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Increase in Child Behavior Problems Resulting from Maternal Smoking during Pregnancy
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ABSTRACT. In this article, the authors investigated the effect of maternal smoking during pregnancy on behavioral problems, which were not mediated by lower birth weight, in offspring at 3 y of age. The authors used the Child Behavior Checklist for ages 2-3 y (CBCL/2-3; Achenbach, Edelbrock and Howell) to assess behavioral problems in 1 377 2- to 3-y-old healthy twin pairs. Soon after the birth of twins, the authors collected pre- and perinatal information, including smoking habits of the mother during pregnancy. The question “Did you smoke during pregnancy?” could be answered by choosing one of three possible options: (1) never, (2) sometimes, or (3) regularly. The authors analyzed the effect of maternal smoking on the Child Behavioral Checklist total score and on several subscale scores for first- and second-born twins separately, and they adjusted for the possible confounding effects of birth weight, socioeconomic status, maternal age, and having been breast- or bottle fed. There was a significant effect of maternal smoking on so-called externalizing behavior problems (oppositional, aggressive, overactive), but not on internalizing behavior problems (withdrawn, depressed, anxious), in both first- and second-born twins. The authors primarily attributed the enhanced externalizing problems to increased aggression. Although boys had higher externalizing (and aggression) scores than girls, the effect of maternal smoking was the same for boys and girls. The authors also discuss whether maternal smoking causes externalizing behavior problems.

SMOKING by a woman while she is pregnant may result in pregnancy complications (i.e., higher perinatal mortality rate; several effects on bodily, emotional, and intellectual development of the child). These effects—or at least some of them—are mediated by the birth weight reducing effect of maternal smoking and, in part, by direct influences of toxic tobacco constituents in organ tissue of the fetus itself. The resulting birth weight reduction is approximately 200–250 g. Low-birth weight children in general (i.e., regardless of the causes of the low birth weight) have a relatively bad prognosis for physical and mental health. Gestational age contributes greatly to the variation in birth weight, but effects of maternal smoking add to the consequences for the child.

The birth weight reducing effects of maternal smoking are the same in singletons as in (individual) twins and triplets. The causative factors, therefore, must be located in the mother (i.e., decreased placental blood flow through placenta to the fetus, a nicotine-produced reduction of intraterine partial pressure of oxygen [pO₂], and a carbon-monoxide-produced decreased oxygen supply to the fetus), rather than in the individual children.

Nevertheless, it must be assumed that toxic tobacco smoke constituents are also transported to the child.
Researchers have shown in several animal studies that exposition of adult female animals during pregnancy has measurable neurophysiological and neuroanatomical effects in the offspring. Peters\textsuperscript{5} determined that 6 mg nicotine/kg · d in drinking water provided to rats throughout pregnancy effected significantly increased adrenergic receptor binding in the cerebral cortex of adult male rat offspring. This receptor binding appeared to involve $\alpha_1$-receptors, rather than $\alpha_2$- or $\beta_2$-subtype receptors.\textsuperscript{10,11}

Slotkin et al.\textsuperscript{12} administered 6 mg/kg · d nicotine by intravenous injection to adult female rats during the first 20 d of gestation. They reported an elevation in activity of the enzyme ornithine decarboxylase (ODC [this enzyme and its metabolites—the polyamines—are major regulators of macromolecule synthesis during replication and differentiation]) in the fetal brain, as well as suppressed deoxyribonucleic acid (DNA) synthesis in the newborn brains—especially in the cerebellum.\textsuperscript{12} In a subsequent study, Slotkin et al.\textsuperscript{13} exposed pregnant female rats to the same dose of nicotine, and they reported that there was an elevation in transmitter turnover in central noradrenergic pathways in the offspring. Slotkin et al. found the strongest effects in late-developing regions (cerebellum), intermediate effects in earlier-developing regions (cerebral cortex), and the weakest effects in regions that mature earliest (midbrain and brainstem).\textsuperscript{13} These adrenergic effects were likely produced by disruption of differentiation of specific cholinergic target cells, which contain nicotine receptors. Van de Kamp and Collins\textsuperscript{14} clearly demonstrated this effect on nicotinic receptors in mice.

In a recent study, Richardson and Tizabi\textsuperscript{15} studied offspring of nicotine-exposed pregnant female rats and found evidence of reductions of dopaminergic activity in the ventral tegmental area (VTA), nucleus accumbens (NAcc), and striatum (STR) of those offspring. Furthermore, Lewis et al.\textsuperscript{16} showed that mice bred selectively for low aggression had lower dopaminergic activity in the NAcc and caudate nucleus than mice from a highly aggressive strain. These observations are not incompatible with those reported by Sexton et al.,\textsuperscript{18} who described the following for children born to mothers who smoked: increased problem behaviors (particularly hyperactivity), poor language development, and delayed general cognitive development.

Another perinatal condition that might be responsible for these types of behavioral effects is being bottle fed during the first weeks of life.\textsuperscript{19} Mothers who smoke during pregnancy tend to bottle feed their child; however, this confounds both of these conditions.\textsuperscript{20} We therefore investigated the prevalence of behavioral problems observed by parents in 3-y-old children and compared it with maternal smoking during pregnancy, corrected for the confounding effects of birth weight and breast/bottle feeding. Because both maternal smoking and the infant's feeding habits (i.e., breast or bottle) are supposedly associated with social class, and because birth weight is related to maternal age, we adjusted the problem behavior-smoking relationship for social class and maternal age.

Method

Subjects. Approximately 45% of all multiple births (mostly twins) in the Netherlands since the end of 1986 have been registered in the Netherlands Twin Register (NTR), which has been kept by the Department of Physiological Psychology at the Free University of Amsterdam. Researchers have registered more than 9 600 twin pairs, varying in age between 2 mo and 8 y; parents of the children have given their written permission for registration. Parents completed several questionnaires about their twins. The first questionnaire, which the parents completed soon after birth, contained questions about birth weight, gestational age, health problems, smoking and drinking habits of the mother during pregnancy, among others. The department mailed a second questionnaire to the parents when the children were between 1.5 and 2 y of age. It contained questions that primarily concerned health and motor development. At the time the children were 3 y of age, the parents filled out the Child Behavior Checklist for 2- to 3-y-old children (CBCL/2-3), developed by Achenbach, Edelbrock, and Howell and translated into Dutch by Verhulst.\textsuperscript{21-23} Investigators mailed this checklist to 7 972 families with twins; parents of 1 377 twin pairs (corresponded with approximately 35% of all Dutch twins in the 2-3 y age category) completed and returned the checklist.

Measures. The CBCL/2-3 is an assessment instrument designed to obtain parental ratings of problem behaviors in 2- to 3-y-old children. The list contains 99 items that describe different behavioral problems. Each item can be endorsed with 0 (not true) or 1 or 2 (true). The answers to the 99 items result in scores on seven behavioral problem categories: oppositional, aggressive, overactive, withdrawn, anxious, sleep problems, and somatic problems. The first three categories contribute collectively to the higher-order problem category, externalizing behavior problems, whereas withdrawn and anxious form the higher-order category, internalizing behavior problems. The sum of all problem categories give one total CBCL score.

Two to 3 y earlier (i.e., in the first-mailed questionnaire sent soon after birth), investigators collected pre- and perinatal information, including the smoking habits of the mother during pregnancy. The question “Did you smoke during pregnancy?” could be answered by the respondent with one of three possible options: never, sometimes, or regularly. In addition, investigators collected information on the following potential confounding factors: birth weight, socioeconomic status, feeding during the first 3 wk (bottle or breast), and maternal age.

Model selection. Preliminary data analysis revealed that distributions of the dependent variables (i.e., CBCL total, externalizing, internalizing, and all the separate problem dimensions) were skewed very positively. To obtain a more symmetric and near-normal distribution, we performed a square-root transformation on each of the dependent variables. For each of the dependent variables and for each child (first- or second-born) separately, we used a model-fitting approach to conduct...
<table>
<thead>
<tr>
<th>Effect</th>
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<th>Externalizing</th>
<th>Internalizing</th>
<th>Aggression</th>
<th>Oppositional</th>
<th>Overactive</th>
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<td></td>
<td>b</td>
<td>t/F*</td>
<td>p</td>
<td>b</td>
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<td>1.229/1.224</td>
<td>1.222/1.221</td>
<td>1.226/1.220</td>
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</table>

*p values were used, unless indicated otherwise.
+t values were used, unless indicated otherwise.
covariance analysis. The starting point in each case was the standard covariance model, with maternal smoking and sex of the child as factors, and (the linear effects of) birth weight, gestational age, SES, and breast feeding (amount) as covariates. We defined SES as the mean of the variables, father's education, mother's education, and profession of the father (Cronbach's \( \alpha = .76 \)). We initially investigated in a stepwise manner whether quadratic terms of the covariates and covariate × covariate interactions significantly improved the fit of the model. We conducted all tests at the \( \alpha = .05 \) level. We finally determined that no extra covariate terms were necessary. We then investigated—for each covariate separately—whether a cell-specific term improved the model fit significantly. After these two steps, we investigated whether the Maternal Smoking × Sex of the Child interaction could be simplified or removed entirely. Because breast feeding never showed a significant effect, we also removed this covariate from all the models. Finally, we investigated whether effects involving maternal smoking could be described more efficiently by a linear component only.

**Results**

Of the 1365 mothers available, 898 (65.8%) had not smoked at all during pregnancy, 198 (14.5%) smoking sometimes, and 269 (19.7%) had smoked regularly. The results of the analyses are shown in Table 1, together with \( R \) and the semi-standardized regression coefficients \( b \) for main factors and covariates. In the case of the factorial main effects, maternal smoking and sex, \( b \) represents the expected increase in the standardized square-root-transformed dependent variable when the independent factor increases by one category. In the case of the (continuous) covariates, \( b \) represents the expected increase in the (transformed) standardized dependent variables per 1 standard deviation increase in the independent variable. In all cases, we could simplify the main effect of maternal smoking by a linear component (i.e., quadratic term was not significant), but the Maternal Smoking × Covariate interactions shown in Table 1 were more complex (especially the SES × Maternal Smoking interaction for CBCL total, internalizing, and overactive). One should realize that for a regression analysis with a significant Maternal Smoking × Covariate interaction, the linear main effect of maternal smoking must be interpreted for an average case.

We attributed the significant effect of smoking on CBCL total score to the contribution of externalizing to CBCL total. The effect of internalizing was much weaker, or negligible. The CBCL total was elevated significantly in boys, compared with girls, and we attributed this to the enhanced (constituting) externalizing score. Maternal smoking was associated significantly with CBCL total and was also the result of the increased externalizing score for children of smoking mothers. Internalizing in boys was not different from that in girls. Because externalizing was the important second-order CBCL factor that was associated with maternal smoking, we analyzed more specifically the constituting first-order factors (i.e., oppositional, aggressive, and overactive). The results (Table 1) showed a very significant effect of sex (i.e., boys scored higher than girls) for aggressive and overactive, and in first-born twins only for oppositional, all of which was confirmed by earlier research. Furthermore, all problem categories that constituted externalizing were associated positively with maternal smoking, aggressive, and particularly oppositional. There appeared to be significant interactions between maternal smoking and SES for some of the problem categories (Table 1).

**Discussion**

The results of this study suggest that toxic tobacco smoke constituents—most likely nicotine—that circulate in maternal blood may pass the placenta and enter the fetal circulation, where they in turn can pass the fetal blood-brain barrier and affect tissue of the central nervous system. Perhaps this was the reason for the increased CBCL problem-behavior scores (particularly aggressive and overactive) in children born to mothers who smoked.

We realize that our data did not allow us to draw this conclusion directly. We had no experimental design that was suitable for inferring causality. Animal experimental evidence, however, as cited earlier, has provided proof that nicotine administered to pregnant animals arrives at several sites of the central nervous system of the offspring and leads to behavioral effects comparable with human externalizing types of behavior. One should realize the possibility that aggressive people tend to smoke and that smoking mothers pass this behavioral feature to their offspring (as is the case with other personality traits). Such a mechanism could produce the results described earlier. Apart from the animal data, which point toward a causal relationship, another argument against the genetic explanation originates from the observation that smoking behavior and hostility (assuming that hosts is strongly related to aggression) are correlated for reasons of shared environmental influences, and not because common genes exist. The incidental interactions between SES and maternal smoking suggest that the effect of smoking on problem behavior was smaller in higher SES categories.

In conclusion, the results of the present study show that maternal smoking during pregnancy has adverse effects on later behaviors of children. In particular, externalizing behavior problems appear to be increased. We think that maternal smoking may directly affect structures in the central nervous system, thus leading to enhanced externalizing behavior (aggression, more specifically) in the offspring.

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References