Background Paper

Association of \textit{in utero} or Postnatal Environmental Tobacco Smoke Exposure and Neurodevelopmental and Behavioral Problems in Children

B. Eskenazi, R. Castorina, School of Public Health, University of California, 140 Warren Hall, Berkeley, CA, USA
Tel: 1 510 642 3496; Fax: 1 510 642 5815; Email: eskenazi@uclink4.berkeley.edu
**Introduction**

Numerous studies have examined whether maternal smoking during pregnancy is associated with behavioral or neurodevelopmental difficulties in children. The commonly accepted mechanism for these effects is altered brain development resulting from fetal hypoxia due to either nicotine in cigarette smoke that acts to reduce blood flow to the fetus or possibly from carbon monoxide which produces higher levels of carboxyhemoglobin\(^1\)\(^-\)\(^2\)\). Nicotine may also target specific neurotransmitter receptors in the fetal brain causing abnormalities in cell proliferation and differentiation\(^3\).

Maternal smoking during pregnancy has been associated in children of preschool age or older with small deficits (less than 10 percent) in general intellectual ability, language/auditory related tasks and in academic achievement\(^4\)-\(^10\). These studies often report dose-related effects. For younger children (age 2 or younger), the association of in utero exposure to maternal smoke is less consistent, although assessment tools may be less sensitive for this age group\(^1\)\(^11\)-\(^14\). However, decreases in auditory habituation and responsiveness have been consistently noted in infants less than one week old exposed to maternal smoke in utero\(^1\)\(^5\), \(^16\).

Previous studies, for the most part, have reported an association between behavioral problems, such as hyperactivity and decreased attention spans, and maternal smoking during pregnancy\(^7\), \(^17\)-\(^22\). Only one study, which had an insufficient number of heavy smokers\(^23\), did not report such a relationship. The association with behavioral problems has been shown in investigations of hyperactive children and controls\(^17\), sibling studies in which the mother smoked in one pregnancy but not in the other\(^7\), and in neuropsychological evaluation of children of smokers and nonsmokers using tests of sustained vigilance and attention\(^20\), \(^22\). Naeye and Peters\(^7\) found that hemoglobin levels in neonates increased with the number of cigarettes their mother smoked during pregnancy, and that children who were more active or who had shorter attention spans had significantly higher hemoglobin levels.

However, the primary aim of this paper is to determine whether environmental tobacco smoke (ETS) exposure to the fetus or child also could be associated with neurodevelopmental or behavioral effects; that is, are there adverse consequences to the child from the mother’s passive exposure to cigarette smoke during pregnancy or the exposure of the child to the smoke of others postnatally? Few of the above studies on neurobehavioral effects of smoking have attempted to separate out the influence of in utero exposure to maternal smoking from the effects of the child’s exposure to ETS postnatally. To determine the independent effect of postnatal ETS exposure would require a large sample size, because women who smoke during pregnancy also tend to smoke afterwards. A review by the California EPA\(^24\) concluded that ETS may pose a neuropsychological developmental hazard. However, since this document was written, a number of new studies have been published. Table 1 presents the 17 studies which have examined the relationship between ETS exposure and neurodevelopment and behavior. In this table, we have included only those studies which attempted to separate out the effects of maternal active smoking from passive ETS smoke exposure by the pregnant mother or the child. We review the most pertinent studies below.

**Academic performance and achievement scores**

Children of smokers have been shown in a couple of studies to perform somewhat more poorly in school than children of nonsmokers. For example, a study of over 3000 14 year olds in Finland\(^25\) found that current paternal smoking (as determined by mailed questionnaire) was at least as strongly related to poorer school performance as maternal smoking during pregnancy, and that this association was dose-related after adjusting for a number of potential confounders such as mother’s smoking habits, socioeconomic status (SES), birth order and gender. Similarly, a U.S. national survey of 7 to 17 year olds found that children of parents who reported smoking at the time of the survey were more likely [odds ratio 1.4 (95% CI 1.1, 1.7)] to have had a history of repeating kindergarten or first grade\(^26\). This study did not obtain information on the exposure of the child to maternal smoke during pregnancy and therefore, we cannot conclude whether the observed association is related to postnatal ETS exposure.

Children of smokers have been compared to children of nonsmokers on standardized tests of academic achievement. Bauman et al.\(^27\) compared the California Achievement Test (CAT) scores of eighth grade children of smokers and children of nonsmokers. They reported a dose-response relationship between total number of cigarettes smoked currently by family members and the children’s overall CAT scores, and found differences between children of smokers and of nonsmokers particularly in spelling and language skills. However, this study did not obtain information on prenatal maternal smoking and therefore, could not determine whether the observed relationship may have been due to maternal smoking during pregnancy. In contrast, Makin et al.\(^28\) used data from the Ottawa Prenatal Prospective Study to
investigate 6 to 9 year old children of nonsmoking mothers who reported being exposed to ETS during pregnancy (maternal ETS exposure), children of nonsmoking mothers not exposed to ETS during pregnancy, and children of mothers who smoked during pregnancy (maternal active smoking). They found that both the children of mothers who were ETS exposed during pregnancy and children of mothers who smoked during pregnancy performed more poorly, in particular, on tests of speech and language, and that there were no clear differences between the two exposed groups; however, they did not have substantially lower scores than children of nonsmokers not ETS exposed on the Wide Range Achievement Test, which assesses spelling, word identification and arithmetic. On a slightly different subset of the Ottawa cohort and using some additional reading tests, neither prenatal maternal ETS exposure in nonsmoking mothers nor postnatal childhood ETS exposure was associated with a discriminant analysis score dominated by reading comprehension. These findings on the same cohort suggest that prenatal maternal and postnatal child ETS exposure may not affect reading or other measures of achievement, but may have effects on other speech and language skills (see below).

Performance on Neuropsychological Tests

A number of studies have evaluated the relationship of maternal ETS exposure during pregnancy and postnatal child ETS exposure and children’s performance on neuropsychologic tests of perception, fine motor skills, language, general cognitive abilities, and visual spatial skills. Again, not all of these studies were designed to separate out the effects of maternal ETS exposure during pregnancy or postnatal child ETS exposure from effects of maternal active smoking during pregnancy, and most could not control for the potentially confounding effects of other factors such as home environment, social class and maternal intelligence. The importance of adequate control for potential confounders is highlighted in a prospective cohort study by Baghurst et al. designed to examine the effects of lead. They found that children of women who smoked after pregnancy compared to those who did not had slightly lower scores at age two years, on the Mental Development Index of the Bayley Scales of Infant Development and at age four, on the General Cognitive Index of the McCarthy Scales of General Abilities and specifically, on the verbal, perceptual, and motor subtests; however, all differences substantially diminished after adjusting for social class, home environment and mother’s intelligence. Maternal active smoking during pregnancy or maternal ETS exposure during pregnancy was not considered in the analyses.

A number of the investigations on neuropsychological functioning of children exposed to ETS during childhood or of mothers exposed to ETS during pregnancy are from the Ottawa Prenatal Prospective Study. Effects of maternal exposure to ETS during pregnancy were examined in children 6 to 9 years old by Makin et al. A two-group discriminant function was able to successfully classify 83% of the children into their respective exposure groups based on their poorer performance particularly in receptive vocabulary (Peabody Picture Vocabulary Test), and factors developed for perceptual organization and freedom from distractibility (from the Wechsler Intelligence Scale for Children-Revised). These differences remained after controlling for social class, but there was no measurement of maternal intelligence or of home environment. In the only study where postnatal ETS exposure was assessed with a biomarker, McCartney et al. found central auditory processing important in receptive language, to be poorer in 110 6 to 11 year old Ottawa children who were ETS exposed postnataally or whose mothers were ETS exposed during pregnancy, and these groups did not differ from each other. These deficits from pre- and postnatal ETS exposure were similar to those seen in children of light active smokers during pregnancy. In contrast, other follow-up investigations of this same cohort which used different assessment tools found that children exposed to ETS during childhood but not children whose mothers were ETS exposed during pregnancy had significant language/auditory processing deficits. Although there were language/auditory deficits among those exposed to ETS during childhood, when analyses were restricted to children of women who did not smoke during pregnancy there were no general cognitive effects (using a discriminant analysis score) of either prenatal maternal ETS exposure or of postnatal child ETS exposure. The timing of exposure during childhood did not influence the results.

Two studies analyzed the data from the Child Health and Development Studies (CHDS), a study of over 20,000 pregnancies which occurred at Northern California Kaiser Permanente between 1959 and 1967. Mothers were interviewed about their smoking habits during pregnancy and serum was collected, and mothers were reinterviewed about smoking habits at follow-up. A portion of these children were evaluated on neurodevelopmental tests at ages five, nine to eleven, and fifteen to seventeen years. Because this data set followed up over 2000 children at each age, it was possible to separate out the effects of passive and active cigarette smoke. In one study, Bauman et al. reported that scores from the
A recent longitudinal study by Williams et al.\textsuperscript{37} of over 4000 4 to 6 year olds in Australia reported that over 25\% of externalizing problems (defined as a child who is argumentative, disruptive, lies or has a bad temper) are due to smoking during pregnancy compared to 16\% due to mother’s smoking when the child is 5 years. However, the authors reported no association between mother’s report of such behavior problems and maternal smoking during late pregnancy nor with smoking at 6 months postnatal. These results controlled for maternal mental health, education level, SES as well as other confounders.

Four studies including those by Weitzman et al.\textsuperscript{35} and Fergussen et al.\textsuperscript{36} reported a relationship between parental smoking and attention disorder with hyperactivity. In an early case-control study\textsuperscript{17} of “methylphenidate sensitive hyperkinetic children” and age, sex, and social class matched dyslexic and...
‘normal’ controls, mothers of cases were found to consume a greater number of cigarettes per day during and after pregnancy than mothers of controls. There were smaller differences in the amount smoked by the fathers either during or after the pregnancy. Eskenazi and Trupin found a dose-relationship between a mother’s ratings of her child’s activity level and the number of cigarettes she reported consuming at the time of child’s assessment at 5 years old, after controlling for prenatal maternal smoking and other confounders. Neither maternal active smoking nor ETS exposure during pregnancy as assessed by serum cotinine levels were related to maternal ratings of the child’s activity level. Furthermore, adjusted regression coefficients for each combination of prenatal -postnatal smoke exposure demonstrated no clear dose-relationship assessment of activity levels.

Is ETS exposure prenatally or postnatally causally related to adverse effects on neurodevelopment or behavior?

The studies outlined in Table 1 suggest that ETS exposure to the mother during pregnancy or to the child during postnatal development may be related to small adverse effects on neurodevelopment or behavior. In particular, three studies have reported poorer academic performance either as measured by school progress or by achievement test scores in relation to paternal, maternal or household smoking as reported at the time of the follow-up during childhood; however, none of these studies adjusted for the potential contribution of in utero maternal active smoke. Seven studies have examined the relationship of postnatal exposure to smoke and performance on a range of cognitive, perceptual, central auditory and linguistic abilities. Of the six studies which controlled for prenatal maternal smoking and showed statistically significant decrements associated with postnatal ETS exposure. Also, two of these studies suggest that children of mothers who smoked only after pregnancy performed somewhat worse than children of mothers who smoked only during pregnancy. Postnatal ETS exposure has been associated with behavioral problems in all three studies which specifically examined behavior problems in children and adequately controlled for home environment and other potentially intervening factors; two of these three studies, however, showed larger associations between behavioral problems and prenatal exposure to maternal smoke than with postnatal child ETS exposure.

There are only three studies which investigated the relationship of maternal ETS exposure during pregnancy and general cognitive performance, two of which were on the same cohort. The first study on the Ottawa cohort reported adverse cognitive effects of maternal ETS exposure during pregnancy as strong as those for active smoking but did not take into account postnatal exposure, whereas the second study showed no relationship between maternal ETS exposure during pregnancy among nonsmokers and general cognitive performance in their children. Similarly, Eskenazi and Trupin assessed maternal ETS exposure by serum cotinine and took into account postnatal exposure, also found no effects.

Assessing whether ETS exposure is causally related to adverse effects on neurodevelopment is difficult for at least three reasons:

1) Results may be explained by uncontrolled confounding.

A complex web of genetic and socioenvironmental factors influence human cognitive development and behavior, and therefore, it is difficult to determine if the relationship between ETS exposure and adverse outcomes is causal and/or direct. For example, postnatal ETS exposure may be linked with otitis media, which can lead to sustained middle ear effusion and hearing loss, which, in turn, could result in language difficulties and academic problems. Similarly, maternal ETS exposure during pregnancy may lower birthweight, which in turn may be related to lowered cognitive abilities and behavioral problems. Given birthweight may be on the causal pathway between ETS exposure and adverse neurodevelopmental outcomes, Baghurst et al. discussed the potential for ‘over-control’ if birthweight remained in the multivariate model.

There are likely to be a number of immeasurable differences between smokers and nonsmokers in personality, home environment, rearing practices, and parental intelligence which cannot be readily ascertained. The investigator may not know and therefore, cannot control for all these factors. The fact that children of ‘quitters’ performed better than those of ‘starters’ in a number of studies suggests that other factors which are related to choosing to begin smoking rather than quitting may confound the results. For example, Eskenazi and Trupin found that women who quit after pregnancy were of higher social class than those who smoked throughout or who started smoking after pregnancy. Leftwich and Collins suggested that depression is related to smoking and that depression may alter childrearing
practices which may affect the child’s development and behavior. Clearly, as proposed by Yerushalmy\textsuperscript{40}, it may be characteristics of the smoker rather than smoking per se that affects development or behavior.

2) Exposure has not been accurately assessed.

Tong and McMichael\textsuperscript{41} noted that most studies have suffered from lack of valid and precise measures of exposure. Misclassification of exposure could be either random or systematic, and therefore, it may be difficult to predict the direction of the bias. Most studies assess level of ETS exposure to the child by asking the mother the amount she smoked or the amount smoked by the father or other household members. Although some studies have suggested that questionnaire data may be valid in assessing ETS exposure, a biomarker of exposure is likely to more accurately reflect exposure from multiple sources in and out of the home\textsuperscript{42, 43}. Correlations between questionnaire data and cotinine measurements range between .4 and .7\textsuperscript{42, 43}. Only two studies to date have employed a biomarker of exposure to assess prenatal\textsuperscript{34} and postnatal\textsuperscript{31} ETS exposure. Given that the half-life of cotinine is relatively short, a single measure in serum, urine or saliva may not accurately assess the extent of exposure throughout pregnancy or childhood.

3) Postnatal ETS exposure and prenatal maternal smoking are often collinear.

Most studies have failed to assess the true independent effects of postnatal ETS exposure. Postnatal ETS exposure is collinear with maternal smoking during pregnancy; that is, most women who smoke during pregnancy continue to smoke after pregnancy. Because of this collinearity, statistically controlling for prenatal exposure may produce artifactual results. To separate out the effects of in utero exposure from postnatal ETS exposure requires large sample sizes of women who smoke only during pregnancy or only during the postnatal period. Furthermore, the effects of ETS exposure may only exist or be apparent when the mother does not smoke during pregnancy\textsuperscript{31}.

Is it biologically plausible that ETS exposure during childhood could cause adverse neurodevelopment or behavior?

It remains possible that ETS exposure during childhood may be hazardous, and potentially more hazardous, to neurodevelopment than in utero exposure to maternal smoking. The routes of exposure of prenatal and postnatal exposure differ: the fetus is exposed transplacentally to compounds absorbed by the mother, while the child is exposed primarily through inhalation. Also, the chemical constituents and their levels differ, to some extent, in ETS and mainstream smoke\textsuperscript{44}. Childhood may be the critical period for neurodevelopmental effects of smoking. Furthermore, exposure during childhood may be longer than the limited time of 9 months for in utero exposure. These differences potentially could explain why those exposed in the postnatal period perform worse than children of nonsmokers.

Perhaps the strongest evidence for a causal relationship between the child’s exposure to ETS and adverse effects on neurodevelopment is from a single animal study. Gospe et al.\textsuperscript{45} exposed pregnant rat dams to sidestream smoke (SS) or filtered air (FA) for 4 hours a day, everyday throughout gestation, and exposed the offspring to either SS or FA for nine weeks postnatally for a total of 4 different exposure conditions: in utero FA-postnatal FA, in utero FA-postnatal SS, in utero SS-postnatal FA, and in utero SS-postnatal SS. After 9 weeks of postnatal exposure, the animals were sacrificed and the brains were divided into forebrain and hindbrain, analyzed for DNA, protein, and cholesterol concentration. Two-way analysis of variance indicated that postnatal SS reduced by 4\% hindbrain DNA concentration, an indicator of cellular density, and increased by 8.9\% the hindbrain protein/DNA ratio, an index of cell size, although the total hindbrain weight was no different. In utero exposure to SS had no effect. This study provides the first clear biologic evidence for an alteration of brain development due to postnatal but not prenatal ETS exposure.

Conclusion

Animal and human data suggest that ETS exposure could cause subtle changes in child neurodevelopment and behavior. However, studies to date are difficult to interpret due to the unknown influence of uncontrolled confounding factors, imprecision in measurements of smoking exposure and collinearity of pre- and postnatal maternal smoking. While evidence exists to suggest that maternal smoking during pregnancy may be associated with deficits in intellectual ability and behavioral problems in children, the impact of prenatal or postnatal ETS exposure remains less clear. However, animal evidence does suggest that effects of postnatal ETS on neurodevelopment and behavior are possible.
<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Study Design</th>
<th>Population</th>
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<th>Outcome / Assessment Instruments</th>
<th>Exposure Definition and Assessment</th>
<th>Prenatal or Postna</th>
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<tbody>
<tr>
<td>Denson et al., 1975</td>
<td>Case-control study</td>
<td>5-15 year olds</td>
<td>N=20 hyperkinetic Children N=20 dyslexic children Control group 1 N=20 healthy children Control group 2</td>
<td>Hyperactivity</td>
<td>Interview (mother) • retrospective report Maternal and paternal pre- and postnatal smoking (cigs/day)</td>
<td>Cigs/day Cases Control 1 Control 2 During pregnancy: paternal 22.2 15.7 18.5 At follow-up: maternal smoking 23.3*** 6.1 8.2 At follow-up: paternal smoking 21.3 14.6 20.7 • No control for prenatal maternal smoking</td>
</tr>
<tr>
<td>Rantakallio et al., 1983</td>
<td>Prospective Finnish Cohort Study</td>
<td>14 year olds</td>
<td>N=1,844 children of Smoking mothers N=1,844 controls</td>
<td>School performance: • Lower level than expected • Ability in theoretical subjects</td>
<td>Mailed questionnaire (mother) • Maternal smoking during 2nd month of pregnancy • Paternal smoking (Never / Former / Present)</td>
<td>• Inverse association of all theoretical subjects with amount father smoked currently*** • Controlled for prenatal maternal smoking</td>
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<tr>
<td>Bauman et al., 1989</td>
<td>Cross-sectional North Carolina 8th graders</td>
<td>8th graders</td>
<td>N=622 children of Smokers N=351 children of non Smokers</td>
<td>California Achievement Test (CAT) • Mathematics • Language • Reading • Spelling</td>
<td>Interview (mother) • Number of cigarettes currently smoked by family members (total) • Maternal breath specimens analyzed for CO for confirmation • Report of sibling smoking by adolescent</td>
<td>Dose-response relationship (ANOVA p&lt;0.001) ( R^2= ) Current total Adjusted: Cigs/day total score ( 0 ) 618.8 ( 1 - 19 ) 610.0 ( 20 - 39 ) 606.8 ( \geq 40 ) 602.9* • Dose-response relations also on subtests particularly for language** and spelling • No control for prenatal maternal smoking</td>
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1 ns=not significant (p>0.05), *p<0.05, **p<0.01, ***p<0.001; if no * is present, not statistically significant.
### Association of Exposure to Environmental Tobacco Smoke *in Utero* and Postnatally and Neurodevelopment and Behavior (cont'd)

<table>
<thead>
<tr>
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<th>Exposure Definition and Assessment</th>
<th>Prenatal or Postnatal Exposure Definition and Assessment</th>
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</thead>
</table>
| Bauman and Flewelling, 1991 33 | Prospective Cohort  Child Health and Development Studies  N California Kaiser  Children followed-up at:  5 years  N=4,939  9-11  N=3,414  15-17  N=2,020 | • Goodenough-Harris Drawing Test  • The Quick Test  • Peabody Picture Vocabulary Test (PPVT)  • Raven Colored Progressive Matrices Test (RAVEN) | Interview (mother)  Prenatal maternal smoking (Yes/No) (Cigs/day)  Parental postnatal smoking at each age of follow-up (Yes/No) (Cigs/day) | Parental postnatal smoker  Adjusted score difference (p<
|                          |               |                                                                            |                                                                                                      |                                                                                                      |                                                                                                                     |
|                         |               |                                                                            |                                                                                                      |                                                                                                      | Parental ETS vs. Nonsmoke  Unadjusted mean score difference:  Sound blending -0.4  PPVT -9.7  TOLD syntax -5.5  WISC-R Freedom -1.2  Pegboard - Dominant -0.4  Draw-a-Man 0.9 (other tests ns)                                                                 |
| Makin et al., 1991 28   | Ottawa Prenatal  Prospective Study  6-9 year olds  N=23 children of nonsmokers (no prenatal ETS)  N=35 children of nonsmokers who were exposed to smoke during pregnancy  N=32 children of Smokers | • Sound blending  • Peabody picture vocabulary test (PPVT)  • Test of Language Development (TOLD)  • Wechsler intelligence scale for children revised (WISC-R)  • Pegboard Fine Motor Test  • Development Drawing Test  • Conner’s Behavior Scale (mother’s rating)  • Goodenough-Harris Draw-a-Man Test  • Wide Range Achievement Test (WRAT) | Interview (mother)  Maternal smoking:  Prenatal (Yes/No)  Postnatal (Yes/No)  Exposure to postnatal ETS  30% of children of nonsmokers  37% of children of ‘passive’ smokers during pregnancy  97% of active smokers children |                                                                                                                  |

1. ns=not significant (p>0.05), *p<0.05, **p<0.01, ***p<0.001; if no * is present, not statistically significant.
Association of Exposure to Environmental Tobacco Smoke *in Utero* and Postnatally and Neurodevelopment and Behavior (cont’d)

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<th>Postnatal maternal smoking</th>
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</thead>
<tbody>
<tr>
<td>Baghurst et al., 1992&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Prospective Port Pirie Cohort Study, Australia N = 550 Evaluated at 2 and 4 years</td>
<td>Bayley Scales of Infant Development (2 years) • Mental Development Index • Motor Scale (MDI) McCarthy Scales of Children’s Abilities (4 years) • General Cognitive Index (GCI)</td>
<td>Interview (mother) • Maternal prenatal smoking (Yes/No) as reported at 1&lt;sup&gt;st&lt;/sup&gt; trimester and 32 weeks • Postnatal maternal smoking (Yes/No) • Paternal smoking (Yes/No)</td>
<td>Score difference (points):</td>
<td><strong>Unadjusted</strong></td>
<td><strong>Adjusted</strong></td>
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<td>Bayley MDI</td>
<td>-2.7*</td>
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<td>PDI</td>
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<td>McCarthy GCI</td>
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<td></td>
<td>verbal</td>
<td>-1.9*</td>
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<td>perceptual</td>
<td>-2.4**</td>
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<td>quantitative</td>
<td>-1.1</td>
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<td>memory</td>
<td>-1.3</td>
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<td>motor</td>
<td>-2.0**</td>
<td>-0.7</td>
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<tr>
<td>Roeleveld et al., 1992&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Retrospective Case-Control 0-15 year olds N=306 cases with unknown etiology N=322 physically Handicapped with known etiology (controls)</td>
<td>Mental retardation (IQ&lt;80)</td>
<td>Maternal/paternal interview for time period from 3 months preconception to 6 months postnatal • Father smoked anything • Father smoked pipe or cigars (Yes/No) • Mother smoked cigarettes (Yes/No)</td>
<td>Score difference (points):</td>
<td><strong>Odds Ratio (95% CI)</strong></td>
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<td>Father smoked</td>
<td>1.2 (0.8,1)</td>
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<td>Father pipe/cigar</td>
<td>2.4 (1.2,5)</td>
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<td></td>
<td>Mother smoked</td>
<td>1.1 (0.8,1)</td>
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<sup>1</sup> ns=not significant (p>0.05), *p<0.05, **p<0.01, ***p<0.001; if no * is present, not statistically significant.
### Association of Exposure to Environmental Tobacco Smoke in Utero and Postnatally and Neurodevelopment and Behavior

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</tr>
</thead>
<tbody>
<tr>
<td>Weitzman et al., 1992</td>
<td>Prospective cohort</td>
<td>US National Longitudinal Survey of Youth</td>
<td>4-11 year olds N=2,256</td>
<td>Behavior Problem Index (BPI) • Antisocial • Anxious/Depressed • Headstrong • Hyperactive • Peer conflict/ Social withdrawn • Immature Rating reported by mother</td>
<td>Interview (mother) Maternal smoking during and/or after pregnancy</td>
<td>Smoked after pregnancy on Adjusted OR (95% CI) for BPI Scores &gt;14: &lt;Pack/day 1.2 (0.9-1.7) ≥Pack/day 2.0 (1.3-3.1)** • At ≥1 pack/day significantly higher rates of all subscales except peer conflict Smoked during and after pregnancy: &lt;Pack/day 1.4 (1.1-1.8)* ≥Pack/day 1.5 (1.1-2.2)* • All subscales significantly higher at ≥1 pack/day</td>
</tr>
<tr>
<td>Fergusson et al., 1993</td>
<td>Prospective cohort</td>
<td>New Zealand 8, 10, 12 year olds N=1265</td>
<td>Adapted from Rutter and Conner’s Scales • Conduct disorder • Attention deficit • Disruptive behavior score Mother (M) and teacher (T) rated</td>
<td>Interview (mother) • Mother smoked during and/or after pregnancy • At delivery, mother’s report of smoking each trimester • After delivery, asked smoking habits each year</td>
<td>Postnatal maternal smoking Standardized regression coefficient (β) Conduct Attention Disruptive disorder deficit behavior M T M T M T (8 years) .1* .07 .08 .09 .1* .08 (10 years) .1 -.01 .1* .002 .1* -.01 (12 years) .1* .01 .09 -.02 .1* .00</td>
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1 ns=not significant (p>0.05), *p<0.05, **p<0.01, ***p<0.001; if no * is present, not statistically significant.
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</tr>
</thead>
</table>
| Byrd and Weitzman, 1994<sup>26</sup> | Cross-sectional Child Health Supplement to 1988 National Health Interview Survey 7-17 year olds N=9,996 | Grade retention - History of repeating kindergarten or first grade | Interview mothers or fathers (10%) Exposure to household cigarette smoke at time of survey (Yes/No) | Prenatal or Postnatal ETS

**Household smoke**

Adjusted OR (95% CI) 1.4 (1.1,1.7)**
- Significant interaction of children’s ETS exposure; deafness or high maternal education
- No control for prenatal maternal smoking

| McCartney et al., 1994<sup>31</sup> | Longitudinal Ottawa Prenatal Prospective Study 6-11 year olds N=110 | Central Auditory Processing Task (SCAN)
- Competing Words Subtest
- Filtered Words Subtest
- Auditory Figure Ground Subtest
- Composite Score | Interview mothers during pregnancy (each trimester) and at 6-11 years
- Maternal smoking during pregnancy
- None
- Light (>0-16 mg nicotine/day)
- Heavy (≥16 mg nicotine/day)
- Maternal passive smoke during pregnancy (hours/wk)
- Child postnatal ETS exposure (maternal questionnaire and urine cotinine) | SCAN Test
(Unadjusted Mean Score)
Nonsmoking Mothers
No ETS ETS Exp
- Competing Words 11.4 10.0
- Composite Score 106.5 103.6
- Group with mother ETS during pregnancy but child exposed performed equal to with both mother and child exposed

| Olds et al., 1994<sup>38</sup> | Prospective Cohort New York 1-4 year olds N=100 | Bayley Mental Development Index, 1 year
- Cattell Scales, 2 years
- Stanford-Binet IQ test, 3 and 4 years | Interview (mother) during pregnancy and at 4 years
- Pre- and postnatal maternal smoking (cigs/day) | Mothers who smoked ≥10 4 years post partum vs. nonsmokers
Adjusted score reduction (points):
- Stanford-Binet at 3 and 4 years: 3.1 (-0.9, 7.1)
- Controlled for prenatal maternal smoking

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<sup>1</sup> ns=not significant (p>0.05), *p<0.05, **p<0.01, ***p<0.001; if no * is present, not statistically significant.

<sup>2</sup> ETS Exposed' refers to women exposed to ETS during pregnancy and/or children who had been exposed to ETS.
<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Age at follow-up</th>
<th>Outcome / Assessment Instruments</th>
<th>Exposure Definition and Assessment</th>
<th>Prenatal or Postnatal Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eskenazi and Trupin, 1995\textsuperscript{34}</td>
<td>Prospective Cohort Study</td>
<td>Child Health and Development Studies N California Kaiser</td>
<td>5 year olds N=2,124</td>
<td>• Peabody Picture Vocabulary Test (PPVT) • Raven’s Colored Progressive Matrices (RAVEN) • Activity Level (mother’s report)</td>
<td>Interview (mother) during pregnancy and age 5 Serum cotinine levels from Pregnancy • No smoking exposure during pregnancy (Cotinine &lt;2 ng/ml) • Maternal ETS exposure during pregnancy (Cotinine $\geq$ 2 ng/ml) • Divided smokers into 4 groups: Nonsmokers, or pre- and/or postnatal smokers</td>
<td>PPVT RAVEN Activity Adjusted mean score OR (9\textsuperscript{4})</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Non-smoker 50.7 10.7 1.0</td>
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<td></td>
<td>Prenatal ETS 51.9 10.8 1.5 (0.7,\textsuperscript{5})</td>
</tr>
<tr>
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<td>Postnatal smoker 49.9 10.4 1.2 (0.6,\textsuperscript{5})</td>
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<td></td>
<td>Pre- + postnatal smoker 50.8 10.6 1.2 (0.9,1)</td>
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<td>Maternal smoking at follow-up (cigs/day): Adjusted regression coefficient PPVT RAVEN Activity SD=8.8 SD=2.4 OR (9 CI)</td>
</tr>
<tr>
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<td></td>
<td>None 0 0 1.0</td>
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<td></td>
<td></td>
<td></td>
<td>1-9 -1.5* -0.5* 1.0 (.6,\textsuperscript{5})</td>
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<td></td>
<td></td>
<td></td>
<td>10-19 -1.3 -.3 1.1 (.8,\textsuperscript{5})</td>
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<td></td>
<td></td>
<td>$\geq$20 -1.3 -.6* 1.6 (.9,\textsuperscript{5})</td>
</tr>
</tbody>
</table>

\textsuperscript{1} ns=not significant (p>0.05), *p<0.05, **p<0.01, ***p<0.001; if no * is present, not statistically significant.
## Association of Exposure to Environmental Tobacco Smoke in Utero and Postnatally and Neurodevelopment and Behavior (cont’d)

<table>
<thead>
<tr>
<th>Authors, Year</th>
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<th>Outcome / Assessment Instruments</th>
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<th>Prenatal or Postnatal ETS</th>
</tr>
</thead>
</table>
| Fried et al., 1997<sup>29</sup> | Prospective Cohort Ottawa Prenatal Prospective Study 9-12 year olds N=131 | 9-12 year olds | Reading and language  
  - Wechsler Intelligence Scale for Children-III (WISC-III)- verbal subtests  
  - Wide Range Achievement Test-Revised (WRAT)  
  - Peabody Picture Vocabulary Test (PPVT)  
  - Fluency Test  
  - Woodcock Reading Mastery Test  
  - Oral Cloze Task  
  - Seashore Rhythm Test  
  - Regular and exception pseudoword task  | Interview mothers during pregnancy (each trimester) and at follow-up  
  - Maternal smoking during pregnancy  
  - None  
  - Light (>0-16 mg nicotine/day)  
  - Heavy (≥16 mg nicotine/day)  
  - Maternal passive smoke exposure during pregnancy (yes/no)  
  - Child postnatal ETS exposure (maternal questionnaire)  | Correlation with Discriminant Analysis Scores  
  - Set 1  
  - Dominated by Reading Comprehension  
  - Maternal smokers and nonsmokers adj r=-.05  
  - Maternal nonsmokers only r=-.03  
  - Postnatal child ETS Exposure  
  - Maternal smokers and nonsmokers adj r=-.09  
  - Maternal nonsmokers only adj r=-.13  
  - No difference by age when exposed during childhood.  |

<sup>1</sup> ns=not significant (p>0.05), *p<0.05, **p<0.01, ***p<0.001; if no * is present, not statistically significant.
### Association of Exposure to Environmental Tobacco Smoke in Utero and Postnatally and Neurodevelopment and Behavior (cont'd)

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</thead>
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<tr>
<td>Fried et al., 1998&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Prospective Cohort Ottawa Prenatal Prospective Study 9-12 year olds N=131</td>
<td>Cognitive Performance • Wechsler Intelligence Scale for Children-III (WISC-III) • Gordon Diagnostic Delay and Vigilance Tasks • Category test • Auditory Working Memory test • Fluency test • Tactual Performance test</td>
<td>Interview mothers during pregnancy (each trimester) and at follow-up • Maternal smoking during pregnancy • None • Light (&gt;0-16 mg nicotine/day) • Heavy (≥16 mg nicotine/day) • Maternal passive smoke exposure during pregnancy (yes/no) • Child postnatal ETS exposure (maternal questionnaire)</td>
<td>Correlation with Discriminant Analysis Scores (Cognitive (Executive Function) Prenatal ETS Exposure • Maternal smokers and nonsmokers • Maternal nonsmokers only Postnatal child ETS Exposure • Maternal smokers and nonsmokers • Maternal nonsmokers only</td>
<td>No difference by age when exposed during childhood.</td>
</tr>
<tr>
<td>Obel et al., 1998&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Longitudinal Cohort Denmark 8 month-old infants N=1,817</td>
<td>Babbling abilities evaluated by health nurses</td>
<td>Questionnaire completed by mother during pregnancy and at 8 months • Maternal pre- and postnatal smoking (cigs/day) • Paternal smoking during pregnancy (hours of maternal exposure/day)</td>
<td>• No difference found in babbling abilities of infants whose mothers began smoking after pregnancy compared to nonsmokers Nonsmokers exposed to pater during pregnancy (hours/day) Non-polysyllable babblers (vs polysyllable babblers) hours/day Relative Risk</td>
<td>0 1 1-4 1.1 5 1.3 No 95% CI reported (ns)</td>
</tr>
</tbody>
</table>

<sup>1</sup> ns=not significant (p>0.05), *p<0.05, **p<0.01, ***p<0.001; if no * is present, not statistically significant.
### Association of Exposure to Environmental Tobacco Smoke in Utero and Postnatally and Neurodevelopment and Behavior (cont'd)

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<th>( \text{Prenatal} )</th>
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</table>
| Williams et al., 1998\(^37\) | Longitudinal Cohort Mater Australia 4-6 year olds N=4,879 | Child behavior check list (shortened CBCL):  - Externalizing problems (EXT) (argumentative, disruptive, lies, temper, etc.)  - Internalizing (INT)  - Social, attentional, thought (SAT) | Interviewed mother 4 times from 1\(^{st}\) prenatal visit to child 5 years  - Smoking assessed for prepregnancy, 1\(^{st}\) prenatal visit, late pregnancy, 6 months, and 5 years | • No adverse association with smoking status postnatal  
Maternal postnatal 5 years  
Adjusted RR >9 cigs/day EXT  
| \(0\) | \(1\)  
| \(1-9\) | \(1.5\)  
| \(10-19\) | \(1.9^*\)  
| \(\geq 20\) | \(1.3\)  |
| \% of children with behavior problems: |  
6.5\% Nonsmoker during pregnancy  
11.3\% Started smoking after pregnancy  
14.7\% Smoked continually | PAR=  
15.5\% of externalizing problems due to smoking at 5 years |

\(^{1}\text{ns}=\text{not significant (p}>0.05), \ ^{*}\text{p}<0.05, \ ^{**}\text{p}<0.01, \ ^{***}\text{p}<0.001; if no * is present, not statistically significant.}
REFERENCES


