We review the potential neurodevelopmental and behavioral effects of children’s prenatal and/or postnatal exposure to environmental tobacco smoke (ETS). Children’s exposure to ETS has been assessed in epidemiologic studies as a risk factor for a variety of behavioral and neurodevelopmental problems including reduced general intelligence ability, skills in language and auditory tasks, and academic achievement, and behavioral problems such as hyperactivity and decreased attention spans. We review 17 epidemiologic studies that have attempted to separate the effects of maternal active smoking during pregnancy from passive ETS smoke exposure by the pregnant mother or the child. Based on the available data, we found that ETS exposure could cause subtle changes in children’s neurodevelopment and behavior. However, studies to date are difficult to interpret because of the unknown influence of uncontrolled confounding factors, imprecision in measurements of smoking exposure, and collinearity of pre- and postnatal maternal smoking. Although some evidence suggests 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.

Keywords: behavior, children, cognition, ETS, exposure, neurodevelopment, postnatal, pregnancy, prenatal, tobacco smoke pollution. Environ Health Perspect 107:991–1000 (1999). [Online 10 November 1999]
http://ehpnet1.niehs.nih.gov/docs/1999/107/991-1000eskenaziabstract.html

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 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 (< 10%) in general intelligence ability, language/auditory-related tasks, and in academic achievement (4–10). These studies often report dose-related effects. For younger children (2 years of age 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 (11–14). However, decreases in auditory habituation and responsiveness have been consistently noted in infants < 1 week old who are prenatally exposed to maternal smoking (13,16).

For the most part, previous studies 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 neuropsychologic evaluations 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 smoked by the mother during her pregnancy, and that children who were more active or who had shorter attention spans had significantly higher hemoglobin levels.

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: are there adverse consequences to the child from the mother’s passive exposure to cigarette smoke during pregnancy or from the postnatal exposure of the child to the smoke of others? Few of the cited studies on the neurobehavioral effects of smoking attempted to separate the influence of in utero exposure to maternal smoking from the effects of the child’s postnatal exposure to ETS. 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 afterward. A review by the California Environmental Protection Agency (24) concluded that ETS may pose a neuropsychologic developmental hazard. However, since this document was written, a number of new studies have been published. Table 1 presents the 17 studies that examined the relationship between ETS exposure and neurodevelopment and behavior. Table 1 includes only those studies that attempted to separate the effects of maternal active smoking from passive ETS smoke exposure by the pregnant mother or the child.

Methods

Published papers, letters, and review articles relating ETS exposure in children to potential neurodevelopmental outcomes were selected by an electronic search of the Medline (National Library of Medicine, Bethesda, MD), BIOSIS (Biosciences Information Service, Philadelphia, PA), and PsycINFO (American Psychological Association, Washington, DC) databases (1975–1998). This search, completed in September 1998, contained the following keywords: tobacco smoke pollution, maternal smoking, prenatal cigarette exposure, passive cigarette exposure, child*, neurobehavior*, behavior, cognitive, cognition, neurodevelopment, neuropsych*, and brain. (An asterisk indicates a search for all terms that contain that word.) We attempted to identify unpublished papers and the results of epidemiologic work performed by state or federal health agencies published as government reports. We reviewed all of the references listed in the articles identified, and 17 studies were selected as relevant to the assessment of prenatal maternal or postnatal child environmental tobacco smoke exposure.
and neurodevelopmental and behavioral problems in children. Only English language papers were reviewed.

**Academic Performance and Achievement Scores**

Table 2 summarizes the studies that assessed the relationship between children's ETS exposure and academic achievement or achievement scores. In a couple of studies, the children of smokers performed more poorly in school than the children of non-smokers. For example, a study of > 3,000 14-year-old children in Finland (25) found that current paternal smoking (as determined by responses to a mailed questionnaire) was at least as strongly related to poorer school performance as maternal smoking during pregnancy. In addition, this association was dose related after adjusting for a number of potential confounders such as the mother’s smoking habits, socioeconomic status (SES), and the child’s birth order and sex. Similarly, a U.S. survey (33) of 7- to 17-year-old children found that the children of parents who reported smoking at the time of the survey were more likely (odds ratio 1.4; 95% confidence interval, 1.1, 1.7) to have repeated kindergarten or first grade. This study did not obtain information on the exposure of the child to maternal smoking during fetal development, and therefore it is difficult to determine 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. (26) compared the California Achievement Test (CAT) scores of eighth-grade children of smokers and nonsmokers. They reported a dose–response relationship between the total number of cigarettes smoked currently by family members and the children’s overall CAT scores, and found differences between the children of smokers and of nonsmokers, particularly in spelling and language skills. However, this study did not obtain information on prenatal maternal smoking; therefore, it could not be determined 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 exposure to ETS during pregnancy (maternal ETS exposure), children of nonsmoking mothers not exposed to

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**Table 1. Association of exposure to environmental tobacco smoke in utero and postnatally and neurodevelopment and behavior.**

| Author/year | Study design, population | Outcome assessment instruments | Exposure definition and assessment | Prenatal or postnatal ETS | Prenatal maternal smoking |
|-------------|--------------------------|--------------------------------|-----------------------------------|---------------------------|---------------------------|
| Dosen et al., 1975 (17) | Case-control study 5-15 years old n = 20 hyperkinetic children n = 20 dyskinetic children (control group 1) n = 20 healthy children (control group 2) Matched on age, sex, and social class | Hypoactivity | Interview (mother), retrospective report Maternal and paternal pre- and postnatal smoking (cigs/day) | Cigs/day | Cigs/day |
| | | | | Cases Control 1 Control 2 | Cases Control 1 Control 2 |
| | | | | During pregnancy: paternal smoke 22.2 15.7 19.5 | At follow-up: maternal smoke 23.3 6.1 8.2 |
| | | | | At follow-up: paternal smoke 21.3 14.6 20.7 | No control for prenatal maternal smoking Inverse association of ability in theoretical subjects with amount father smoked currently Controlled for prenatal maternal smoking Lower level than expected |
| Rantakallio et al., 1983 (28) | Prospective Finnish Cohort Study 14 years old n = 1,844 children of smoking mothers n = 1,844 controls Matched on maternal 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 second month of pregnancy Paternal smoking (never/former/present) | | |
| | | | | | |
| Bauman et al., 1989 (28) | Cross-sectional North Carolina 8th graders n = 627 children of smokers n = 351 children of nonsmokers | | | | |
| | | | | | |
| Bauman et al., 1991 (27) | Prospective cohort Child Health and Development Studies Northern California Kaiser Children followed up at ages 5 years n = 4,939 9-11 n = 3,414 15-17 n = 2,029 | CAT Mathematics Language Reading Spelling | Interview (mother) Number of cigarettes currently smoked by family members (total) Maternal breath specimen analyzed for CO for confirmation Report of sibling smoking by adolescent | | |
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*continued, next page*
ETS during pregnancy, and children of mothers who smoked during pregnancy (maternal active smoking). Makin et al. (28) found that both the children of mothers who were ETS exposed during pregnancy and the children of mothers who smoked during pregnancy performed more poorly, particularly on tests of speech and language, and that there were no clear differences between the two exposed groups. However, the children did not have substantially lower scores on the Wide Range Achievement Test than the children of nonsmokers that were not exposed to ETS. This test assesses spelling, word identification, and arithmetic. A slightly different subset of the Ottawa cohort, with the addition of some additional reading tests, showed that neither prenatal maternal ETS exposure in nonsmoking mothers nor postnatal childhood ETS exposure was associated with a discriminant analysis score dominated by reading comprehension (37). 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.

**Performance on Neuropsychologic 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 (Table 3). Again, not all of these studies were designed to separate the effects of maternal ETS exposure during pregnancy or postnatal child ETS exposure from the 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. (29) designed to examine the effects of lead. They found that children of women who smoked after pregnancy as compared to those who did not had slightly lower scores at 2 years of age on the Mental Development Index of the Bayley Scales of Infant Development, and at 4 years of age, on the General Cognitive Index of the McCarthy Scales of General Abilities. Specifically, the verbal, perceptual,

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**Table 1. Continued.**

| Author/year | Study design, population age at follow-up | Outcome assessment instruments | Exposure definition and assessment | Results | Prenatal or postnatal ETS | Prenatal maternal smoking |
|-------------|-------------------------------------------|-------------------------------|-----------------------------------|---------|---------------------------|----------------------------|
| Makin et al., 1991 (28) | Ottawa Prenatal Prospective Study 6-9 years old 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 | Interview (mother) Maternal smoking: Prenatal (yes/no) Postnatal (yes/no) Exposure to postnatal ETS 30% of children of nonsmokers (mother’s rating) ‘passive’ smokers during pregnancy 57% of active smokers children | | Prevalent ETS vs. nonsmokers Unadjusted mean score difference: Postnatal ETS | Smokers vs. nonsmokers Unadjusted mean score difference: Sound blending PPVT TOLD WISC-R Development drawing test Conner’s behavior scale (mother’s rating) Goodenough-Harris Draw-a-Man Test WRAT | |
| Baghurst et al., 1992 (29) | Prospective Follow-up Study, Australia n = 550 Evaluated at 2 and 4 years old | Bayley Scales of Infant Development (2 years) MDI Motor scale McCarthy Scales of Children’s Abilities (4 years) GCI | Interview (mother) Maternal prenatal smoking (yes/no) as reported at first trimester and 32 weeks Postnatal maternal smoking (yes/no) Paternal smoking (yes/no) | | Postnatal maternal smoking Score difference (points) | Prevalent ETS vs. nonsmokers Unadjusted mean score difference: Postnatal ETS | Smokers vs. nonsmokers Unadjusted mean score difference: Sound blending PPVT TOLD WISC-R Development drawing test Conner’s behavior scale (mother’s rating) Goodenough-Harris Draw-a-Man Test WRAT |
| Reeveeld et al., 1992 (30) | Retrospective case-control 0-15 years old n = 300 cases with unknown etiology n = 326 physically handicapped with known etiology (controls) | Mental retardation (IQ < 80) | Maternal/paternal interview for time period from 3 months to 3 years postnatal Fetal smoking anything Fetal smoking pipe or cigars (yes/no) Mother smoked cigarettes (yes/no) | | No control for prenatal maternal smoking | Prevalent ETS vs. nonsmokers Unadjusted mean score difference: Postnatal ETS | Smokers vs. nonsmokers Unadjusted mean score difference: Sound blending PPVT TOLD WISC-R Development drawing test Conner’s behavior scale (mother’s rating) Goodenough-Harris Draw-a-Man Test WRAT |
| Weitzman et al., 1992 (31) | Prospective cohort U.S. National Longitudinal Survey of Youth 4-11 years old n = 2,156 | BPI Anssociative Anxious/depresed Headstrong Hyperactive Peer conflict social withdrawal Immature Rating reported by mother | Interview (mother) Maternal smoking during and/or after pregnancy | | Smoked after pregnancy only: | Prevalent ETS vs. nonsmokers Unadjusted mean score difference: Postnatal ETS | Smoked during pregnancy Adj OR for BPI scores > 14 (95% CI) < 1 pack/day 1.2 (0.9, 1.7) ≥ 1 pack/day 2.0 (1.3, 3.1)* At ≥ 1 pack/day significantly higher at all subscales except poor conflict Smoked during and after pregnancy: < 1 pack/day 1.4 (1.1, 1.8)* ≥ 1 pack/day 1.5 (1.1, 2.2)* All subscales significantly higher at ≥ 1 pack/day | Smoked during pregnancy Adj OR for BPI scores > 14 (95% CI) < 1 pack/day 1.8 (1.0, 2.5)* ≥ 1 pack/day 0.4 (0.1, 1.6) No subscales significantly higher at ≥ 1 pack/day | | continued, next page |
and motor subtests, scores were lower; 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 neuropsychologic functioning of children exposed to ETS during childhood or of mothers exposed to ETS during pregnancy are from the Ottawa Prenatal Prospective Study (28,34,37,38). Effects of maternal exposure to ETS during pregnancy were examined in children 6–9 years of age by Makin et al. (28). A two-group discriminant function successfully classified 83% of the children into their respective exposure groups based on their poorer performance, particularly in receptive vocabulary (Peabody Picture Vocabulary Test; PPTV), and on 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. (34) found limited evidence for a slight decrease in central auditory processing important in receptive language in 6- to 11-year-old Ottawa children whose mothers were exposed to ETS during pregnancy regardless of whether the children were exposed. 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 (37,38) of this same cohort, which used different assessment tools, found that children exposed to ETS during childhood but not children whose mothers were exposed to ETS during pregnancy had lower scores on tests of language/auditory processing (37). Although there were lower language/auditory scores 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 (38). The timing of exposure during childhood did not influence the results.

Two studies (27,36) analyzed the data from the Child Health and Development

Table 1. Continued:

| Author/year | Study design, population age at follow-up | Outcome assessment instruments | Exposure definition and assessment | Results |
|-------------|------------------------------------------|---------------------------------|----------------------------------|---------|
| Ferguson et al., 1993 (37) | Prospective cohort New Zealand 8, 10, 12 years old n = 1,255 | Adapted from Rutter and Connors’s scales Conduct disorder Attention deficit Disruptive behavior score | Mother and teacher rated | Postnatal maternal smoking Standardized regression coefficient (β) Conduct disorder M/T | Prenatal or postnatal ETS
| Byrd and Whitman, 1994 (39) | Cross-sectional Child Health Supplement to 1988 National Health Interview Survey 7–17 years old 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) | Conduct disorder M/T
| McCartney et al., 1994 (34) | Longitudinal Ottawa Prenatal Prospective Study 6–11 years old n = 110 | SCAN Competing words subtest Filtered words subtest Auditory figure ground subtest | Interview mothers during pregnancy (each trimester) and at 6–11 years of age Maternal smoking during pregnancy (mg nicotine/day) None: Light (<10–15) Heavy (>15) | Maternal smoking
| Olds et al., 1994 (39) | Prospective cohort New York 1–4 years n = 100 | Bayley MDI, 1 year of age Cattell scales, 2 years of age Stanford-Binet IQ test, 3 and 4 years of age | Group with mother ETS exposed during pregnancy but child not ETS exposed performed equal to group with both mother and child ETS exposed Mothers who smoked ≥ 10 cigs/day at 4 years postpartum vs. non-smokers Adjusted score reduction (95% CI) for Stanford-Binet at 3 and 4 years of age (points): 3.1 (4.9, 7.1) Controlled for prenatal maternal smoking | Linear dose–response relationship with competing words subtest and composite score by prenatal maternal smoking Mothers who smoked ≥ 10 cigs/day at 34 weeks gestation vs. non-smokers Adjusted score reduction (95% CI) for Stanford-Binet at 3 and 4 years of age (points): 3.2 (1.1, 5.4) No significant reduction in mental development scores (adjusted to 1 or 2 years of age Greater effect of smoking at end of pregnancy than earlier |
reported that scores from the PPVT and Raven's Colored Progressive Matrices Test of more than 3,000 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 of these groups performed better than the 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 birth weight, 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).

Table 1. Continued.

| Author/year | Study design, population at follow-up | Outcome assessment instruments | Exposure definition and assessment | Results | Prenatal or postnatal ETS | Prenatal maternal smoking |
|-------------|--------------------------------------|---------------------------------|-----------------------------------|---------|--------------------------|---------------------------|
| Eskanazi and Trope, 1995 (28) | Prospective cohort Child Health and Development Studies in Northern California Kaiser | PPVT Raven Activity serum cotinine levels from pregnancy | Interview (mother) during pregnancy and at 5 years of age No smoking exposure during pregnancy (cotinine > 2 mg/mL) | Prenatal ETS 51.9 10.6 1.5 (0.7, 3.3) Postnatal smoker 49.9 10.4 1.2 (0.6, 2.2) Pre- and postnatal smoker 50.8 10.6 1.2 (0.9, 1.7) | PPVT Raven Activity Adj mean score OR (95% CI) 0.75* 11.3 1.5 (0.7, 3.1) | PPVT Raven Activity Adj mean score OR (95% CI) 0.75* 11.3 1.5 (0.7, 3.1) |

Fried et al., 1997 (37) Prospective cohort Ottawa Prenatal Study 9–12 years old \( n = 131 \)

| Author/year | Study design, population at follow-up | Outcome assessment instruments | Exposure definition and assessment | Results | Prenatal or postnatal ETS | Prenatal maternal smoking |
|-------------|--------------------------------------|---------------------------------|-----------------------------------|---------|--------------------------|---------------------------|
| Fried et al., 1998 (38) | Prospective cohort Ottawa Prenatal Study | Cognitive performance WISC III: Verbal, Maternal smoking during pregnancy | Interview mothers during pregnancy (each trimester) and at follow-up Maternal smoking during pregnancy | Prenatal ETS exposure Maternal smokers and nonsmokers, adj \( r = -0.05/adj r = -0.04 \) Postnatal child ETS exposure Maternal smokers and nonsmokers, adj \( r = 0.05/adj r = 0.10 \) Maternal nonsmokers only, adj \( r = 0.13/adj r = 0.31 \) | Adjusted mean scores (standard error) | Maternal smoking None Light Heavy |

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The authors presented 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 Raven or PPVT scores.

### Behavioral Assessment

Prenatal and postnatal exposure to cigarette smoke have been examined in relation to children’s behavioral problems (Table 4). 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. (32) of more than 2,000 children aged 4–11 who participated in the National Longitudinal Survey of Youth, parental reports of children’s behavior on the Behavior Problem Index (including subscale measures of antisocial behavior, depression and anxiety, headstrong personality, hyperactivity, and immaturity) were dose related to the amount smoked by mothers among those who only smoked after pregnancy or those who smoked both before and after pregnancy. There was no clear dose–response relationship with prenatal maternal smoking only, possibly because only a few of the 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, maternal education, self-esteem, and intelligence. Another study (32) of more than 1,000 New Zealand children followed up at 8, 10, and 12 years of age 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 of an index of conduct disorder, attention deficit, and disruptive behavior measures. After accounting for the collinearity of prenatal and postnatal smoking, Ferguson et al. (32) found that in 13 of the 18 regression equations, there was an association between smoking during pregnancy and behavioral outcomes.

### Table 4. Continued.

| Author/year | Study design, population age at follow-up | Outcome assessment instruments | Exposure definition and assessment | Prenatal or postnatal ETS | Results | Prenatal maternal smoking |
|-------------|------------------------------------------|---------------------------------|-----------------------------------|---------------------------|---------|----------------------------|
| Obst et al., 1998 [30] | Longitudinal cohort Denmark Infants, 6-months old n = 1,817 | Babbling abilities evaluated by health nurses | Questionnaire completed by mother during pregnancy and at 8 months of age Maternal pre- and postnatal smoking (cigs/day) Maternal smoking during pregnancy (hours of maternal exposure/day) | No difference found in babbling abilities of infants whose mothers began smoking after pregnancy as compared to nonsmokers Non-smokers exposed to paternal smoking during pregnancy (hours/day) Nonpoly/nonpoly bidders vs. polypolys bidders | Hr/day | RR |
| | | | | | | |
| Williams et al., 1998 [43] | Longitudinal cohort Queensland Australia 4–8-years old n = 4,879 | Shortened CBCL, EXT (problems, argumentative, disruptive, lies, temper, etc.) | Interviewed mother four times from first prenatal visit to child at 5 years of age Smoking assessed for pre-pregnancy, first prenatal visit, late pregnancy, 6 months, and 5 years of age | No 95% CI reported (NS) No adverse association with smoking status at 6 months postnatal Maternal postnatal smoking at 5 years of age Adjusted RR > 90th percentile Cigs/day EXT INT SAT | 0 1 | 1–4 |
| | | | | | 5 13 |

Abbreviations: adj; adjusted; ANOVA, analysis of variance; BPI, Behavior Problem Index; CAT, California Achievement Test; cigs; cigarettes; CBCL, Child Behavior Checklist; CI, 95% confidence interval; CO, carbon monoxide; Discrim, discriminant; ETS, environmental tobacco smoke; EXT, externalizing; GCI, General Cognitive Index; INT, Internalizing, M, mother; MDI, Mental Development Index; NS, not significant (p > 0.05); OR, odds ratio; PAR, population attributable risk; PDI, Psychomotor Development Index; PPVT, Peabody Picture Vocabulary Test; Raven, Raven’s Colored Progressive Matrices test; RR, relative risk; SAT, social, attentional, thought; SCAN, central auditory processing task; T, teacher; TOLD, Test of Language Development; WISC-III, Wechsler Intelligence Scale for Children, III; WISC-R, Wechsler Intelligence Scale for Children- Revised; WRAT, Wide Range Achievement Test.

*ETS exposed refers to women exposed to ETS during pregnancy and/or children who had been exposed to ETS. *Dominted by reading comprehension. **Dominted by language/auditory.

\[ *p < 0.05 \] **p < 0.01 \]
but only six regression models showed the effects of smoking after pregnancy, 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. (40) of more than 4,000 Australian children 4–6 years of age reported that more than 25% of externalizing problems (defined as a child who is argumentative, disruptive, lies, or has a bad temper) are due to smoking during pregnancy, as compared to 10% due to mother’s smoking when the child is 5 years of age. However, the authors reported no association between the mother’s report of such behavior problems and maternal smoking during late pregnancy or with smoking at 6 months postpartum. These results controlled for maternal mental health, education level, SES, and other confounders.

Four studies, including those by Weitzman et al. (31) and Fergussen et al. (32), reported a relationship between parental smoking and attention disorder with hyperactivity. In an early case–control study of methylphenidate-sensitive hyperkinetic children and age-, sex-, and social-class matched dyslexic and normal controls, mothers of cases consumed a greater number of cigarettes per day during and after pregnancy than mothers of controls (17). There were smaller differences in the amount smoked by the fathers either during or after the pregnancy. Eksenazi and Trupin (36) 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 the child’s assessment at 5 years of age, after controlling for prenatal maternal smoking and other confounders. Neither maternal active smoking nor ETS exposure during pregnancy 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.

### Table 2. Summary of studies assessing children’s ETS exposure and academic performance and achievement scores.

| Author/Year               | Age of Child | Measurement                          | ETS Exposure | Control for Maternal Smoking During Pregnancy | Direction of Effect | Data Quality |
|---------------------------|--------------|--------------------------------------|--------------|-----------------------------------------------|---------------------|--------------|
| Rantakallio et al., 1983  | 14 years     | School performance                   | Postnatal    | Yes                                           | ↓                    | ++++         |
| Bauman et al., 1989       | 8th graders  | California Achievement Test          | Postnatal    | No                                            | ↓                    | ++++         |
| Makin et al., 1991        | 6–9 years    | Speech and Language Tests            | Prenatal     | Yes                                           | ↓                    | ++++         |
| Byrd and Weitzman, 1994   | 7–17 years   | Grade retention                      | Postnatal    | No                                            | ↑                    | ++++         |
| Fried et al., 1997        | 9–12 years   | Reading comprehension                | Prenatal     | Yes                                           | =                    | ++++         |
|                           |              |                                      | Postnatal    | Yes                                           |                      |              |

ETS, environmental tobacco smoke. Data quality is based on whether studies meet the following seven conditions: adjusted for potential confounding; adjusted for prenatal maternal smoking; had clearly defined criteria for selection of the study population; provided data in the paper; provided concurrent control data; provided dose information or refined exposure categories; and/or used a biomarker of exposure.

*Prenatal ETS exposure is defined by the mother’s exposure during pregnancy to smoke by either her husband or by others. Postnatal ETS exposure is defined by child’s exposure to smoke by the mother, father, or other household members (Table 1 shows exact definitions). ↑ or ↓, adverse effect reported—arrow represents direction of effect; =, no adverse effect found. ++++, six conditions met; ++++, five conditions met; +++, four conditions met.

### Table 3. Summary of studies assessing children’s ETS exposure and neuropsychologic assessment.

| Author/Year               | Age of Child | ETS Exposure | Control for Maternal Smoking During Pregnancy | Affected Domain | Data Quality |
|---------------------------|--------------|--------------|-----------------------------------------------|----------------|--------------|
| Bauman and Flewelling, 1991| 5, 9–11, and 15–17 years | Postnatal | Yes                                           | ↓ PPVT         | ++++         |
| Makin et al., 1991        | 6–9 years    | Prenatal     | Yes                                           | ↓ Raven        | ++++         |
| Baghurst et al., 1992     | 2 and 4 years| Postnatal    | No                                            | ↑ Mental retardation (IQ < 80) | ++++         |
| Roeleveld et al., 1992    | 0–15 years   | Prenatal     | No                                            | ↑ Mental retardation (IQ < 80) | ++++         |
| McCartney et al., 1994    | 6–11 years   | Prenatal     | Yes                                           | ↓ Mental retardation (IQ < 80) | ++++         |
| Olds et al., 1994         | 1–4 years    | Postnatal    | Yes                                           | ↓ Stanford-Binet IQ | ++++         |
| Eksenazi and Trupin, 1995 | 5 years      | Prenatal     | Yes                                           | ↓ PPVT         | ++++         |
| Fried et al., 1997        | 9–12 years   | Prenatal     | Yes                                           | ↓ Language/auditory processing | ++++         |
| Fried et al., 1998        | 9–12 years   | Prenatal     | Yes                                           | ↓ Language/auditory processing | ++++         |
| Obel et al., 1998         | 8 months (infants) | Postnatal | Yes                                           | ↓ General cognitive performance | ++++         |

Abbreviations: ETS, environmental tobacco smoke; IQ, intelligence quotient; PPVT, Peabody Picture Vocabulary Test; Raven, Raven’s Colored Progressive Matrices test; WISC-R, Wechsler Intelligence Scale for Children-Revised. Data quality is based on whether studies meet the following seven conditions: adjusted for potential confounding; adjusted for prenatal maternal smoking; had clearly defined criteria for selection of the study population; provided data in the paper; provided concurrent control data; provided dose information or refined exposure categories; and/or used a biomarker of exposure.

*Prenatal ETS exposure is defined by the mother’s exposure during pregnancy to smoke by either her husband or by others. Postnatal ETS exposure is defined by child’s exposure to smoke by the mother, father, or other household members (Table 1 shows exact definitions). ↑ or ↓, adverse effect reported—arrow represents direction of effect; =, no adverse effect found; ~, trend reported for group, not statistically significant. ++++, all seven conditions met; ++++, six conditions met; ++++, five conditions met; +++, four conditions met. No effect observed when analyses were restricted to women who did not smoke during pregnancy.
Is ETS Exposure Causally Related to Adverse Neurodevelopment?

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 (25,26,33) 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, only one of these studies adjusted for the potential contribution of in utero maternal active smoking (25). Seven studies examined the relationship of postnatal exposure to smoke and performance on a range of cognitive, perceptual, central auditory, and linguistic abilities (27,29,34–38). Of the six studies that controlled for prenatal maternal smoking (27,34–38), half (27,36,37) show clear decrements associated with postnatal ETS exposure. Also, two of these studies (27,36) suggest that the children of mothers who smoked only after pregnancy performed somewhat worse than the children of mothers who smoked only during pregnancy. Eskenazi and Trupin (36) suggest that this effect may be due to potential misclassification of exposure or to the fact that women who begin to smoke after pregnancy may be different in ways that affect the child’s cognitive development (e.g., sociodemographic, cognitive). Furthermore, ETS exposure during childhood may be more hazardous to neurodevelopment than in utero exposure to maternal smoking. Postnatal ETS exposure has also been associated with behavioral problems in all three studies that specifically examined behavior problems in children (31,32,40) and adequately controlled for home environment and other potentially intervening factors; two of these three studies (32,40), however, showed larger associations between behavioral problems and prenatal exposure to maternal smoke than with postnatal child ETS exposure.

There are only three studies that investigated the relationship of maternal ETS exposure during pregnancy (28,36,38) 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 (28) but did not take into account postnatal exposure, whereas the second study (38) showed no relationship between maternal ETS exposure during pregnancy among nonsmokers and general cognitive performance in their children. Similarly, Eskenazi and Trupin (36) 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, as described below.

Results may be explained by uncontrolled confounding. A complex web of genetic and socioenvironmental factors influence human cognitive development and behavior; 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 (24), which can lead to sustained middle ear effusion and hearing loss, that in turn could result in language difficulties and academic problems. Similarly, maternal ETS exposure during pregnancy may lower birth weight (41–43), which in turn could potentially be related to lowered cognitive abilities and behavioral problems. Because birth weight may be on the causal pathway between ETS exposure and adverse neurodevelopmental outcomes, Baghurst et al. (29) discussed the potential for over control if birth weight remained in the multivariate model.

There are likely to be a number of immeasurable differences between smokers and nonsmokers (personality, home environment, other environmental or personal exposures [lead, alcohol], child-rearing practices, and parental intelligence) that cannot be readily ascertained. Not controlling for these factors is likely to bias the results toward finding an effect. The investigator may not know and therefore cannot control for all of these factors. The fact that in a number of

Table 4. Summary of studies assessing children’s ETS exposure and behavior outcomes.

| Author/year                        | Age of child | ETS exposure | Control for maternal smoking during pregnancy | Affected domain | Data quality |
|------------------------------------|--------------|--------------|-----------------------------------------------|-----------------|-------------|
| Weitzman et al., 1992 (37)         | 4–11 years   | Postnatal    | Yes                                           | Behavior Problem Index | ++++        |
|                                    |              |              |                                               | ↑ Antisocial     |             |
|                                    |              |              |                                               | ↑ Anxious/depressed |             |
|                                    |              |              |                                               | ↑ Headstrong     |             |
|                                    |              |              |                                               | ↑ Hyperactive    |             |
|                                    |              |              |                                               | ↑ Peer conflict/social withdrawal |             |
|                                    |              |              |                                               | ↑ Immature      |             |
|                                    |              |              |                                               | Conduct disorder|             |
|                                    |              |              |                                               | ↑ Mother’s report|             |
|                                    |              |              |                                               | ↑ Teacher’s report|             |
|                                    |              |              |                                               | ↑ Attention deficit|            |
|                                    |              |              |                                               | ↑ Mother’s report|             |
|                                    |              |              |                                               | ↑ Teacher’s report|             |
|                                    |              |              |                                               | Disruptive behavior|          |
|                                    |              |              |                                               | ↑ Mother’s report|             |
|                                    |              |              |                                               | ↑ Teacher’s report|             |
|                                    |              |              |                                               | Internalizing   |             |
|                                    |              |              |                                               | ↑ Social, emotional, thought |             |
|                                    |              |              |                                               | ↑ Externalizing behavior problems |             |
|                                    |              |              |                                               | Activity level (mother’s report) |             |
|                                    |              |              |                                               | ↑ Activity level|             |
|                                    |              |              |                                               | ↑ Hyperactivity |             |
| Fergusson et al., 1993 (32)        | 8, 10, 12 years | Postnatal    | Yes                                           |                | ++++        |
| Williams et al., 1998 (40)         | 4–6 years    | Postnatal    | Yes                                           |                | ++++        |
|                                    |              |              |                                               | ↑ Mother’s report|             |
|                                    |              |              |                                               | ↑ Teacher’s report|             |
|                                    |              |              |                                               | ↑ Attention deficit|            |
|                                    |              |              |                                               | ↑ Mother’s report|             |
|                                    |              |              |                                               | ↑ Teacher’s report|             |
|                                    |              |              |                                               | Disruptive behavior|          |
|                                    |              |              |                                               | ↑ Mother’s report|             |
|                                    |              |              |                                               | ↑ Teacher’s report|             |
|                                    |              |              |                                               | Internalizing   |             |
|                                    |              |              |                                               | ↑ Social, emotional, thought |             |
|                                    |              |              |                                               | ↑ Externalizing behavior problems |             |
|                                    |              |              |                                               | Activity level (mother’s report) |             |
|                                    |              |              |                                               | ↑ Activity level|             |
|                                    |              |              |                                               | ↑ Hyperactivity |             |
| Eskenazi and Trupin, 1995 (36)     | 5 years      | Prenatal     | Yes                                           |                | ++++        |
| Denson et al., 1975 (17)           | 5–15 years   | Postnatal    | No                                            |                | +++         |

ETS, environmental tobacco smoke. Data quality is based on whether studies meet the following seven criteria: adjusted for potential confounding; adjusted for prenatal maternal smoking; had clearly defined criteria for selection of the study population; provided data in the paper; provided concurrent control data; provided dose information or refined exposure categories; and/or used a biomarker of exposure.

*Prenatal ETS exposure is defined by the mother’s exposure during pregnancy to smoke by either her husband or by others. Postnatal ETS exposure is defined by child’s exposure to smoke by the mother, father, or other household members (Table 1 shows exact definitions). #, adverse effect reported—arrow represents direction of effect; = no adverse effect found. ***, all seven conditions met; ***, six conditions met; ***, five conditions met; ***, four conditions met.
studies, children of mothers who quit smoking performed better than those of mothers who started smoking suggests that other factors which are related to choosing to begin smoking rather than quitting may confound the results. For example, Eskenazi and Trupin (36) found that women who quit smoking after pregnancy were of higher social class than those who smoked throughout or who started smoking after pregnancy. Leftwich and Collins (44) suggested that depression is related to smoking and that depression may alter child-rearing practices, which may affect the child's development and behavior. Clearly, as proposed by Yerushalmy (45), it may be the characteristics of the smoker rather than the smoking per se that affects development or behavior.

Exposure has not been accurately assessed.

Tong and McMichael (46) noted that most studies have suffered from a lack of valid and precise measures of exposure. Misclassification of exposure could be either random or systematic, and therefore, it is difficult to predict the direction of the bias. However, if women exposed to ETS do not accurately report their exposures, results would be biased towards the null. Most studies assess levels 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 inside and outside of the home (47,48). Correlations between questionnaire data and cotinine measurements range between 0.4 and 0.7 (47,48). Only two studies to date have used a biomarker of exposure to assess prenatal (36) and postnatal (34) ETS exposure. Because 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.

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; most women who smoke during pregnancy continue to smoke after pregnancy. Because of this collinearity, statistically controlling for prenatal exposure may produce artifactual negative results. To separate 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 (34).

Biological Plausibility of ETS Exposure Causing Adverse Neurodevelopment

It is possible that ETS exposure during childhood may be hazardous, and potentially more hazardous, to neurodevelopment than during in utero exposure to maternal smoking. The routes of exposure to prenatal and postnatal maternal smoking differ: the fetus is exposed transplacentally to compounds absorbed by the mother, whereas the child is exposed primarily through inhalation. Also, the chemical constituents and their levels differ, to some extent, in ETS and mainstream smoke (49). Childhood may be the critical period for neurodevelopmental effects of smoking. Furthermore, exposure during childhood may be longer than the 9 months of in utero exposure. These differences 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. (50) exposed pregnant rat dams to side-stream smoke (SS) or filtered air (FA) for 4 hr/day, every day throughout gestation, and exposed the offspring to either SS or FA for 9 weeks postnatally for a total of four different exposure conditions: in utero FA-postnatal FA, in utero FA-postnatal SS, in utero SS-postnatal FA, and in utero SS-postnatal SS. No dose-related effects were observed in the dams as a result of SS exposure during pregnancy (51). After 9 weeks postnatal exposure, the animals were sacrificed and the brains were divided into forebrain and hindbrain and 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 not 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 because of the unknown influence of uncontrolled confounding factors, imprecision in measurements of smoking exposure, and collinearity of pre- and postnatal maternal smoking. Although 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.

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