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Background Paper

Association of *in utero* or Postnatal Environmental Tobacco Smoke Exposure and Neurodevelopmental and Behavioral Problems in Children

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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 differentiation³.

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 achievement⁴⁻¹⁰. 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 group¹¹⁻¹⁴. However, decreases in auditory habituation and responsiveness have been consistently noted in infants less than one week old exposed to maternal smoke *in utero*^{15, 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 smokers²³, did not report such a relationship. The association with behavioral problems has been shown in investigations of hyperactive children and controls¹⁷, sibling studies in which the mother smoked in one pregnancy but not in the other⁷, and in neuropsychological evaluation of children of smokers and nonsmokers using tests of sustained vigilance and attention^{20, 22}. Naeye and Peters⁷ 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 EPA²⁴ 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 Finland²⁵ 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 grade²⁶. 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 comprehension²⁹. 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.³⁰ 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.²⁸ 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.³¹ found central auditory processing important in receptive language, to be poorer in 110 6 to 11 year old Ottawa children who were ETS exposed postnatally 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^{29,32} 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 deficits²⁹. 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 exposure³². The timing of exposure during childhood did not influence the results.

Two studies^{33, 34} 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.³³ reported that scores from the

Peabody Picture Vocabulary (PPVT) and Ravens Colored Progressive Matrices Test of over 3000 9 to 11 year old children of mothers who smoked during pregnancy, but who quit afterwards, were similar to those of children of mothers who did not smoke during pregnancy or at follow-up; however, both these groups performed better than children of women who reported smoking at both points (maternal active smoking during pregnancy and postnatal child ETS exposure), and these, in turn, performed better than children of women who reported smoking only at the follow-up exam (postnatal child ETS exposure only). The authors found a dose-response relationship between the scores on both tests and level of parental smoking at follow-up (as reported by the mother). These differences were observed after controlling for maternal smoking during pregnancy, mother's performance on the PPVT, the child's birthweight, maternal and paternal education, and family income as well as other variables. No clear relationships were observed for parental or maternal prenatal smoking and test scores at age 5 years or at ages 15 to 17 years (PPVT only).

The second study which used the CHDS dataset, by Eskenazi and Trupin³⁴, is the only study in the literature to use a biomarker of exposure, cotinine measured in serum, to estimate passive and active smoke exposure during pregnancy, and to clearly assess the independent effects of prenatal and early childhood exposure. They found that children born to nonsmoking mothers who were exposed to ETS during pregnancy did not differ on the Raven and PPVT at age 5 from children born to nonsmokers who were not exposed to ETS. However, children whose mothers did not smoke during pregnancy, but who did smoke during childhood, had lower Ravens and PPVT scores than children of other women who did not smoke at either time. Children of mothers who smoked only during pregnancy but then quit, had the highest scores. These results controlled for multiple confounders including maternal and paternal education, and social class, but could not control for maternal intelligence or aspects of the home environment, since these were not assessed at the five year follow-up. The authors present the adjusted regression coefficients for each combination of prenatal (as determined by serum cotinine levels) - postnatal smoke exposure (number of cigarettes per day as reported by the mother) and there was no clear dose-relationship with either Ravens or PPVT scores.

Behavioral Assessment

Prenatal and postnatal exposure to cigarette smoke have been examined in relation to children's behavioral problems. It is not clear from many of these studies whether the critical period for effects is during pregnancy from prenatal exposure to active maternal smoking and/or from child postnatal ETS exposure. In a study by Weitzman et al. of over 2000 4 to 11 year olds participating in the National Longitudinal Survey of Youth³⁵, parental report of their child's behavior on the Behavior Problem Index (including subscale measures of antisocial behavior, depression and anxiety, headstrong personality, hyperactivity, and immaturity) was dose-related to amount smoked by mothers among those who only smoked after pregnancy, or smoked both before and after pregnancy. There was no clear dose-response relationship with prenatal maternal smoking only, possibly because very few mothers (n=19) smoked more than one pack during pregnancy and did not smoke afterwards. This study did examine the potential confounding effects of SES, home environment, and maternal education, self-esteem and intelligence. Another study³⁶ of over 1000 New Zealand children followed up at age 8, 10 and 12 years, attempted to replicate this study. One concern of the previous study was that the results may be due to information bias in that mothers who smoke may rate their children more negatively. Therefore, the New Zealand study included children's ratings by the mother as well as by the teacher on an index comprised of measures of conduct disorder, attention deficits and disruptive behavior. After accounting for the collinearity of prenatal and postnatal smoking, they found that in 13 of the 18 regression equations, there were significant associations between smoking during pregnancy and behavioral outcomes, but in only 6 regression models were the effects of smoking after pregnancy statistically significant, and all of these were based on maternal report. This study also controlled for many measures of SES, home environment and parenting.

A recent longitudinal study by Williams et al.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.³⁵ and Fergusson et al.³⁶ reported a relationship between parental smoking and attention disorder with hyperactivity. In an early case-control study¹⁷ 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 Trupin³⁴ 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 smoke²⁵⁻²⁷. Seven studies have examined the relationship of postnatal exposure to smoke and performance on a range of cognitive, perceptual, central auditory and linguistic abilities^{29-34,38}. Of the six studies which controlled for prenatal maternal smoking^{29,31-34,38}, half^{29,33,34} show statistically significant decrements associated with postnatal ETS exposure. Also, two of these studies^{33, 34} 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 children³⁵⁻³⁷ and adequately controlled for home environment and other potentially intervening factors; two of these three studies^{36, 37}, 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^{28, 32, 34} 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 smoking²⁸ but did not take into account postnatal exposure, whereas the second study³² 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 effects³⁴.

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 media²⁴, 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.³⁰ 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 Trupin³⁴ 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 Collins³⁹ 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 Yerushalmy⁴⁰, 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 McMichael⁴¹ 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^{42, 43}. Correlations between questionnaire data and cotinine measurements range between .4 and .7^{42, 43}. Only two studies to date have employed a biomarker of exposure to assess prenatal³⁴ and postnatal³¹ 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 pregnancy³¹.

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 smoke⁴⁴. 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.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 1. Association of Exposure to Environmental Tobacco Smoke *in Utero* and Postnatally and Neurodevelopment

Authors, Year	Study Design Population Age at follow-up	Outcome / Assessment Instruments	Exposure Definition and Assessment	Prenatal or Postnatal
Denson et al., 1975 ¹⁷	Case-control study 5-15 year olds N=20 hyperkinetic Children N=20 dyslexic children Control group 1 N=20 healthy children Control group 2 • Matched on age, sex and social class	Hyperactivity	Interview (mother) • retrospective report Maternal and paternal pre- and postnatal smoking (cigs/day)	Cigs/day <u>Cases</u> <u>Control 1</u> <u>Control 2</u> During pregnancy: paternal 22.2 15.7 18.5 At follow-up: maternal sm 23.3*** 6.1 8.2 At follow-up: paternal sm 21.3 14.6 20.7 • No control for prenatal maternal smoking
Rantakallio et al., 1983 ²⁵	Prospective Finnish Cohort Study 14 year olds N=1,844 children of Smoking mothers N=1,844 controls • Matched on marital status, age, parity and place of residence	School performance: • Lower level than expected • Ability in theoretical subjects Questionnaire (mailed)	Mailed questionnaire (mother) • Maternal smoking during 2 nd month of pregnancy • Paternal smoking (Never / Former / Present)	• Inverse association of al in theoretical subjects w amount father smoked currently*** • Controlled for prenatal maternal smoking
Bauman et al., 1989 ²⁷	Cross-sectional North Carolina 8 th graders N=622 children of Smokers N=351 children of non Smokers	California Achievement Test (CAT) • Mathematics • Language • Reading • Spelling	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	Dose-response relationship (ANOVA p<0.001) R ² =0.1 Current total Adjusted : <u>Cigs/day</u> <u>total score</u> 0 618.8 1 - 19 610.0 20 - 39 606.8 ≥40 602.9* • Dose-response relationsh also on subtests particul for language** and spell • No control for prenatal maternal smoking

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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Authors, Year	Study Design Population Age at follow-up	Outcome / Assessment Instruments	Exposure Definition and Assessment	Prenatal or Postnatal												
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	<ul style="list-style-type: none"> • 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) <table border="1"> <thead> <tr> <th>Age</th> <th>PPVT</th> <th>RAVEN</th> </tr> </thead> <tbody> <tr> <td>5</td> <td>-0.1</td> <td>-0.1</td> </tr> <tr> <td>9-11</td> <td>-1.6***</td> <td>-0.9*</td> </tr> <tr> <td>15-17</td> <td>-0.9</td> <td></td> </tr> </tbody> </table> (other tests ns) <ul style="list-style-type: none"> • Linear dose-response relationship at age 9-11 years with PPVT and Raven by level of parental smoking • Adjusted for prenatal maternal smoking • 9-11 years scores on PPVT/Ravens: Nonsmoker Quitters (postnatal) > Smokers (pre- and postnatal) > Starters 	Age	PPVT	RAVEN	5	-0.1	-0.1	9-11	-1.6***	-0.9*	15-17	-0.9	
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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	<ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • 30% of children of nonsmokers • 37% of children of 'passive' smokers during pregnancy • 97% of active smokers children 	Prenatal ETS vs. Nonsmoker Unadjusted mean score difference <table border="1"> <tbody> <tr> <td>Sound blending</td> <td>-0.4</td> </tr> <tr> <td>PPVT</td> <td>-9.7</td> </tr> <tr> <td>TOLD syntax</td> <td>-5.5</td> </tr> <tr> <td>WISC-R Freedom</td> <td>-1.2</td> </tr> <tr> <td>Pegboard - Dominant</td> <td>-0.4</td> </tr> <tr> <td>Draw-a-Man</td> <td>0.9</td> </tr> </tbody> </table> (other tests ns) <ul style="list-style-type: none"> • Most profound effects in spelling and language • No control for postnatal ETS exposure 	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
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Baghurst et al., 1992 ³⁰	Prospective Port Pirie Cohort Study, Australia N = 550 Evaluated at 2 and 4 years	Bayley Scales of Infant Development (2 years) <ul style="list-style-type: none"> • Mental Development Index • Motor Scale (MDI) McCarthy Scales of Children's Abilities (4 years) <ul style="list-style-type: none"> • General Cognitive Index (GCI) 	Interview (mother) <ul style="list-style-type: none"> • Maternal prenatal smoking (Yes/No) as reported at 1st trimester and 32 weeks • Postnatal maternal smoking (Yes/No) • Paternal smoking (Yes/No) 	<p>Postnatal maternal smoking</p> <p>Score difference (points):</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">Unadjusted</th> <th style="text-align: center;">Adjusted</th> </tr> </thead> <tbody> <tr> <td>Bayley MDI</td> <td style="text-align: center;">-2.7*</td> <td style="text-align: center;">-0.6</td> </tr> <tr> <td>PDI</td> <td style="text-align: center;">-0.9</td> <td style="text-align: center;">-0.2</td> </tr> <tr> <td>McCarthy</td> <td></td> <td></td> </tr> <tr> <td>GCI</td> <td style="text-align: center;">-3.5*</td> <td style="text-align: center;">-0.5</td> </tr> <tr> <td>verbal</td> <td style="text-align: center;">-1.9*</td> <td style="text-align: center;">-0.2</td> </tr> <tr> <td>perceptual</td> <td style="text-align: center;">-2.4**</td> <td style="text-align: center;">-0.7</td> </tr> <tr> <td>quantitative</td> <td style="text-align: center;">-1.1</td> <td style="text-align: center;">0.2</td> </tr> <tr> <td>memory</td> <td style="text-align: center;">-1.3</td> <td style="text-align: center;">0.6</td> </tr> <tr> <td>motor</td> <td style="text-align: center;">-2.0**</td> <td style="text-align: center;">-0.7</td> </tr> </tbody> </table> <p>• No control for prenatal maternal smoking</p>		Unadjusted	Adjusted	Bayley MDI	-2.7*	-0.6	PDI	-0.9	-0.2	McCarthy			GCI	-3.5*	-0.5	verbal	-1.9*	-0.2	perceptual	-2.4**	-0.7	quantitative	-1.1	0.2	memory	-1.3	0.6	motor	-2.0**	-0.7
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motor	-2.0**	-0.7																																
Roeleveld et al., 1992 ⁴⁶	Retrospective Case- Control 0-15 year olds N=306 cases with unknown etiology N=322 physically Handicapped with known etiology (controls)	Mental retardation (IQ<80)	Maternal/paternal interview for time period from 3 months preconception to 6 months postnatal <ul style="list-style-type: none"> • Father smoked anything • Father smoked pipe or cigars (Yes/No) • Mother smoked cigarettes (Yes/No) 	<p style="text-align: center;">Odds Ratio (95% CI)</p> <table style="width: 100%; border-collapse: collapse;"> <tbody> <tr> <td>Father smoked</td> <td style="text-align: center;">1.2</td> <td style="text-align: center;">(0.8, 1.6)</td> </tr> <tr> <td>Father pipe/cigar</td> <td style="text-align: center;">2.4</td> <td style="text-align: center;">(1.2, 5.0)</td> </tr> <tr> <td>Mother smoked</td> <td style="text-align: center;">1.1</td> <td style="text-align: center;">(0.8, 1.4)</td> </tr> </tbody> </table> <p>• No control for timing of exposure</p>	Father smoked	1.2	(0.8, 1.6)	Father pipe/cigar	2.4	(1.2, 5.0)	Mother smoked	1.1	(0.8, 1.4)																					
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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 B

Authors, Year	Study Design Population Age at follow-up	Outcome / Assessment Instruments	Exposure Definition and Assessment	Prenatal or Postnata
Weitzman et al., 1992 ³⁵	Prospective cohort US National Longitudinal Survey of Youth 4-11 year olds N=2,256	Behavior Problem Index (BPI) • Antisocial • Anxious/Depressed • Headstrong • Hyperactive • Peer conflict/ Social withdrawn • Immature Rating reported by mother	Interview (mother) Maternal smoking during and/or after pregnancy	Smoked after pregnancy on Adjusted OR (95% CI) for BI Scores >14: <hr/> <Pack/day 1.2 (0.9-1.7) ≥Pack/day 2.0 (1.3-3.1)** • At ≥ 1 pack/day significant higher rates of all subscale <u>except</u> peer conflict Smoked during and after pregnancy: <Pack/day 1.4 (1.1-1.8)* ≥Pack/day 1.5 (1.1-2.2)* • All subscales significantly higher at ≥ 1 pack/day
Fergusson et al., 1993 ³⁶	Prospective cohort New Zealand 8, 10, 12 year olds N=1265	Adapted from Rutter and Conner's Scales • Conduct disorder • Attention deficit • Disruptive behavior score Mother (M) and teacher (T) rated	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	Postnatal maternal smoking Standardized regression coefficient (β) Conduct disorder Attention deficit Disruptive behavior <u>M T M T M T</u> (8 years) .1* .07 .08 .09 .1* .08 (10 years) .1 -.01 .1* .002 .1* -.01 (12 years) .1* .01 .09 -.02 .1* .00 • Controlled for prenatal maternal smoking

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 B

Authors, Year	Study Design Population Age at follow-up	Outcome / Assessment Instruments	Exposure Definition and Assessment	Prenatal or I
Byrd and Weitzman, 1994 ²⁶	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)	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 ³¹	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 Mother: 110.0 ETS Exposed: 103.6 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 ³⁸	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. non-smokers: Adjusted score reduction (95% CI) for Stanford-Binet at 3 and 4 years (points): 3.1 (-0.9,7.1) • Controlled for prenatal maternal smoking

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

[‡] ETS Exposed' refers to women exposed to ETS during pregnancy and/or children who had been exposed to ETS.

Association of Exposure to Environmental Tobacco Smoke *in Utero* and Postnatally and Neurodevelopment and Behavior

Authors, Year	Study Design Population Age at follow-up	Outcome / Assessment Instruments	Exposure Definition and Assessment	Prenatal or Postnatal
				Adjusted mean score OR (95% CI)
Eskenazi and Trupin, 1995 ³⁴	Prospective Cohort Child Health and Development Studies N California Kaiser 5 year olds N=2,124	<ul style="list-style-type: none"> • Peabody Picture Vocabulary Test (PPVT) • Raven's Colored Progressive Matrices (RAVEN) • Activity Level (mother's report) 	Interview (mother) during pregnancy and age 5 Serum cotinine levels from Pregnancy <ul style="list-style-type: none"> • No smoking exposure during pregnancy (Cotinine <2 ng/ml) • Maternal ETS exposure during pregnancy (Cotinine ≥2 ng/ml) • Divided smokers into 4 groups: Nonsmokers, or pre- and/or postnatal smokers 	PPVT RAVEN Activity <u>Adjusted mean score OR (95% CI)</u> Nonsmoker 50.7 10.7 1.0 Prenatal ETS 51.9 10.8 1.5 (0.7, 2.5) Postnatal smoker 49.9 10.4 1.2 (0.6, 2.2) Pre- + postnatal smoker <u>50.8 10.6 1.2 (0.9, 1.5)</u> Maternal smoking at follow-up (cigs/day): Adjusted regression coefficients PPVT RAVEN Activity <u>SD=8.8 SD=2.4 OR (95% CI)</u> None 0 0 1.0 1-9 -1.5* -.5* 1.0 (.6, 1.6) 10-19 -1.3 -.3 1.1 (.8, 1.4) ≥20 -1.3 -.6* 1.6 (.9, 2.7)

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 B

Authors, Year	Study Design Population Age at follow-up	Outcome / Assessment Instruments	Exposure Definition and Assessment	Prenatal or Postnatal ETS
Fried et al., 1997 ²⁹	Prospective Cohort Ottawa Prenatal Prospective Study 9-12 year olds N=131	Reading and language <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • Maternal smoking during pregnancy <ul style="list-style-type: none"> • 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 Ana Set 1 Dominated by by Reading Comprehension Prenatal ETS Exposure <ul style="list-style-type: none"> • Maternal smokers and nonsmokers adj r=-.05 .004 • Maternal nonsmokers only r=-.03 Postnatal child ETS Exposure <ul style="list-style-type: none"> • Maternal smokers and nonsmokers adj r=-.09 • Maternal nonsmokers only adj r=-.13 • No difference by age when expo childhood.

[†] 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 B

Authors, Year	Study Design Population Age at follow-up	Outcome / Assessment Instruments	Exposure Definition and Assessment	Prenatal or Postnatal E								
				Scores								
Fried et al., 1998 ³²	Prospective Cohort Ottawa Prenatal Prospective Study 9-12 year olds N=131	Cognitive Performance <ul style="list-style-type: none"> • 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 	Interview mothers during pregnancy (each trimester) and at follow-up <ul style="list-style-type: none"> • Maternal smoking during pregnancy <ul style="list-style-type: none"> • 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 Scores Cogniti (Executive Func Prenatal ETS Exposure <ul style="list-style-type: none"> • Maternal smokers and nonsmokers • Maternal nonsmokers only Postnatal child ETS Exposure <ul style="list-style-type: none"> • Maternal smokers and nonsmokers • Maternal nonsmokers only <ul style="list-style-type: none"> • No difference by age when during childhood. 								
Obel et al., 1998 ⁴⁷	Longitudinal Cohort Denmark 8 month-old infants N=1,817	Babbling abilities evaluated by health nurses	Questionnaire completed by mother during pregnancy and at 8 months <ul style="list-style-type: none"> • Maternal pre- and postnatal smoking (cigs/day) • Paternal smoking during pregnancy (hours of maternal exposure/day) 	<ul style="list-style-type: none"> • No difference found in babbling abilities of infants whose mothers began smoking after pregnancy compared to nonsmokers <p>Nonsmokers exposed to pater during pregnancy (hours/day)</p> <p>Non-polysyllable babblers (vs. polysyllable babblers)</p> <table border="1"> <thead> <tr> <th>hours/day</th> <th>Relative Risk</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>1</td> </tr> <tr> <td>1-4</td> <td>1.1</td> </tr> <tr> <td>5</td> <td>1.3</td> </tr> </tbody> </table> <p>No 95% CI reported (ns)</p>	hours/day	Relative Risk	0	1	1-4	1.1	5	1.3
hours/day	Relative Risk											
0	1											
1-4	1.1											
5	1.3											

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 B

Authors, Year	Study Design Population Age at follow-up	Outcome / Assessment Instruments	Exposure Definition and Assessment	Prenatal								
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	<ul style="list-style-type: none"> • No adverse ass smoking status postnatal <p>Maternal postn 5 years Adjusted RR >9 cigs/day EXT</p> <table border="1"> <tr><td>0</td><td>1</td></tr> <tr><td>1-9</td><td>1.5</td></tr> <tr><td>10-19</td><td>1.9*</td></tr> <tr><td>≥ 20</td><td>1.3</td></tr> </table> <p>% of children wi behavior probler 6.5% Nonsmok pregnanc 11.3% Started si pregnanc 14.7% Smoked c</p> <p>PAR= • 15.5 % of exte problems due 5 years</p>	0	1	1-9	1.5	10-19	1.9*	≥ 20	1.3
0	1											
1-9	1.5											
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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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