# A dose-response relationship between maternal smoking during late pregnancy and adult intelligence in male offspring

**Erik Lykke Mortensen[a,b], Kim Fleischer Michaelsen[c], Stephanie A. Sanders[d,e] and June Machover Reinisch[a,d]**

*[a]Danish Epidemiology Science Centre, Institute of Preventive Medicine, Copenhagen University Hospital, [b]Department of Health Psychology, Institute of Public Health, University of Copenhagen, Copenhagen, [c]Department of Human Nutrition, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark, [d]The Kinsey Institute for Research in Sex, Gender, and Reproduction, and [e]Department of Gender Studies, Indiana University, Bloomington, IN, USA*

*Correspondence:*
Associate Professor Erik Lykke Mortensen, Department of Health Psychology, Institute of Public Health, University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark.
E-mail: e.l.mortensen@pubhealth.ku.dk

## Summary

An association between maternal smoking during pregnancy and cognitive and behavioural development has been observed in several studies, but potential effects of maternal smoking on offspring adult intelligence have not been investigated. The objective of the present study was to investigate a potential association between maternal smoking during pregnancy and offspring intelligence in young adulthood. Adult intelligence was assessed at the mean age of 18.7 years by a military draft board intelligence test (Børge Priens Prøve) for 3044 singleton males from the Copenhagen Perinatal Cohort with information regarding maternal smoking during the third trimester coded into five categories (about 50% of the mothers were smokers). The following potential confounders were included as covariates in multivariable analyses: parental social status and education, single mother status, mother's height and age, number of pregnancies, and gestational age. In separate analyses, birthweight and length were also included as covariates.

Maternal cigarette smoking during the third trimester, adjusted for the seven covariates, showed a negative association with offspring adult intelligence ($P = 0.0001$). The mean difference between the no-smoking and the heaviest smoking category amounted to 0.41 standard deviation, corresponding to an IQ difference of 6.2 points [95% confidence interval 0.14, 0.68]. The association remained significant when further adjusted for birthweight and length ($P = 0.007$). Both unadjusted and adjusted means suggested a dose-response relationship between maternal smoking during pregnancy and offspring adult intelligence. When subjects with missing data were excluded, essentially the same results were obtained in the reduced sample ($n = 1829$). These results suggest that smoking during pregnancy may have long-term negative consequences on offspring adult intelligence.

## Introduction

Several studies have demonstrated lower birthweight and birth length in offspring of mothers who smoke during pregnancy and most studies also suggest a dose-response relationship between cigarette consumption during pregnancy and offspring birthweight.[1–3] While some studies have found evidence that the negative effects of maternal smoking may persist during childhood, a recent large study found no weight differences between offspring of smoking and non-smoking mothers at the age of 6 months.[1] Partial or complete catch-up during the first years of life has also been observed in a majority of other studies.[4–7] Despite the apparent early catch-up growth, maternal smoking during pregnancy may still have subtle consequences for long-term development. Surprisingly, few studies have investigated the possible associations between smoking during pregnancy and adult development.[8]

An association between maternal smoking during pregnancy and behaviour problems in childhood has been suggested.[9,10] Childhood behaviour problems may persist into adulthood since an association between maternal smoking and adult criminality has been observed for both males[11,12] and females.[13] This last study also demonstrated a relationship between maternal smoking during pregnancy and hospitalisation for substance abuse in both male and female adult offspring.[13] If smoking during pregnancy has long-term consequences for offspring psychological and social development, it is important to identify the underlying mechanisms.[14] Smoking during pregnancy may affect the development of the brain and consequently the child's intellectual and cognitive development. This hypothesis is supported by studies that have found an association between smoking during pregnancy and early childhood cognitive ability and academic achievement.[8] However, to our knowledge, there has been only one study suggesting a possible negative association between smoking during pregnancy and offspring educational achievement at the age of 23.[15] School achievement is generally closely associated with IQ,[16] but there are no specific reports on the relationship between maternal smoking and offspring adult intelligence.

The purpose of the present study was to investigate possible long-term consequences of smoking during pregnancy on offspring adult intelligence.

## Methods

### The Copenhagen Perinatal Cohort

The Copenhagen Perinatal Cohort consists of 9125 individuals born at the National University Hospital from October 1959 to December 1961. Demographic, socio-economic, prenatal and postnatal medical information was recorded prospectively during pregnancy, at delivery and at a 1-year follow-up. Information on smoking during pregnancy (with emphasis on cigarette consumption during the third trimester) was collected by a physician who interviewed the mothers while they were pregnant and during the first few days after delivery.[17]

### Draft records

With the exception of individuals with disqualifying diseases (e.g. epilepsy and diabetes) and those who volunteer for military service, all Danish males are required to appear before the draft board when they become liable for conscription at the age of 18. Draft board records contain information on weight, height, and intelligence. Draft information has been located for a majority of the male members of the cohort by the Prenatal Development Project.[18]

Intelligence is assessed by Børge Priens Prøve (BPP). The BBP is a 45-min group intelligence test comprised of four subtests (letter matrices, verbal analogies, number series, and geometric figures) with a total score ranging from 0 to 78. The draft records only include the total score which correlates 0.82 with the Full Scale WAIS IQ (Wechsler's Adult Intelligence Scale),[19] indicating that the BPP is a highly valid measure of general intelligence.[20] Like most measures of intelligence, the distribution of BPP total scores is approximately normal.

### Current sample

The Perinatal Cohort comprises 4668 male infants. Maternal smoking data were available for 4575 (98%) mothers, and draft records for 3773 (81%) male subjects. Information on maternal smoking and complete draft records were available for 3175 individuals. From this sample, 102 twins and 29 second-born siblings were excluded because data for twin pairs and siblings are not statistically independent and because relationships between some of the covariates and adult intelligence may be different in twins and singletons. Consequently, the subsample of the Perinatal Cohort analysed in the present study included 3044 singleton males who appeared before the draft board at a mean age of 18.7 years (SD 1.3, range 16–26 years). This final sample represented 71% of the 4280 males surviving the first 4 weeks of life. The percentage of smokers among mothers in the sample was slightly lower than among the 1595 mothers excluded due to lack of data or twin births (50 and 54%, respectively, $P = 0.008$), but among smokers the median daily cigarette consumption was 6.5 for both included and excluded mothers and a Mann-Whitney test showed no significant group difference ($P = 0.37$).

### Data analysis

When the Perinatal Cohort was established, maternal cigarette consumption in the third trimester was recorded in the following five categories:[17] (1) no smoking; (2) <3 cigarettes daily; (3) 3–10 cigarettes daily; (4) 11–20 cigarettes daily; (5) >20 cigarettes daily (Table 1).

**Table 1.** Relation between covariates and maternal smoking during pregnancy

| | Daily cigarette consumption | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | <3 | 3–10 | 11–20 | >20 | *n* | *P*-value |
| Number of subjects | 1517 | 204 | 882 | 397 | 44 | 3044 | |
| Social status | 4.3 | 4.1 | 3.8 | 3.7 | 3.2 | 2475 | <0.0001 |
| Breadwinner's education | 2.5 | 2.5 | 2.3 | 2.3 | 2.3 | 2457 | <0.0001 |
| Single mother (%) | 33 | 46 | 40 | 41 | 57 | 3043 | <0.0001 |
| Maternal height (cm) | 162.9 | 163.1 | 162.6 | 163.1 | 162.2 | 3015 | 0.37 |
| Mother's age (years) | 26.1 | 24.4 | 25.4 | 26.6 | 26.2 | 3027 | 0.0001 |
| No. of pregnancies | 1.8 | 1.7 | 1.9 | 2.0 | 2.0 | 3038 | 0.002 |
| Gestational age (week) | 39.3 | 39.3 | 39.0 | 38.9 | 39.9 | 2449 | 0.02 |
| Birthweight (g) | 3426 | 3408 | 3166 | 3136 | 3084 | 3043 | <0.0001 |
| Birth length (cm) | 52.0 | 51.8 | 50.8 | 50.6 | 50.4 | 3042 | <0.0001 |

The *P*-value for the percentage of single mothers refers to a chi-square test of differences among smoking categories. For the remaining variables, *P*-values refer to the overall *F*-tests of differences among the means of the smoking categories. Social status and breadwinner's education were coded on 1–8 and 1–4 point scales respectively (see text below).

The outcome measure was adult intelligence (BPP score) from the draft records and, in addition, three analyses of the association between maternal smoking and adult intelligence were conducted. Firstly, the unadjusted BPP means for the five smoking categories were analysed. Secondly, the BPP means were adjusted for parental social status, breadwinner's education, single mother status, mother's height, mother's age, number of pregnancies, and gestational age. Thirdly, an analysis was conducted that also adjusted the BPP means for birthweight and birth length. The SPSS linear regression and analysis of variance routines (SPSS Inc, Chigaco, IL) were used to analyse unadjusted and adjusted mean differences among the five smoking categories. The level of significance was set at 0.05.

We have previously developed a statistical model to predict adult intelligence from pre- and perinatal variables in the Copenhagen Perinatal Cohort.[21] In the current sample, the following six variables were significantly associated with adult intelligence test scores: parental social status [a combined 1–8 point scale based on breadwinner's occupation, breadwinner's education, type of income (wage/salary) and quality of housing],[17] breadwinner's education (coded on a 1–4 point scale),[17] single-mother status (yes or no), mother's height, mother's age, number of pregnancies (including the present). Mother's height and mother's age showed significant non-linear associations with BPP scores, and to reflect possible non-linearity, the regression models included squared deviations from the mean for these two variables (all quantitative variables were included in regression models as continuous variables). Preliminary analyses showed no significant interactions between any of the covariates and maternal smoking with respect to BPP score.

In the first series of analyses, we deliberately excluded birthweight and length, since a large number of studies show short-term effects of maternal smoking on fetal growth. Consequently, statistical adjustment for these variables would remove part of the variance associated with smoking. In our data, we also observed a statistically significant association between maternal smoking and estimated length of gestation, but this effect was relatively small, and we included gestational age as a covariate for a more conservative estimate of effect. A second series of analyses also included birthweight and length. Table 2 presents adjusted means for the five maternal smoking groups for regression models based on seven and nine covariates and dummy coding of the cigarette consumption categories (cf. Table 1).

For most covariates, the missing data rate was <1%, but the missing data rates for gestational age, social status, and breadwinner's education were 20%, 19%, and 19% respectively. Since about 40% of the sample had missing data on one or more predictor variables, it was decided to present analyses based on overall mean substitution for missing values and including dummy variables for missing data on gestational age, social status, and breadwinner's education.[22] Mean imputation may lead to underestimation of standard errors,[23] and although there were no missing data for maternal smoking and BPP scores, all analyses were replicated using the Amos program[24] to obtain maxi-

**Table 2.** Observed and adjusted means for BPP intelligence test scores in relation to maternal smoking

| | Daily cigarette consumption | | | | | |
|---|---|---|---|---|---|---|
| | 0 | <3 | 3–10 | 11–20 | >20 | *P*-value |
| Total sample ($n = 3044$) | | | | | | |
| Mean BPP score | 41.2 | 39.9 | 38.5 | 37.8 | 34.1 | <0.0001 |
| SD | 11.3 | 11.8 | 11.4 | 11.4 | 10.2 | |
| 1st adjusted mean | 40.6 | 39.9 | 39.2 | 38.5 | 35.9 | 0.0001 |
| 2nd adjusted mean | 40.4 | 39.8 | 39.4 | 38.8 | 36.4 | 0.007 |
| Reduced sample ($n = 1829$) | | | | | | |
| Mean BPP score | 41.9 | 40.6 | 38.8 | 38.0 | 34.1 | <0.0001 |
| SD | 11.2 | 12.0 | 11.7 | 11.8 | 9.9 | |
| 1st adjusted mean | 41.3 | 40.8 | 39.7 | 38.5 | 36.2 | 0.004 |
| 2nd adjusted mean | 41.1 | 40.8 | 39.9 | 38.6 | 36.6 | 0.005 |

The 1st adjusted means are adjusted for parental social status, breadwinner's education, single mother status, mother's height, mother's age, number of pregnancies, and gestational age.
The 2nd adjusted means are additionally adjusted for birthweight and length.
The significance levels for both the unadjusted and adjusted means refer to the overall *F*-tests of significance of mean differences among the five smoking categories.

mum likelihood parameter estimates based on all available data and using a reduced sample, comprising only the 1829 individuals without missing data.

Contrasts were calculated to evaluate the significance of differences between pairs of means and between combinations of means.[22,25] For tests of trend, interval midpoints were used to code smoking during the third trimester (0, 1.5, 6.5, 15.5, and 25 cigarettes daily) and power polynomials were calculated.[22] Finally, logistic regression was used to evaluate the adjusted relative risks of obtaining a BPP score below the median of the total sample.

The associations between individual covariates and BPP scores were not a primary focus of the study, and collinearity among the covariates was not expected to seriously affect the estimation of the effects of maternal smoking. The largest squared multiple correlation between an individual covariate and all the other covariates was 0.69 for birth length in the model with birthweight and birth length included and 0.57 for social status in the model without the latter two variables. Excluding highly correlated covariates only resulted in small changes in the regression coefficients associated with maternal smoking.

## Results

Table 1 presents the number of subjects in the five cigarette consumption categories. About 50% of the mothers were smokers, and although the majority smoked between 3 and 10 cigarettes daily, a substantial proportion (29%) of the smokers consumed more than 10 cigarettes daily.

The relationship between covariates and maternal smoking categories is addressed in Table 1. It reveals significant mean differences among smoking categories for all variables except maternal height. Smoking in the third trimester was clearly associated with single mother status, lower social status, and lower educational level (the last two variables are semiquantitative, but Kruskal-Wallis tests confirmed the association). The data in Table 1 also reveal highly significant differences in mean birthweight and length among the five smoking categories. There were no significant differences between the 'no-smoking' and the '<3 cigarettes daily' groups, but significant differences between these two groups and the remaining three groups (which show no significant differences among themselves).

Table 2 presents the results for the BPP intelligence test. The three analyses revealed significant associations between maternal smoking and offspring intelligence. For all three analyses, tests of linear and quadratic trend showed only significant linear trend ($P < 0.0001$). Moreover, the patterns of means suggested a dose-response relationship between maternal smoking and offspring intelligence. Both the unadjusted and the adjusted means showed quite dramatic differences in intelligence test scores between the 'no-smoking' and the heaviest smoking category

($P < 0.0001$ and $P = 0.003$ for the unadjusted and adjusted means respectively). Compared with the standard deviation of the total sample (11.4), the 4.7 BPP points adjusted difference amounted to 0.41 standard deviation [95% confidence interval (CI) 0.14, 0.68]. A typical IQ scale[19] has a mean of 100 and a standard deviation of 15, and thus 0.41 BPP standard deviation corresponds to about 6.2 IQ points. Compared with the offspring of 'no-smoking' mothers, the adjusted relative risks (odds ratios) of obtaining a BPP score below the median of the total sample was 3.4 among offspring of mothers in the heaviest smoking category [95% CI 1.6, 7.0]. Differences between the 'no-smoking' category and the other three groups were considerably smaller, but clearly significant for both the unadjusted and adjusted means for the '3–10' and the '11–20 cigarettes daily' categories ($P = 0.002$ and $P = 0.0004$ for the two adjusted means). The second row of adjusted means in Table 2 shows that including birthweight and birth length as covariates resulted in only slightly smaller differences among smoking categories.

The adjusted difference between the mean BPP of the 'no-smoking' category and the offspring of all smoking mothers was 1.5 ($P < 0.0001$) and compared with the offspring of no-smoking mothers, the relative risk for offspring of smoking mothers of obtaining a BPP score below the median of the total sample was 1.3 ($P = 0.003$).

Maximum likelihood estimation confirmed the results described above. Thus, both the overall effect of maternal smoking and the linear trend between maternal smoking category and offspring intelligence remained significant at the 0.0005 and the <0.0001 level. Table 2 also presents analyses based on the reduced sample without missing data. Both the patterns of BPP mean scores and the levels of significance are fully consistent with the results obtained for the full sample.

An anonymous reviewer of a previous version of this paper pointed to the relatively wide age range of the sample and raised the question of whether the effects of maternal smoking may be related to offspring age at the time of appearing before the draft board. A series of additional analyses suggested that this is not the case: there are no significant differences in mean age among smoking categories and the overall effect of smoking barely changes when age at testing is included as a covariate. This was also the case when the subsample in the narrow age range 18–22 was analysed (about 96% of the sample was in this age range).

## Discussion

Our results reveal significant long-term effects of maternal smoking during pregnancy on mental development. According to the results in Table 2, maternal smoking during pregnancy was associated with lower adult intelligence and there appeared to be a dose-response relationship between maternal smoking and offspring intelligence. Although the mean BPP score for the '>20 cigarettes daily' category is based on a relatively small subsample, the results do suggest that daily smoking of a pack or more of cigarettes during the third trimester of pregnancy may have serious consequences for offspring long-term intellectual development.

A number of studies that evaluated intellectual ability and academic achievement in childhood support the supposition that maternal smoking may have long-term consequences for offspring intellectual development.[8] Some of these studies observed deficits in cognitive abilities or academic achievement associated with maternal smoking in children who were 7 years or older.[26–31] On the other hand, two studies detected no cognitive deficits in middle childhood associated with maternal smoking during pregnancy,[32,33] and although intelligence is stabilised quite early,[34] children of smoking mothers might conceivably overcome their intellectual deficits (as they apparently overcome fetal growth retardation). However, our findings, like the majority of childhood studies, suggest that this is not the case. They are supported by a recent small sample study showing an association between maternal smoking and intelligence assessed in early adolescence[35] and a large-scale study demonstrating an association between maternal smoking and educational achievement at age 23.[15]

The observed relationship between maternal smoking and long-term cognitive development may be an effect of smoking during pregnancy or an effect of factors that we were unable to control statistically. Alcohol consumption was very rare among Danish women when the Perinatal Cohort was established and was therefore not registered systematically (this was also the case for illegal substance use).[17] However, we consider it unlikely that sporadic alcohol consumption among the mothers of the cohort can explain our results since studies show effects of maternal smoking on cognitive functioning in childhood and early adolescence even when maternal alcohol consumption and marijuana use are controlled statistically.[35–37]

The same studies also demonstrated that exposure to cigarette smoking after birth is an unlikely explanation for the association between maternal smoking during pregnancy and offspring cognitive development. Although other postnatal factors might also be associated with maternal smoking, effects of exposure to prenatal smoking were observed in studies that tried to control aspects of the home environment[35–38] and, in addition, twin studies as well as adoption studies have questioned the importance of the home environment for long-term intellectual development.[39] We have previously demonstrated that adult intelligence is associated with duration of breastfeeding in the Perinatal Cohort,[21] but an analysis including this factor as a covariate essentially showed the same results as those presented in Table 2.

One earlier study was able to control for maternal intelligence, and in that investigation a significant negative effect of smoking during pregnancy on offspring cognitive development at age four was still documented.[38] Nevertheless, the putative effects of maternal smoking on offspring intelligence may be confounded by the influence of parental intelligence. For several reasons we believe that this type of confounding is unlikely to account for the current findings.

Firstly, although we did not have direct measures of parental intelligence, it is reasonable to conclude that our measures of parental education and social status provide valid substitute indices. The average correlation between parent IQ and offspring IQ has been reported to be 0.42.[39] In our sample, the multiple correlation between parental education and social status and the BPP score of their offspring was 0.45, and the bivariate correlations with the offspring BPP score were 0.41 and 0.43 for parental education and social status respectively. Multiple correlations of education and social status with parental IQs might be even higher, and thus inclusion of parental education and social status as covariates is likely to have removed a substantial part of the variance in offspring IQ associated with parental IQ.

Secondly, it is important to observe that we found evidence of a dose-response relationship between maternal smoking and offspring intelligence. Consequently, parental intelligence could only explain the results in Table 2 if there was a systematic, negative association between parental IQ and amount of smoking even within educational and social classes (these variables were controlled as covariates). Such an association may not be entirely unlikely among low-status mothers (i.e. awareness of potential harmful effects of smoking could have been less prevalent and, thus, more strongly associated with maternal intelligence among low-status mothers), but such a pattern seems much less likely for well-educated high-status mothers. It is therefore remarkable that the patterns of mean test scores for the five smoking categories were similar in low and high social status subsamples and that formal statistical tests showed no interaction between smoking and social status. Thus, the association between maternal smoking and offspring intelligence seems as strong in high social status children as in low social status children.

Thirdly, it should be remembered that fully half of the mothers in the Perinatal Cohort smoked during pregnancy, which strongly suggests that few mothers were aware that smoking might be harmful to the fetus. At the time of the establishment of the cohort, Danish women were not being warned against smoking during pregnancy, and thus it is unlikely that the mothers' smoking habits were related to their intelligence. In fact, in 1962, a leading contemporary American authority recommended a daily cigarette for bowel regulation during pregnancy.[40]*

Effects of smoking during pregnancy on offspring cognitive development may be direct (i.e. effects on fetal brain development) or indirect (e.g. consequences of pregnancy complications or fetal growth retardation). Including both birthweight and length as covariates still revealed a significant, although somewhat smaller association between maternal smoking and adult intelligence (Table 2); thus, it appears that the effect of maternal smoking on offspring intelligence was largely independent of the effect on fetal physical growth. A previous study of the association between smoking during pregnancy and adult criminality in the Perinatal Cohort included weighted pregnancy and delivery complication scales as covariates.[11] In our sample, these scales were significantly associated with smoking, and it is possible that maternal smoking may affect the rate of pregnancy and delivery comp-

*In a chapter entitled Minor Complaints of Pregnancy, Guttmacher in 1962[40] gave the following advice on constipation: '. . . Try to develop the habit of a regular unhurried visit to the bathroom at the same hour each day, preferably after breakfast. Smoking a cigarette while on such an excursion may help.'

lications.[41] However, a series of analyses that included these two covariates as well as a binary indication of prescribed maternal medication during pregnancy[11] demonstrated essentially the same results as the analysis presented here.

Thus, it seems justified to assume that part of the effect of maternal smoking on offspring cognitive development is a direct result of the effect of substances in cigarette smoke on the fetal central nervous system. More specifically, maternal smoking may reduce uteroplacental circulation and cause fetal hypoxia[8,38] which may particularly affect the development of the brain and thus subsequent intellectual development.

For the Copenhagen Perinatal Cohort, any explanation of the effects of maternal smoking during pregnancy must not only consider the negative association with adult intelligence, but also the association with adult criminal behaviour and substance use.[13] Since intelligence is related to a broad range of behavioural and psychological characteristics,[42] the association between maternal smoking and intellectual development may explain some of the reported behavioural effects in offspring of mothers who smoke during pregnancy, such as behaviour problems in childhood[9,10] and criminal behaviour in adults.[11,14]

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