Special Article

Effect of Maternal Cigarette Smoking on Pregnancy Complications and Sudden Infant Death Syndrome

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Background. The purpose of this study was to estimate the annual morbidity and mortality among fetuses and infants that can be attributed to the use of tobacco products by pregnant women.

Methods. Published research reports identified by literature review were combined in a series of meta-analyses to compute pooled risk ratios, which, in turn, were used to determine the population attributable risk.

Results. Each year, use of tobacco products is responsible for an estimated 19,000 to 141,000 tobacco-induced abortions, 32,000 to 61,000 infants born with low birthweight, and 14,000 to 26,000 infants who require admission to neonatal intensive care units. Tobacco use is also annually responsible for an estimated 1900 to 4800 infant deaths resulting from perinatal disorders, and 1200 to 2200 deaths from sudden infant death syndrome (SIDS).

Conclusions. Tobacco use is an important preventable cause of abortions, low birthweight, and deaths from perinatal disorders and SIDS. All pregnant women should be advised that smoking places their unborn children in danger. The low success rate of smoking cessation among pregnant women suggests that efforts to reduce the complications of pregnancy attributable to tobacco use by pregnant women should focus on preventing nicotine addiction among teenaged girls.

Key words. Abortion (tobacco-induced); infant, low birthweight; infant mortality; pregnancy; sudden infant death; smoking, tobacco. (*J Fam Pract 1995; 40:385-394*)

The cigarette is the only legal consumer product that injures or kills a sizable proportion of its users when used as intended by the manufacturer. The harm caused by the cigarette is not limited to the user, however, as unborn children and infants are sometimes harmed by other people's use of smoking tobacco.

An investigation was undertaken to assess the morbidity and mortality among children that can be attributed to cigarette smoking, ie, tobacco-induced abortions, low birthweight, perinatal deaths, sudden infant death syndrome (SIDS), otitis media, asthma, cough, lower respiratory tract illness, and fire injuries. This report is limited to the effects of cigarette smoking on the incidence of SIDS and complications of pregnancy.

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Methods

A review of the medical literature was conducted to identify conditions causing illness or death among children as a result of the use of smoking tobacco by other people. A manual literature search was conducted to locate all relevant studies published in English on the above-listed conditions.

All published articles were included, regardless of year of publication, except for a few studies addressing the effects of smoking on pregnancy outcome that predated the microfilm archives at the University of Massachusetts Medical School library.

Studies were included in the meta-analysis if either a case-control or cohort design was used on an appropriate population, and data were provided in a form allowing for

the construction of 2×2 tables. Studies were excluded if data presented in different parts of the published paper conflicted and it could not be determined which data were correct. A few studies of special populations were excluded because the results could not be generalized to the general population.

Meta-analysis is a statistical method used to combine the data from a number of different studies on the same topic. For each of the effects of smoking on pregnancy outcome that were considered here, separate meta-analyses were performed using the method of DerSimonian and Laird.[1] Case-control studies produce a measure of risk termed the odds ratio (OR), and meta-analysis combines such studies to produce a pooled OR. Meta-analysis of cohort studies produces a pooled relative risk (RR). All results were adjusted for the preliminary test of study homogeneity. This procedure takes into account the variability among studies and produces a more conservative result.

A valid meta-analysis does not include bias in the selection of studies to be included. A bias toward positive results might arise if negative studies are less likely to be submitted or accepted for publication, if published negative studies are less likely to provide usable data, or if published negative studies are more likely to have been missed by our literature search.

To assess the potential role of selection bias, a calculation was performed to determine the number of extra neutral studies (ENS) that would be needed to reduce the pooled risk to a point that would no longer be statistically significant ($P>.05$). The size of each added study was identical to the average study size for the condition under consideration. The subjects in the ENS were divided evenly among cases and controls and among exposed and unexposed populations to result in an odds ratio or relative risk of 1.0. Knowledge regarding the number of ENS required to negate the results of the meta-analysis allows the reader to judge the likelihood that the observed results are due to the exclusion of unpublished studies, overlooked studies, or studies with unpublished data.

Since cohort and case-control studies were analyzed separately, pooled estimates of both the RR and the OR are possible for some conditions. As a rule, the RR provides a more conservative estimate of risk. Therefore, when a choice was available, the pooled RR estimates were used to calculate attributable morbidity and mortality.

The pooled estimate of risk (R) and data on the proportion of US children who are exposed (p) were used to derive an estimate of the proportion of cases that are attributable to the exposure (a).

$$a=\frac{p\,(R-1)}{p\,(R-1)+1}$$

National incidence or prevalence data (i) for each condition were then used to estimate the actual number of cases attributable to the exposure in the United States each year (n):

$$n=a\times i$$

Results are reported with 95% confidence intervals (CI). A P value of $<.05$ was used as a measure of statistical significance. It is possible that subgroup or multivariate analysis by a study's authors would produce statistically significant findings, but significant results would not be produced by the 2×2 tables constructed for the meta-analysis. In this report, references to statistical significance in the text refer to the results reported by the study's authors, while such references in the tables apply to the significance of the 2×2 tables.

Results

Prevalence of Smoking During Pregnancy

Studies relying on self-reports have produced estimates of 18.4% and 19.0% for the prevalence of smoking among pregnant women.[2,3] In one study, the self-reported smoking rate was 19% for pregnant women and 30% for women of reproductive age (18 to 44 years) who were not pregnant.[3] This study implies a quit rate of approximately 37%. In the 1986 Linked Telephone Survey,[4] 39% of smokers reported quitting during pregnancy, but the prevalence of smoking after pregnancy was almost the same as it was before pregnancy (30% and 32%, respectively).

These self-reported quit rates of 37% and 39% are far higher than those measured in clinical trials in which cessation has been validated biochemically.[5,6] In two separate studies in which cotinine levels were measured, 8% of women receiving standard obstetrical care quit smoking, while 14% of those receiving intensive smoking cessation assistance were successful in quitting.[5,6] The authors conclude that the unvalidated self-report surveys cited above grossly underestimate the true prevalence of smoking during pregnancy.

Taking the rates for smoking among women of reproductive age (18 to 44 years) during 1989 (30%) and allowing for a 10% smoking cessation rate during pregnancy produces an estimated 27% prevalence of smoking among pregnant women.[3] In 1988, the National Health Interview Survey measured a period prevalence of smoking among pregnant women of 28.8%.[7] To estimate the

Table 1. Studies Comparing the Incidence of Spontaneous Abortion Between Smokers and Nonsmokers

Study Author and Reference	Year of Publication	Study Site	Study Design	No. of Pregnancies	OR	RR	Sig
OLane[15]	1963	USA	Cohort	883	—	1.34	Yes
Zabriski[16]	1963	USA	Cohort	5619	—	1.43	Yes
Kullander and Kallen[17]	1971	Sweden	Cohort	5348	—	1.38	Yes
Murphy and Mulcahy[18]	1974	Ireland	Cohort	12,013	—	1.22	Yes
Kline et al[19]	1977	USA	Case-control	883	1.78	—	Yes
Himmelberger et al[20]	1978	USA	Cohort	12,914	—	1.17	Yes
Stein et al[21]	1981	USA	Case-control	4088	1.44	—	Yes
Hemminki et al[22]	1983	Finland	Cohort	2709	—	.96	No
Sevelan et al[23]	1985	Finland	Case-control	445	1.09	—	No
Ericson and Kallen[24]	1986	Sweden	Case-control	1249	1.17	—	No
Sandahl[25]	1989	Sweden	Case-control	1947	1.27	—	Yes
Armstrong et al[26]	1992	Canada	Cohort	47,146	—	1.25	Yes
Windham et al[27]	1992	USA	Case-control	1923	1.10	—	No
Pooled OR=1.32 (CI=1.18–1.48), $P<.001$, ENS=23							
Pooled RR=1.24 (CI=1.19–1.30), $P<.001$, ENS=18							

NOTE: OR>1 or RR>1 implies increased risk of spontaneous abortion associated with maternal smoking.
OR denotes odds ratio; RR, relative risk; Sig, P<.05; CI, confidence interval; ENS, extra neutral studies.

disease burden related to smoking during pregnancy, 18.4% and 27% will be used as the respective low and high estimates of the prevalence of smoking during pregnancy.

Tobacco-Induced Abortions

Twenty studies comparing the spontaneous abortion rates of smokers and nonsmokers were found. Two of the studies, one with positive findings and one with negative findings, were excluded because the data presented were self-contradictory.[8,9] Three studies that showed statistically significant odds ratios of 1.71, 1.83, and 2.6 for smoking and fetal loss were excluded because tobacco-induced abortions were pooled with neonatal deaths and stillbirths.[10–12] Two additional studies showing nonsignificant increases in spontaneous abortion among smokers did not provide data.[13,14] These exclusions left 13 studies that could be included in the meta-analysis (Table 1).[15–27] Although two studies computed adjusted rates, crude data had to be used in the meta-analysis, which lowered the study's estimated risk in one case and raised it in the other.[22,27]

As depicted in Table 1, the association of smoking with miscarriage has been suspected for more than 30 years, and has been well established for more than 20 years. While the studies have differed markedly in size, the results have been fairly consistent. The association of miscarriage with smoking remains after controlling for age, parity, previous miscarriages, alcohol consumption, ethnicity, education, and employment status.[19,26]

Three additional factors decrease the likelihood that the association of smoking with abortion is confounded by an unknown factor. First, a dose-response relationship between smoking and abortion has been demonstrated.[21,26] Second, pathological studies reveal that smokers are more likely to abort chromosomally normal embryos than are nonsmokers.[21,28] Third, former smokers do not experience increased rates of miscarriage.[21]

The lack of significant findings in some studies may be attributable to very low levels of consumption. Three Finnish studies[9,22,23] showed no risk of miscarriage associated with smoking, but daily consumption levels among Finnish women are far below those of their American counterparts. The inclusion of two of these studies in the meta-analysis may result in an underestimation of the risk for American women.[22,23]

The pooled RR for the cohort studies was 1.24 (CI=1.19 to 1.30, $P<.001$, ENS=18). The pooled OR was 1.32 (CI=1.18 to 1.48, $P<.001$, ENS=23).

The actual number of abortions caused by smoking each year can be estimated if it is known how many spontaneous abortions occur annually in the United States. This number must be determined indirectly since there are no reliable national data. When only those pregnancies that are not terminated by elective abortion are considered, between 20% and 62% of pregnancies end in spontaneous abortion.[29–32] Four prospective studies using serial biochemical measures have documented a total of 217 losses and 342 successful deliveries for a ratio of 63 spontaneous losses to every 100 births.[29–32] Most of the spontaneous losses occurred before the woman knew she was pregnant. Consequently, there were only 15 clinically recognized spontaneous abortions per 100 births. The most recent of these studies used a highly specific hormonal assay that is more sensitive than those available to earlier researchers.[32] In this study, there was a ratio of 46 losses for every 100 live births; of these, only 14 were clinically recognized as miscarriages.[32]

Table 2. Studies Comparing Low Birthweight Rates Between Smokers and Nonsmokers

Study Author and Reference	Year of Publication	Study Site	Study Design	No. of Subjects	OR	RR	Rate/1000* S	Rate/1000* NS	Sig
Simpson[39]	1957	USA	Cohort	7499	—	1.74	111.3	64.0	Yes
Frazier et al[40]	1961	USA	Cohort	2523	—	1.67	186.4	112.0	Yes
Savel and Roth[41]	1962	USA	Cohort	1415	—	1.64	98.8	60.2	Yes
Jarvinen and Osterlund[42]	1963	Finland	Cohort	2568	—	1.31	56.7	43.2	No
O'Lane[15]	1963	USA	Cohort	1031	—	2.31	118.3	51.2	Yes
Zabriski[16]	1963	USA	Cohort	2000	—	2.59	99.3	38.4	Yes
Yerushalmy[43]	1964	USA	Cohort	6747	—	2.01	77.0	38.3	Yes
Underwood et al[44]	1967	US Navy	Cohort	48,494	—	1.56	89.1	57.0	Yes
Rantakallio[45]	1969	Finland	Cohort	11,742	—	1.73	60.7	35.0	Yes
Comstock et al[46]	1971	USA	Case-control	654	1.99	—	111.0†	59.0†	Yes
Kullander and Kallen[17]	1971	Sweden	Cohort	4124	—	1.53	50.0	32.6	Yes
Yerushalmy[47]	1971	USA	Cohort	13,083	—	1.98	77.1	39.0	Yes
Andrews and McGarry[48]	1972	UK	Cohort	14,534	—	1.98	76.2	38.4	Yes
Niswander[49]	1972	USA	Cohort	37,576	—	1.62	129.6	79.6	Yes
Rush and Kass[50]	1972	USA	Cohort	972	—	1.54	146.9	95.2	Yes
Cope et al[51]	1973	Australia	Cohort	4067	—	1.66	98.1	59.1	Yes
Fedrick and Anderson[52]	1976	UK	Cohort	16,381	—	1.97	24.7	12.5	Yes
Meyer et al[53]	1976	Canada	Cohort	50,097	—	1.76	87.2	49.4	Yes
Guzick et al[54]	1984	USA	Cohort	2865	—	1.50	101.8	67.8	Yes
Hopkins et al[55]	1990	USA	Cohort	74,139	—	2.09	95.3	45.7	Yes
Ahlborg and Bodin[12]	1991	Sweden	Cohort	3396	—	1.90	21.6	11.4	Yes
McDonald et al[56]	1992	Canada	Cohort	40,445	—	2.61	93.8	36.0	Yes
Li et al[5]	1993	USA	Cohort	1201	—	1.43	156.0	109.0	Yes
Pooled RR=1.82(CI=1.67–1.97), *P<.001, ENS=9*									

**Rate per 1000 births of infants weighing <2500 g.*
†Comstock's estimates.
OR denotes odds ratio; RR, relative risk; S, maternal smokers; NS, maternal nonsmokers; Sig, P<.05; CI, confidence interval; ENS, extra neutral studies.

There were more than 4.1 million live births in the United States in 1990.[2] Applying the more conservative ratio of 46 losses per 100 live births results in an estimated 1,886,000 spontaneous abortions among US women each year, of which 574,000 are clinically recognized.

All the studies in the meta-analysis concern clinically evident abortions. The literature provides no evidence that the abortifacient effects of smoking are limited to pregnancies that have become clinically apparent. However, to produce a "best-case" calculation, it was assumed that smoking has no adverse effects on preclinical pregnancies. A best-case calculation, which uses the lower limit of the 95% CI for the RR (1.19) and the lowest estimate of the prevalence of smoking during pregnancy (18.4%), applied only to clinically recognized pregnancies, produces an estimate of 19,000 clinically recognized tobacco-induced abortions in the United States annually. Using this calculation, smoking would be the cause of 3% of miscarriages.

A "worst case" estimate, which uses the upper limit of the CI for the RR (1.30) and the highest estimate of the prevalence of smoking during pregnancy (27%), applied to both clinical and preclinical abortions, produces an estimate of 141,000 tobacco-induced abortions in the United States annually. Using this calculation, smoking would be the cause of 7.5% of miscarriages.

Low Birthweight

Low birthweight (<2500 g) is a major factor in infant mortality and the cost of neonatal care in the United States. Disorders related to low birthweight are the leading cause of death among black infants in the United States.[33] In 1990, approximately 295,000 infants weighing less than 2500 g were born, representing 7.2% of all births.[2]

Thirty studies concerning maternal smoking and low birthweight were reviewed. Seven were excluded from the meta-analysis for the following reasons: the data were insufficient,[13,34–36] the study design did not meet our criteria,[11,37] and the data were already included in another study.[38]

While all 23 studies included in the meta-analysis defined low birthweight as <2500 g, two limited their analyses to premature infants (less than 37 weeks' gestation), while another limited analysis to term infants (>37 weeks' gestation) (Table 2).

The association between low birthweight and maternal smoking has been one of the most consistent findings reported in the medical literature. This association is independent of maternal age, alcohol and drug use, education, employment, parity, prenatal care, socioeconomic status, and weight.[36,39,40] Twenty-two of the 23 studies

demonstrated a statistically significant association because of a relatively high risk ratio, a high prevalence of smoking among the study populations, and a high baseline rate of low-weight births.

The meta-analysis reveals a pooled RR of 1.82 (CI=1.67 to 1.97, $P<.001$, ENS=9), which is consistent with an odds ratio of 1.90 calculated by McIntosh[57] 10 years earlier.

If the prevalence of smoking during pregnancy is taken as 18.4% and the lower end of the 95% CI for the RR is used for a best-case calculation, 11% of low-weight births (some 32,000 cases annually) would be attributable to maternal smoking.

If the prevalence of smoking during pregnancy is considered to be 27%, and the upper limit of the 95% CI of the RR (1.97) is used for a worst-case calculation, 21% of low-weight births (61,000 annually) could be attributed to maternal smoking.

Oster and colleagues[58] estimated that 41.8% of smoker's infants weighing <2500 g at birth require admission to the neonatal intensive care unit. If this is accurate, maternal smoking would cause an estimated 14,000 to 26,000 admissions of newborns to neonatal intensive care units.

The additional costs for each low birthweight infant admitted to neonatal intensive care units because of maternal smoking during pregnancy has been estimated to range from $12,104 to $30,935.[59] Therefore, maternal smoking during pregnancy results in additional neonatal intensive care costs of between $164 million and $792 million each year.

Infant deaths due to low birthweight are included in the perinatal mortality figures.

Perinatal Mortality

Perinatal deaths include stillborn infants and infants who die shortly after birth. In 1988, there were 13.8 deaths of infants between a gestational age of 20 weeks and 28 days of life per 1000 live births in the United States.[60] With over 4.1 million births annually, 56,580 perinatal deaths would be expected.[61]

Forty-two studies concerning perinatal mortality were reviewed. Seventeen studies were excluded from the meta-analysis for the following reasons: the data were insufficient,[15,34,42,44,62–65] the data were already included in another report on the same population,[43,46,48,66–68] perinatal deaths could not be distinguished from abortions or infant deaths,[10,11] or the study design did not meet our criteria.[11,37]

The 25 studies included in the meta-analysis employed a variety of definitions for the terms stillbirth and neonatal death (Table 3). Definitions of stillbirth varied to include fetal deaths after the first trimester, after 20 weeks' gestation, and after 28 weeks' gestation, and infants weighing more than 600 g at birth. Neonatal deaths were defined as the death of a liveborn infant during the first day, week, 27 days, or 28 days. Most of the studies did not define these terms.

The association of maternal smoking with neonatal deaths has been shown to be independent of maternal age, parity, race, education, and marital status.[65,79] The increased risk of perinatal death with maternal smoking is due primarily to two factors: an increased rate of placental abruption and an increased rate of delivering immature infants of low birthweight.[48,68,74,79]

In contrast to the literature on low birthweight, the association of smoking with increased perinatal mortality has not been consistently documented. Of the 25 studies included in this analysis, only 11 demonstrated a statistically significant increase in risk, which can be attributed to a low relative risk and a very low baseline perinatal mortality rate. Butler[72] estimated that with a smoking prevalence of 31% and a RR of 1.28, a study of perinatal mortality would require 23,000 subjects to have a 90% probability of demonstrating statistical significance at the $P<.05$ level. A study of neonatal mortality alone would require 70,000 subjects.[72] Based on these criteria, 13 of the 14 negative studies reviewed in this investigation had inadequate statistical power.

The meta-analysis revealed a pooled RR of 1.26 (CI=1.19 to 1.34, $P<.001$, ENS=12) and a pooled OR of 1.23 (CI=1.12–1.41, $P<.001$, ENS=1) for perinatal mortality related to maternal smoking. McIntosh calculated an odds ratio of 1.25 for stillbirths and 1.22 for neonatal deaths.[57]

Despite the large number of negative studies, the literature supports a firm conclusion that maternal smoking is associated with an increased risk of perinatal mortality.

The variety of definitions of perinatal death among these studies, and the lack of a definition in most, interjects uncertainty into the calculations of the number of perinatal deaths attributable to maternal smoking. The magnitude of the RR for perinatal mortality (1.26) is nearly identical to that seen for spontaneous abortion (1.24). Since the risk of smoking-related pregnancy loss appears to be fairly constant throughout pregnancy, the gestational age that is used as the definition as to when perinatal deaths begin should have only a minimal effect on the outcome of these calculations.

If the prevalence of maternal smoking is considered to be 18.4%, and the lower end of the 95% CI around the pooled RR (1.19) is used in a best-case calculation, 3.4% of perinatal deaths (1900 deaths annually) would be attributable to maternal smoking.

Table 3. Studies Comparing Perinatal Mortality Rates Between Women Who Smoked During Pregnancy and Those Who Did Not

Study Author and Reference	Year of Publication	Study Site	Study Design	No. of Subjects	Fetal/ Infant Deaths	OR	RR	Perinatal Mortality* S	Perinatal Mortality* NS	Sig
Lowe[69]	1959	United Kingdom	Cohort	1823	47	—	1.28	30.0	23.4	No
Frazier et al[40]	1961	USA	Cohort	2763	95	—	1.44	42.5	29.5	No
Savel and Roth[41]	1962	USA	Cohort	1415	31	—	0.71	18.0	25.4	No
Comstock and Lundin[70]	1967	USA	Case-control	772	396	1.23	—			No
Underwood et al[44]	1967	US Navy	Cohort	48,494	981	—	1.05	20.8	19.7	No
Rantakallio[45]	1969	Finland	Cohort	11,742	273	—	1.01	23.4	23.2	No
Bailey[71]	1970	New Zealand	Cohort	1174	21	—	0.97	17.5	18.1	No
Kullander and Kallen[17]	1971	Sweden	Cohort	5740	120	—	1.43	25.2	17.7	Yes
Yerushalmy[47]	1971	USA	Cohort	13,083	170	—	1.07	13.7	12.7	No
Butler et al[72]	1972	United Kingdom	Case-control	21,788	6553	1.44	—	—	—	Yes
Niswander et al[49]	1972	USA	Cohort	38,736	1453	—	1.12	39.8	35.4	Yes
Rush and Kass[50]	1972	USA	Cohort	3276	113	—	1.42	41.0	28.8	No
Cope et al[51]	1973	Australia	Cohort	4067	94	—	1.32	27.8	21.1	No
Fabia[73]	1973	Canada	Cohort	6932	103	—	1.24	16.7	13.5	No
Murphy and Mulcahy[18]	1974	Ireland	Cohort	10,715	468	—	1.35	50.9	37.6	Yes
Goujard et al[74]	1975	France	Cohort	9169	100	—	2.53	23.3	9.2	Yes
Meyer et al[53]	1976	Canada	Cohort	50,097	1303	—	1.25	29.3	23.5	Yes
Targett et al[75]	1977	Australia	Cohort	3000	43	—	1.41	17.7	12.6	No
Rantakallio[76]	1978	Finland	Cohort	3688	92	—	1.09	26.0	23.9	No
Schramm[35]	1980	USA	Cohort	67,701	1130	—	1.32	19.9	15.1	Yes
Rush and Cassano[77]	1983	United Kingdom	Cohort	15,739	339	—	1.34	25.2	18.7	Yes
van der Velde and Treffers[78]	1985	Netherlands	Cohort	597	7	—	6.35	20.7	3.3	No
Malloy et al[79]	1988	USA	Cohort	305,581	1739	—	1.33	6.9	5.2	Yes
Rush et al[80]	1990	United Kingdom	Cohort	48,462	1131	—	1.32	27.0	20.4	Yes
Ahlborg and Bodin[12]	1991	Sweden	Cohort	3294	122	—	1.67	48.1	28.7	Yes
				Pooled OR=1.23(CI=1.12–1.41), $P<.001$, ENS=1						
				Pooled RR=1.26(CI=1.19–1.34), $P<.001$, ENS=12						

**Deaths per 1000 births. Definitions of "perinatal" differed among studies.*
OR denotes odds ratio; RR, relative risk; S, maternal smokers; NS, maternal nonsmokers; Sig, P<.05; CI, confidence interval; ENS, extra neutral studies.

If the prevalence of maternal smoking is considered to be 27%, and the upper range of the 95% CI (1.34) is used in a worst-case calculation, 8.4% of perinatal deaths (4800 deaths annually) would be attributable to maternal smoking.

Sudden Infant Death Syndrome

After congenital anomalies, SIDS is the most common cause of death among infants in the United States, accounting for 5417 deaths in 1990.[81]

It is surprising that the association between maternal smoking and SIDS is not common knowledge. It was first reported in 1966, and since then, an additional 15 studies[79,82–96] have confirmed this association, with ORs ranging from 1.6 to 4.5 (Table 4). In one study, the OR was 13 for the subpopulation of infants dying before 8 weeks of age.[92]

Two studies were excluded from the meta-analysis because data on the same population were included in another report,[90,93] and three studies[87,88,92] did not provide sufficient data (Table 4). One report was on two separate populations, and both sets of data were included.[96] Almost all these studies classified exposure based on whether the mother smoked during pregnancy. Since almost all women who smoke during pregnancy continue to do so after giving birth, such studies offer little insight into the relative roles of in utero exposure and involuntary smoking after birth.

Schoendorf and Kiely[96] compared three groups: mothers who did not smoke, mothers who smoked both during and after pregnancy, and mothers who smoked only after delivery. Smoking during and after pregnancy was associated with a threefold increased risk of SIDS, while exposure only after delivery resulted in odds ratios of 2.2 to 2.4. Postnatal exposure to smoke from persons other than the mother was associated with an increased risk of 1.4 among whites but not among blacks. Therefore, the risk of SIDS is increased by both maternal smoking during pregnancy and exposure to environmental tobacco smoke after delivery. After delivery, maternal smoking appears to pose a greater danger than does paternal smoking, probably because of the greater amount of time infants spend with their mothers. Since exposure to environmental tobacco smoke after birth clearly increases the risk of SIDS, all the other studies of SIDS reviewed here may have underestimated the role of smok-

Table 4. Studies Comparing the Incidence of Sudden Infant Death Syndrome Among the Offspring of Women Who Smoked and Those Who Did Not Smoke During Pregnancy

Study Author and Reference	Year of Publication	Study Site	Study Design	No. of Cases	No. of Controls	OR	Sig
Steele and Langworth[82]	1966	Canada	Case-control	79	154	2.49	Yes
Schrauzer et al[83]	1975	USA	Case-control	46	38	2.41	No
Bergman and Wiesner[84]	1976	USA	Case-control	56	86	2.15	Yes
Naeye et al[85]	1976	USA	Case-control	125	375	1.57	Yes
Lewak et al[86]	1979	USA	Case-control	34	14,823	4.40	Yes
Hoffman et al[89]	1988	USA	Case-control	757	757	3.79	Yes
Malloy et al[79]	1988	USA	Case-control	372	305,358	2.93	Yes
McGlashan[91]	1989	Tasmania	Case-control	167	334	4.48	Yes
Haglund and Cnattingius[94]	1990	Sweden	Case-control	190	279,748	2.13	Yes
Mitchell et al[95]	1991	New Zealand	Case-control	125	492	3.31	Yes
Schoendorf and Kiely[96]	1992	USA	Case-control	214	2645	4.07	Yes
			Case-control	175	2999	2.94	Yes

Pooled OR=2.98(CI=2.51–3.54), $P<.001$, ENS=17

NOTE: OR>1 implies increased incidence of SIDS associated with maternal smoking during pregnancy. OR denotes odds ratio; Sig, P<.05; CI, confidence interval; ENS, extra neutral studies.

ing by classifying infants who had postnatal exposure to maternal smoking as unexposed controls.

Four studies have examined the issue of paternal smoking and SIDS. Bergman and Wiesner[84] reported an OR of 1.53 ($P>.05$) for paternal smoking but did not control for maternal smoking. McGlashan[91] reported an OR of 1.73 ($P=.05$) for paternal smoking, with a dose-response relationship, and a greater risk when both parents smoked than if only one smoked. In a very small study, Lewak and co-workers[86] reported no effect of paternal smoking on SIDS outcome. Schoendorf and Kiely[96] demonstrated a definite risk related to exposure to environmental tobacco smoke from the mother but not from other household members. Conclusions about the role of paternal smoking in SIDS cannot be made at this time.

The association of SIDS with maternal smoking persists when controlling for birth order, date of birth, sex, gestational age, low birthweight, place of birth, race, maternal age, parity, occupation, and socioeconomic status.[83,85,89]

Meta-analysis produced a pooled estimate of the OR of 2.98 (CI=2.51 to 3.54, $P<.001$, ENS=17) for maternal smoking during pregnancy. This is the largest risk ratio for any of the diseases studied.

If the prevalence of maternal smoking is considered to be 18.4% and the lower range of the 95% CI around the pooled OR (2.51) is used in a best-case calculation, maternal smoking is responsible for 21.7% of SIDS deaths, or 1178 in 1990.

If the prevalence of maternal smoking is considered to be 27% and the upper range of the CI (3.54) is used in a worst-case calculation, maternal smoking is responsible for 40.7% of SIDS deaths, or 2203 in 1990.

Conclusions

This analysis reveals strong evidence of the detrimental effects of maternal tobacco use during and after pregnancy (Table 5). Each year the use of tobacco products by pregnant women results in the deaths of 19,000 to 141,000

Table 5. The Effect of Maternal Cigarette Smoking on Pregnancy Complications and Sudden Infant Death Syndrome

Fetal/Infant Outcome	Type of Study	No. of Studies	Pooled Risk	CI	*P* Value	ENS	% of All Cases	No. of Cases
Spontaneous abortion	Cohort	7	1.24	1.19–1.30	<.001	18	3–8	19,000–141,000
	Case-control	6	1.32	1.18–1.48	<.001	23		
Low birthweight	Cohort	22	1.82	1.67–1.97	<.001	9	11–21	32,000–61,000
	Case-control	1	1.99	1.74–2.28	<.001			
Perinatal mortality	Cohort	23	1.26	1.19–1.34	<.001	12	3–8	1900–4800
	Case-control	2	1.23	1.12–1.41	<.001	1		
SIDS	Case-control	12	2.98	2.51–3.54	<.001	17	22–41	1200–2200

NOTE: Pooled risk is a relative risk for cohort studie and an odds ratio for case-control studies. CI denotes confidence interval; ENS, extra neutral studies; SIDS, sudden infant death syndrome.

fetuses and 3100 to 7000 infants. By comparison, in 1990, child abuse and homicide resulted in the deaths of 1222 children up to the age of 14.[81] At least three times as many infants die of SIDS caused by maternal smoking as are killed as a result of homicide or child abuse.[81] While deliberate violence and abuse are very serious concerns, cigarettes kill many more children.

Between 32,000 and 61,000 infants are born with low birthweight each year because of maternal smoking. Some 14,000 to 26,000 of these infants require intensive care after birth.

The most dramatic effect of maternal smoking is on the risk of SIDS, which is tripled by maternal smoking. About two thirds of the SIDS deaths among the children of women who smoke while pregnant are attributable to their smoking.

Surprisingly, the wide range of numbers reported in this investigation is related to uncertainty about the proportion of women who smoke while pregnant.

A few limitations of this analysis should be highlighted. One limitation of meta-analysis is that it is usually impossible to adjust the pooled results to take into account potentially confounding factors because of differences in methodology between studies. The role of confounding factors is more easily addressed in individual studies. When adjustment for confounding factors was made in the individual studies considered here, the risk was just as often observed to increase after adjustment as not. Therefore, it is unlikely that the magnitude of the pooled risks reported here would be substantially different were such an adjustment possible. Nevertheless, readers should be aware that the estimates of disease burden presented here were not adjusted either upward or downward to account for the role of potential confounding factors.

Another caveat is that computations of attributable risk assume causality. A comprehensive discussion of causality is beyond the scope of this report; however, nothing in the many studies reviewed would lead us to suspect that tobacco is not a causal factor in any of the conditions considered here.

Some authors using the meta-analytic technique have chosen to screen studies for inclusion based on selected quality criteria. This approach was rejected because it would certainly result in accusations from the tobacco industry that the data were manipulated to bias the results.

A bias against the publication of neutral studies could not be ruled out. Also, some published studies did not provide sufficient data to be included in the meta-analyses. Therefore, a novel approach was used to assess the likelihood that the omission of neutral studies could have altered the outcome of the analysis. "Ghost" studies were used in a statistical analysis to simulate the effect of including neutral studies. The computation of the ENS was not used as a test of significance or validity and is offered only to provide the reader with an additional perspective on the data. This analysis suggests that, with all of the conditions considered here, it would be extremely unlikely that a publication bias is important.

In the consideration of publication bias, it was assumed that negative studies would be less likely to be published than positive studies. In light of recent allegations that the tobacco industry has suppressed the publication of medical research with positive findings,[97] it must also be considered that publication bias might conceal the magnitude of the risk.

The low success rates of smoking cessation intervention among pregnant women[5,6] even with intense efforts suggest that efforts to reduce these complications of pregnancy should focus on preventing nicotine addiction among teenaged girls.

The magnitude of the morbidity and mortality inflicted on fetuses and infants by smoking tobacco is a poignant reminder that use of tobacco products affects many innocent individuals who have not chosen to assume the risks involved. Since there is no safe level of tobacco use, the term "tobacco abuse" as applied to adult patients is inaccurate. The term might be more appropriately used to describe the morbidity and mortality inflicted on children through the manufacture, sale, and use of tobacco products.

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