

Developmental Toxicity II: Postnatal Manifestations

4.1 INTRODUCTION In this section we examine associations between ETS exposure and three outcomes occurring after the neonatal period: Sudden Infant Death Syndrome (SIDS), neuropsychological development, and physical growth.

The discussion of each outcome begins with a brief review of studies that assessed the effect of active smoking by the mother during pregnancy. Although reviewing active smoking effects is not the purpose of this document, the review of these studies provides a context within which to consider the results of the studies of ETS exposure.

The brief review of active smoking effects is followed by detailed descriptions of epidemiologic studies of ETS exposure and their outcomes. Pertinent animal studies are then described. The section concludes with a discussion of overall evidence on the impact of ETS exposure and the endpoint.

4.1.1 Confounding in Studies of Child Development The issue of adequate control of confounding is central in attempting to identify causal factors in child development. Smokers as a group appear to differ from nonsmokers in many ways that may influence child development (Broman *et al.*, 1987). For example, smokers are more likely to be of lower socioeconomic status, to be less educated (Fiore *et al.*, 1989; Pierce *et al.*, 1989; Escobedo *et al.*, 1990), to drink alcohol (Kuzma and Kissinger, 1981), and are less likely to breast-feed their infants (Goodine and Fried, 1984) than are nonsmokers. Differences between smokers and nonsmokers with respect to personality and emotional tone have also been observed (Waal-Manning and de Hammel, 1978; Haines *et al.*, 1980; Frerichs *et al.*, 1981). Fried and Watkinson (1988) have reported that the home environments of smokers are on average less conducive to optimal child development. These associations may confound the relationship between ETS exposure and child development.

Adjustment for potential confounders must be done carefully or incomplete control may result. For example, Rantakallio (1983) discovered that within each social class stratum used in her analysis, mothers who smoked were more disadvantaged in terms of employment, family intactness, and health status than were nonsmoking mothers. Conversely, a smoking effect may be concealed through adjustment for intervening variables. For example, adjusting for birthweight could obscure an effect attributable to smoking, if smoking exerts the effect through lowered birthweight.

The above-mentioned factors make it very difficult to examine the association between ETS exposure and developmental outcomes in children. Nevertheless, postnatal ETS exposure of the child may be an important or even the most relevant route of exposure to tobacco smoke components for some outcomes. Identifying an adverse outcome associated with exposure to ETS could have significant implications for public health. Using data from the 1988 National Health Interview Study, Overpeck and Moss (1991) estimated that 49 percent of all U.S. children under 5 years of age are regularly exposed to tobacco smoke after birth by their mother or another member of their household. It is important to distinguish the effects of prenatal and postnatal exposure to tobacco smoke components because approximately two-thirds of women who quit smoking while they are pregnant restart after the birth of the child (Gillies *et al.*, 1988). Identification of any adverse developmental effects due solely to postnatal ETS exposure may help motivate women who quit smoking during pregnancy to remain non-smokers after their babies are born.

4.2 SUDDEN INFANT DEATH SYNDROME Sudden Infant Death Syndrome (SIDS) is generally defined as the sudden death of any infant which is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death (Beckwith, 1970). The diagnosis of SIDS is usually restricted to infants aged 1 month to 1 year, but investigators sometimes expand the age-at-death criterion. In the United States and other developed countries, SIDS is the most common cause of post-neonatal death. Maternal risk factors that have been identified include young age, high parity, low socioeconomic status, cigarette smoking, and illicit drug use; risk factors in the infant include male sex, black or American Indian race, prematurity, low birthweight, a history of recent illness, having a "near-miss SIDS episode," having a sibling who died of SIDS, not breast feeding, and sleeping in the prone position; other risk factors include the winter season (Kraus and Bulterys, 1991; Guntheroth and Spiers, 1992).

4.2.1 Overview of Human Studies of SIDS and Maternal Smoking During Pregnancy Active maternal smoking during pregnancy has been consistently found to be a significant risk factor for SIDS with odds ratios (for any versus no maternal smoking) ranging from 1.6 to 4.4. Many studies, particularly the earlier ones, did not adequately control for potential confounders (Steele and Langworth, 1966; Schrauzer *et al.*, 1975; Naeye *et al.*, 1976; Bergman and Wiesner, 1976; Lewak *et al.*, 1979); others had problems with potential selection bias (Bergman and Wiesner, 1976) or incomplete assessment of maternal smoking status (Rintahaka and Hirvonen, 1986). However, there have been two case-control studies (Hoffman *et al.*, 1987 and 1988; Mitchell *et al.*, 1991 and 1992) and two population-based cohort studies (Malloy *et al.*, 1988; Haglund and Cnattingius, 1990) that have been large and reasonably well controlled, adjusting for at least maternal age, parity, race, and socioeconomic status or maternal educational level. In these studies, maternal smoking during pregnancy remained a significant independent risk factor for SIDS with adjusted ORs ranging from 1.8 to 2.5. The effect of maternal smoking on risk of SIDS is independent of birthweight, as demonstrated by Hoffman *et al.* (1987), Malloy *et al.* (1988), Kraus *et al.* (1989), Wierenga

et al. (1990), and Li and Daling (1991). Some investigators have suggested that the residual effect of maternal smoking during pregnancy after adjusting for birthweight could represent an effect of postnatal ETS exposure to the child (Kraus *et al.*, 1989; Dwyer and Ponsonby, 1992).

Several investigators (Steele and Langworth, 1966; Naeye *et al.*, 1976; Kraus *et al.*, 1989; Bulterys *et al.*, 1990; Haglund and Cnattingius, 1990; Malloy *et al.*, 1992) have noted an increase in SIDS risk with increasing levels of maternal smoking during pregnancy. The exception (a re-analysis of the Hoffman case-control study described in Malloy *et al.* (1992)) had used maternal smoking during the first trimester as its measure of exposure. It may be that the risk of SIDS associated with maternal active smoking varies depending on the timing and duration of exposure.

4.2.2 Human Studies of SIDS and ETS Exposure

4.2.2.1 ETS Exposure of the Mother During Pregnancy

No studies were found that specifically examined the relationship of ETS exposure of the mother during pregnancy to the subsequent risk of SIDS in the infant.

4.2.2.2 Postnatal ETS Exposure

Ten studies were found that examined the relationship between SIDS and postnatal ETS exposure (Table 4.1). Some of these studies were reviewed by the U.S. Environmental Protection Agency (1992).

Bergman and Wiesner (1976)

Bergman and Wiesner (1976) conducted a small case-control study of SIDS in King County, Washington. Cases and controls were matched on date of birth, sex, and race; there was no adjustment for other co-variables. Exposure was ascertained retrospectively by a mailed questionnaire. The study's case participation rate was poor (56 of 100 identified cases versus 86 of 100 identified controls) with non-responding mothers more likely to be young and to live in poor neighborhoods. This probably led to an underestimation of the proportion of smokers among the cases. The authors ascertained the level of maternal smoking both during and after pregnancy and the level of paternal smoking (timing unspecified). They found an overall crude OR for any maternal smoking during pregnancy of 2.2 (95% CI = 1.0-4.5), and for any maternal smoking after pregnancy of 2.4 (95% CI = 1.2-4.8). There was a large degree of overlap between the "smoking during" and "smoking after" groups: of the smoking mothers, the mothers of only one case and four controls did not smoke both during and after pregnancy. The effect of maternal smoking after pregnancy was independent of level of maternal education, but was present only among mothers ≤ 25 years old. Among the infants of these young mothers, there was evidence of a dose-response effect, with ORs of 3.8 (95% CI = 1.2-11.8) and 7.7 (95% CI = 1.4-52.4) for < 20 cigarettes and ≥ 20 cigarettes per day, respectively. Paternal smoking had an OR of 1.5 (95% CI = 0.7-3.2). Maternal smoking was not controlled for in the analysis of paternal smoking.

McGlashan (1989)

McGlashan (1989) conducted a case-control study of virtually all unexplained infant deaths in Tasmania from 1980 to 1986. Parents of the 167 cases were interviewed as part of routine grief counseling by public health nurses. Two controls were matched to each case by date of birth and

Table 4.1
Sudden Infant Death Syndrome (SIDS) Studies that Assessed some Source of Postnatal ETS Exposure

Authors (year) Location	Study Size	Exposure Group Comparison		Comments
		Exposure Group ¹	Odds Ratio (95% CI)	
Bergman & Wiesner (1976) United States (King County, Washington)	56 cases, 86 controls	• Any vs. no MS during pregnancy	2.2 (1.0-4.5)	Matched on sex, race. Poor study participation. Virtually all mothers who smoked in pregnancy also smoked afterwards.
		* Any vs. no MS after pregnancy	2.4 (1.2-4.8)	
		* Any vs. no PS	1.5 (0.7-3.2)	
McGlashan (1989) Tasmania	167 cases, 334 controls	• Any vs. no MS during pregnancy	1.9 (1.2-2.9)	Matched on sex; no other adjustment. ORs were calculated from table; author presented results of a matched analysis that were different. Virtually all mothers who smoked in pregnancy also smoked afterwards.
		* Any vs. no MS in child's first year	1.9 (1.2-2.9)	
		* Any vs. no PS	"significantly increased"	
Mitchell <i>et al.</i> (1991) New Zealand	128 cases, 503 controls (subset of Mitchell <i>et al.</i> (1993))	• Any vs. no MS during pregnancy (from medical records)	2.7 (crude)	Controlled for many demographic and social factors, breastfeeding, season, and sleeping position. Strong dose-response noted in crude analysis. Virtually all mothers who smoked in pregnancy also smoked afterwards.
		* Any vs. no recent MS (from interview)	3.0 (crude) 1.8 (1.0-3.3; adj)	
Nicholl & O'Cathain (1992) United Kingdom	242 cases, 251 controls	• Any vs. no MS during pregnancy	2.1 (1.5-3.1)	Matched for date and place of birth. Controlled for spousal smoking only. Effect of PS increased as infants' ages increased.
		* Any vs. no PS	1.6 (1.1-2.4)	

Table 4.1 (Continued)

Authors (year) Location	Study Size	Exposure Group ¹	Odds Ratio (95% CI)		Comments
			White	Black	
Schoendorf & Kiely (1992) United States (U.S. National Maternal and Infant Health Survey)	435 cases, 6,000 controls	• Any vs. no MS during and after pregnancy	3.1 (2.3-4.2)	3.1 (2.2-4.3)	Restricted to infants with birth weights ≥2,500 g. Controlled for maternal age, education, and marital status. Smokers in "during and after" category were heavier smokers than smokers in the "after only" category
		* Any vs. no MS after pregnancy only	1.8 (1.0-3.0)	2.3 (1.5-3.7)	
		* Other household smokers (vs. no other household smokers)	1.4 (1.0-1.9)	0.9 (0.7-1.3)	
Mitchell <i>et al.</i> (1993) New Zealand	485 cases, 1,800 controls	* Any vs. no recent MS	1.7 (1.2-2.3)		The first 3 ORs are adjusted for region season, breastfeeding, and bed shar- ing; mother's marital status, SES, age, and smoking during pregnancy; infant's age, sex, birthweight, race, and sleep- ing position; and where appropriate, smoking by the mother, father, and other household numbers.
		* Any vs. no PS	1.4 (1.0-1.8)		
		* Any vs. no other household smokers	1.2 (0.8-1.6)		
		* MS cigs/day:	<u>No PS</u>	<u>PS</u>	
		0	1.0 (ref)	1.0 (0.6-1.6)	
1-19	2.6 (1.7-3.8)	4.4 (3.3-6.0)			
≥20	3.4 (2.0-5.8)	7.4 (4.9-11.1)			

¹ Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (•) denotes non-ETS exposure.

Table 4.1 (Continued)

Authors (year) Location	Study Size	<u>Exposure Group Comparison</u>		Comments	
		Exposure Group ^{1,2}	Odds Ratio (95% CI)		
Klonoff-Cohen <i>et al.</i> (1995) United States (Southern California)	200 cases, 200 controls		<u>Unadjusted</u>	<u>Adjusted</u>	Adjusted ORs were controlled for birth weight, routine sleep position, medical conditions at birth, prenatal care, breast feeding, and maternal smoking during pregnancy.
		* Any MS	3.1 (1.8-5.6)	2.3 (1.0-5.0)	
		* Any same-room MS	6.2 (2.6-14.6)	4.6 (1.8-11.8)	
		* Any PS	3.5 (2.0-6.3)	3.5 (2.0-6.3)	
		* Any same-room PS	9.2 (3.7-23.2)	8.5 (3.3-21.6)	
		* Any household smoking	3.8 (2.3-6.4)	3.5 (1.8-6.8)	
		* Any same-room household smoking	6.2 (3.3-11.7)	5.0 (2.4-11.0)	
		Total number of household smokers:			
		1	3.1 (1.8-5.5)	3.0 (1.5-6.0)	
		2	5.2 (2.5-10.7)	5.3 (1.9-14.5)	
		3	8.1 (1.5-44.5)	5.1 (0.7-36.6)	
		Total cig exposure/day:			
1-10	2.3 (1.1-4.7)	2.4 (1.1-5.4)			
11-20	3.5 (1.7-7.1)	3.6 (1.5-8.8)			
≥21	12.6 (4.3-37.1)	22.7 (4.8-107.2)			

Table 4.1 (Continued)

Authors (year) Location	Study Size	Exposure Group Comparison		Comments
		Exposure Group ¹	Odds Ratio (95% CI)	
Blair <i>et al.</i> (1996) United Kingdom	195 cases, 780 controls	* Any vs. no PS	2.5 (1.5-4.2)	Matching by age and region. First OR is adjusted for maternal age, marital status, SES, maternal smoking, drug and alcohol use, gestational age, sleeping position, and breast feeding.
		* PS/no MS vs. no PS or MS	3.4 (2.0-5.9)	
		* Household cigs/day: 0	1.0	
		1-19	2.5 (1.3-4.7)	
		20-39	4.0 (2.4-6.6)	
		≥40	7.6 (4.0-14.3)	

¹ Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (•) denotes non-ETS exposure.

² All odds ratios are for postnatal exposure and are relative to infants with no smoke exposure.

sex. Parents of controls were interviewed much later after pregnancy than were parents of cases, introducing a potential source of recall bias. The levels of maternal smoking during pregnancy and throughout the baby's first year of life, as well as levels of paternal smoking, were ascertained. As in the Bergman and Wiesner (1976) study, there was virtually complete overlap between the women who smoked during pregnancy and who smoked during the infants' first year of life, with ORs for both forms of maternal smoking of 1.9 (95% CI = 1.2-2.9). No clear dose-response relationship was seen. The author also stated that cases were significantly more likely than controls to have a father who smoked, or to have either a mother or father who smoked, but the actual data were not presented. There was no adjustment for co-variates.

Mitchell et al. (1991) Results from the first year of a 3-year case-control study of SIDS in New Zealand were reported in Mitchell *et al.* (1991). The interim report included 128 SIDS cases and 503 controls. Cases were well-defined and study participation was over 80 percent. Information regarding all major risk factors for SIDS except for maternal illicit drug use was either obtained through an interview with the parents (conducted on average one month after the death of the case infant) or abstracted from medical records. Maternal smoking status was assessed two ways: as a yes/no variable abstracted from the obstetric record and as the average number of cigarettes smoked per day in the two weeks prior to interview. Neither of these approaches are ideal—the first method would underestimate exposure if a smoking history was not consistently obtained, and the second method might overestimate smoking among mothers of cases if they were smoking more due to the stress of recently losing a baby. Nevertheless, both methods resulted in very similar crude ORs of 2.7 and 3.0, respectively. In a multivariate analysis incorporating most known risk factors for SIDS except maternal smoking during pregnancy, any maternal smoking in the 2 weeks prior to interview had an OR of 1.8 (95% CI = 1.0-3.3). There was no data presented regarding smoking by the father or other family members.

Nicholl and O'Cathain (1992) Nicholl and O'Cathain (1992) conducted a study of 242 SIDS cases and 251 controls drawn from a larger study of post-neonatal mortality in the United Kingdom. The authors calculated independent risks of SIDS for maternal smoking during pregnancy and for smoking by the mother's partner. Smoking by the partner was associated with an OR of 1.6 (95% CI = 1.1-2.4) whereas smoking (during pregnancy) by the mother was 2.1 (95% CI = 1.5-3.1). This analysis controlled for spousal smoking but did not control for any other potential confounders. In the subset of infants whose fathers smoked and whose mothers were nonsmokers, the OR for paternal smoking was 1.4 (95% CI = 0.8-2.4). The researchers did not ascertain maternal smoking status after pregnancy, nor did they distinguish partner's smoking level during and after the pregnancy. In a secondary analysis, the infants were divided into four subgroups by age at death of the case-infant. As the infants' ages increased, the independent ORs associated with partners' smoking increased, from 1.5 at <8 weeks to 2.6 at ≥24 weeks. Conversely, the ORs associated with maternal smoking decreased (from 4.0 to 1.4) as infants' ages increased (confidence intervals were not

given). The authors suggested that this pattern implies that prenatal exposure to maternal active smoking components may be more important for younger infants, and postnatal ETS exposure more important for older infants. Their finding that maternal smoking was less important than partner's smoking in infants ≥ 24 weeks of age is problematic, since most mothers who smoked during pregnancy presumably also exposed their infants to ETS by continuing to smoke after delivery. However, the numbers in each age category were small and the point estimates are probably imprecise.

Schoendorf and Kiely (1992) The first study to independently examine maternal smoking during and after pregnancy was published by Schoendorf and Kiely (1992). They performed a case-control analysis of data from the 1988 National Maternal and Infant Health Survey. Within this dataset, 201 black and 234 white autopsied SIDS cases were identified from death certificates; approximately 3,000 controls for each race were used. The analysis was restricted to infants weighing $\geq 2,500$ grams at birth. Mothers were questioned regarding their level of cigarette consumption during pregnancy and at the time of interview, and from their responses categorized as nonsmokers, smokers after pregnancy only, or smokers during and after pregnancy. After adjustment for maternal age, education, and marital status, maternal smoking only after pregnancy had an OR of 1.8 (95% CI = 1.0-3.0) for whites and 2.3 (95% CI = 1.5-3.7) for blacks. The risk of SIDS among infants of women who smoked both during and after pregnancy was 3.1 (95% CI = 2.3-4.2) and 3.1 (95% CI = 2.2-4.3) for whites and blacks respectively. The ORs for "passive" (postnatal) and "combined" (pre- and postnatal) exposure were not directly comparable, as mothers who smoked during and after pregnancy tended to smoke more cigarettes per day than mothers who smoked only after pregnancy. The authors also examined the risk of SIDS in relation to the presence of other smokers in the household. In whites, household smoking was significantly associated with SIDS (OR = 1.4, 95% CI = 1.0-1.9), but no relationship was seen in blacks (OR = 0.9, 95% CI = 0.7-1.3). This latter analysis controlled for mother's smoking status only.

Mitchell et al. (1993) Final results from the New Zealand case-control study were published in Mitchell *et al.* (1993). The study's catchment area covered 78 percent of all live births in New Zealand during the 3-year study period. Four hundred eighty-five SIDS cases were compared to 1,800 controls. Case infants were much more likely than were control infants to have mothers who had smoked in the 2 weeks prior to interview (OR = 4.1, 95% CI = 3.3-5.1). The OR decreased to 1.7 (95% CI = 1.2-2.3) but was still significant at the $p = 0.05$ level after adjusting for region, season, breastfeeding, and bed sharing; mother's marital status, socioeconomic status, age, and smoking during pregnancy; infant's age, sex, birthweight, race, and sleeping position; and smoking by the father and other household members. Although results were adjusted for maternal smoking during pregnancy, less than 10 percent of the mothers changed their smoking behavior through pregnancy and the first year of the infant's life. There was a strong dose-response relationship observed between amount smoked by the mother and risk of SIDS (these ORs were not adjusted for any co-variates). The researchers also

found a significant relationship between recent paternal smoking and SIDS, with a crude OR of 2.4 (95% CI = 1.9-3.0) and an adjusted OR of 1.4 (95% CI = 1.0-1.8; adjusted for maternal smoking as well as the other co-variables listed previously). They did not see a dose-response relationship for paternal smoking. Among infants whose mothers did not smoke (131 cases and 1,081 controls), there appeared to be no difference in SIDS risk between infants whose fathers smoked and those with non-smoking fathers (OR = 1.0, 95% CI = 0.6-1.6). However, having a smoking father appeared to substantially increase the risk of SIDS among infants whose mothers smoked. The authors speculated that non-smoking mothers may be more likely than smoking mothers to insist that fathers smoke away from the child.

Mitchell *et al.* also looked at the relationship between the number of smokers in the household and the risk of SIDS. Having any other smokers in the household—excluding the parents—resulted in a crude OR of 1.5 (95% CI = 1.2-2.0) and an adjusted OR of 1.2 (95% CI = 0.8-1.6). When parents were included, there was a strong dose-response relationship between the number of household smokers and the risk of SIDS.

Milerad et al. (1994) Milerad *et al.* (1994) published a small case-report study of autopsied SIDS cases. Sixteen consecutive cases with no other positive histological or other findings at post-mortem had pericardial fluid tested for cotinine, a nicotine metabolite often used to quantify exposure to tobacco smoke. Nine of the 16 (56.3 percent) cases had pericardial cotinine levels indicative of moderate to heavy ETS exposure (cotinine 2.2-156.9 ng/ml). Swedish national surveys report that 18 percent of Swedish women smoke after having a baby, thus more of the autopsied SIDS cases were exposed than would be expected using national data. This small descriptive study has a number of limitations, including the lack of information on the actual smoking practices of the SIDS cases' family members, and the lack of controls. However, to date this is the only study to look at a biomarker of tobacco exposure in SIDS.

Mitchell et al. (1995) Mitchell *et al.* (1995) describes a follow-up study to the New Zealand case-control SIDS study (Mitchell *et al.*, 1991) designed to examine the risk of maternal smoking by considering where the smoking took place. As location of smoking had not been determined in the original interview, a questionnaire was mailed to all participants. Mothers who smoked were asked whether they had usually, sometimes, or never smoked in various parts of their home. Non-Europeans had a poor response rate and were excluded. Of the European participants, 60.3 percent of the case parents and 76.9 percent of the control parents responded. Non-respondents were more likely than respondents to be smokers, younger, and of a lower occupational group. There was no discernible pattern in risk between locations or between smoking frequency, with ORs associated with maternal smoking ranging from 1.7 to 3.0. Mothers who smoked but claimed they never did so in the house had a higher risk of SIDS (OR = 5.1; 95% CI = 1.5-15.4) than did mothers who smoked in the house (OR = 2.2; 95% CI = 1.4-3.5), but the number of women in the group who never smoked in the house was very small ($n = 18$). There was no control for potential confounders. The

authors felt that the increased risk even among women who did not smoke in the home suggested that risk was primarily from *in utero* exposure. However, this conclusion was driven by a very small group of women, and there was no accounting for the smoking habits of other family members. The authors themselves cautioned that there may be societal pressures for smokers to report not smoking in the home; also, in previous analyses of their own data, they saw an effect of paternal smoking. Thus, they stated that their results should not be interpreted to mean that ETS exposure after birth is not important.

Haglund et al. (1995) Although the study by Haglund *et al.* (1995) did not measure postnatal ETS exposure, it is included here because the authors felt it had implications for the issue of pre- versus postnatal exposure. The authors linked the Swedish death register to the Medical Birth Register to create a cohort of over 800,000 infants, of whom 749 died of SIDS. Maternal smoking (yes/no) at the first prenatal visit was included in the birth registry. The authors found that the winter season and maternal smoking were both independent risk factors for SIDS, but that the excess risk due to smoking did not vary by season (*i.e.*, risks for the winter season and smoking were simply additive). The excess relative risk of smoking was approximately 3.5 for early SIDS deaths (7-90 days) and 2.5 for late SIDS deaths (91-364 days). They speculated that exposure to ETS would be likely to vary by season, and thus stated that “possibly the effect of smoking is prenatal rather than the result of passive smoking after birth.” They did not have any direct information about the infants’ exposure to tobacco smoke after birth, nor did they present any evidence that ETS exposure would vary significantly by season.

Klonoff-Cohen et al. (1995) Klonoff-Cohen *et al.* (1995) conducted a large case-control study (200 SIDS cases and 200 controls) that had the most extensive assessment of exposure to tobacco smoke of any SIDS study to date. The investigators assessed quantitatively the amount smoked by the mother during each trimester of pregnancy and after birth, by the father during and after pregnancy, and by other live-in adults and day-care providers; they also assessed the proximity of these individuals to the infant as they smoked. They also inquired about smoking and breastfeeding practices. Results were adjusted for several potential confounders including maternal smoking during pregnancy, birthweight, sleep position, breastfeeding, and medical conditions. Every measure of ETS exposure was associated with increased SIDS risk. The adjusted OR for postnatal maternal smoking was 2.3 (95% CI = 1.0-5.0). Paternal smoking had an adjusted OR of 3.5 (95% CI = 1.9-6.3). Although the OR for paternal smoking was higher than the OR for maternal smoking, the high correlation between maternal smoking during and after pregnancy probably resulted in an underestimate of the effect of maternal smoking after pregnancy when adjusting for smoking during pregnancy. Increased risk was also seen with increasing number of household smokers and with total cigarette exposure per day (see Table 4.1). Furthermore, the risk associated with smoking increased when the comparison was restricted to smoking in the same room as the infant. For example, the adjusted OR for postnatal maternal smoking increased from 2.3 to 4.6 (95% CI = 1.8-

11.8) when restricted to same-room exposure. Similarly, the adjusted OR for any household smoking increased from 3.5 (95% CI = 1.8-6.8) to 5.0 (95% CI = 2.4-11.0). The authors concluded, "These data suggest that exposure to tobacco smoke after birth, after adjusting for prior fetal exposure, is associated with an increased risk of SIDS."

Klonoff-Cohen *et al.* also examined the interaction between breastfeeding and maternal smoking. As expected, breastfeeding was protective for SIDS among nonsmokers (adjusted OR = 0.4, 95% CI = 0.2-0.8). No protective effect of breastfeeding was seen among the smokers, although there were only 22 women who both smoked and breastfed their infants (adjusted OR = 1.4, 95% CI = 0.2-12.0).

Blair et al. (1996) A recently published case-control study by Blair *et al.* (1996) corroborated the findings of Klonoff-Cohen *et al.* The study documented significant, dose-related increases in SIDS risk for the three main measures of household smoke that were examined: the number of smokers in the household, the hours of smoke exposure to the infant daily, and the number of cigarettes smoked daily in the household. The latter variable yielded results quite similar to those of Klonoff-Cohen *et al.*, with ORs for 1-19, 20-39, and ≥ 40 cigarettes per day of 2.5, 4.0, and 7.6, respectively. They also demonstrated elevated risk in families where the mother was a nonsmoker and either the father (OR = 3.4, 95% CI = 2.0-5.9) or another family member (OR not given but $p = 0.007$) smoked. These analyses were unadjusted for potential confounders. In a multivariate analysis that controlled for sleep position, breast feeding, socioeconomic status indicators, maternal smoking, and other factors, paternal smoking remained an independent risk factor (OR = 2.5, 95% CI = 1.5-4.2). The authors calculated that the population-attributable risk for SIDS associated with smoking by at least one parent was 61 percent (this included the effect of smoking by the mother during pregnancy). An interesting feature of this study was that it was conducted in England after the 1991 "Back to Sleep" campaign. This campaign, which sought to reduce the prevalence of risk factors for SIDS, particularly putting infants to sleep in the prone position, had been associated with a fall in the incidence of SIDS in the United Kingdom (Wigfield and Fleming, 1995).

4.2.3 Animal Studies of SIDS and Tobacco Smoke Exposure

There is no established animal model for SIDS. However, Slotkin *et al.* (1995) proposed a rat model for SIDS based upon changes in neurochemical function and increased hypoxia-induced mortality of rat pups prenatally exposed to nicotine. According to the model, prenatal exposure to nicotine causes lasting neurochemical changes, which in turn place an infant at greater risk for cardiorespiratory failure during neonatal apneic episodes. A direct link between specific nicotine-induced neurochemical changes and the observed increase in hypoxia-induced mortality has not yet been established. However, in other studies (Milerad *et al.*, 1995), nicotine was found to attenuate the ventilatory response to hypoxia in neonatal lambs, suggesting that neurochemical effects of nicotine could alter either the sensitivity of the carotid body to carbon dioxide or the central processing of chemo-receptor input in the brain.

4.2.4 Discussion and Conclusions

Existing data indicate a causal relationship between maternal smoking in general and risk of SIDS. Numerous studies have consistently found maternal smoking to be a significant predictor of SIDS, with ORs from well-controlled studies ranging from 1.8 to 3.1. A meta-analysis performed by DiFranza and Lew (1995) on studies of SIDS among offspring of women who smoked and who did not smoke during pregnancy (regardless of smoking status after pregnancy) found a pooled OR of 2.98 (95% CI = 2.51-3.54). Several investigators (but not all) have found clear dose-response relationships between the number of cigarettes smoked per day during pregnancy and SIDS risk. Although the etiology of SIDS is not fully understood, a favored current hypothesis is that chronic fetal hypoxia impairs development of the fetal central nervous system, leading to abnormal control of cardio-respiratory activity (Harper and Frysinger, 1988). Maternal smoking during pregnancy promotes fetal hypoxia through placental insufficiency or by increasing the concentrations of carbon monoxide and carboxyhemoglobin in the fetus (U.S. DHHS, 1980). In support of this hypothesis is the finding by Bulterys *et al.* (1990) that low hematocrit during pregnancy becomes an important predictor of SIDS as the level of maternal smoking increases. Exposure to nicotine may also alter an infant's catecholamine metabolism and response to hypoxia (Milerad and Sundell, 1993), an effect recently demonstrated in rats (Slotkin *et al.*, 1995).

Ten epidemiologic studies have attempted to specifically examine the relationship between ETS exposure and SIDS. These studies have looked at smoking by the mother after pregnancy, paternal smoking, household smoking, and smoking during different seasons. In three studies that looked at maternal postnatal smoking (Bergman and Wiesner, 1976; McGlashan, 1989; Mitchell *et al.*, 1991), extensive overlapping between women smoking during and after pregnancy precluded any attempt to identify an independent relationship to ETS exposure. Haglund *et al.* (1995) speculated that because the risk associated with maternal smoking did not rise in the winter, when indoor ventilation might be poorer, prenatal tobacco exposure might be more important than postnatal exposure. They did not, however, measure postnatal maternal smoking, nor did they provide evidence that ETS exposure is greater in the winter. In Mitchell *et al.* (1993), a significant association between postnatal maternal smoking and SIDS remained after adjustment for smoking during pregnancy and other co-variates. However, the number of smokers who had not smoked during pregnancy was very small. Mitchell *et al.* later attempted to refine their assessment of maternal smoking by reinterviewing their subjects about location of smoking (Mitchell *et al.* 1995). Although the authors interpreted their finding that never smoking inside the home did not reduce the risk of SIDS as implying that prenatal exposure is more important than postnatal exposure, the numbers in this group were very small. In addition, they did not link location of smoking to the location of the infant. Schoendorf and Kiely (1992) took advantage of the recent trend for women who are smokers to quit smoking during pregnancy by comparing infants of women who smoked primarily only after pregnancy with infants of non-smoking mothers. Their adjusted OR (1.8) was quite similar to the adjusted OR (1.7) calculated by Mitchell *et al.* (1993). Bulterys (1993) pointed out that most

of the women who smoked “after pregnancy only” also smoked during the first few weeks of pregnancy; thus, it was possible, though not likely, that the increased risk was due to ETS exposure or to maternal active smoking early in pregnancy. Klonoff-Cohen *et al.* (1995), in a fairly large study with detailed exposure assessment and good control of potential confounding, reported an adjusted OR for postnatal maternal smoking of 2.3. This value is also consistent with the ORs seen in Mitchell *et al.* (1993) and Schoendorf and Kiely (1992). In addition, Klonoff-Cohen *et al.* (1995) found that the risk associated with maternal smoking increased when the exposed group was restricted to those women who smoked in the same room as their infant, implying that more concentrated exposure increased risk.

Six papers examined the association between paternal smoking and SIDS. Two (Bergman and Wiesner, 1976; McGlashan, 1989) found that crude ORs for paternal smoking were slightly elevated, but no adjustment for maternal smoking had been made. The third paper to examine paternal smoking (Nicholl and O’Cathain, 1992) found a significantly elevated risk of SIDS independent of maternal smoking. The risk associated with paternal smoking increased with the age of the infant, suggesting that passive exposure of the infant was important. They also found an increased risk of SIDS in families where the father but not the mother smoked, although the confidence interval included unity (OR = 1.4, 95% CI = 0.8-2.4). Lack of control for potential confounders somewhat reduces confidence in their findings. Mitchell *et al.* (1993) looked extensively at smoking among fathers. Overall, paternal smoking remained associated with SIDS even after controlling for maternal smoking and a number of other co-variables. However, the risk did not vary with the amount smoked by the father, and in families where the mother did not smoke, the presence of a smoking father did not appear to increase SIDS risk. The authors presented a plausible explanation for this pattern of results, namely that in families where the mother does not smoke, the father may be less likely to smoke near the infant; however, this speculation remains to be confirmed. Klonoff-Cohen *et al.* (1995) found an increased risk of SIDS associated with paternal smoking independent of maternal smoking. Their OR (3.5) was somewhat higher than Nicholl and O’Cathain and Mitchell *et al.* (1.6 and 1.4 respectively), but this difference could have been due to differences in the time fathers spent with their children. Klonoff-Cohen *et al.* found some evidence of a dose-response in that the risk increased substantially when the analysis was restricted to those fathers who smoked in the same room as their infant. Blair *et al.* (1996) was able to demonstrate significantly increased SIDS risk in families where the father smoked but the mother was a nonsmoker (OR = 3.4, compared to families where neither parent smoked). In a fully adjusted model, any paternal smoking conferred an OR of 2.5, which was between the ORs reported by Mitchell *et al.* and Klonoff-Cohen *et al.*

Four studies looked at household smoke exposure and SIDS. Schoendorf and Kiely (1992) found that among white infants there was an increased risk of SIDS associated with the presence of smokers other than the mother in the household; no such association was seen among black infants. With the information available to them, Schoendorf and Kiely (1992) were not able to explain why no association was seen among blacks.

Mitchell *et al.* (1993) found a dose-response relationship (unadjusted) between the number of smokers in a household and the risk of SIDS. The adjusted OR for the presence of any smokers other than the parents in the household was small (1.2) and the confidence interval included unity. These non-parental smokers might have spent less time with the infant, however. Klonoff-Cohen *et al.* (1995) looked extensively at household smoke exposure, measuring it as total number of household smokers, and as total cigarette exposure per day. A dose-response relationship between ETS and SIDS was seen with both these measures: adjusted ORs for 1-10, 11-20, and ≥ 21 cigarettes/day were 2.4, 3.6, and 22.7, respectively. Blair *et al.* (1996) found very similar dose-related risks for household cigarette exposure, although their results were unadjusted for possible confounding.

One study in Sweden, Milerad *et al.* (1994), examined cotinine levels in the pericardial fluid of a small number of consecutively autopsied SIDS cases. They found cotinine levels indicating ETS exposure in over half of the cases, a proportion approximately three times higher than would be expected given the percentage of Swedish women who report smoking postnatally. Although limited, this study provides further corroboration of the association between ETS and SIDS seen in other studies.

There is some evidence that suggests a relationship between ETS and SIDS is biologically plausible. Hoppenbrouwers *et al.* (1981) found an association between air pollution levels and incidence of SIDS, suggesting that airborne contaminants may play a role in the etiology of SIDS. Since tobacco smoke is a major contributor to indoor air pollution, ETS could influence SIDS risk through mechanisms similar to those of other air pollutants. ETS may impair respiratory control through chronic carbon monoxide (Watkins and Strobe, 1986) and nicotine exposure (Milerad and Sundell, 1993), and ETS can directly affect lung function (U.S. DHHS, 1986). Finally, exposure to ETS increases the likelihood of respiratory tract infections in infants (as discussed in the chapter *Respiratory Health Effects*) which in turn may increase the risk of SIDS. These hypotheses remain to be confirmed.

In conclusion, the strength of the Klonoff-Cohen *et al.* and Blair *et al.* studies, their consistency with two earlier well-conducted studies (Mitchell *et al.*, 1993; and Schoendorf and Kiely, 1992), and the identification of dose-response relationships provide sufficient evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS.

4.2.4.1 Risk Attributable to ETS Exposure In a large epidemiological study that addressed several potential confounders (Klonoff-Cohen *et al.*, 1995), an OR of 3.5 (1.8-6.8) was found for ETS exposure resulting from any household smoking. Pierce *et al.* (1994) estimated that, in 1993, 17.3 percent of children under the age of five were exposed to ETS in California households. Following DiFranza and Lew (1996), from the proportion exposed to ETS (p) and relative risk (R , which is approximated by the OR), the proportion of cases attributable (a) to ETS exposure can be estimated:

$$a = p(R - 1) / (p(R - 1) + 1)$$

Thus, of the 398 cases of SIDS in California occurring in 1995, 30 percent—or 120 cases—may be attributed to ETS exposure. Nationally, 40-55 percent of children may live in households with ETS exposure (Pirkle *et al.*, 1996; Overpeck and Moss, 1991; Greenberg *et al.*, 1989), and 4,669 cases of SIDS occurred in 1993 (U.S. Bureau of the Census, 1996). Thus, 50-58 percent of SIDS cases nationally (1,868-2,708 deaths in 1993) may be attributed to ETS exposure.

4.3 COGNITION AND BEHAVIOR IN CHILDREN

The determinants of cognitive ability and behavior in children are extremely complex. A wide array of genetic, social, and environmental factors are thought to influence neuropsychological development, including parental intellectual and emotional make-up, socioeconomic status, nutritional status, quality of the home environment, number and spacing of siblings, birth order, sex, and maternal intake of alcohol during pregnancy. Many of these factors do not act independently of each other, but instead create a web of influence that can be very difficult to untangle.

4.3.1 Cognition and Behavior in Children whose Mothers Smoked During Pregnancy

A number of epidemiological studies have examined the association between active maternal smoking during pregnancy and cognition and behavior in children. These have been reviewed

4.3.1.1 Studies of Children whose Mothers Smoked During Pregnancy

in Rush and Callahan (1989), Rush (1992), and Tong and McMichael (1992). In the following summary of the literature, studies of cognition in infants, pre-schoolers, and older children are discussed, followed by a review of behavioral studies.

Infant neuropsychological development is often assessed using the Bayley Scales of Infant Development, an administered test that includes mental, psychomotor, and behavioral components (Bayley, 1969). Garn *et al.* (1980) examined the Bayley scores of over 43,500 infants enrolled in the National Collaborative Perinatal Project and found that the proportion with low mental and motor scores increased as maternal cigarette consumption increased. The association was very small until maternal consumption exceeded 20 cigarettes per day; there was no control for potential confounders. Streissguth *et al.* (1980) failed to find significant relationships between maternal smoking (converted to a nicotine score) and Bayley scores after adjusting for gestational age and maternal education, parity, alcohol and caffeine intake. Whether non-significant relationships existed could not be determined from the data presented. Gusella and Fried (1984) found modest negative correlations between nicotine consumption and psychomotor, verbal comprehension, and fine motor indices (the range of Pearson correlation coefficients (r) was -0.11 to -0.22), controlling only for father's education. Only the relationship with verbal comprehension was significant (exact p -values were not calculable from data presented).

Fried and Watkinson (1988) studied a larger sample from the same cohort studied by Gusella and Fried (1984), weighted so that children with heavier exposure to prenatal tobacco and alcohol would be over-represented. They found that after adjustment for the quality of the home environment (assessed by the Home Observation for Measurement of the

Environment (HOME) test), maternal alcohol use, and various demographic factors, differences between 2-year-old children of smokers and nonsmokers diminished to nearly nil (the HOME test measures a variety of characteristics of the home environment and maternal-child interaction and is strongly correlated with many measures of child development (Siegel, 1982)). Thus, this study suggests that most, if not all, of the negative association between maternal smoking during pregnancy and scores on the Bayley exam can be explained by confounding by other variables.

Two studies have evaluated pre-school children using the McCarthy Scales of Children's Abilities. The McCarthy is an administered test with verbal, perceptual, quantitative, general cognitive, memory, and motor subscales, and is a good predictor of school performance (Kaufman and Kaufman, 1977). Fried and Watkinson (1990) found negative correlations between nicotine consumption during pregnancy and all subscales, particularly the verbal subscale (approximate 10 percent decrement among children of heavy smokers). These differences were adjusted for HOME score only. The investigators also found comparable decreases in Peabody Picture Vocabulary Test scores (a test of receptive vocabulary) and the expressive language component of the Reynell Developmental Language Scales. Sexton *et al.* (1990) compared children born to women who quit smoking during pregnancy with children of persistent smokers. One-third of the mothers were "quitters" and two-thirds of the mothers had smoked throughout pregnancy. Children of persistent smokers had adjusted scores that were 2 to 4 percent lower than scores of children of quitters; the effect was most pronounced in the verbal and general cognitive indices. Control variables included a variety of demographic factors, family characteristics, maternal use of alcohol during pregnancy, maternal smoking after pregnancy, and the child's birthweight, gestational age, and health status. Similar results were seen using the Minnesota Child Development Inventory. Thus, in both studies of pre-schoolers there was a pattern of decreased McCarthy scores, especially in the verbal subscale.

Conversely, two studies that used data from the Kaiser Permanente Child Health and Development Studies, Bauman *et al.* (1991) and Eskenazi and Trupin (1995), failed to find an association between smoking during pregnancy and lowered scores on the Peabody Picture Vocabulary Test and the Raven Colored Progressive Matrices Test. Bauman *et al.* defined smoking status using interview data, whereas Eskenazi and Trupin used serum cotinine levels measured in mid-pregnancy. These studies were large (over 1,500 subjects) and well-controlled, including adjustment for postnatal smoke exposure.

The association between maternal smoking during pregnancy and impairments of cognition and school achievement in older children are generally consistent, although the decrements are small and not always statistically significant. A longitudinal study of 17,000 British children found modest but statistically significant dose-related delays in reading, math, and general ability at 7, 11, and 16 years, and a lower level of educational attainment at age 23 (Davie *et al.*, 1972; Butler and Goldstein, 1973; Fogelman, 1980; Fogelman and Manor, 1988). The decrements were

approximately halved after adjusting for a variety of demographic factors and birthweight. In studies derived from the National Collaborative Perinatal Project, Hardy and Mellits (1972) and Naeye and Peters (1984) found adjusted decrements of two to four percent among children of smokers on the spelling and reading sections of the Wide Ranging Achievement Test; Naeye and Peters (1984) also found an increasing effect with number of cigarettes smoked. Nichols and Chen (1981) found a 25 percent increased risk (unadjusted) of learning difficulties among children of heavy smokers (≥ 20 cigarettes per day). In their crude analysis, risk varied with dose; however, the association between maternal smoking and learning difficulties diminished to non-significance in the final multivariate model. In an uncontrolled analysis, Dunn *et al.* (1977) found that children of mothers who smoked during pregnancy scored approximately 3 percent lower on the Wechsler Intelligence Scale than did children of nonsmokers.

None of these studies of older children controlled for maternal alcohol intake during pregnancy, parental intelligence, quality of the home environment, or current smoking status of the child or family members. In an attempt to control for unassessed genetic and environmental factors, Naeye and Peters (1984) also conducted a sibling pair comparison, balanced for birth order, in which the mother smoked during one pregnancy and not the other. This study again found achievement test scores 2-5 percent lower among children of smoking mothers. Changes in marital status or outside employment did not explain the association.

Behavioral problems such as hyperactivity have been inconsistently reported in studies of children with prenatal exposure to maternal active smoking. Dunn *et al.* (1977) found that male children of mothers who smoked during pregnancy were judged by their teachers to have more problems with behavior, social development, and temperament (uncontrolled analysis; proportions were not given). In their work with the large National Collaborative Perinatal Project, Nichols and Chen (1981) found that school-aged children of women who smoked more than 20 cigarettes per day during pregnancy had a 28 percent increased risk of hyperkinetic-impulsive behavior. Naeye and Peters (1984) found that children's attention span decreased and level of activity increased as the number of cigarettes smoked per day by the mother during pregnancy increased, even after adjustment for demographic factors, gestational age, and breast feeding. Similar results were found in the sibling pair comparison.

The findings of Landesman-Dwyer *et al.* (1981) did not support an association between maternal active smoking during pregnancy and hyperactive behavior. They scored 4-year-olds on a large number of behaviors during a 3-hour observation period in the children's homes. There were no differences noted between children of smokers and children of nonsmokers after adjustment for sex, birth order, maternal alcohol use, and HOME score. However, smoking mothers rated their children as "intense", "persistent", and "willing to approach strangers" more often than did nonsmoking mothers. Similarly, in a large, well-controlled study, Eskenazi and Trupin (1995) failed to find an association between smoking during pregnancy and "active" behavior as reported by the mother. Unlike the other

studies, this study also adjusted for the child's exposure to tobacco smoke after birth. Thus, of all the studies described in this section, their results are the only ones likely to represent the effect of prenatal exposure alone.

Three groups of investigators have used computer-controlled "vigilance tasks" to evaluate attention, impulsivity, and reaction time in children. Poor vigilance performance is related to childhood hyperactivity (Porrino *et al.*, 1983). Streissguth *et al.* (1984), controlling for birth order and maternal education, nutrition, and caffeine and alcohol intake, found that maternal nicotine consumption in pregnancy was significantly associated in a dose-related manner with poorer attention span. Kristjansson *et al.* (1989) found that increased activity levels were more common in children of mothers who smoked during pregnancy, even after adjustment for age, sex, income, maternal education, alcohol and marijuana use, and post-natal smoke exposure. In a larger sample drawn from the same cohort as Kristjansson *et al.* (1989), Fried *et al.* (1992) found that vigilance parameters reflecting impulsiveness and attention, as well as the McCarthy memory subscale, significantly discriminated between children whose mothers were non-, light, and heavy smokers in a discriminant function analysis. Smoking mothers were also more likely to report impulsive and hyperactive behavior in their children, but the difference was not significant ($p > 0.10$). No adjustments for co-variates were made, as the authors stated that no potentially confounding variables were associated with both smoking and the outcome variables.

4.3.1.2 Discussion of Evidence from Studies in Children whose Mothers Smoked During Pregnancy

Most studies of cognitive development demonstrated small decrements, especially in language skills, in children whose mothers smoked during pregnancy. Where data were presented to make the calculation possible, differences associated with maternal smoking ranged from about 2 to 5 percent (Sexton *et al.*, 1990; Hardy and Mellits, 1972; Naeye and Peters, 1984; Rantakallio, 1983). In most studies that found an association, dose-response relationships were also noted. Studies of infants tended not to show effects after adjustment for co-variates, whereas studies of older children tended to show significant effects. The relative lack of association seen in studies of infants may reflect the fact that studies of infants tended to be better controlled than studies of older children. This hypothesis is supported by the results of Baghurst *et al.* (1992), Bauman *et al.* (1991), and Eskenazi and Trupin (1995), all well-controlled negative studies of older children. Alternatively, effects of active maternal smoking during pregnancy may become more "measurable" as children mature, and their intellectual functions become more complex.

Eight of ten studies of behavior and active maternal smoking during pregnancy have shown increased activity level and decreased attention span in children of smokers. Of the four studies with good control of potential confounders (Landesman-Dwyer *et al.*, 1981; Weitzman *et al.*, 1992; Naeye and Peters, 1984; Eskenazi and Trupin, 1995), Weitzman *et al.* (1992) and Naeye and Peters (1984) found significant behavioral impairments in children of smokers. However, Weitzman's outcome measure was based on mothers' reports, making it possible that the effect of smoking was due to

differences in mothers' interpretations of their children's behavior, rather than differences in the actual behavior of the children. This possibility is supported by Landesman-Dwyer *et al.* (1981) who reported no differences in objective measures of children's behavior related to maternal smoking during pregnancy, but found smoking-related differences in mothers' assessments of their children's behavior.

It is biologically plausible that smoking during pregnancy could eventually lead to neuropsychological deficits. One hypothesis is that chronic hypoxia impairs fetal brain development. There are several mechanisms by which maternal smoking can make the fetus hypoxic. Maternal smoking exposes the fetus to both nicotine and carbon monoxide. Nicotine reduces uteroplacental blood flow and carbon monoxide produces carboxyhemoglobin, both of which reduce oxygen delivery to fetal tissues (Lehtovirta and Forss, 1978; Cole *et al.*, 1972). Supporting this hypothesis is the finding by Naeye and Peters (1984) that among children of smoking mothers, those with behavioral abnormalities had had significantly higher neonatal hemoglobin levels (a sign of chronic fetal hypoxia) than had children with normal behavior. Furthermore, nicotine has been shown to have direct adverse effects on the developing brain (Lichtensteiger *et al.*, 1988). Although the few animal studies of exposure to mainstream or sidestream smoke that have been reported do not provide supportive data, the large literature on the effects on animals of prenatal exposure to carbon monoxide and nicotine do suggest that adverse impacts of these agents on postnatal neurobehavior is biologically plausible.

In summary, there is some evidence from reasonably well-controlled studies that maternal smoking during pregnancy is adversely associated with measures of cognition and behavior in children. Dose-response relationships were demonstrated in several studies, and an adverse effect is biologically plausible. However, most of the studies that found significant relationships failed to control for smoke exposure after birth, thus it is difficult to determine if the findings are truly related to smoking during pregnancy, or are in fact related to smoking after pregnancy. Studies that did control for postnatal smoke exposure tended to find no association between prenatal smoke exposure and cognition or behavior. Furthermore, smoking is also known to be strongly associated with many social and environmental characteristics that adversely influence neuropsychological development (Overpeck and Moss, 1991; Fried and Watkinson, 1988). That fact, along with the small size of the associations seen between maternal smoking and neuropsychological outcomes, makes it particularly difficult to rule out the possibility of a spurious effect due to undercontrolled confounding.

4.3.2 Cognition and Behavior in Children whose Mothers were Exposed to ETS During Pregnancy

Makin et al. (1991)

Two papers that addressed ETS exposure of the mother during pregnancy were identified.

Makin *et al.* (1991) administered an extensive neuropsychological test battery to children of women who were active smokers, exposed to ETS, and not exposed to ETS during pregnancy. Assessment of

exposure to ETS was prospective but imprecise, as it was ascertained by ask-

ing subjects during pregnancy “Are you regularly exposed to a smoke-filled environment?” There were less than 35 children in each exposure group. Measures of language, intelligence, and attention were outcomes that significantly distinguished non-exposed, ETS-exposed, and active-smoking mothers in a discriminant function analysis. Scores of children of ETS-exposed mothers tended to fall between scores of children of non-exposed and active-smoking mothers. No adjustment was made for potential confounders, as the authors stated that none were related to both tobacco smoke exposure and outcome.

Eskenazi and Trupin (1995) The Child Health and Development Studies were conducted from 1959 to 1967 among women and children who received their health care at the Kaiser Permanente Medical Center of Oakland, California. Pregnant women were interviewed and gave serum samples, which were stored. The children of these pregnancies were administered various neurobehavioral tests at ages 5, 9-11, and 15-17 years. Eskenazi and Trupin (1995) measured cotinine, a nicotine metabolite, in the stored serum samples and examined the results in relation to the 5-year neurobehavioral scores. There were a total of 2,124 mother/child pairs included in this analysis, of whom 1,348 were considered to have no tobacco exposure during pregnancy (nonsmokers with cotinine levels <2 ng/ml) and 68 were classified as having ETS exposure during pregnancy (nonsmokers with cotinine levels from 2-10 ng/ml). The remainder were classified as either active smoking during pregnancy only, active smoking after pregnancy only, or active smoking during and after pregnancy. Forty-three women were excluded because of cotinine levels that did not correspond to their self-reported smoking status. There have been some questions raised about the validity of the definition of ETS exposure used in this study (see discussion of Eskenazi *et al.*, 1995 in Section 3.2.2.4). The neurobehavioral tests examined in this study included the Peabody Picture Vocabulary Test (PPVT), the Raven Colored Progressive Matrices Test (tests of vocabulary and nonverbal reasoning, respectively), and the child’s activity level as rated by the mother. Children whose mothers were exposed to ETS during pregnancy did not have Raven or PPVT scores that differed significantly from the scores of children with no smoking exposure, even after adjustment for race, birth order, preschool attendance, parents’ education, socioeconomic status, and other factors. The OR for “active” behavior among children whose mothers were exposed to ETS during pregnancy was somewhat elevated (adjusted OR = 1.5), but the confidence interval included unity (95% CI = 0.7-3.1).

4.3.3 Cognition and Behavior in Children Exposed to ETS Postnatally

Of seven studies of neuropsychological development that have assessed effects of some measure of postnatal ETS exposure, four focused on cognitive ability and two focused on behavioral outcomes. One examined both. These seven studies are reviewed below and summarized in Table 4-2.

4.3.3.1 Studies of Cognition and Postnatal ETS Exposure

Rantakallio (1983)

Rantakallio (1983) conducted a nested exposure-control study within the Finnish Cohort Study. Women who had smoked through the second month of pregnancy ($n = 1,819$) were matched on age, parity, marital status, and residence to nonsmoking pregnant women. When their off-

spring were 14 years of age, information regarding the children's health and school performance and the fathers' smoking status was obtained by a mailed questionnaire. As an outcome measure Rantakallio devised a six-point score based on school performance in "theoretical subjects." The method by which this score was derived was not explained. The magnitude of the association seen with maternal smoking during pregnancy was comparable to other studies of prenatal exposure, with an adjusted difference in mean performance score between children of heavy smokers and nonsmokers of approximately 2.5 percent (this is an estimate from a figure, data were not presented). In a regression analysis that included social class, family size, maternal age and education, and sex of the child as co-variates, both maternal and paternal smoking were significant predictors of the school performance score. Paternal smoking was a slightly stronger predictor of score (standardized coefficient = -0.068) than maternal smoking during pregnancy (standardized coefficient = -0.049). It was unclear if paternal smoking represented current smoking status or smoking at the time of the pregnancy. The smoking status of the mother after the second month of pregnancy, and the current smoking status of the child or other family members were not ascertained.

Bauman et al. (1989) Bauman and coworkers conducted two studies that looked at current smoking by the parents and other family members. The first study (Bauman *et al.*, 1989) was a re-analysis of data collected in 1980 to investigate social and psychological determinants of smoking among eighth-graders in one North Carolina school district. The students had been interviewed regarding their own smoking behavior, and their mothers had been given a questionnaire which ascertained the total number of cigarettes smoked per day by all family members. Smoking status of the students and mothers was validated by analysis of breath samples for carbon monoxide. For this study, the analysis was restricted to the 973 students who denied being smokers themselves and who had alveolar carbon monoxide levels of <9 ppm. The students were later routinely administered the California Achievement Test (CAT) by their school. In the crude analysis, scores for the total battery and each of the four subtest scores (math, language, reading, and spelling) decreased as family smoking increased over four categories (zero, 1-19, 20-39, and ≥ 40 cigarettes per day). The differences by smoking level were all statistically significant ($p < 0.001$). After adjustment for eight co-variates, including age, sex, race, and parents' educational level, generally consistent inverse relationships between family smoking and test scores remained. However, the associations between the math and reading subscores were no longer significant at the $p = 0.05$ level. The magnitude of difference in scores was not large. For example, the mean adjusted total CAT score was 618.8 for children of nonsmoking families and 602.9 for children in the heaviest family smoking category—a difference of about 3 percent of the range for these test scores. The language subscores also differed by approximately 3 percent, whereas the spelling subscores differed by about 6 percent. There was no adjustment for maternal smoking status during pregnancy.

Bauman et al. (1991) The second study (Bauman *et al.*, 1991) was done using data from the examinations of children at ages 5, 9-11, and 15-17 years (referred

to as the 5, 10, and 16-year examinations) enrolled in the Kaiser Permanente Child Health and Development Studies. This dataset allowed the authors to control for maternal smoking during pregnancy, as well as a number of other pertinent co-variates. Sample sizes for each of the examinations ranged from 2,020 (the 16-year exam) to 4,939 (the 5-year exam). Parental smoking status was obtained by periodic interviews with the mothers, but fathers' smoking had to be interpolated for the 5- and 16-year examinations. Twelve to thirty percent of the children had missing parental smoking information and were excluded from the analysis. Cognitive tests performed at the 5-year exam included the Peabody Picture Vocabulary Test (PPVT), the Raven Colored Progressive Matrices Test (a test of reasoning ability), the Quick Test (another test of receptive vocabulary), and the Goodenough-Harris Draw-A-Man test of intellectual maturity. Ten-year-olds were administered the PPVT and Raven test, and the 16-year-olds were administered the PPVT only.

The authors first examined mean test scores by mother's prenatal smoking (yes/no) and current smoking (yes/no). For all Raven and PPVT exams, mean scores were 3-10 percent lower in children of current smokers, independent of maternal smoking status during pregnancy ($p < 0.001$). Conversely, there was little difference in mean scores by prenatal smoking status after stratification by current parental smoking (No difference by smoking status was seen in the Quick Test or Draw-A-Man, and the authors did not consider these tests further). The investigators then examined the effect of current parental smoking after adjustment for multiple confounders, including mothers' smoking during pregnancy, age, sex, race, low birthweight, and parents' education, occupation, and income. For the 16-year exam, active smoking by the child was also included in the regression. Again, current parental smoking had a negative effect on PPVT and Raven scores whereas the mother's smoking during pregnancy had a negligible effect.

The results were significant only at the 10-year examination, where a 3-5 percent decrement in test scores was seen. The authors speculated that the loss of significance at the 5- and 16-year exams may have been related to their method of interpolating smoking status, which would have biased results toward the null. The adjusted scores for the 10-year PPVT and Raven examinations displayed a dose-response relationship over four categories of parental smoking ($p < 0.01$ for linear trend).

Baghurst et al. (1992) Baghurst *et al.* (1992) conducted a longitudinal study that examined maternal smoking during and after pregnancy. Their study cohort had been assembled for the primary purpose of assessing the effect of lead exposure upon cognition. Of the 723 infants enrolled in the study at birth, 548 were still enrolled at the age of 4 years. Each child was administered the Bayley exam at age 2 and the McCarthy exam at age 4. One hundred and sixty children had been exposed to prenatal maternal smoking, and 232 were exposed postnatally to ETS (most of these were also exposed prenatally). In the crude analysis, both prenatal and postnatal maternal smoking were associated with lower scores on all Bayley and McCarthy subscales. The decrements in scores seen with postnatal smoking

Table 4.2
Cognition in Children: Studies that Assessed some Source of Postnatal ETS Exposure

Authors (year) Location	Design (n) Age at Follow-up	Outcome Assessment	Tobacco Exposure Comparison ^{1,2}		Comments
			Exposure Group	Results	
Rantakallio (1983) Finland	Prospective (1,763 prenatally exposed, 1,781 controls) 14 year olds	School ability in theoretical sub- jects	<ul style="list-style-type: none"> • MS during pregnancy: <10 cig/day vs. 0 ≥10 cig/day vs. 0 * Any vs. no PS 	Change in score: -1.8% -2.5% ^^ Inverse association	MS adjusted for sex, maternal age, parental height, SES, and family size. PS also adjusted for prenatal exposure and maternal education.
Bauman <i>et al.</i> (1989) United States (North Carolina)	Prospective (973) 8th graders	California Achievement Test	<ul style="list-style-type: none"> * Cig/day smoked by family: 	Mean total score: 0 618.8 1-19 610.0 20-39 606.8 >40 602.9 ^	Nonsmoking children only (con- firmed by breath CO). Adjusted for age, sex, parental education, some psych characteristics. No control for SES, prenatal exposure.
Bauman <i>et al.</i> (1991) United States (California)	Prospective (1,500-2,800) 5,10,16 year olds	PPVT RAVEN	<ul style="list-style-type: none"> * Any vs. no parental smoking at age: 	Score difference: PPVT RAVEN 5 -0.06 -0.14 10 -1.55^^ -0.89^ 16 -0.92	Up to 30% had missing values for parental smoking. Father's smok- ing interpolated at ages 5 and 16. Adjusted for age, sex, race, birth weight, SES, income, parental education, prenatal exposure, and (in 16-year-olds) active smoking. Dose-response seen with PPVT scores in 10-year-olds.

Table 4.2 (Continued)

Authors (year) Location	Design (n) Age at Follow-up	Outcome Assessment	Tobacco Exposure Comparison ^{1,2}		
			Exposure Group	Results	Comments
Baghurst <i>et al.</i> (1992) Port Pirie, Australia	Prospective (548) 2 and 4 year olds	Bayley (at 2 years) McCarthy (at 4 years)	* Any vs. no maternal postnatal smoking	Score difference: Bayley MDI -0.55 McCarthy GCI -0.45 verbal -0.17 perceptual -0.67 quantitative -0.21	Adjusted for SES, maternal IQ, and HOME score. No control for prenatal exposure. Adjustment caused score differences to drop 65-90% and lose statistical signifi- cance.
Eskenazi and Trupin (1995) California	Prospective (2,124) 5 year olds	PPVT RAVEN	<ul style="list-style-type: none"> • No smoke exposure * Maternal ETS during pregnancy • MS during pregnancy * MS after pregnancy * MS both during and after pregnancy * Current cig/day smoked by mother: <li style="padding-left: 20px;">1-9 <li style="padding-left: 20px;">10-19 <li style="padding-left: 20px;">≥20 	Mean score: <u>PPVT</u> <u>RAVEN</u> 50.7 10.7 51.9 10.8 52.5 [^] 11.3 [^] 49.9 10.4 50.8 10.6 Score difference from children of nonsmoking mothers <u>PPVT</u> <u>RAVEN</u> -1.5 [^] -0.5 [^] -1.3 -0.3 -1.3 -0.6 [^]	Adjusted for parents' education, socioeconomic status, race, birth order, preschool attendance, and other factors. Adjusted for above factors as well as prenatal exposure

¹ Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (o) denotes on-ETS exposure; PPVT-Peabody Picture Vocabulary Test; RAVEN-Raven Colored Progressive Matrices Test; MDI-Mental Development Index of the Bayley Scales of Infant Development; GCI-General Cognitive Index of the McCarthy Scales of Children's Abilities; HOME-Home Observation for Measurement of the Environment.

² ns = not significant ($p > 0.05$), [^] $p < 0.05$, ^{^^} $p < 0.01$, ^{^^^} $p < 0.001$, n = study size.

were consistent with other studies (ranging from 2.4-4.1 percent) and were generally statistically significant. In contrast, differences associated with prenatal maternal smoking were smaller and not statistically significant. A dose-response relationship was seen between level of maternal smoking after pregnancy and the Mental Development Index of the Bayley exam. There was no attempt to calculate the effect of postnatal maternal smoking independent of prenatal maternal smoking. When the analysis of postnatal smoking was adjusted for socioeconomic status, HOME score, and the mother's intelligence quotient, test score differences dropped by 65-90 percent to near nil and lost statistical significance. In the final regression model (which also included sex, birthweight, number of siblings, and breast- versus bottle-feeding), neither maternal nor paternal smoking was associated with any subscale score.

Eskenazi and Trupin (1995) Similar to Bauman *et al.* (1991), Eskenazi and Trupin (1995) also conducted a re-analysis of data from the Child Health and Development Studies to examine the relationship between cognition and postnatal ETS exposure. Although Eskenazi and Trupin used serum cotinine levels during pregnancy to determine ETS exposure of the mother (see section 4.3.2), interview information was used to classify smoking status at the child's 5-year examination. In addition to categorizing children as being exposed to active maternal smoking during pregnancy only (prenatal exposure), after pregnancy only (postnatal exposure), or during and after pregnancy, the number of cigarettes smoked by the mother per day at the time of the 5-year examination was evaluated. Unlike Bauman *et al.*, paternal smoking was not considered, and results from the 10- and 16-year examinations were not included. Raven and PPVT scores for children with prenatal or postnatal exposure only were not significantly lower than scores for children with no smoking exposure. In contrast, Raven and PPVT scores for children with both pre- and postnatal exposure were lower ($p < 0.05$) than those for children with no exposure; however, the differences in mean scores disappeared after adjustment for parent's education, socioeconomic status, race, birth order, preschool attendance, and other factors. When the number of maternal cigarettes smoked per day was examined, mean scores on both the Raven and the PPVT among children of smoking mothers were generally lower than the mean scores among children of nonsmoking mothers; this was true whether the model was unadjusted, adjusted for prenatal exposure only, or adjusted for prenatal exposure and a variety of other co-variates. However, no clear dose-response relationship was seen in any of the models (see Table 4.2). Because of the lack of a dose-response relationship, the authors felt that the effect seen in children of smoking mothers could potentially be explained by uncontrolled social and environmental factors.

4.3.3.2 Studies of Behavior and Postnatal ETS Exposure

Denson et al. (1975)

Denson et al. (1975) conducted a small case-control study comparing 20 hyperkinetic children with dyslexic and normal controls, matched for sex, age, and social class (Table 4.3). Parental cigarette consumption at the time of interview and during pregnancy was ascertained by interview with the mother. The mean number of cigarettes smoked per day during pregnancy was greater in mothers of cases than in mothers of normal controls

(14.3 vs. 6.3 cigarettes/day, $p < 0.05$). The difference was more pronounced when consumption at the time of interview was compared (23.3 vs. 8.2 cigarettes/day, $p < 0.001$). Sixteen of the twenty case mothers smoked during pregnancy (80 percent), but the number of control mothers who smoked was not given (thus ORs cannot be calculated). The fathers of cases smoked slightly more than fathers of controls, both during pregnancy (22.2 vs. 18.5 cigarettes/day) and at interview (21.3 vs. 20.7 cigarettes/day), but the differences were not significant. There was no control for confounding other than matching, and there was no attempt to separate pre- and postnatal exposure.

Weitzman et al. (1992) Weitzman *et al.* (1992) attempted to examine the separate contributions of pre- and postnatal exposure. The investigators examined children of women who had been enrolled in the National Longitudinal Survey of Youth in 1979. A total of 2,256 children aged 4 to 11 years were studied. Maternal smoking was categorized as none, only during pregnancy (there were only 132 children in this group), only after pregnancy, and during and after pregnancy. Since the smoking categories were derived from the mother's smoking status during pregnancy and in 1984, exposure misclassification among the smokers probably occurred. Thus, some mothers in the "only during pregnancy" group may have smoked in pregnancy and for several years afterwards as long as they quit before 1984. Mothers completed a Behavior Problem Index (BPI) survey regarding their children's activities and social relationships. A large number of potential confounders were included in the analysis, including demographic factors, birthweight, current health status of mother and child, HOME score, and maternal education, intelligence, use of alcohol during pregnancy, self-esteem, and employment. Paternal or family smoking was not assessed.

The investigators found that smoking was associated with BPI score in a dose-related manner in two groups of children with mothers who smoked: children whose mothers smoked after pregnancy only, and children whose mothers smoked both during and after pregnancy. In the small group of children whose mothers smoked during pregnancy only, smoking 1-20 cigarettes per day was also associated with higher BPI scores, but not significantly so ($p = 0.13$). The adjusted differences in BPI score were fairly comparable across the three categories of exposure. A similar pattern of results was seen when odds ratios for extreme scores on the BPI were calculated. Since the outcome measure was assessed by the mother, differences in BPI may have reflected different perceptions of behavior by smoking mothers rather than altered behavior of the child.

Eskenazi and Trupin (1995) In addition to examining the effects of tobacco smoke during and after pregnancy on cognition, Eskenazi and Trupin (1995) used data from the Child Health and Development Studies to examine the relationship between behavior and postnatal ETS exposure. Their measure for "active" behavior was based on three questions from a 42-item behavioral inventory completed by the mother at her child's 5-year examination. If the mother felt that her child had more energy than most, hated to sit still, and disliked playing quietly, the child was rated as "active." Overall, 17.3 percent of the children were rated as active by their mothers. Analyses

Table 4.3
Behavior in Children: Studies that Assessed some Source of Potential ETS Exposure

Authors (year) Location	Design (n) Age at Follow-up	Outcome Assessment	Tobacco Exposure Comparison ¹	Results	Comments ¹
Denson <i>et al.</i> (1975) Saskatchewan	Retrospective (20 cases, 40 controls) 5-15 year olds	Hyperactivity	<ul style="list-style-type: none"> • MS during pregnancy * PS during pregnancy * Current MS * Current PS 	Parents of cases smoked more cig/day than parents of controls. $p < 0.05$ only for MS.	Matched by age,sex, and minimally by SES, no other adjustment for potential confounders. ORs could not be calculat- ed from data presented.
Weitzman <i>et al.</i> (1992) US National Longitudinal Survey of Youth	Prospective (2,256) 4-11 year olds	Behavior Problem Index >14 (rating by mother)	MS in cig/day: <ul style="list-style-type: none"> • Pregnancy only: <ul style="list-style-type: none"> <20 vs. 0 ≥20 vs. 0 * Post-preg only: <ul style="list-style-type: none"> <20 vs. 0 ≥20 vs. 0 * Both: <ul style="list-style-type: none"> <20 vs. 0 ≥20 vs. 0 	OR (95% CI): 1.6 (1.0-2.5) 0.4 (0.1-1.6) 1.2 (0.9-1.7) 2.0 (1.3-3.1) 1.4 (1.1-1.8) 1.5 (1.1-2.2)	Only 19 women in high- dose pregnancy-only cate- gory thus estimate unsta- ble. Adjusted for age, sex, race, birth weight, health, HOME, income, and maternal education, intelli- gence, self-esteem, mari- tal status, alcohol use in pregnancy, employment.

Table 4.3 (Continued)

Authors (year) Location	Design (n) Age at Follow-up	Outcome Assessment	Tobacco Exposure Comparison ¹	Results OR (95% CI)		Comments ¹	
Eskenazi and Trupin (1995) California	Prospective (2,124) Five year olds	Rated "active" by mother	• No smoke exposure	1.0	1.0	Adjusted for parents' education, socioeconomic status, race, birth order, preschool atten- dance, and other factors.	
			* Maternal ETS during pregnancy	1.6 (0.7-3.3)	1.5 (0.7-3.1)		
			• MS during pregnancy only	1.1 (0.6-2.0)	1.0 (0.5-1.9)		
			* MS after pregnancy only	1.4 (0.8-2.7)	1.2 (0.6-2.2)		
			* MS during and after pregnancy	1.6 (1.2-2.1)	1.2 (0.9-1.7)		
			* Current cig/day smoked by mother:	<u>Unadjusted</u>	<u>Adjusted</u>		Adjusted for above factors as well as prenatal exposure
			1-9	1.2 (0.7-1.9)	1.0 (0.6-1.7)		
10-19	1.5 (0.9-2.3)	1.1 (0.8-2.0)					
≥20	1.8 (1.2-2.6)	1.6 (0.9-2.8)					

¹ Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (•) denotes non-ETS exposure; HOME-Home Observation for Measurement of the Environment-Short Form, n-study size.

analogous to those described in the previous section on cognition were performed. The OR for active behavior was somewhat elevated among children with postnatal exposure only, and with prenatal and postnatal exposure, although the effect diminished with adjustment for co-variables (unadjusted OR for pre- and postnatal exposure = 1.6, 95% CI = 1.2-2.1; adjusted OR = 1.2, 95% CI = 0.9-1.7). When maternal cigarettes/day were examined, the ORs for active behavior increased with increasing exposure. This dose-response relationship was seen whether the model was unadjusted, adjusted for prenatal exposure only, or adjusted for prenatal exposure and a variety of other co-variables. However, the effect diminished and lost statistical significance in the full model (see Table 4.3). Despite the presence of a modest dose-response relationship, the authors felt they could not rule out uncontrolled confounding as an explanation for their findings.

4.3.4 Animal Studies of Cognition and Behavior and Tobacco Smoke Exposure

Behavioral teratology studies in animals examine postnatal behavioral function after developmental exposures to toxicants. Bertolini *et al.* (1982) reported an enhanced rate of learning of an active avoidance task in offspring of rats exposed to mainstream tobacco smoke daily during gestation. Studies using sidestream smoke have been reported only in abstract form (Lindsay *et al.*, 1985; Mactutus *et al.*, 1993) and do not present enough information for evaluation. There is a large literature concerning the effects of prenatal exposure to nicotine and carbon monoxide on postnatal behavior; these data are discussed in a recent review (Mactutus, 1989).

4.3.5 Discussion and Conclusions

The evidence that ETS exposure of a nonsmoking pregnant woman can result in neuropsychologic deficits in the child, though very limited, is inconclusive. One small study (Makin *et al.*, 1991) found an association between ETS exposure of nonsmoking mothers during pregnancy and decrements in their offspring's test scores. However, a much larger study that used a biomarker to ascertain ETS exposure (Eskenazi and Trupin, 1995) failed to find any associations between ETS exposure during pregnancy and three measures of cognition and behavior.

The five studies that have looked at postnatal ETS exposure and cognitive endpoints in children have shown inconsistent results. Four of the studies (Rantakallio, 1983; Bauman *et al.*, 1989 and 1991; Eskenazi and Trupin, 1995) found modest decrements in performance by ETS-exposed children, even after adjustment for a variety of other factors. Dose-response relationships were reported in the two Bauman *et al.* studies, but were not seen in Eskenazi and Trupin. The findings of Bauman *et al.* (1991) were internally inconsistent in that associations were not seen at all ages, and results differed for two tests of receptive language (the PPVT and the Quick Test). None of these studies adjusted for parental intelligence or characteristics of the home environment. In the fourth study, Baghurst *et al.* (1992), in their crude analysis, also found decrements in test scores associated with maternal smoking after pregnancy. However, these decrements disappeared after adjustment for several powerful confounders, including socioeconomic status, HOME score, and maternal IQ.

Of the three studies that examined postnatal ETS exposure and children's behavior, Denson *et al.* (1975) was too small and poorly conducted to

allow any conclusions to be drawn. On the other hand, Weitzman *et al.* (1992) conducted a large, well-controlled study that enabled prenatal exposure to maternal active smoking and postnatal ETS exposure to be examined independently. They found significant, dose-related associations between most categories of postnatal maternal smoking and a behavior problem index. Eskenazi and Trupin (1995) also found modest, dose-related associations between postnatal ETS exposure and “active” behavior. Both studies used a mother-reported outcome; thus, they were unable to determine if maternal smoking was associated with differences in the children’s behavior or in the mothers’ perceptions.

Proposed mechanisms through which ETS could affect a child’s neuropsychological development include a direct effect of nicotine (a stimulant) upon the central nervous system, and adverse impacts of chronic exposure to carbon monoxide. Exposure to ETS increases concentrations of carboxyhemoglobin in the blood (Huch *et al.*, 1980; Jarvis *et al.*, 1983), and increased ambient carbon monoxide levels adversely affect mental functioning in humans (National Research Council, 1977; World Health Organization, 1979). As noted above, the large literature on the effects on animals of prenatal exposure to carbon monoxide and nicotine suggest that adverse impacts of these agents on postnatal neurobehavior is biologically plausible.

In conclusion, there are very few studies that have examined the relationship of neuropsychological development to postnatal ETS exposure of the child, independent of prenatal exposure to maternal active smoking. Two studies of behavior (Weitzman *et al.*, 1992; Eskenazi and Trupin, 1995) did a reasonably good job of separating postnatal from *in utero* exposure and also controlled for other pertinent co-variates. These studies found adverse relationships associated with childhood ETS exposure. With respect to cognitive development, one well-controlled study showed no association with ETS, but four other fairly well controlled studies showed modest decrements associated with ETS. No conclusions regarding causality can be made on the basis of these studies, but they do provide suggestive evidence that ETS exposure may pose a neuropsychological developmental hazard.

4.4 POSTNATAL PHYSICAL DEVELOPMENT When evaluating studies of postnatal physical development, it should be kept in mind that growth varies not only with genetic influences (*e.g.*, sex and parental height) and nutrition, but also with social factors such as socioeconomic status, birth order, and family size (Goldstein, 1971).

4.4.1 Postnatal Physical Development of Children whose Mothers Smoked During Pregnancy Active maternal smoking during pregnancy can cause significant decreases in birthweight (U.S. DHHS, 1980). There is also evidence that body length at birth is affected by smoking during pregnancy (Persson *et al.*, 1978). Birthweight, which is also a significant predictor of physical development, may be an intervening variable between prenatal exposure to tobacco smoke and growth. There may also be an effect of prenatal exposure to tobacco smoke independent of birthweight. A review of the topic is contained in Rush and Callahan (1989).

4.4.1.1 Studies of Children whose Mothers Smoked During Pregnancy

Several studies, some involving thousands of children, have examined the relationship between maternal smoking during pregnancy and height, and have found that children of smokers are slightly shorter than children of nonsmokers. The largest height decrements were seen in studies by Dunn *et al.* (1976) and Naeye (1981). Dunn *et al.* (1976), in an uncontrolled study, reported differences of 1.6-2.0 cm for normal birth-weight children aged 4-6.5 years. Naeye (1981), in a sibling pair comparison, found the offspring of smoke-exposed pregnancies were 1.7 cm shorter than their non-exposed siblings. Among studies of pre-pubertal children that controlled for a variety of social factors, height decrements for offspring of maternal heavy smokers (at least 10 cigarettes per day) ranged from 0.7-1.0 cm (Hardy and Mellits, 1972; Goldstein, 1971; Butler and Goldstein, 1973; Wingerd and Schoen, 1974; Eskenazi and Bergmann, 1995). The last four papers reported mean heights of children whose mothers were moderate smokers to be intermediate between those of children whose mothers were heavy smokers and nonsmokers.

Fox *et al.* (1990) compared 3-year-old children of women who smoked throughout pregnancy with children of women who had quit and also found an adjusted height difference of 1.0 cm. Studies of the British National Child Development Study cohort at 16 and 23 years of age have shown that the effect of maternal smoking during pregnancy appears to persist beyond puberty, although the size of the effect is not consistent (Fogelman, 1980; Fogelman and Manor, 1988). The sole exception to this pattern was reported by Fried and O'Connell (1987), who failed to find a significant negative correlation between children's height and mothers' smoking status during pregnancy. The point estimate was not presented, so the direction of the association is not known. However, a subsequent larger study taken from the same cohort found children of heavy smokers to be significantly shorter than children of nonsmokers (Fried and Watkinson, 1988). The presentation of data did not allow a specific height difference to be identified.

The effect of adjusting height differences for birthweight has been explored in four study populations. Goldstein (1971), and Fogelman and Manor (1988), using data from the National Child Development Study, found that adjusting for birthweight reduced height differences by 30-60 percent. Fox *et al.* (1990) corroborated this finding, calculating a 50 percent reduction of effect. The studies by Hardy and Mellits (1972) and Eskenazi and Bergmann (1995) reported that differences in height were virtually eliminated when birthweight was taken into account.

Hardy and Mellits (1972), Dunn *et al.* (1976), Naeye (1981), Fried and Watkinson (1988) and Fox *et al.* (1990) also examined prenatal exposure to maternal smoking and children's weight. All five studies found small negative associations with maternal smoking, but the effect was significant only in Naeye's sibling pair comparison. Both Fox *et al.* (1990) and Hardy and Mellits (1972) reported that the effect disappeared when birthweight was controlled.

4.4.1.2 Discussion of Evidence from Studies on Physical Development in Children whose Mothers Smoked During Pregnancy

Investigators have consistently observed a height decrement of 0.7-1.0 cm among children of women who smoked at least 10 cigarettes per day during pregnancy. Fox *et al.* (1990) demonstrated a similar effect when comparing children of quitters and persistent smokers. Dose-response relationships have also been consistently observed. Although very small, the effect appears to be independent of sex, parental height, socioeconomic status, birth order, and family size. One study (Eskenazi and Bergmann, 1995) also controlled for postnatal exposure to ETS. This, together with the lack of evidence associating ETS exposure with height growth (see below) and Berkey *et al.*'s (1984) finding that ETS exposure was not related to rate of growth, suggests that the effect is specifically associated with *in utero* exposure to maternal active smoking.

Half or more of the effect on height appears to be related to reductions in birthweight among offspring of smokers. As maternal smoking is known to cause reductions in birthweight, and as birthweight is a predictor of height (Goldstein, 1971), it is plausible that *in utero* exposure to maternal active smoking could result in small reductions in height growth.

Five poorly controlled studies have found small inverse relationships between maternal smoking during pregnancy and children's postnatal weight growth. More work is required before any conclusions can be drawn regarding the effect of active smoking during pregnancy and children's weight.

In summary, the evidence suggests that the relationship between active maternal smoking during pregnancy and impaired height growth of approximately one centimeter in the pre-adolescent child may be causal. Dose-response relationships have been repeatedly demonstrated, and there are plausible mechanisms to explain the association.

4.4.2 Postnatal Physical Development of Children Exposed to ETS

One study was found that examined the relationship of ETS exposure of the mother to the height of the child at 5 years of age.

4.4.2.1 ETS Exposure of the Mother During Pregnancy

Eskenazi and Bergmann (1995)

Eskenazi and Bergmann (1995) reanalyzed data from the Kaiser Permanente Child Health and Development Studies that were conducted in Oakland, California from 1959 to 1966. The authors measured cotinine, a nicotine metabolite, in stored serum samples taken from women in mid-pregnancy. Of the 2,622 women included in this study, 1,610 were considered to have no tobacco exposure during pregnancy (nonsmokers with cotinine levels <2 ng/ml) and 77 were classified as having ETS exposure during pregnancy (nonsmokers with cotinine levels from 2-10 ng/ml). The children's heights were measured within 6 months of their fifth birthday; the measurements were then extrapolated using linear regression to their height at exactly 5 years. Children of ETS-exposed pregnancies were on average 0.4 cm higher than non-smoke-exposed children (95% CI = -0.5-1.4) after adjustment for birth weight, gestational age, race, sex, birth order, and maternal height, body mass index, education, and age.

4.4.2.2 Postnatal ETS Exposure Six studies have evaluated the association between some indicator of postnatal ETS exposure and height (Table 4.4). No studies were found of ETS exposure and children's postnatal weight growth.

Rona et al. (1981 and 1985) Three studies have been conducted by Rona and colleagues using cross-sectional data from the ongoing British National Study of Health and Growth. In their initial study of 4,961 primary school children in England and Scotland, Rona *et al.* (1981) found an inverse association between the number of people smoking more than five cigarettes per day at home and the standardized height of the child. Height differences could not be calculated from the data presented. Results remained significant after adjustment for birthweight, age, sex, social class, and parental height. Prenatal exposure to tobacco smoke was not assessed.

Rona *et al.* (1985) refined their exposure assessment by ascertaining the total number of cigarettes per day smoked at home by both parents. Forty-three percent of fathers, and 34 percent of mothers smoked in this sample. After adjusting for prenatal exposure to maternal smoking, parental height, infant birthweight, age, sex, degree of overcrowding, and number of siblings, children of smokers were still slightly but significantly shorter than non-exposed children ($p < 0.01$). The adjusted height decrement was small—approximately 0.2 cm for every 10 cigarettes smoked at home. Father's smoking, mother's current smoking, and smoking during pregnancy were all independently associated with height.

In Chinn and Rona (1991), the study was varied by using an even larger cohort of over 11,000 school children and including more co-variables in the analysis, including social class, ethnicity, and receiving school meals. No association was seen between number of cigarettes smoked at home and height. The investigators then repeated the analysis using their 1985 database and found that the height difference, although still negative, diminished by a third and was no longer statistically significant. They concluded that postnatal ETS exposure has no effect on children's height.

Rantakallio (1983) Rantakallio (1983) studied over 2,800 Finnish 14-year-olds, evenly divided as to prenatal exposure status. The adjusted height decrement associated with maternal smoking during pregnancy was approximately -0.9 cm (estimated from a figure), consistent with estimates calculated by other investigators. In a regression analysis that included demographic and socioeconomic factors, prenatal exposure status, and maternal height, paternal smoking status was negatively related to children's height ($p = 0.07$). The size of the standardized coefficients for maternal smoking during pregnancy and paternal smoking were roughly equivalent. There was no adjustment for birthweight.

Berkey et al. (1984) Berkey *et al.* (1984) examined height and height growth rate in a longitudinal study of 9,273 children aged 6-11 years (the same study is also described in Ferris *et al.*, 1985). The study's main intent was to examine the health effects of air pollution. The authors found a very significant dose-related decrease in height with increasing current maternal cigarette consumption. Children of mothers who smoked ≥ 10 cigarettes per day were 0.7 cm shorter than children of nonsmokers, after adjusting for age, sex,

parent's education, and use of gas for cooking in the home. There was no adjustment for prenatal exposure to maternal smoking or birthweight, thus it is likely that the effect associated with current maternal smoking actually reflected the effect of smoking during pregnancy. The similarity of the height decrement to decrements seen in studies of maternal smoking during pregnancy supports this interpretation. A nonsignificant association was seen with paternal smoking, with an adjusted height decrement of 0.1 cm among children of fathers smoking ≥ 10 cigarettes per day. Over an average of 4 years of observation per child, there was no association of either mother's or father's smoking with the child's rate of growth, which led the authors to suggest that the height differences were due to *in utero* or early life exposure.

Eskenazi and Bergmann (1995) As described in the previous section, Eskenazi and Bergmann (1995) used data from the Child Health and Development Studies to examine the relationship between maternal smoking and height of the child at age 5 years. They used information from interviews with the mothers during pregnancy and at their child's 5-year examination to categorize smoke exposure as prenatal only, postnatal only, and pre- and postnatal. Children with prenatal exposure only, and those with pre- and postnatal exposure were 0.3 cm and 0.5 cm shorter than children of nonsmokers, respectively (prenatal exposure, 95% CI = -1.1-0.5; pre- and postnatal exposure, 95% CI = -0.9 to -0.1; adjusted for race, sex, birth order, and maternal education, age, height, and body mass index). These differences diminished to -0.01 and -0.02 cm after also controlling for birthweight and gestational age. In contrast, children with postnatal exposure only were on average 0.5 cm taller than children of nonsmokers, though this difference was not statistically significant (95% CI = -0.3-1.3). The authors concluded that any height decrements seen in children of smokers were probably related to *in utero* exposure rather than postnatal exposure.

4.4.3 Animal Studies of Postnatal Physical Development and Tobacco Smoke Exposure No studies on this topic that used mainstream smoke were located. One study (Tachi and Aoyama, 1988b) purports to deal with the effects of "sidestream" tobacco smoke on postnatal growth in rats. Exposures began at weaning (21 days postnatal) and continued through adulthood (54 days of age). Rats mature sexually at 35-45 days of age. Reduced growth rates in smoke-exposed animals were reported within a few days of initiation of the exposure. Growth was determined by daily weighing during the study and determination of organ weights at the conclusion of the study. A control group was exposed to carbon monoxide levels comparable to those experienced by the group exposed to tobacco smoke. However, no pair-fed controls were included. Pair-fed controls are important in establishing that the exposure protocols did not lead to reduced food intake due to disruption of normal feeding routines or general malaise.

4.4.4 Discussion and Conclusions Using paternal smoking as a proxy for postnatal ETS exposure, Rantakallio (1983) and Berkey *et al.* (1984) found very small, nonsignificant negative correlations with height after adjusting for maternal smoking. Berkey *et al.* (1984) found no association between current maternal or paternal smoking and the rate of growth, suggesting that

Table 4.4
Height Growth in Children: Studies that Assessed some Source of Postnatal ETS Exposure

Authors (year) Location	Design (n) Ages at Follow-up	Source/Amount of Tobacco Exposure ¹	Height Difference in cm	Comments
Rona <i>et al.</i> (1981) United Kingdom	Cross-section (4,961) 5-11 year olds	*Number of people smoking >5 cig/day at home	Inverse association ($p < 0.05$)	Adjusted for age, sex, parental heights, # sibs, SES, birth weight. No control for prenatal exposure.
Rona <i>et al.</i> (1985) United Kingdom	Cross-section (5,903) 5-11 year olds	*Every 10 cig/day smoked at home by parents	-0.2 ($p < 0.01$)	Adjusted for age, sex, location, parental heights, # sibs, prenatal exposure, birth weight.
Chinn & Rona (1991) United Kingdom	Cross-section (11,224) 5-11 year olds	*Total cig/day smoked at home by parents	No significant association	Adjusted for same covariates as above, plus SES, ethnicity, school meals.
Rantakallio (1983) Finland	(1,763 prenatally ex- posed, 1,781 controls) 14 year olds	•MS during pregnancy: <10 cig/day vs. 0 ≥10 cig/day vs. 0 *Any vs. no PS	-0.6 -0.9 ($p < 0.05$) Inverse association (ns)	MS adjusted for sex, maternal age, parental height, SES, and family size. PS also adjusted for prenatal exposure and maternal education.
Berkey <i>et al.</i> (1984); Ferris <i>et al.</i> (1985) United States	Longitudinal cohort (9,273) 6-11 year olds	Current cig/day: •MS <10 vs. 0 ≥10 vs. 0 •PS ≥10 vs. 0 ≥10 vs. 0	-0.5 -0.7 ($p < 0.001$) -0.04 -0.1 (ns) No association between MS or PS and rate of growth	Adjusted for age, sex, location, parental education, gas cooking. No control for parental height, prenatal exposure, birth weight.

Table 4.4 (Continued)

Authors (year) Location	Design (n) Ages at Follow-up	Source/Amount of Tobacco Exposure ¹	Height Difference in cm		Comments
Eskenazi and Trupin (1995) California	Prospective (2,622) 5 year olds	*Maternal ETS during pregnancy	<u>Model I</u>	<u>Model II</u>	Model I adjusted for race, sex, birth order, and maternal edu- cation, age, height, and body mass index.
		•MS during pregnancy only	0.5 (-0.5-1.4)	0.4 (-0.5-1.3)	
		*MS after pregnancy only	-0.3 (-1.1-0.5)	-0.01 (-0.8-0.8)	Model II adjusted for the above factors and birth weight and gestational age.
		*MS during and after pregnancy	0.5 (-0.3-1.3) -0.5 (-0.9 to -0.1)	0.5 (-0.3-1.3) -0.02 (-0.4-0.4)	

¹ Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (•) denotes non-ETS exposure; n-study size.

height decrements seen in children of smokers reflect differences that exist at birth. In corroboration of this interpretation, Eskenazi and Bergmann (1995) found no height decrement among children with postnatal ETS exposure only; they also found that the height decrement seen among children whose mothers smoked during and after pregnancy disappeared after controlling for birth weight and gestational age.

In Rona *et al.* (1985) and Chinn and Rona (1991), a reasonably good measure of ETS exposure was obtained (number of cigarettes smoked at home by parents), and analyses were controlled for prenatal exposure to maternal active smoking. These studies found an extremely small ETS effect (-0.2 cm) and no effect, respectively. When the 1985 data were reanalyzed using the same methods employed for the 1991 data, the height decrement diminished by a third and lost statistical significance. These results imply that if any effect of ETS exposure on height exists, it is vanishingly small.

Although there are plausible mechanisms through which ETS exposure could impact postnatal height growth (*e.g.*, impairment of appetite, increased frequency of illness), there is little to no epidemiological evidence that ETS exposure has a significant effect on height growth of children. A single animal study of postnatal sidestream smoke exposure did find reduced growth rates in exposed animals; however, the lack of pair-fed controls in this study limits the conclusions which can be drawn from its results.

4.5 RESPIRATORY DEVELOPMENT AND FUNCTION The impact of ETS exposure on the respiratory tract has been reviewed by a number of authoritative bodies (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992). Several acute and chronic non-cancer respiratory health effects of ETS have been observed, including exacerbation of childhood asthma, acute lower respiratory tract illness, middle ear infection, and chronic respiratory symptoms in children. Also, while the results from all studies are not wholly consistent, there is substantial evidence that childhood exposure to ETS affects lung growth and development, as measured by small but statistically significant decrements in pulmonary function tests. Drawing on the above-mentioned reviews, as well as more recent literature, these impacts are discussed at length in the Chapter entitled *Respiratory Health Effects of Exposure to Environmental Tobacco Smoke*.

4.6 CHAPTER SUMMARY AND CONCLUSIONS Interest in Sudden Infant Death Syndrome (SIDS) stems from numerous studies demonstrating that infants of smoking mothers have an increased risk of SIDS. There is adequate epidemiological evidence of a causal relationship between maternal smoking in general and risk of SIDS. In most of the studies examining the relationship between ETS exposure and SIDS, it was not possible to separate the effects of postnatal ETS exposure from those of prenatal exposure to maternal active smoking. Recent findings of elevated risk of SIDS associated with postnatal ETS exposure independent of maternal smoking in reasonably well controlled epidemiological studies provide compelling evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS.

Although studies have shown fairly consistently that maternal smoking during pregnancy is adversely associated with measures of cognition and behavior in children, very few studies have examined these effects in relation to children's postnatal ETS exposure. One study of behavior which did a reasonably good job of separating postnatal from *in utero* exposure and controlled for other pertinent co-variables found significant adverse relationships associated with childhood ETS exposure. With respect to cognitive development, the best controlled study showed no association with postnatal ETS exposure, but three other fairly well-controlled studies showed modest decrements associated with postnatal ETS exposure. A single small study of nonsmoking pregnant women found an association of ETS exposure during pregnancy with decrements in their offspring's test scores. While conclusions regarding causality cannot be made on the basis of these studies, they do suggest that ETS exposure may pose a neuropsychological developmental hazard.

While small but consistent effects of active maternal smoking during pregnancy on physical growth of offspring have been demonstrated in a number of studies, there is no epidemiological evidence that postnatal ETS exposure has a significant effect on the height growth of children after controlling for prenatal exposure to maternal active smoking. Although a relatively small number of studies have addressed this issue, to date there is no evidence that postnatal ETS exposure is an independent and significant hazard to height growth in humans.

Further evidence of developmental toxicity of ETS exposure on respiratory outcomes is provided in Chapter 6, which presents substantial evidence that childhood exposure to ETS affects lung growth and development, exacerbates childhood asthma, and causes acute lower respiratory tract illness, middle ear infection and chronic respiratory symptoms in children.

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