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# Secondhand Smoke and Adverse Fetal Outcomes in Nonsmoking Pregnant Women: A Meta-analysis

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**KEY WORDS**

secondhand smoke, environmental tobacco smoke, fetal outcomes, congenital malformations, systematic review, meta-analysis

**ABBREVIATIONS**

OR—odds ratio
CI—confidence interval

Dr Leonardi-Bee participated in the study conception, design, identification of studies, data collection, study selection, data extraction, analysis, and interpretation of the data, writing of the protocol, and drafting and revision of the article; Professor Britton participated in the study conception, design and interpretation of the data, and critical revision of the article for important intellectual content and approved the final version to be published; and Dr Venn participated in the study conception, design, identification of studies, data collection, study selection, data extraction, analysis, and interpretation of the data, and critical revision of the article for important intellectual content and approved the final version to be published.

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## abstract

FREE

**OBJECTIVE:** To determine the risk of adverse fetal outcomes of secondhand smoke exposure in nonsmoking pregnant women.

**METHODS:** This was a systematic review and meta-analysis in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We searched Medline and Embase (to March 2009) and reference lists for eligible studies; no language restrictions were imposed. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by using random-effect models. Our search was for epidemiologic studies of maternal exposure to secondhand smoke during pregnancy in nonsmoking pregnant women. The main outcome measures were spontaneous abortion, perinatal and neonatal death, stillbirth, and congenital malformations.

**RESULTS:** We identified 19 studies that assessed the effects of secondhand smoke exposure in nonsmoking pregnant women. We found no evidence of a statistically significant effect of secondhand smoke exposure on the risk of spontaneous abortion (OR: 1.17 [95% CI: 0.88–1.54]; 6 studies). However, secondhand smoke exposure significantly increased the risk of stillbirth (OR: 1.23 [95% CI: 1.09–1.38]; 4 studies) and congenital malformation (OR: 1.13 [95% CI: 1.01–1.26]; 7 studies), although none of the associations with specific congenital abnormalities were individually significant. Secondhand smoke exposure had no significant effect on perinatal or neonatal death.

**CONCLUSIONS:** Pregnant women who are exposed to secondhand smoke are estimated to be 23% more likely to experience stillbirth and 13% more likely give birth to a child with a congenital malformation. Because the timing and mechanism of this effect is not clear, it is important to prevent secondhand smoke exposure in women before and during pregnancy. *Pediatrics* 2011;127:000

Active maternal smoking during pregnancy is well recognized as a cause of fetal mortality[1] and morbidity that arises from being small for gestational age (<10th centile for body weight corrected for gestation),[2] low birth weight (<2500 g),[1] and premature birth (<37 weeks' gestation).[3] Birth weights of infants of mothers who smoked during pregnancy are ~250 g less than those born to nonsmoking mothers.[2,4,5] Smoking during pregnancy has been associated also with increased risks of congenital malformations, particularly heart defects, limb-reduction defects, kidney/urinary tract defects, and cleft lip and palate defects.[6]

Because secondhand smoke involves exposure to the same range of tobacco smoke toxins experienced by active smokers, although at lower levels, it is likely that exposure to secondhand smoke also causes some or all of these complications but with lower levels of relative risk. Therefore, secondhand smoke exposure to the mother during pregnancy may also have important health effects on fetal health. After a recent systematic review and meta-analysis, we reported that secondhand smoke exposure in nonsmoking pregnant women decreases birth weight by 33 g and increases the risk of low birth weight (<2500 g).[7] However, the effect of maternal secondhand smoke exposure on other fetal outcomes, including mortality and congenital malformations, is less widely known.

Therefore, we now report the results of a systematic review and meta-analysis of all of the world evidence available to quantify the effect of maternal secondhand smoke exposure during pregnancy on a range of adverse fetal outcomes including spontaneous abortion, fetal death, stillbirth, and major congenital malformations. This work was conducted as part of a more extensive review of the effects of passive smoking in children for the Royal College of Physicians.[6]

## PATIENTS AND METHODS

### Methods of the Systematic Review

We attempted to identify any comparative case-control, cross-sectional, or cohort epidemiologic studies that assessed the effect of secondhand smoke exposure in mothers during pregnancy. Randomized controlled trials of smoking cessation in either parent were excluded. Secondhand smoke exposure was defined as contact with secondhand smoke from any source (domestic, occupational, or other sources) measured through self-reported smoking status of the father/partner, self-reported maternal exposure to secondhand smoke, or biochemically measured maternal exposure to secondhand smoke. We excluded populations from studies for which the effect of secondhand smoke exposure was assessed in actively smoking pregnant women.

### Outcome Measures

We assessed the effects of maternal secondhand smoke exposure on spontaneous abortion (miscarriage, death before 20 weeks' gestation), stillbirth (death between 20 weeks' gestation and birth), perinatal mortality (death after 20 weeks' gestation or within the first week of life), neonatal mortality (death within 28 days of live birth), or congenital malformations. Studies that assessed only birth weight and/or prematurity were excluded, because a comprehensive systematic review on these topics was recently published.[7]

### Search Strategy

We performed comprehensive searches based on 2 electronic databases, Medline (from 1966 to March 2009) and Embase (from 1980 to March 2009), by using the Centre for Reviews and Dissemination guidelines.[8] The following search terms were used ($ indicates truncation): fetal death, spontaneous abortion, malformations, pregnancy complications, infant mortality, stillbirth (passive or second hand or second-hand or involuntary or parent$ or maternal or mother$ or paternal or father$ or household$) and (smok$ or tobacco$ or cigarette$ or cotinine$). We also scanned previous reviews, editorials, and reference lists of the identified articles. We imposed no language restrictions on the searches, and translations were sought where necessary.

### Study Selection

Two authors (Drs Venn and Leonardi-Bee) checked the eligibility of the articles by independently reviewing the titles and abstracts and excluding irrelevant articles after each stage. The full text of the studies that were regarded as potentially eligible were obtained and assessed independently by 2 authors (Drs Venn and Leonardi-Bee) to decide which ones met the inclusion criteria; discrepancies were resolved through discussion. For all of the included studies, 2 authors (Drs Venn and Leonardi-Bee) independently extracted data by using a previously piloted data-extraction form and scored methodologic quality by using the Newcastle-Ottawa Assessment Scale.[9] This scale assesses the selection of the study sample (for case-control or cohort studies, maximum of 4 points; for cross-sectional studies, maximum of 3 points); the comparability of the sample groups (maximum of 2 points); and the ascertainment of either the exposure (for case-control and cross-sectional studies, maximum of 3 points) or outcome (for cohort studies, maximum of 3 points).

### Statistical Analysis

Tabulated data, unadjusted estimates, or adjusted estimates were extracted from the included publications; ad-

**TABLE 1** Characteristics of the Included Studies

| Study | Design | Ascertainment of Secondhand Smoke Exposure | Source of Secondhand Smoke Exposure | Outcome Assessed | Methodologic Quality Score | Geographic Area Studied |
|---|---|---|---|---|---|---|
| Ahlborg and Bodin[42] | Prospective cohort | Self-report | Home, work | Stillbirth | 8 | Sweden |
| Carmichael et al[30] (2005) | Population-based case-control | Self-report | Home, work | Congenital malformations | 7 | United States |
| Carmichael et al[29] (2008) | Population-based case-control | Self-report | Any | Congenital malformations | 7 | United States |
| Comstock and Lundin[31] | Cross-sectional | Self-report | Father | Neonatal mortality | 4 | United States |
| George et al[43] | Population-based case-control | Plasma cotinine | Any | Spontaneous abortion | 9 | Sweden |
| Honein et al[32] | Population-based case-control | Self-report | Any | Congenital malformations | 7 | United States |
| Kharrazi et al[33] | Retrospective cohort | Serum cotinine | Any | Stillbirth | 8 | United States |
| Little et al[44] | Population-based case-control | Self-report | Father, any | Congenital malformations | 5 | United Kingdom |
| Mau and Netter[45] | Cross-sectional | Self-report | Father | Perinatal mortality | 2 | Germany |
| Meeker et al[47] | Cross-sectional | Self-report | Father, work, any | Spontaneous abortion | 5 | United States |
| Mishra et al[39] | Cross-sectional | Self-report | Any | Stillbirth | 5 | India |
| Nakamura et al[38] | Cross-sectional | Self-report | Any | Spontaneous abortion | 2 | Brazil |
| Peppone et al[34] | Cross-sectional | Self-report | Any | Stillbirth | 4 | United States |
| Uncu et al[46] | Cross-sectional | Self-report | Father | Stillbirth, congenital malformations | 3 | Turkey |
| Venners et al[40] | Prospective cohort | Self report | Father | Spontaneous abortion | 6 | China |
| Wasserman et al[35] | Population-based case-control | Self-report | Father | Congenital malformations | 7 | United States |
| Windham et al[36] (1992) | Population-based case-control | Self-report | Father, any | Spontaneous abortion | 8 | United States |
| Windham et al[37] (1999) | Prospective cohort | Self-report | Father, work, any | Spontaneous abortion | 8 | United States |
| Zhang et al[41] | Population-based case-control | Self-report | Father | Congenital malformations | 6 | China |

justed estimates were used in preference, when available. For studies with similar outcomes, meta-analyses were performed to estimate weighted measures of effect across studies by using random-effect models, because we anticipated high levels of heterogeneity between the estimates of the studies because of inherent biases in the study designs. We compared the impact of maternal secondhand smoke exposure with no maternal secondhand smoke exposure on the outcome measures by using the most inclusive definition of secondhand smoke exposure. In addition, we performed sensitivity analyses by restricting the analysis to studies that assessed the direct effect of secondhand smoke exposure from the infant's father (paternal exposure). Outcomes are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity between studies was assessed by using recognized methods ($I^2$ index).[10] When moderate-to-high levels of heterogeneity ($I^2 > 50\%$) were detected between studies, subgroup analyses relating to methodologic quality of the studies were performed to explore the reasons for heterogeneity. A score of $\geq 6$ was used to distinguish higher-quality from poorer-quality studies.

Publication bias was assessed by using a simple funnel plot when adequate numbers of studies were included in the meta-analyses. Analyses were performed by using Review Manager 5.0.23 (RevMan) (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). *P* values of $<.05$ were deemed statistically significant. The systematic review was conducted in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[11]

### Ethics

Ethical approval was not required for this study.

## RESULTS

### Overview of Included Studies

From an initial 4275 articles identified in the searches, 279 had potentially eligible titles, 80 had potentially eligible abstracts, and 34 had potentially eligible full texts. After scrutinizing the full texts, 19 of these studies were found to meet all of the inclusion criteria for inclusion in this review (Table 1; Fig 1). The remaining 15 studies were excluded from the analysis because they assessed secondhand smoke exposure in actively smoking pregnant women.[12–28]

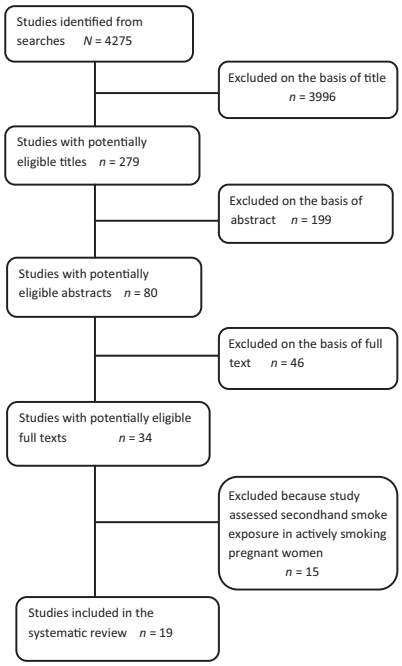


**FIGURE 1**
Flow diagram of included and excluded studies.

Ten of the 19 included studies were conducted in North America,[24,29–37] 1 in South America,[38] 3 in Asia,[39–41] and 5 in Europe.[42–46] Eight studies used a case-control design, 7 were cross-sectional, and 4 were cohort studies. The majority of studies assessed maternal exposure to secondhand smoke by self-report, but 2 studies measured serum[33] and plasma[43] cotinine levels.

The Newcastle-Ottawa Assessment Scale scores for methodologic quality of the included studies ranged from 2 to 9 (median: 6). Scores below 7 tended to arise from failure to adjust for confounding factors and using self-reported ascertainment of tobacco exposure. There was no evidence of publication bias identified for the association between exposure to secondhand smoke and the risk of spontaneous abortion.

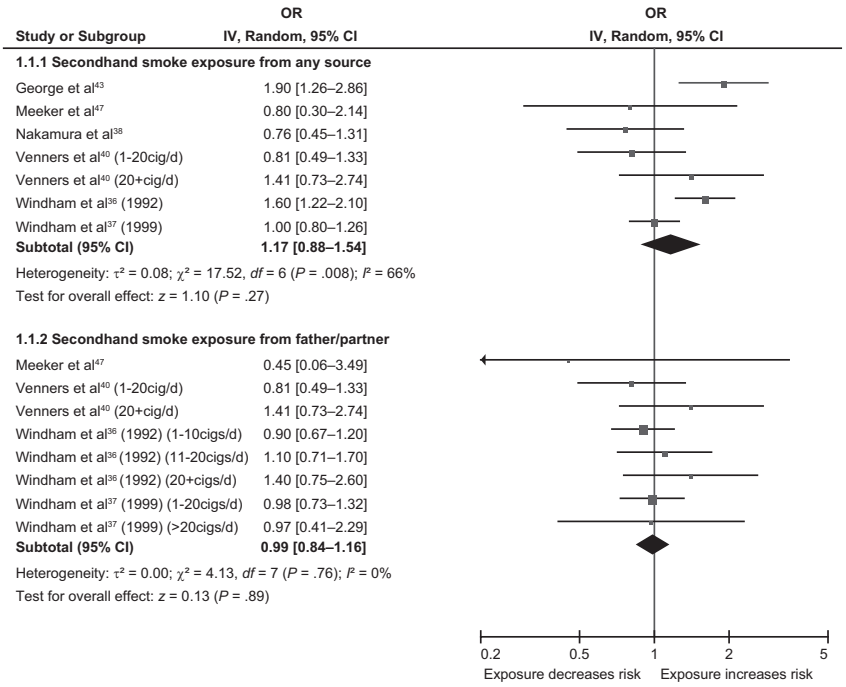


**FIGURE 2**
Forest plot of secondhand smoke exposure and the risk of spontaneous abortion. IV indicates inverse variance method; cig, cigarettes; *df*, degrees of freedom.

## Spontaneous Abortion

Seven studies assessed the relation between secondhand smoke exposure and the risk of spontaneous abortion,[36–38,40,43,45,47] 5 of which were based on exposure from the infant's father (paternal smoking).[36,37,40,45,47] Data from 1 study could not be included in the meta-analyses because of the lack of detailed data within the publication.[45] The excluded study found that paternal smoking of ≥10 cigarettes per day did not significantly increase the risk of spontaneous abortion. The risk of spontaneous abortion was unrelated to either overall secondhand smoke exposure (OR: 1.17 [95% CI: 0.88–1.54]; $I^2 = 66\%$; 6 studies) (Fig 2) or exposure from the infant's father (OR: 0.99 [95% CI: 0.84–1.16]; $I^2 = 0\%$; 4 studies) (Fig 2). A similar nonsignificant finding was seen from a sensitivity analysis that was based on high-quality studies (exposure to overall secondhand smoke, OR: 1.28 [95% CI: 0.94–1.75]; 4 studies; and exposure to paternal smoke, OR: 0.99 [95% CI: 0.85–1.17]; 3 studies).

## Stillbirth and Perinatal and Neonatal Mortality

The effect of secondhand smoke exposure on the risk of stillbirth was assessed in 5 studies.[33,34,39,42,46] Data from 1 study could not be included in the meta-analysis because of how the data were reported.[39] The excluded study reported a nonsignificant increase in risk of stillbirth with exposure to any secondhand smoke (OR: 1.05 [95% CI: not reported). Overall exposure to secondhand smoke was significantly associated with a 23% increase in the risk of stillbirth (95% CI: 1.09–1.38; $I^2 = 0\%$; 4 studies) (Fig 3). A sensitivity analysis based on higher-quality studies resulted in similar estimates of effect for the association (OR: 1.18 [95% CI: 0.88–1.59; 2 studies). Only 1 study assessed the effect of paternal smoking[46]; a nonsignificant but nearly fourfold increase in risk (OR: 3.81 [95% CI: 0.42–34.30]) was reported.

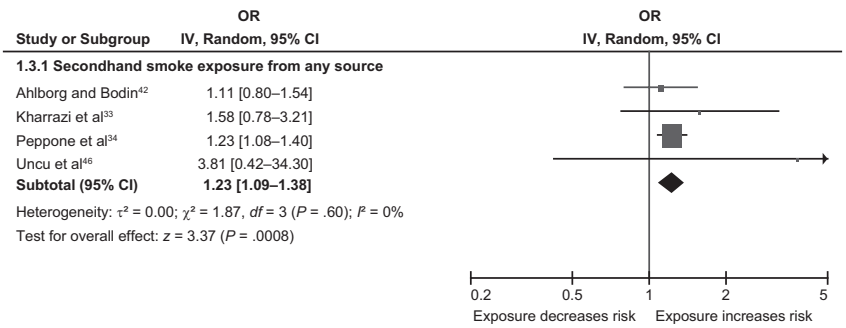


**FIGURE 3**
Forest plot of secondhand smoke exposure and the risk of stillbirth. IV indicates inverse variance method; cig, cigarettes; *df*, degrees of freedom.

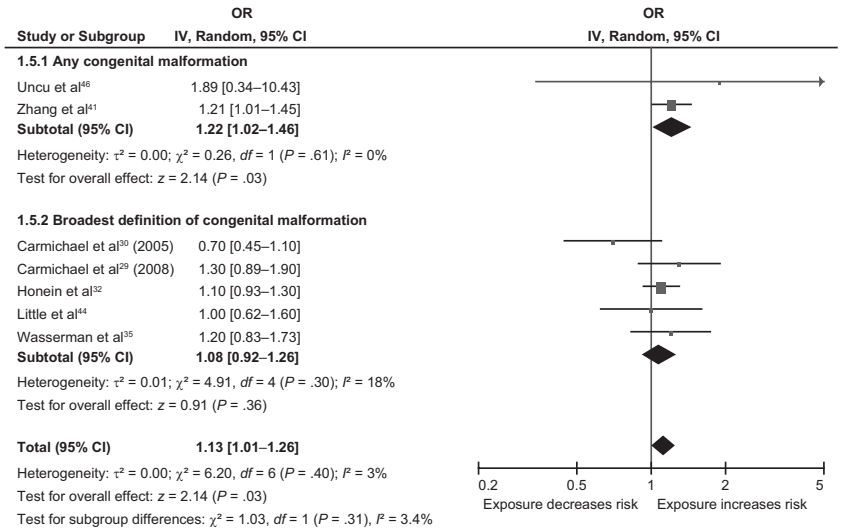


**FIGURE 4**
Forest plot of secondhand smoke exposure and the risk of congenital malformation. IV indicates inverse variance method; cig, cigarettes; *df*, degrees of freedom.

Only 2 studies assessed the association between secondhand exposure to smoke (paternal smoking) and the risk of perinatal or neonatal mortality.[31,45] No significant association was seen between paternal smoking and the risk of perinatal mortality (OR: 1.07 [95% CI: 0.48–2.38][45]) and neonatal mortality[31] (data not reported).

## Congenital Malformations

Seven studies assessed the association between maternal secondhand smoke exposure and congenital malformations.[29,30,32,35,41,44,46] Five of these studies examined a single type of malformation,[29,30,32,35,44] and the other 2 used a broader definition of any malformation.[41,46] A pooled analysis revealed that exposure to any secondhand smoke was significantly associated with a 13% increase in risk of a congenital malformation (95% CI: 1.01–1.26; $I^2 = 3\%$; 7 studies) (Fig 4). Restricting the meta-analysis to the 2 studies,[41,46] which specifically examined the risk of developing any congenital malformation, revealed a significant 22% increase in the risk of any congenital malformation (95% CI: 1.02–1.46; $I^2 = 0\%$; 2 studies) (Fig 4).

### *Heart Defects*

Two studies were identified that assessed the effect of secondhand smoke exposure on the risk of cardiac defects,[35,41] both of which measured exposure to father's smoking but examined different outcomes. Paternal smoking was not found to significantly increase risks of cardiac defects, namely conotruncal heart defects (OR: 1.30 [95% CI: 0.85–2.10][35]) and ventricular septal defect (OR: 0.60 [95% CI: 0.17–2.10][41]) (Table 2).

### *Musculoskeletal Defects*

Two studies that assessed the effect of secondhand smoke exposure on the risk of musculoskeletal defects were identified.[35,41] A 50% significant reduction in the risk of numerical deformities with paternal smoking (95% CI: 0.25–1.00) was reported; however, the same study revealed a borderline significant increase in varus/valgus deformities of the feet, including clubfoot (OR: 1.80 [95% CI: 0.97–3.30]). In addition, paternal smoking was not associated with brachydactylia/adactylia (OR: 1.6 [95% CI: 0.4–6.1])[41] or limb-reduction defects (OR: 1.2 [95% CI: 0.75–1.9]).[35]

### *Defects of the Genitourinary Systems*

Two studies that assessed the effect of secondhand smoke exposure on the risk of genitourinary system defects were identified.[30,41] A pooled analysis revealed no significant association between overall secondhand smoke exposure and hypospadias (OR: 0.73 [95% CI: 0.52–1.04]; $I^2 = 0\%$; 2 studies[30,41]); no significant association was seen from the individual study that also assessed exposure to parental smoking and hypospadias (OR: 0.79 [95% CI: 0.45–1.38][41]). However, paternal smoking was associated with a borderline significant increase in the risk of cryptorchidism (OR: 1.55 [95% CI: 0.95–2.54][41]) but had no effect on polycystic kidney or indeterminate gender.

### *Defects of the Central Nervous System*

Two studies assessed the impact of secondhand smoke exposure on the risk of central nervous system defects[35,41] but examined different outcomes. One study revealed no significant increase in the risk of neural tube defects in relation to overall exposure to secondhand smoke (OR: 1.20 [95% CI: 0.83–1.73]) or exposure to paternal smoke (OR: 1.15 [95% CI: 0.78–1.68]).[35] The other study found that, overall, secondhand smoke exposure nonsignificantly doubled the risk of anencephaly (OR: 2.10 [95% CI: 0.90–4.90]) and spina bifida (OR: 1.90 [95% CI: 0.70–9.40]) but had no effect on hydrocephalus or microcephaly.[41]

### *Defects of the Face, Eyes, Ears, and Neck*

Four studies assessed the effect of secondhand smoke exposure on the risk of defects of the face, eyes, ears, and neck[29,32,41,44] but generally examined different outcomes. A pooled analysis of 2 studies revealed no association between overall secondhand smoke exposure and the risk of orofa-

cial clefts (OR: 1.09 [95% CI: 0.93–1.27]; $I^2 = 0\%$).[32,44] Individual studies found that exposure to secondhand smoke was not associated with risks of craniosynostosis (OR: 1.30 [95% CI: 0.89–1.90][29]), anomalies of the eye, anomalies of the external ear, microtia or absence of ear, or nasal bone absence.[41]

### *Other Congenital Malformations*

One study also examined the association between secondhand smoke exposure and the risk of other defects and revealed no significant effect of paternal smoking on the risk of hemangioma, pigmentary anomalies of the skin, Down syndrome (trisomy 21), diaphragmatic hernia, or lung hypoplasia/aplasia.[41]

## DISCUSSION

Tobacco smoke contains a wide range of toxins and carcinogens; therefore, exposure of pregnant women to passive smoke is a cause for concern in relation to both maternal and fetal health. However, the magnitude of any health effect is likely to be small and, therefore, difficult to detect in individual studies. This systematic review and meta-analysis is, to our knowledge, the first to attempt to synthesize the existing world literature to provide summary estimates of these effects. We found that maternal secondhand smoke exposure was significantly associated with an increased risk of stillbirth and congenital malformation. The available number of studies that have examined specific malformations was small, but effects just short of significance were seen for varus/valgus deformities of the feet, cryptorchidism, and anencephaly. Generally, relatively low levels of heterogeneity were detected between the results of the studies, which indicates that the effects were robust to the definition and quantity of secondhand smoke exposure identified within the studies. We have not attempted to distinguish the effects of secondhand smoke exposure at different stages of pregnancy or the quantity of secondhand smoke exposure because of an insufficient number of studies that reported this level of detail. However, we have separated, when possible, the effects of secondhand smoke identified as arising from paternal smoking as distinct from other sources.

The findings from this review are generalizable, because we performed comprehensive search strategies of all of the literature worldwide, although the majority of them were conducted in the United States or Europe. We attempted to explore reasons for heterogeneity between the studies by performing subgroup analyses based on methodologic quality, when sufficient data permitted, and found results similar to those of the overall analyses. However, there are likely to be confounding factors for which we have been unable to adjust, because we relied on the factors adjusted for in the original analyses; therefore, we were unable to completely adjust for the effects of socioeconomic status or ethnicity, which could have been potential confounders. However, the most common confounders adjusted for within the individual studies were maternal age, education, ethnicity, alcohol use, and previous outcome (eg, stillbirth).

Active smoking during pregnancy has been found to increase the risk of birth defects between 10% and 34%[6] and the risk of stillbirth between 20% and 34%.[48] The effects of secondhand smoke exposure are likely to be substantially smaller, because typical secondhand smoke exposure consists of only ~1% of typical active smoking exposure.[49] However, the relation between exposure and effect is not necessarily linear, as is the case for the effect of secondhand smoking on mean birth weight, which is ~17% to 20% that of active smoking. However, our estimates were substantially higher than this, which possibly indicates the potential for publication bias being present in this meta-analysis.

The effects of secondhand smoke on adverse fetal outcomes are likely to be a result of the impact of side-stream smoke, which is the primary component of secondhand smoke exposure and has been shown to be more harmful than mainstream smoke[50] because it contains greater concentrations of the toxins that are harmful to the fetus. The mechanism by which secondhand smoke exposure could exerts its effects could be the mother's exposure to side-stream smoke during a particular period during pregnancy and/or during the preconception period or could be the direct effect of active smoking by the father on spermatogenesis, thereby inducing genotoxic effects.[51] The importance of this study is that, irrespective of the true magnitude of these effects, secondhand smoke exposure to a mother while pregnant is likely to have serious adverse risks because of the increased risk for congenital malformations and stillbirths.

## CONCLUSIONS

Our results provide confirmatory evidence that there are further adverse effects of maternal secondhand smoke exposure during pregnancy on the health of the fetus through increased risks of congenital malformations, stillbirths, and possibly other adverse fetal outcomes. These results highlight the importance of smoking prevention and cessation to focus on the father in addition to the mother during the preconception period and during pregnancy.

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