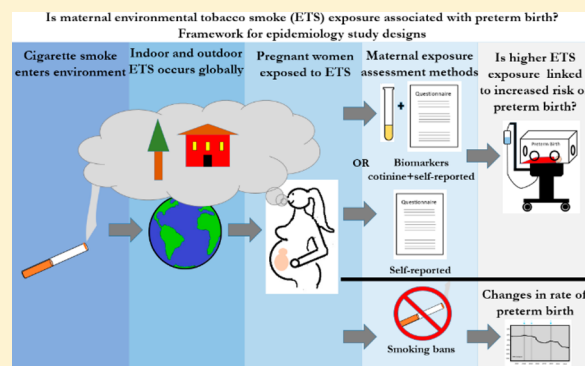


# Trends in Environmental Tobacco Smoke (ETS) Exposure and Preterm Birth: Use of Smoking Bans and Direct ETS Exposure Assessments in Study Designs

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**ABSTRACT:** For decades, many studies have linked maternal smoking to an increased risk of preterm birth. As a result, the scientific community has long hypothesized that exposure to environmental tobacco smoke (ETS), commonly referred to as second-hand smoke, is also associated with an increased risk of preterm birth. Multiple studies have examined this proposed association through different strategies and approaches. Recently, a small number of epidemiology studies have examined preterm birth trends before and after the implementation of antismoking legislation in various jurisdictions. We found that these studies have largely revealed a significant trend of decreasing population-level preterm birth rates after the implementation of smoking bans. However, most of the studies reviewed did not distinguish the impact of maternal smoking from ETS in their analyses, making it difficult to specifically evaluate the effects of smoking bans on ETS exposure. Other studies have taken the approach of directly measuring maternal ETS exposure and associations with preterm birth within particular study populations. In contrast to smoking ban studies, the latter group of studies had more inconclusive results. The use of a variety of exposure assessment methods ranging from different self-reporting techniques to biomarker measurements posed a challenge to compare studies. We evaluate current scientific literature for evidence of an association between maternal ETS exposure and risk of preterm birth. We also discuss the strengths and weaknesses of the different approaches to study this association as well as methods used for ETS exposure assessment. We propose that more studies, specifically, evaluating rates of preterm birth among nonsmoking women before and after smoking bans, are needed as well as using better ETS exposure assessments methods in studies measuring maternal ETS exposure.



## INTRODUCTION

Preterm birth is both a common and devastating adverse health outcome with global impacts. On average, approximately 11.1% of all babies born globally are classified as preterm. In 2010 alone, an estimated 15 million babies were born prematurely worldwide, including over half a million in the United States.<sup>1</sup> The World Health Organization generally defines preterm birth as a woman giving birth before 37 weeks gestation.<sup>2</sup> Babies who are born prematurely face a myriad of health complications upon arrival, which greatly increase their likelihood of death. These include factors such as lung immaturity, gastrointestinal feeding intolerance, skin problems including the inability to regulate body temperature, immune system deficiencies, and cardiovascular, hearing, and vision problems.<sup>3</sup> Complications from preterm birth are the leading cause of death in children under the age of 5.<sup>2</sup> These complications are not just limited to the days and weeks after birth. Premature babies often face a lifetime of chronic health problems and devastating disabilities that cost an estimated twenty-six billion dollars per year in the United States alone.<sup>3</sup>

## ENVIRONMENTAL TOBACCO SMOKE

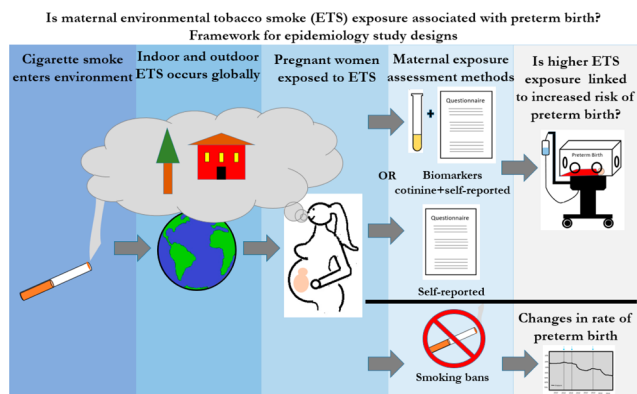
The scope of the preterm birth problem makes it a pressing global public health issue and as a result, extensive research has been conducted on potential causes for many decades. One potential cause of preterm birth that has been examined in the past few decades is environmental tobacco smoke (ETS). ETS, also known as secondhand smoke or passive smoke, is defined as any smoke from a tobacco-containing product that is emitted into the ambient air through the exhalation of an active smoker (mainstream smoke) or through the burning end of a lit cigarette (side stream smoke). Exposure to ETS primarily occurs in indoor environments such as at home, in cars, or in restaurants.<sup>4</sup> However, it can also occur outdoors such as near the entrances of smoke-free buildings or bus stops.<sup>4</sup> Although a wealth of evidence dating back to the 1950s indisputably links active maternal smoking to preterm birth, considerably less research has examined the relationship between ETS and preterm birth.<sup>5</sup> The comparatively small number of studies

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examining associations between ETS and preterm birth have examined the issue utilizing different strategies and approaches (Figure 1).



**Figure 1.** Framework for epidemiological study designs evaluating associations between maternal ETS exposure and preterm birth. Studies specifically evaluating maternal ETS exposure and risk of preterm birth use different methods to assess or quantify individual level maternal ETS exposure. These methods include maternal self-reporting via interviews or questionnaires or a combination of biomarker biochemical validation and self-reporting. Studies specifically evaluating ETS exposure and population level changes in preterm birth rate use data before and after the implementation of smoking bans.

## ■ ANTISMOKING LEGISLATION

As a result of the overwhelming evidence of adverse health outcomes and mortality attributed to smoking, in the past several decades, a number of different types of smoking bans have been implemented across different parts of the world. These regulations vary widely in their details, scope, enforcement, and geography. For example, some of the bans cover only bars and restaurants, while others also include parks, public spaces, and workplaces. In addition, bans apply to whole countries, individual states, counties, or cities.<sup>6</sup> Timing and implementation of the antismoking regulations have varied. In Scotland, a single ban passed at one point in time and was implemented in phases over the course of years.<sup>7</sup> In other examples, different bans were passed at different times or a single ban was passed and implemented at one time. As the number of smoking bans continues to increase, it is necessary to assess the effects of these bans in reducing smoking-related morbidities.

## ■ EVIDENCE FROM ANTISMOKING LEGISLATION AND PRETERM BIRTH STUDIES

Several epidemiology studies have examined the potential association between maternal ETS exposure and the risk of preterm birth by using the strategy of evaluating preterm birth trends before and after the implementation of antismoking legislation locally, regionally, and nationally. To characterize the results thus far of smoking bans and preterm birth studies, we searched PubMed to identify relevant studies. Different combinations of keywords were entered into the regular search bar. These keywords included “smoking bans”, “anti-smoking legislation”, “tobacco control”, “smoking regulation”, “smoke-free legislation”, “preterm birth”, “birth outcomes”, “neonatal outcomes”, “gestation”, and “premature”. In addition, we identified studies using citations from the Been et al. meta-analysis

review.<sup>6</sup> All studies that examined the associations of anti-smoking laws with preterm birth rates were included in the analysis. We identified five studies, which are discussed here.<sup>7–11</sup> In addition to preterm birth, most of the studies included evaluations of other outcomes such as low birth weight, small for gestational age, maternal smoking, and childhood asthma. Only the sections of the studies relevant to the preterm birth outcome were evaluated.

Each of the five studies was conducted on populations in northern and western Europe and the United States. They encompassed geographical areas ranging from nations (Norway, Ireland) to regions (Flanders, Belgium, and Scotland) to cities (Pueblo and El Paso, Colorado). The earliest smoking ban was implemented in 2003 and the last in 2010. Three of the five studies assessed laws with one implementation date that banned smoking in workplaces and public places.<sup>8–10</sup> One study assessed laws that were passed at the same time and were implemented in three phases over the course of four years, also banning smoking in workplaces and public places.<sup>7</sup> One study assessed a law that built upon a previous ban on smoking in workplaces and public places by adding bans in restaurants and bars.<sup>11</sup> The studies all used retrospectively available routine health data collected during and after pregnancies to perform their analyses. Interrupted time series and difference-in-difference study designs were used. All of the studies identified increased odds of preterm birth after the implementation of each ban. Several studies also reported gradual (slope) changes in preterm birth rates. These logistic regression models also included adjustment for several confounders. The most commonly included confounders in final regression models were: parity (4 studies), sex of baby (3 studies), age of mother (3 studies), alcohol consumption (2 studies), and marital status (2 studies).<sup>7–11</sup>

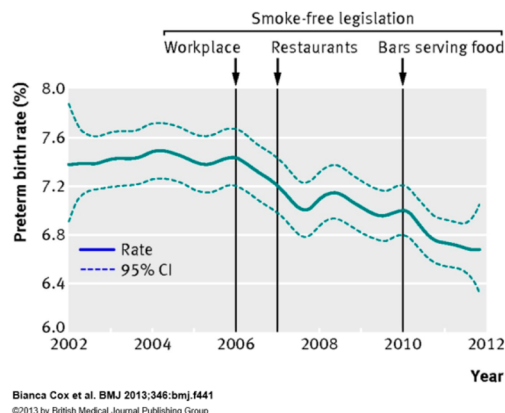
These studies have largely revealed a significant trend of decreasing population-level preterm birth rates after the implementation of smoking bans. The results of the five studies are summarized in Table 1. Four of the five studies showed overall immediate (step) statistically significant reductions in the rates of preterm birth,<sup>7–10</sup> while the fifth study showed a trend toward a reduction that was not significant.<sup>11</sup> The largest reduction in the overall preterm birth rate category was  $-25\%$  [95% confidence interval:  $-41.0\%$ ,  $-4.0\%$ ] reported by Kabir et al.,<sup>8</sup> while the smallest reduction was  $-0.59\%$  [95% CI:  $-2.63\%$ ,  $1.49\%$ ] reported by Cox et al. following the first ban of three implemented over the course of the study. Even though Cox et al. reported relatively small, insignificant reductions after the first and third bans were implemented, their final model for overall preterm birth rate, which included all three bans, was a larger significant reduction of  $-3.18\%$  [95% CI:  $-5.38\%$ ,  $-0.94\%$ ].<sup>7</sup> By contrast, Cox et al. reported significant reductions in the spontaneous preterm birth rate category following the implantation of each of the three smoking bans as well as a reduction of  $-3.13\%$  [95% CI:  $-4.37\%$ ,  $-1.87\%$ ] in their final model for the spontaneous category (Figure 2).<sup>7</sup> In addition to Cox et al., Bhardawaj et al. also reported a reduction that was not statistically significant of  $-2.55\%$  [90% CI:  $-5.52\%$ ,  $0.42\%$ ].<sup>11</sup> Page et al., who looked at a city-wide smoking ban in Colorado found a large  $-23.1\%$  [95% CI:  $-40.1$ ,  $-1.3$ ]<sup>10</sup> reduction in preterm birth rates, while Mackay et al. found a modest overall reduction of  $-11.72\%$  [95% CI:  $-15.87\%$ ,  $-7.35\%$ ].<sup>9</sup> A meta-analysis conducted by Been et al. in 2014 is consistent with our finding that these studies have largely revealed a significant trend of decreasing

Table 1. Summary of Smoking Bans and Preterm Birth Studies

first author	location of study	population	year of ban	details of smoking ban	preterm birth definition	immediate change in preterm birth rate (overall adjusted) <sup>a</sup>	findings
Page <sup>10</sup>	USA: Pueblo and El Paso, CO	470 000	2003	workplaces and public places in Pueblo; none in El Paso	preterm <37 weeks	−23.1% [95% CI: −40.1, −1.3]	Postban: Preterm birth rates reduced by 23.1% in Pueblo compared to El Paso preban.
Bharadwaj <sup>11</sup>	Norway	4 950 000	2004	restaurants and bars; previous ban on workplaces and public places	preterm <36 weeks	−2.55% <sup>b</sup> [95% CI: −5.52, 0.42]	Postban: Preterm birth rates reduced by 2.55% in mothers working in bars and restaurants.
Kabir <sup>8</sup>	Ireland	4 580 000	2004	workplaces and public places	preterm <37 weeks	−25% [95% CI: −41.0, −4.0]	Postban: Preterm birth rates reduced by 25%.
MacKay <sup>9</sup>	United Kingdom: Scotland	5 300 000	2006	workplaces and public places	among smokers and nonsmokers: mild preterm <37 weeks; moderate preterm <34 weeks; extreme preterm <32 weeks stratified by current smokers	−11.72% [95% CI: −15.87, −7.35]	Among both smokers and nonsmokers: Postban: Preterm birth rates reduced by 11.72%.
Cox <sup>7</sup>	Belgium: Flanders	6 250 000	2006	Phase I: workplaces and public places	stratified by nonsmokers	−5.51% [95% CI: −13.84, 3.63]	Among currently smoking mothers: Postban: Preterm birth rates reduced by 5.51%.
					preterm <37 weeks; very preterm <32 weeks	−15.44% [95% CI: 21.02, −9.47]	Among never smoking mothers: Postban: Preterm birth rates reduced by 15.44%.
					overall, −0.59% <sup>b</sup> [95% CI: −2.63, 1.49]; spontaneous, −3.24% [95% CI: −4.40, −2.07]	Phase I Postban: Preterm birth rates reduced by 0.59% overall and 3.24% for spontaneous preterm birth.	
				Phase II: restaurants	preterm <37 weeks; very preterm <32 weeks	overall: −2.28% [95% CI: −4.37, −0.15]; spontaneous, −3.69% [95% CI: −4.81, −2.55]	Phase II Postban: Preterm birth rates reduced by 2.28% overall and 3.69% for spontaneous preterm birth.
					preterm <37 weeks; very preterm <32 weeks	overall, −1.24% <sup>b</sup> [95% CI: −3.05, 0.60]; spontaneous, −3.36% [95% CI: −4.73, −1.9]	Phase III Postban: Preterm birth rates reduced by 1.24% overall and 3.36% for spontaneous preterm birth.
				all phases	preterm <37 weeks; very preterm <32 weeks	overall, −3.18% [95% CI: −5.38, −0.94]; spontaneous, −3.13% [95% CI: −4.37, −1.87]	All phases postban: preterm birth rates reduced by 3.18% overall and 3.13% for preterm birth.

<sup>a</sup>*p* < 0.05. <sup>b</sup>Not statistically significant; absolute change.

Time trend in rate of spontaneous preterm deliveries (with 95% confidence interval) in Flanders, 2002–11, with vertical lines indicating stepwise implementation of smoke-free legislation.



**Figure 2.** Change in rate of spontaneous preterm deliveries before and after the sequential implementation of three smoking bans in Flanders, Belgium between 2006 and 2010. Reproduced from Impact of a stepwise introduction of smoke-free legislation on the rate of preterm births: analysis of routinely collected birth data, Cox, B., Martens, E., Nemery, B., Vangronsveld, J., and Nawrot, T. S, Vol. 346, Page f441, Copyright 2013 with permission from BMJ Publishing Group Ltd.<sup>7</sup>

preterm birth rates after the implementation of smoking bans. Been et al. included data from four of the five studies summarized here in their meta-analysis of over 1.3 million births.<sup>6</sup> They found a significant reduction of  $-10.4\%$  [95% CI:  $-18.8\%$ ,  $-0.2\%$ ] in the rate of preterm births after the implementation of smoking bans.<sup>6</sup>

A key limitation of this group of studies looking at the effects of smoking bans on preterm birth rates is the fact the majority of them were not able to differentiate the effects of the bans on active maternal smoking exposure versus secondhand exposure because the researchers used previously collected health data and had no input into what questions were asked of the mothers.<sup>7,8,10</sup> Only two of the studies were able to report on preterm birth rates for women who never smoked versus current smokers.<sup>9,11</sup> Bhardawaj et al. reported no significant reduction for either group (but the stratified estimates were not shown), while MacKay et al. showed a significant reduction in preterm birth rates for both current smokers and never-smokers.<sup>9,11</sup> Interestingly, they reported that never-smokers showed a three-fold greater reduction in preterm births rates at  $-15.44\%$  [95% CI:  $-21.02\%$ ,  $-9.47\%$ ] than current smokers at  $-5.51\%$  [95% CI:  $-13.84\%$ ,  $3.63\%$ ].<sup>9</sup> This underscores the substantial need for more studies that are able to specifically examine the effects of smoking bans on nonsmoking women. Such studies could use smoking bans as a proxy for reduced ETS exposure and eliminate similar exposures that active smokers receive from their direct smoking.

### ■ ETS EXPOSURE ASSESSMENT METHODS

In addition to the small group of studies using the smoking ban approach to study changes in preterm birth rates at a population level, a considerably larger group of studies has taken the approach of directly measuring maternal ETS exposure and associations with preterm birth within particular study populations. These studies faced substantial challenges in developing methods for accurately measuring ETS exposure among pregnant women.<sup>4</sup> These challenges exist because assessing individual exposure accurately is difficult and many individual variables affect bodily absorption and disposition of ETS. A few

of these challenges include assessing intensity and duration of exposure, repetitive or noncontinuous exposure, cumulative effects, knowledge of exposure, indoor ventilation, and outdoor weather patterns.<sup>4,12</sup> Despite these challenges, the number of studies assessing ETS and preterm birth has markedly increased since 2000 by utilizing methods that have been evolving since they were first conceived in the 1960s.

### ■ SELF-REPORTING: INTERVIEWS AND QUESTIONNAIRES

The most widely used method for assessing exposure to ETS has been through self-reporting by utilizing either interviews or self-reported questionnaires. The self-reporting methodology has many strengths including its noninvasive nature, its cost-effectiveness and feasibility in larger studies and developing countries, and its ease of obtaining large amounts of information in short periods of time. In particular, recent studies have done a better job than older studies of more accurately classifying and stratifying exposure levels over the course of the entire pregnancy and categorizing the severity of preterm birth. These efforts aim to establish a dose–response relationship, account for confounding, and gain detailed information on exposure sources.

Despite the widespread use of self-reporting, many limitations for this method exist. These include early studies using too few simplistic questions about exposure, no classification of levels, location, intensity, or duration of ETS exposure, differences in how variables are defined and stratified, and a wide array of methods for obtaining self-reported information.<sup>12–17</sup> In addition, inaccuracies in self-reporting have led to high misclassification rates between nonETS-exposed and ETS-exposed pregnant women as shown by studies using biochemical validation of self-reported ETS exposure information.<sup>18</sup> The limitations that exist with using this method alone to classify ETS exposure have prompted the development and use of another assessment method, biomarkers.

### ■ ETS EXPOSURE MEASUREMENTS: BIOMARKERS

Biomarkers are measurable indicators of the presence of substances or their metabolites in the human body.<sup>19</sup> In contrast to self-reported exposure information, which can offer imprecise information on potential exposure levels, biomarkers provide tangible proof of exposure and quantifiable measurements of the amount absorbed into the body from the exposure.<sup>4</sup> For a specific biomarker to provide an accurate and precise quantification of an exposure, it should ideally meet several criteria. These criteria include specificity to the exposure, a relationship to the specific substance within the exposure that is thought to cause adverse health outcomes, a sufficiently long half-life, and a laboratory technique for quantification with a reasonable level of detection.<sup>20</sup>

Cotinine, the primary metabolite of nicotine, has emerged as both a highly accurate and practical biomarker to use when assessing ETS exposure because it has been shown to have a high sensitivity and specificity to tobacco smoke.<sup>20</sup> Cotinine is a relatively stable molecule specific to tobacco smoke exposure. Its half-life is approximately 20 h, making it detectable in serum, saliva, and urine for 3 to 4 days after exposure and in hair for 1–2 months.<sup>21,22</sup> Cotinine, as a metabolite of nicotine, is also readily distributed in all tissues, which implies that its presence indicates exposure in all compartments of the body.<sup>20,23,24</sup> Even early studies confirmed the high correlation of cotinine levels in



Table 2. Summary of Maternal ETS Exposure and Preterm Birth Studies

first author	year	cohort size	location of study	exposure assessment method	ETS exposure definition	association?	odds ratio
Martin <sup>12</sup>	1986	3891	USA: MA	in-person interview	exposed more than 2 h per week	no	NO OR given: ETS exposed preterm birth rate: 4.64%; ETS nonexposed preterm birth rate: 4.66%
Mathai <sup>28</sup>	1992	994	India	in-person questionnaire	1 household member smokes	no	NO OR; ETS exposure: 5–8% preterm birth rate; non-ETS exposed 3–8% preterm birth rate
Fortier <sup>14</sup>	1994	4644	Canada	phone interview, post pregnancy (up to 6 weeks)	exposed more than 1 h per week	no	ETS exposed at work: 0.92 [CI: 0.64–1.31]
						no	ETS exposed at home: 0.93 [CI: 0.58–1.51]
						no	ETS exposed at home and work: 0.98 [CI: 0.56–1.73]
Windham <sup>17</sup>	2000	4454	USA: CA	phone interview, early pregnancy	exposed more than 1/2 h per day	yes (not significant)	Low ETS (05–6.5hrs/day) and Very Preterm (<35wks): 1.5 [CI: 0.90–2.5];
						yes (not significant)	Low ETS (05–6.5hrs/day) and Preterm (<37wks): 1.1 [CI: 0.79–1.6]
						yes (not significant)	High ETS (>7 h/day) and Very Preterm (<35wks): 2.4 [CI: 1.0–5.3]
						yes (not significant)	High ETS (>7 h/day) and Preterm (<35wks): 1.6 [CI: 0.87–2.9]
Jaakkola <sup>26</sup>	2001	389	Finland	questionnaire at clinic, post pregnancy and maternal hair nicotine, post pregnancy	<0.75 $\mu\text{g/g}$ hair nicotine concentration	yes (not significant)	Hair nicotine: (0.75–<4.00 $\mu\text{g/g}$ ): 1.30 [CI: 0.30–5.58]
						yes	Hair nicotine: (>4.00 $\mu\text{g/g}$ ): 6.12 [CI: 1.31–28.7]
						no	ETS at home: 0.65 [CI: 0.06–6.81]
						yes (not significant)	ETS at work: 2.35 [CI: 0.50–11.1]
						yes	ETS exposure home/work: 8.89 [CI: 1.05–75.3]
Kharazmi <sup>27</sup>	2004	3669	USA: CA	questionnaire at clinic, post pregnancy and maternal serum cotinine (15–19 weeks pregnant)	<0.026 ng/mL serum cotinine concentration	no	Serum cotinine: (0.026–0.053 ng/mL): 0.90 [CI: 0.48–1.66]
						no	(0.054–0.0096 ng/mL): 0.76 [CI: 0.40–1.42]
						no	(0.097–0.235 ng/mL): 0.68 [CI: 0.35–1.30]
						yes	(>0.235 ng/mL): 1.78 [CI: 1.01–3.13]
Ashford <sup>29</sup>	2010	210	USA: KY	questionnaire and hair maternal cotinine	answered yes to any exposure question	yes (not significant)	ETS exposure: 2.3 [CI: 0.96–5.96]
Crane <sup>13</sup>	2011	11 852	Canada	questions asked by physician at first prenatal visit	any exposure-cutoff not defined	Very Preterm (<34 Wks), yes (not significant); Preterm (<37 Wks), not reported	Very Preterm (<34 Wks): 1.87 [CI: 1.00–3.53]
Qiu <sup>16</sup>	2013	10 094	China	in-person interview, post pregnancy (1–3 days postdelivery)	exposed more than 1/2 h per month	yes	ETS During Whole Pregnancy: Very Preterm (<32 Wks): 1.98 [CI: 1.41–2.27];
						no	Moderate Preterm (32–36 wks): 0.98 [CI: 0.81–1.19]
						yes (not significant)	Preterm (32–36wks): 1.12 [CI: 0.95–1.32]
Miyake <sup>15</sup>	2013	1565	Japan	2 questionnaires (1 during pregnancy, 1 post pregnancy)	at least 1 person in home or at work smoked during first questionnaire	no	ETS at home: 0.91 [CI: 0.48–1.65]
						no	ETS at work: 0.97 [CI: 0.36–2.23]

bodily fluids and known tobacco exposure. In a study conducted in 1983, Haley et al. found that daily cotinine levels in

plasma and saliva samples taken from smokers correlated very highly with the number of cigarettes they reported smoking

when compared with another metabolite.<sup>25</sup> Although biomarkers have been shown to be highly effective tools for measuring ETS exposure, they alone still cannot solely be used to assess ETS exposure because they do not provide any contextual information about the possible sources of ETS exposure or information about variables that could confound any associations discovered between ETS exposure and preterm birth.<sup>20</sup>

To address the deficits in both self-reporting and biomarker methodology, the best study design that has emerged in the past decade is one that utilizes a combination of both methods to capture the most accurate information about ETS exposure.<sup>26</sup> Carefully considered and detailed questions about ETS exposure and possible confounders are combined with biomarker measurements of cotinine in bodily fluids or nicotine in hair. Although the combined study design is the gold standard, for very large epidemiology studies and studies where biochemical validation is not feasible, well-designed self-reported-based study designs are still used and viewed as acceptable. Finally, a few other methods for ETS exposure assessment have undergone limited testing but show great potential to detect ETS exposure even more precisely and accurately than the methods currently available. One method, the use of personal exposure monitoring devices, has been shown to accurately capture ETS exposure. However, the technology needs improvement, and the costs are substantial.<sup>4,20</sup>

## ■ EVIDENCE FROM DIRECT ETS EXPOSURE ASSESSMENT AND PRETERM BIRTH STUDIES

Studies that have taken the approach of directly measuring maternal ETS exposure and incidences of preterm birth within particular study populations have largely utilized the exposure assessment methods outlined above. To characterize the results thus far of maternal ETS exposure and preterm birth studies, we searched PubMed to identify relevant studies. Different combinations of keywords were entered into the regular search bar. These keywords included “environmental tobacco smoke”, “ETS”, “passive smoke”, “secondhand smoke”, “passive tobacco smoke”, “preterm birth”, “birth outcomes”, “neonatal outcomes”, “gestation”, and “premature”. Several studies were identified using the works cited section of the Meeker and Benedict review and several of the original research articles.<sup>4</sup> All studies that examined an association between ETS exposure and preterm birth were included in the summary. In addition to the primary predictor and outcome of interest, some of the studies included other predictors such as active smoking and other outcomes such as birth weight; however, only the relevant parts of those studies were reviewed. Ultimately, ten studies were included in the analysis.<sup>12–17,26–29</sup>

Overall, the studies assessing the association between ETS exposure and preterm birth showed inconclusive results. The results are summarized in Table 2. All of the studies except Martin and Bracken and Mathai et al. used logistic regression for statistical analysis and included variables that could potentially confound any association found between ETS exposure and preterm birth. The odd ratios comparing the odds of giving birth prematurely among non-ETS exposed versus different levels of ETS exposed pregnant were obtained.<sup>13–17,26,27,29</sup> Some of the studies, such as Martin and Bracken, Crane et al., and Kharrazi et al., conducted initial univariate analyses between the individual maternal characteristics and ETS exposure status, which were displayed on the distribution tables, to identify possible confounders. They used *t* tests or Wilcoxon

sign-ranked tests for continuous variables and Chi square or Fisher's exact tests for categorical variables.<sup>12,13,27</sup> The most commonly included confounders were parity, maternal age, BMI, employment status, and education level (each of 4 studies), history of pregnancy complications, sex of baby, alcohol consumption, and marital status (each of 3 studies).<sup>13–17,26,27,29</sup>

The earlier studies that used simple self-reporting methodology all showed no significant association between ETS exposure and preterm birth.<sup>12,15,28</sup> The more recent studies that use more sophisticated self-reporting methodology showed mixed results. The Windham et al. study calculated odds ratios for four groups stratified based on high and low ETS exposure and preterm and very preterm birth. The odds ratio for very preterm and preterm births, respectively, among mothers with high versus low ETS exposure were 2.4 [95% CI: 1.0–5.3] and 1.5 [95% CI: 0.90–2.5].<sup>17</sup> Two other studies, Qiu et al. and Crane et al., both evaluated large cohorts of over 10 000 people each and saw similar results. Qiu et al. reported an odds ratio of 1.98 [95% CI: 1.41–2.76], and Crane reported 1.87 [95% CI: 1.00–3.53], specifically for their respective very preterm birth categories.<sup>13,16</sup> Neither study found strong or significant associations for preterm or moderate preterm birth categories.<sup>13,16</sup> Miyake et al. also found no association.<sup>15</sup>

Studies that combined self-reporting and biomarker measurements in their study designs collectively showed results that indicate a relationship between preterm birth and ETS exposure. One study, Ashford et al., which used maternal hair cotinine and a questionnaire to assess ETS exposure, reported a trending association with an odds ratio of 2.3 [95% CI: 0.96–5.96].<sup>29</sup> Kharrazi et al. used an extremely sensitive detection assay for serum cotinine measurements and observed an odds ratio for preterm birth of 1.78 [95% CI: 1.01–3.13], but only within the group with the highest ETS exposure confirmed by serum cotinine levels above 0.235 ng/mL.<sup>27</sup> The results of Kharrazi et al. suggested that very low ETS exposure is not associated with preterm birth, but higher levels may be associated.<sup>27</sup> Jaakkola et al. used hair nicotine to quantify ETS exposure and reported the highest odds ratio of these studies, 6.12 [95% CI: 1.31–28.7], suggesting a strong association between ETS exposure above 4.00 µg/g in hair and preterm birth. However, below that threshold, the results were not significant.<sup>26</sup> Jaakkola et al. also simultaneously calculated odds ratios based on self-reported ETS exposure from the same study participants. Only those who reported ETS exposure both at home and at work had a statistically significant odds ratio of 8.89 [95% CI: 1.05–75.3], while the other odds ratios were not significant.

Our assessment of studies examining the association between ETS exposure and preterm birth differs somewhat from a meta-analysis conducted by Leonardi-Bean et al., which concluded that there is no association between ETS exposure and preterm birth.<sup>30</sup> The meta-analysis included studies published prior to 2008 and did not include results based on the stratification of different prematurity categories such as very preterm.<sup>30</sup> In our assessment, we included several large studies published after 2008 that reported either a significant or trending association between ETS exposure and very preterm birth categories.<sup>13,16</sup> This evidence, in addition to the evidence of a positive association from several combined self-reporting and biomarker studies, led us to interpret the evidence available thus far as being inconclusive.<sup>26,29</sup>

## DISCUSSION AND CONCLUSION

Preterm birth is a severe adverse health outcome that may have lifelong health implications for babies. Assessing possible causes of increased risk of preterm birth is essential for identifying public health interventions that can reduce incidence of preterm birth.<sup>6</sup> In the past several decades, numerous studies have examined a potential association between ETS and risk of preterm birth through different strategies and approaches. The small number of studies that have used the approach of examining preterm birth trends before and after the implementation of antismoking legislation have largely demonstrated a significant trend of decreasing population-level preterm birth rates. Unfortunately, most of these studies do not differentiate the impact of maternal smoking from ETS in their analyses, making it difficult to specifically evaluate the effects of smoking bans on ETS exposure. The larger group of studies that have taken the approach of directly measuring maternal ETS exposure and calculating associations of ETS and preterm birth within particular study populations has had much more inconclusive results. They have utilized both self-report exposure assessment methods and biomarker measurements.<sup>4,20,26</sup> Although the information revealed about the association between ETS exposure and preterm birth in the studies that have been conducted thus far serves as a starting point, more research must be done to clarify the nature of a potential association and to develop appropriate public health interventions. On the basis of this review, we propose that more studies specifically evaluating rates of preterm birth among non-smoking women before and after smoking bans are needed as well as use of better ETS exposure assessments methods in studies measuring maternal ETS exposure.

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### Notes

The authors declare no competing financial interest.

## ABBREVIATIONS

ETS, environmental tobacco smoke

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