Prenatal and Postnatal Environmental Tobacco Smoke Exposure and Children's Health

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ABSTRACT. Children's exposure to tobacco constituents during fetal development and via environmental tobacco smoke (ETS) exposure is perhaps the most ubiquitous and hazardous of children's environmental exposures. A large literature links both prenatal maternal smoking and children's ETS exposure to decreased lung growth and increased rates of respiratory tract infections, otitis media, and childhood asthma, with the severity of these problems increasing with increased exposure. Sudden infant death syndrome, behavioral problems, neurocognitive decrements, and increased rates of adolescent smoking also are associated with such exposures. Studies of each of these problems suggest independent effects of both pre- and postnatal exposure for each, with the respiratory risk associated with parental smoking seeming to be greatest during fetal development and the first several years of life. *Pediatrics* 2004;113:1007–1015; *environmental tobacco smoke, children, prenatal, otitis media, asthma, SIDS.*

ABBREVIATIONS. ETS, environmental tobacco smoke; SIDS, sudden infant death syndrome; OM, otitis media; EPA, Environmental Protection Agency; NCI, National Cancer Institute.

The effect of maternal smoking during pregnancy on children's birth weight has been recognized since 1957,[1] and the first report concerning the adverse effects of environmental tobacco smoke (ETS) on children's health was published in 1967.[2] Since that time, >150 studies of the effects of ETS on respiratory illness in children alone have been published.[3] A similarly large, although generally newer body of work, clearly links both prenatal maternal smoking and ETS exposure to ear infections, sudden infant death syndrome (SIDS), behavioral problems, and neurocognitive deficits. Aligne and Stoddard[4] estimated the annual excess in deaths in children younger than 5 years as a result of tobacco smoke exposure at close to 6000, exceeding deaths as a result of all injuries combined. Children's exposure to tobacco constituents during fetal development and via ETS exposure during childhood is perhaps the most ubiquitous and hazardous of children's environmental exposures.

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CHILDREN'S VULNERABILITY TO ETS EXPOSURE

Respiratory and Ear Infections

Exposure of children to ETS in the home increases the incidence of middle ear disease, asthma, wheeze, cough, phlegm production, bronchitis, bronchiolitis, pneumonia, and impaired pulmonary function, and it has also been associated with snoring,[5] adenoid hypertrophy,[6] tonsillitis, and sore throats.[7] In 4 of 5 studies, the incidence of tonsillectomy was doubled for children who live in households with smokers.[7–11] Maternal smoking is associated with an increased incidence of wheezing illness up to 6 years of age with an odds ratio of 1.31.[12]

It has been suggested that parental smoking might be associated with respiratory infections in children because the parents themselves are more likely to bring home a respiratory infection. This mechanism would not explain why parental smoking increases the risk and severity of respiratory syncytial virus bronchiolitis in infants.[13,14] Even when controlling for parental symptoms, birth weight, and family size, bronchitis and pneumonia are more common during the first year of life in smoking households.[15,16] Parental symptoms do not account for the increased incidence of cough among children of smokers.[17,18]

In smoking households, children are at greater risk of hospitalization for respiratory illness.[19,20] A meta-analysis concluded that ETS was associated with an approximate doubling of the risk of lower respiratory tract infection in children, with the risk declining after the age of 2.[21] Smoking during pregnancy seems to add an additional risk to that associated with postnatal exposure to ETS.[22] Maternal smoking during pregnancy has been associated with an odds ratio of 3.8 for infant death as a result of respiratory disease (excluding conditions related to prematurity).[23]

ETS increases both the prevalence and the severity of asthma.[12] Several authors have argued that the evidence regarding ETS and asthma is strong enough to conclude that the relation is causal, although the mechanism has not been established.[24–26] In a meta-analysis, the risk of developing asthma was 1.37 if either parent smoked.[12] Household smoking increases the frequency of attacks,[27] the number of emergency department visits,[28] and the risk of intubation.[29] The relationship between parental smoking and asthma has stood up when controlled for a long

list of potential confounders, including gender, age, urbanization, education, crowding, dampness, mold, cooking fuel, parental respiratory symptoms, parental asthma, and the child's smoking.[30–32] A strong indicator that the association is not attributable to unmeasured confounders is reports that asthma severity has improved in children when exposure was reduced.[33]

Several authoritative reviews have concluded that parental smoking has adverse effects on pulmonary function in children.[26,34,35] A meta-analysis of 21 studies found a reduction in forced expiratory volume in 1 second of 1.4%, midexpiratory flow rate of 5%, and end expiratory flow rates of 4.3%.[36] It is likely that some of this effect is attributable to in utero exposure as smoking during pregnancy has adverse effects on pulmonary function measured in the neonatal period.[37] Postnatal ETS exposure has been associated with small declines in pulmonary function as well, but the mechanism of damage has not been identified.[19]

The epidemiologic data regarding a possible link between ETS and otitis media (OM) has been reviewed several times by federal agencies: the Surgeon General,[34] the National Research Council,[38] the US Environmental Protection Agency (EPA),[26] and the National Cancer Institute (NCI)/California EPA.[35] The NCI report concluded that "overall, the epidemiologic data strongly support a relationship between ETS exposure in the home and either acute OM or OM with effusion, particularly among children under 2 years of age." In addition, a thorough peer-reviewed, systematic, quantitative meta-analysis of 11 papers on acute OM, 9 on recurrent OM, 5 on middle ear effusion, and 9 on surgery for OM with effusion was published in 1998.[12] It concluded, "Evidence for middle ear disease is remarkably consistent, with pooled odds ratios if either parent smoked of 1.48 (1.08–2.04) for recurrent OM, 1.38 (1.23–1.55) for middle ear effusion, and 1.21 (.95–1.53) for surgery for OME. Odds for acute OM are in the range 1.0 to 1.6. There is likely to be a causal relationship between parental smoking and both acute and chronic middle ear disease in children."[12]

Three additional papers with strong designs for investigating the ETS—OM association have been published since 1997.[39–41] These 3 found relative risks ranging from 1.9 to 3.9. One used hair cotinine measurements, home visits, and inspection of physician medical records on a subset of the participants to validate the exposure and outcome information.[40] Another used an objective definition of both exposure and outcome, with ETS measurement by urine cotinine and OM assessment by direct examination by an ears, nose, and throat specialist.[41] The third studied a large prospective cohort recruited before birth and found that prenatal smoking is more important than postnatal smoking with respect to OM risk.[39]

SIDS

SIDS is the leading cause of death of infants 1 month to 1 year of age in the United States.[42] Multiple potential risk factors have been identified.[35,43] The incidence in developed countries has declined dramatically during the 1990s, after public health campaigns advising parents to place sleeping infants on their back.[44] Now that fewer infants sleep prone, maternal smoking is the major suspected risk factor for SIDS.

The epidemiologic data regarding a possible link between ETS and SIDS has been reviewed several times by federal agencies, as well as by the World Health Organization: the Surgeon General (1986),[34] US EPA (1992),[26] NCI/California EPA (1999),[35] and World Health Organization (1999).[45] The NCI report concluded that "existing data indicate a causal relationship between maternal smoking in general and SIDS." In addition, a thorough, peer-reviewed, systematic, quantitative review of 39 studies, including 10 cohort studies and 29 case-control studies, was published in the medical literature in 1997.[46] It concluded, "Maternal smoking doubles the risk of sudden infant death syndrome. The relationship is almost certainly causal. The epidemiologic evidence points to a causal relationship between SIDS and postnatal exposure to environmental tobacco smoke."[46] The distinction between effects of prenatal versus postnatal exposure was believed to warrant additional investigation.

Five studies published since the above-cited reviews provide new information.[47–51] These recent studies were conducted after the switch to supine sleeping and the resulting decline in SIDS deaths. The odds ratios reported by these studies, ranging from 3.3 to 6.0, are higher than had been previously reported. Investigations that quantified smoking found a significant dose–response relation between smoking and SIDS. One study[49] found that smoking cessation during pregnancy reduces the risk of SIDS. Bed-sharing (infant co-sleeping with the mother) seems to be a risk for SIDS only when the mother also smokes, even after controlling for alcohol use and other risk factors.[51]

Effects of Maternal Smoking on Intrauterine Growth

In 1957, Simpson reported an adverse effect of maternal smoking on birth weight.[1] Subsequent studies have confirmed this finding and demonstrated a direct dose-response effect.[52–58] The effect on birth weight is attributable more to intrauterine growth retardation than to preterm delivery.[58] Kramer et al[57] estimated the effect of prenatal maternal smoking as a 5% reduction in relative weight per pack of cigarettes smoked per day. Cigarette smoking is the single most important factor affecting birth weight in developed countries.[58] Meyer and Comstock[59] reported that the effect of maternal cigarette smoking on infant birth weight was an average reduction of 150 to >300 g. Maternal and paternal smoking both are associated with lower birth weight, with maternal smoking having a greater effect.[60,61] A randomized controlled intervention study demonstrated that reduction of smoking during pregnancy improves the infant birth weight.[62]

Prenatal maternal smoking affects the fetus in a number of ways that may result in chronic hypoxia and low birth weight. Placental vascular resistance is

often increased when women smoke during pregnancy.[63,64] Maternal smoking is associated with alterations of protein metabolism and enzyme activity in fetal cord blood.[65,66] Cigarette smoking during pregnancy transiently lowers maternal uterine blood flow and reduces flow of oxygen from the uterus to the placenta.[67] Increased levels of carboxyhemoglobin are found in both maternal and fetal blood when the mother smokes during pregnancy, and this can lead to fetal hypoxia[68] and the fetus experiences chronic hypoxic stress, as evidenced by elevated hematocrit levels.[69]

Poor intrauterine growth has a lasting effect on subsequent growth[70] and development of children,[71] including an increased risk of emotional and behavioral problems,[72–75] and lowered cognitive abilities and hyperactivity.[76,77] A recent paper also indicated decrements in IQ associated with lower birth weight in children born with weight >2500 g.[78]

In rats, in utero exposure to nicotine has been shown to have a teratologic effect on neuronal development in the brain.[79] Prenatal exposure results in profound alterations in neurotransmitter disposition, which are evident in specific neuronal pathways and which persist after birth.[80] Although nicotine has been the prime focus of animal studies on this topic, tobacco smoke is composed of thousands of chemicals and the contributions of individual chemicals is unknown.

In humans, maternal smoking increases the likelihood for a child to be born with a small head circumference.[81] Children who are born to smoking mothers experience catch-up growth in weight and partial catch-up growth in length, but the differences in head circumference persist to at least 5 years of age.[82] No difference in head circumference measurements was found when women who are pregnant stop smoking before 32 weeks' gestation.[83]

BEHAVIOR AND COGNITIVE FUNCTIONING

The impact of prenatal and postnatal exposure to tobacco smoke on human behavior and neurologic development has been reviewed in 6 recent articles.[35,84–88] The literature strongly suggests that such exposures lead to negative behavioral and neurocognitive effects in children.[89–91]

Adverse Behavioral Outcomes

Studies of children whose mothers smoked during pregnancy have consistently demonstrated that such children have higher rates of behavior problems than those not exposed. Olds[84] noted that 10 of 11 human studies reviewed found increased rates of child behavior problems and attention-deficit/hyperactivity disorder–like behaviors even after controlling for many potential confounders.[84,92–103] Follow-up in these studies has varied from the newborn period through adolescence.

Fried et al[104] reported increases in hypertonicity, tremors, and startles among neonates who were prenatally exposed. Longo[105] found evidence for neonatal hyperactivity. In a study by Brook et al,[106] maternal smoking during pregnancy was associated with negativity in 2-year-old children, and Williams et al[107] reported that it was associated with externalizing behavior problems.

Weitzman et al[102] in the United States and Fergusson et al[93] in New Zealand, examining longitudinal data, found that maternal smoking was associated with increased ratios of behavior problems, even after controlling for numerous potential confounders. The latter study used both teacher and mother reports, thereby eliminating the potential problem that smoking mothers may be less tolerant of children's behaviors and more likely to report them as abnormal. A clear dose–response relationship between amounts smoked during pregnancy and behavior problems was found in both studies. Rantakallio et al[97] found an association between prenatal cigarette smoking and later delinquency in a Finnish birth cohort study, and Wakschlag et al[103] in a prospective study in the United States found that boys aged 7 to 12 were more likely to be referred for psychiatric care for conduct disorder when their mothers smoked during pregnancy.

Cognitive Impairments and School Performance

Prenatal exposure to maternal smoking has been shown to adversely affect children's performance on intelligence and achievement tests, as well as performance in school, although the findings in this area are not as consistent as those for increased rates of behavior problems. Butler and Goldstein[108] demonstrated that children whose mothers smoked 10 or more cigarettes per day were between 3 and 5 months delayed in reading, mathematics, and general ability. A number of studies demonstrate similar effects,[93,95,96,109–112] whereas some found effects to virtually disappear after controlling for confounders.[113–115] In families in which mothers smoked during some but not all pregnancies, exposed children performed worse on intelligence tests than their unexposed siblings.[113] Similarly, children of women who quit smoking during pregnancy have been found to score higher on tests of cognitive ability than children whose mothers smoked throughout pregnancy.[94]

Infants who are born to maternal smokers have decreased rates of auditory habituation and increased sound thresholds.[116] By ages 3 and 4 years, language development has been found to be adversely affected by maternal cigarette smoking[94]; these findings are dose related and have persisted through 12 years of age.[112] A study by Olds et al[117] found that smoking 10 or more cigarettes per day during pregnancy was independently associated with decreased Stanford-Binet IQ scores of 4.35 points, when controlling for many potential confounders. The same investigators also demonstrated that the adverse effects of smoking during pregnancy seem to be prevented or ameliorated by smoking cessation.[118] Denson et al,[119] in a case-control study, showed hyperactivity to be associated with maternal smoking in a dose–response relationship. Milberger et al[98] also found that prenatal tobacco exposure contributes to children's attention-deficit/hyperactivity disorder. Rantakallio[109] reported that data from a 1966 birth cohort of 1819 Finnish children

demonstrated that parental smoking was associated with lower mean scores on "theoretical subjects based on school reports." Byrd et al[120] demonstrated that children of smoking parents are more likely to repeat kindergarten or first grade.

Critical Windows of Exposure

In many studies involving smoking mothers, it has not been clear whether the adverse effect of parental smoking on children's health was attributable to in utero damage to the developing fetus or to exposure to ETS after birth. Both mechanisms may be involved. Studies that control for low birth weight and other manifestations of prenatal smoking may mask a real effect of maternal smoking. Current smoking several years after delivery may not be a good marker of exposure if the woman temporarily stopped smoking during a period of pregnancy critical for causing damage.

Many studies have observed that the respiratory risk associated with parental smoking seems to be greatest at younger ages.[25,121,122] Fetal development seems to represent a critical time of pulmonary vulnerability. Smoking during pregnancy has been associated with decreased pulmonary function in the neonatal period in several studies.[37,123,124] Animal studies have confirmed that maternal smoke exposure during pregnancy has an adverse impact on fetal lung development.[125] The risk of pneumonia and bronchitis in relation to ETS exposure is highest during the preschool years and seems to peak during the first year of life.[15,16,126–129] The risk of hospitalization for respiratory illness seems to be greatest in the first 6 months of life.[128] The effect of ETS on bronchial hyperresponsiveness seems to be strongest when the exposure occurs early in life.[130] Cough in relation to parental smoking seems to decline after age 13.[131]

It is not clear why the adverse respiratory consequences of parental smoking decline as children grow older. It may reflect that children spend less time in the presence of parents as they progress from infancy to adolescence, and, consequently, exposure to ETS declines with age.[132,133]

Studies of parental smoking and OM, SIDS, neurocognitive development, and children's behavior as cited previously all suggest independent effects of both pre- and postnatal exposure. The mechanisms by which maternal smoking during pregnancy and children's ETS exposure are associated with respiratory illness, SIDS, neurocognitive decrement, and behavior problems have not been established; therefore, it remains unknown why vulnerability changes with age.

Biological Mechanisms/Plausibility

Suggested mechanisms by which maternal smoking during pregnancy and children's ETS exposure might cause asthma include an irritant effect, increased bronchial hyperreactivity, alterations in circadian variations in pulmonary function, or a heightened sensitivity to allergens.[32,134,135] The California EPA/NCI report hypothesized 4 mechanisms whereby ETS might increase Eustachian tube dysfunction and thereby contribute to OM: 1) decreased mucociliary clearance promoting entry of microbes, 2) hyperplasia of adenoids reducing Eustachian tube patency, 3) mucosal swelling reducing eustachian tube patency, and 4) increased frequency of upper respiratory infections causing 1 to 3 above.[35] In addition, there is evidence that ETS impairs immune system function, increases the risk of low birth weight and birth defects, and promotes the growth of oral bacteria, all of which could contribute to OM.[136–138]

Establishing a biological mechanism by which passive smoking causes SIDS is hampered by the lack of consensus as to which pathophysiologies are directly linked to SIDS. With the available data, it is difficult to distinguish the effect of active maternal smoking during pregnancy from that of postnatal ETS exposure of the infant. However, clear evidence for a nonmaternal ETS effect arises from 6 studies that examined SIDS and paternal smoking in which the mother is a nonsmoker. The pooled unadjusted relative risk from these studies is 1.4.[45] A recent case-controlled study found differences in nicotine in the lungs of infants who died of SIDS and infants who died of other causes.[139]

As noted in the sections on intrauterine growth and animal studies, there are several very plausible biological mechanisms by which maternal smoking during pregnancy and early passive ETS exposure of children might result in behavioral and neurocognitive problems.

MEASUREMENT OF EXPOSURE TO ETS

Exposure to ETS may vary from season to season, day to day, or even hour to hour. The optimal time frame for the assessment of exposure is unknown. For example, in considering the effect of ETS on middle ear disease, should the cumulative lifetime exposure to ETS be assessed; just the exposure over the preceding days, weeks, or months; or just prenatal exposure? Survey instruments for measuring exposure to ETS have been developed and validated against environmental measures of exposure.[140]

The search continues for an ideal biomarker of exposure to ETS. The same biochemical measures that have been used to measure active smoking have also been used to measure ETS exposure.[141] Nicotine is metabolized within hours to cotinine. Because of its short half-life of 2 hours, measures of nicotine in the serum or saliva reflect only exposures during the past day.[142] The measurement of nicotine in hair may provide long-term exposure information but requires additional development and standardization.[143] Cotinine can be measured in saliva, blood, or urine. With its longer half-life, cotinine measures exposure during the preceding few days but does not seem to offer an advantage over exposure data based on parental smoking histories.[129] The measurement of cotinine in meconium may reflect exposures during a more extended time period.[144] Carbon monoxide and thiocyanate can indicate ETS exposure, but these tests are nonspecific as carbon monoxide exposure can result from multiple sources and thiocyanate can originate from dietary sources.[145] Because of its

longer half-life and specificity for ETS exposure, cotinine is currently the biomarker of choice.[141]

Are Low Levels of ETS Exposure Without Risk?

There are no data to indicate that low levels of exposure to ETS are harmless. Corbo et al[146] did not find evidence of a threshold effect in examining the impact of occasional ETS exposure on pulmonary function. Although the clinical relevance of the small decrements in pulmonary function observed in this study is unclear, the authors comment, "This suggests that there is no threshold dose of ETS below which an effect will not occur."[146] If there is a threshold exposure level, it might be different for the various conditions attributed to ETS exposure. For example, a theoretical threshold exposure that did not increase the risk of middle ear disease might still leave a child at risk for asthma. Many studies have demonstrated dose–response relationships between ETS exposure and respiratory, behavioral, and cognitive problems.[128]

It would be hazardous to base conclusions about a threshold effect on current data. Our ability to measure ETS exposure is crude. Many methods have been used, but all can result in significant misclassification of exposure that reduces the power of all studies to detect effects at low levels of exposure.[35] Most studies have used questionnaires to determine exposure, collecting such data as the number of smokers who live with the child, the number of cigarettes smoked indoors, and the number of rooms in the house.[31] Sometimes the mother's smoking status during pregnancy is used as a measure of ETS exposure throughout childhood. Problems arise in cross-sectional studies. Murray and Morrison[147] demonstrated that ETS exposure declined over time in a population of individuals with asthma, which he attributed to parental education about the impact of ETS. Meinert et al[148] found that if a child had airway disease, then the mother was less likely to start smoking and more likely to quit. These desirable outcomes lead to a situation in which smoking is relatively more common in households with healthy children, creating the impression in cross-sectional studies that ETS provides a protective effect. In 1 study, the parents of children with chronic respiratory conditions withheld the truth about the extent of their child's exposure to ETS,[132] and in another, 9% of self-reported nonsmoking mothers had serum cotinine levels indicative of active smoking.[149] Without an accurate measure of exposure, conclusions about a possible threshold dose would be very hazardous.

With most pollutants, it is progressively more costly to achieve lower and lower levels of exposure. In the case of ETS, the opposite is true. Although efforts to reduce the concentration of tobacco smoke pollutants through ventilation or filtration are expensive, completely eliminating tobacco smoke at its source by prohibiting smoking where children may be present costs nothing and can result in revenue savings as a result of decreased cleaning costs.

CAN WE EXTRAPOLATE FROM ANIMAL AND ADULT DATA?

Experimental animal studies can eliminate bias and confounding and provide the foundation for the biological plausibility of toxic effects on neurocognitive development in humans arising from specific agents in tobacco smoke. At present, the animal data are sufficiently strong to suggest roles for nicotine[150–160] and carbon monoxide[161–166] in causing neurocognitive and behavioral problems in children. The animal data also support a conclusion that adolescents are more vulnerable to nicotine than adults. In adolescent rats, nicotine increases the density of nicotinic acetylcholine receptors in the midbrain to a much greater extent than in adult animals, and the changes are more persistent in adolescents.[167] In adolescent rats, nicotine induces cell damage in the hippocampus, and in both mice and rats, adolescents demonstrate greater impairment in reward system function after nicotine exposure.[167–171] Although animal studies clearly demonstrate negative effects of prenatal exposure on fetal lung and brain development, epidemiologic studies are the most appropriate method for determining the risks associated with ETS in humans.

It is inappropriate to estimate the damage to nonsmokers on the basis of morbidity and mortality data regarding active smoking because the chemical makeup of sidestream smoke differs from the mainstream smoke inhaled by the smoker.[35]

Children and adults differ in their vulnerability to ETS. Adults are at risk of myocardial infarction,[172] whereas children are at risk for a variety of respiratory tract conditions and neurodevelopmental problems. Extrapolation from adults to children for the risk of heart disease is illogical because of the extreme rarity of this condition in children. Both populations share a risk of asthma. Although a handful of studies have associated ETS exposure with asthma in adults, the literature concerning the effects of ETS on asthma in children is far more extensive. Thus, there is no basis or utility for extrapolating the risk of ETS from adults to children. Although a dose–response relationship between ETS exposure and reduced pulmonary function has been observed in adults,[173] the literature concerning this effect in children is far more extensive.[36]

POLICY IMPLICATIONS

There is a consensus in the pediatric and the public health communities that the evidence concerning the adverse health effects of ETS for children are strong enough to warrant active intervention to reduce or eliminate children's exposure to ETS. Appropriate measures include the elimination of smoking in children's homes and all forms of transportation used by children. Additional measures include the elimination of smoking in all public places where children are present, including in all child care settings and schools. Multiple settings where pregnant women and children receive services, such as the obstetrician's office; hospital nurseries; children's primary care services; dental services; Women, Infants, and

Children program; certified child care settings; and Head Start programs, should be equipped to identify, counsel, and refer smoking parents for smoking cessation services.

FUTURE RESEARCH

Future research should investigate how we can be more effective in lowering exposure, preventing smoking initiation, and facilitating smoking cessation. Better epidemiologic data are needed on the effect of maternal smoking cessation and alterations in asthma and OM prevalence and severity, neurocognition and behavior problems, and the incidence of SIDS. Better clarification of the potential roles of prenatal tobacco and postnatal ETS exposure and children's behavior disorders and neurocognitive functioning also is needed.

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