA’s scores) other than tobacco effects suggesting different causal mechanisms. Another limitation was that we did not measure cotinine levels in the mother or child’s serum, which, if anything, would have diminished the strength of our findings.

The strengths of this study are that it is a population-based birth cohort study with repeated prospective surveys of parental smoking habits with moderate levels of tobacco exposure. Studies of this type are sparse and more human studies are needed to complement findings relating to biologically plausible mechanisms which have been demonstrated in animal design studies.

In conclusion, our findings are consistent with previous studies suggesting a negative association between maternal smoking habits during pregnancy and subsequent cognitive development in the child. We identified some cognitive sub-areas related to verbal and quantitative abilities, working memory and executive function in which may benefit from
increased stimulation during early infancy in those children who have been exposed to high levels of tobacco smoke during pregnancy.

Acknowledgement
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