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Review

Maternal Active Smoking During Pregnancy and Low Birth Weight in the Americas: A Systematic Review and Meta-analysis

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Abstract

Introduction: Smoking during pregnancy may negatively impact newborn birth weight. This study investigates the relationship between maternal active smoking during pregnancy and low birth weight in the Americas through systematic review and meta-analysis.

Methods: A literature search was conducted through indexed databases and the grey literature. Case-control and cohort studies published between 1984 and 2016 conducted within the Americas were included without restriction regarding publication language. The article selection process and data extraction were performed by two independent investigators. A meta-analysis of random effects was conducted, and possible causes of between-study heterogeneity were evaluated by meta-regressions and subgroup analyses. Publication bias was assessed by visual inspection of Begg's funnel plot and by Egger's regression test.

Results: The literature search yielded 848 articles from which 34 studies were selected for systematic review and 30 for meta-analysis. Active maternal smoking was associated with low birth weight, $OR = 2.00$ (95% CI: 1.77–2.26; $I^2 = 66.3\%$). The funnel plot and Egger's test ($p = .14$) indicated no publication bias. Meta-regression revealed that sample size, study quality, and the number of confounders in the original studies did not account for the between-study heterogeneity. Subgroup analysis indicated no significant differences when studies were compared by design, sample size, and regions of the Americas.

Conclusion: Low birth weight is associated with maternal active smoking during pregnancy regardless of the region in the Americas or the studies' methodological aspects.

Implications: A previous search of the major electronic databases revealed that no studies appear to have been conducted to summarize the association between maternal active smoking during pregnancy and low birth weight within the Americas. Therefore, this systematic review may help to fill the information gap. The region of the Americas contains some of the most populous countries in the world; therefore, this study may provide useful data from this massive segment of the world's population.

Introduction

The prevalence of active smoking among pregnant women is estimated to be up to 25% worldwide.[1] In countries of the Americas, this prevalence varies according to the regions. In 2010, the prevalence of active smoking among pregnant women in the United States was 10.7% varying between 5.1% and 28.7% depending on the country's State.[2] In the same year, this prevalence in Canada was 23.0%, reaching up to 59.3% in the Northern Territories.[3] A study conducted in seven Latin American countries between 2001 and 2012 showed prevalence of tobacco consumption among pregnant women equals to 2.1% (95% confidence interval [CI]: 1.2–3.2).[4] In Mexico, the prevalence of active smoking during pregnancy was 3.0% in 2013[5] and in Brazil it varied between 9.0% and 23.3% between 1991 and 2011 according to the investigated city.[6–9]

Maternal active smoking during pregnancy negatively impacts birth weight and increases the risks of miscarriage, ectopic pregnancy, placental abruption, preterm birth, intrauterine growth restriction, congenital anomalies, respiratory disorders, and behavioral impairments.[10]

Birth weight is an easily obtained measure of gestational conditions and fetal development. Low birth weight is defined by the World Health Organization as a birth weight bellow 2500 grams regardless of gestational age.[11] Low birth weight interferes with newborn survival and negatively affects both childhood and adult life. It can be life-threatening in the neonatal period, can predispose to infections, delayed fetal growth and development, and can result in future predisposition to metabolic chronic diseases.[12–14]

The average incidence of low birth weight in developed countries is 7%, while in developing countries it is approximately 15%.[15] Low birth weight may result from a shorter gestational period (prematurity), restriction in intrauterine growth or from a combination of both. Some factors associated with these events include social, economic, cultural, genetic, nutritional and psychological issues, as well as maternal lifestyle choices.[16]

The frequency of smoking during pregnancy has fallen during recent years. However, smoking is still an important risk factor for low birth weight, mainly in developed countries.[17] The negative effects of maternal smoking on birth weight are due to the action of nicotine. This substance acts upon the maternal cardiovascular system, releasing catecholamines, which provoke tachycardia, peripheral vasoconstriction, and decreased placental flow. This results in low levels of oxygen and nutrients delivered to the placenta. This can substantially decrease cytotrophoblast mitotic potential, thus causing fetal growth restriction.[18–21]

Tobacco smoking by women at childbearing age and its negative outcomes have been a concern in maternal-fetal medicine since the 1960s.[22] Most primary studies have shown measures of association between smoking and low birth weight. However, because of population and methodological differences, these measures may vary among countries. Therefore, we aim to conduct a systematic review with meta-analysis to investigate the relationship between maternal active smoking and low birth weight in the region of the Americas.

Methods

This study is registered at the International Register of Prospective Systematic Reviews (PROSPERO) under the CRD number 42015027690.

Eligibility Criteria

We included case-control and cohort studies that examined the relationship between maternal active smoking[23] and low birth weight and that were conducted in countries of the Americas. Low birth weight was defined as a birth weight below 2500 grams.

We excluded pilot studies, studies conducted with illegal drug users, with Human Immunodeficiency Virus (HIV), positive women, with homeless people, and studies involving ethnicity.

Study Selection

The literature search for potential eligible studies was performed in April 2016 using the following electronic databases: Medline, Embase, LILACS, SciELO, Web of Science, and Scopus. There were no restrictions regarding language or publication date. The retrieved studies were assessed and classified according to the eligibility criteria.

The search strategy used for MEDLINE (via PubMed) was: ("smoking" [Mesh] OR "smoking" [TIAB] OR "tobacco smoking" [TIAB] OR "tobacco use disorder" [TIAB]) AND ("Pregnancy" [Mesh] OR "Pregnancy" [TIAB] OR "Pregnant Women" [TIAB] OR "gravidity" [TIAB] OR "maternal exposure" [Mesh] OR "maternal exposure" [TIAB]) AND ("Infant, Low Birth Weight" [Mesh] OR "Infant, Low Birth Weight" [TIAB] OR "Low Birth Weight" [TIAB]) AND ("case-control studies" [Mesh] OR "case-control studies" [TIAB] OR "retrospective studies" [Mesh] OR "retrospective studies" [TIAB] OR "case-control study" [TIAB] OR "Study, case-control" [TIAB] OR "Studies, case-control" [TIAB] OR "case-comparison studies" [TIAB] OR "cohort studies" [Mesh] OR "cohort studies" [TIAB]) AND ("Caribbean region" [TIAB] OR "Central America" [TIAB] OR " Belize" [TIAB] OR "Costa Rica" [TIAB] OR "El Salvador" [TIAB] OR "Guatemala" [TIAB] OR "Honduras" [TIAB] OR "Nicaragua" [TIAB] OR "Panama" [TIAB] OR "Gulf of Mexico" [TIAB] OR "North America" [TIAB] OR "Canada" [TIAB] OR "Greenland" [TIAB] OR "Mexico" [TIAB] OR "United States" [TIAB] OR "South America" [TIAB] OR "Argentina" [TIAB] OR "Bolivia" [TIAB] OR "Brazil" [TIAB] OR "Chile" [TIAB] OR "Colombia" [TIAB] OR "Ecuador" [TIAB] OR "French Guiana" [TIAB] OR "Paraguay" [TIAB] OR "Peru" [TIAB] OR "Suriname" [TIAB] OR "Uruguay" [TIAB] OR "Venezuela" [TIAB] OR "Latin America" [TIAB]). This search strategy was considered the pattern strategy for this review and was adapted to other electronic databases. In addition, reference lists from the selected studies and from the grey literature were hand searched, and when necessary, the authors were contacted to provide more information about the studies.

After the exclusion of duplicate studies, two reviewers (PPdSP and FAFM) independently reviewed the titles and abstracts of the studies. All disagreements were settled by consensus between the authors.

Data Extraction

A standardized form was used to extract the following data from the studies: title, first author name, country and city of the study, dates of data collection and publication of the article, sample characteristics (size, sampling method, and age of the women), measurement of active smoking and outcome, duration of follow-up in cohort studies, confounding variables, and the estimated risk with respective CIs. The authors (PPdSP and FAFM) independently performed the data extraction.

Quality Assessment

The validated Newcastle-Ottawa Scale was used to analyze the methodological quality of the included studies.[24] This scale is recommended by the Cochrane Collaboration for use with observational studies, such as cohort and case-control designs. The scale addresses three perspectives: (1) group selection, (2) group comparability, and (3) determination of any exposure or outcome for case-control or cohort studies. Each question receives one point (marked as a star *), except for the comparability item, which may receive one or two points. The maximum total score is nine points. A total score between one and three indicates a low quality study, between four and six, a moderate quality study, and from seven to nine points, a high quality study.

Data Synthesis

The variables of interest were infants with low birth weight born to active smoking and nonsmoking women. The odds ratio (*OR*) was the risk estimation measure, with a 95% CI. A random effect meta-analysis was performed using the inverse variance method.

The between-study heterogeneity was assessed by using a chi-squared test with a significance level of $p < .10$. This p value was adopted instead of the frequently used $p < .05$ because the chi-squared test has low power when a small number of studies or small sample sizes are considered in meta-analyses.[25] The I-squared statistics (I^2) was assessed according to Higgins and Thompson.[25] When the I^2 was greater than 50% it was classified as high heterogeneity, when it was between 25% and 50% as moderate heterogeneity, and when it was less than 25% as low level of heterogeneity.

Possible causes for heterogeneity between studies were investigated through meta-regression, subgroup, and sensitivity analysis. The meta-regression investigated the influence of the methodological quality score, sample size, and number of confounders in the studies. The subgroup analyses were performed by: regions of the Americas (North, Central, and South), type of study (prospective cohort vs. retrospective cohort vs. case-control), sample size (<1000 vs. >1000) and study quality (moderate vs. high).

Publication bias was assessed by the visual inspection of Begg's funnel plot and by the Egger's regression test at $p < .05$.[26] We used STATA software (version 13.0) for all statistical analyses.

Results

Study Selection

The search of databases yielded 881 studies, and 11 were obtained by the reference lists of selected studies (Figure 1). Of these, 239 were duplicates that were excluded from the analysis. After the independent assessment of titles and abstracts, 57 studies were selected for full-text reading, resulting in 34 studies included in the review. These 34 studies are covered in only 33 articles, as one article gave information about two studies.[27]

Study Characteristics

The total population of the original studies was 3 259 833 women (Table 1). Nineteen studies were conducted within South America, 10 in North America, and five in Central America. Most studies included women regardless of their age, and in only one study the sample set consisted of women younger than 19 years.[22] From 34 studies, 26 took place in hospitals or maternity wards, six in settings such as clinics and primary care units,[30–35] and three collected data from secondary databases.[29,36,37]

The oldest study was published in 1986 in the United States of America.[22] Five studies were published in the 1990s[30,38,39,45,46] and the rest was published between 2000 and 2016. Eighteen articles are case-control studies, eleven are retrospective cohort studies, and five are prospective cohort studies.

Eleven studies contained data on exposure and outcome, making it possible to calculate an association measure. Eight studies showed only gross measure data,[27,31,40–42,44,53,58] seven contained adjusted measure data,[22,30,36–39,43] and seven contained both gross and adjusted measure data.[28,34,45,48,51,55,57] The most frequently occurring

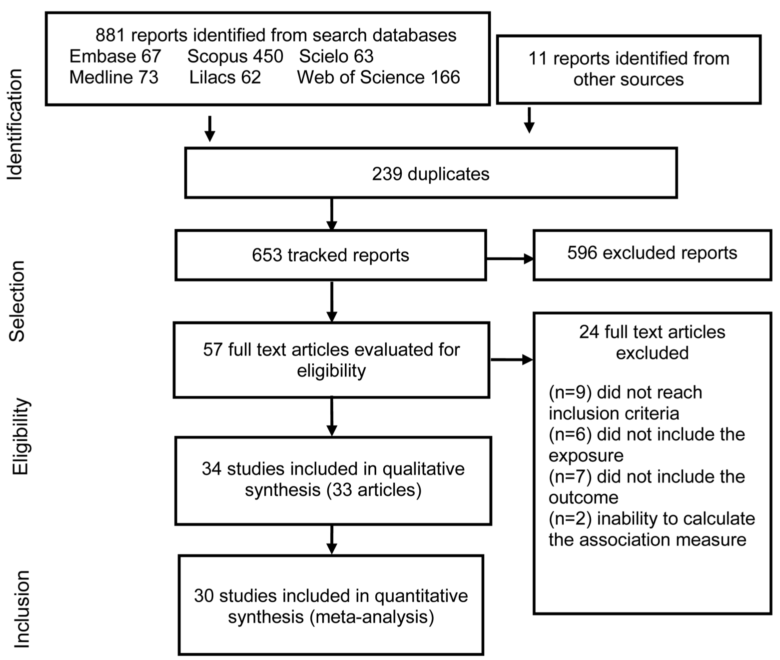

Figure 1. Flowchart of article eligibility and final inclusion in this systematic review.

Table 1. Characteristics of the Included Studies

First author/year	Country	Data collection period	*N*	Data collection site	Data collection source	Quality of the study
Prospective cohort						
Veloso, 2014[27]	Brazil	1997–1998	2426	Public and private hospitals	Database, interview and Medical record	8
Veloso, 2014[27]	Brazil	2010	5040	Public and private hospitals	Database, interview and Medical record	8
Solla, 1997[38]	Brazil	1987–1989	1023	Public and private maternities	Interview and medical record	8
Shiono, 1995[30]	United States	1984–1989	7470	University clinics	Interview	7
McDonald, 1992[39]	Canada	—	40 445	Public and private hospitals	Database	5
Retrospective cohort						
Lundsberg, 2015[31]	United States	1996–2000	4484	Hospitals and clinics	Interview and medical record	7
Dietz, 2010[36]	United States	2002	2 995 747	Database	Database	9
Mehaffey, 2010[40]	Canada	2003–2005	918	Hospital	Medical record	6
Pogodina, 2009[41]	United States	2004–2005	2206	University hospital	Interview	6
Tiago, 2008[42]	Brazil	2003–2005	489	University hospital	Medical record	6
Silva, 2006[43]	Brazil	1994	2749	Public and private hospitals	Database, interview and medical record	8
Okah, 2005[37]	United States	1990–2002	78 358	Database	Database	9
Barbieri, 2000[44]	Brazil	1978–1994	5492	Public and private hospitals	Interview e anthropometry	7
Horta, 1997[45]	Brazil	1993	5166	Public and private maternities	Interview and medical record	9
Silva, 1992[46]	Brazil	1978–1979	6557	Public and private hospitals	Interview e anthropometry	7
Scholl, 1986[22]	United States	1984	775	University hospital	Database	7
Case-control						
Souza, 2016[47]	Brazil	2009–2011	951	Public hospitals	Interview and hospital record	7
Fonseca, 2012[48]	Brazil	2004–2008	1046	University hospital	Hospital record	9
Pérez-Rivera, 2010[32]	Cuba	2000–2008	1046	Public primary care unit	Medical record	6
López, 2010[33]	Cuba	2003–2008	82	Public primary care unit	Medical record	5
Franciotti, 2010[49]	Brazil	2009	244	Public hospital	Interview and Medical record	5
Coutinho, 2009[34]	Brazil	1986–2004	43 944	Public primary care unit	Medical record	7
Cruz, 2009[50]	Brazil	2003	548	Public hospitals	Interview and medical record	5
Araújo, 2007[51]	Brazil	1998–2004	600	Public hospital	Medical record	7
Siqueira, 2007[52]	Brazil	2004–2005	1277	Public hospital	Interview and medical record	5
Bassani, 2007[53]	Brazil	—	915	Public hospital	Interview and medical record	5
Hujoel, 2006[29]	United States	1993–2000	3965	Database	Database	6
Moliterno, 2005[28]	Brazil	—	151	Public hospital	Interview and medical record	5
Cruz, 2005[54]	Brazil	2003	302	Public hospital	Interview and medical record	5
Torres-Areola, 2005[55]	Mexico	1996	728	Public hospitals	Interview and medical record	7
Domínguez, 2005[35]	Cuba	2001–2003	119	Primary care unit	Hospital record	5
Escobar, 2002[56]	Cuba	1997–2002	2201	Public hospital	Interview and medical record	7
Bicalho, 2002[57]	Brazil	1994–1995	708	Public maternity	Interview and anthropometry	7
Valladares, 2002[58]	Nicaragua	1996	303	University hospital	Interview	5

confounding variables in the original studies were: age, income, education, marital status, pre-gestational weight, number of pregnancies, previous history of low birth weight, gestational morbidities, and the number of prenatal consultations.

The original studies collected information about maternal active smoking during pregnancy through interviews, patient records, and databases. In most studies, birth weight was collected from patient records, medical records, and databases. Anthropometric measurements were performed in only three studies.[44,46,57]

Nineteen studies were classified as high quality, and the mean quality score of the studies in this review was 6.6, with scores varying from 5 to 9 points. No studies were excluded due to low quality.

Association Between Maternal Active Smoking During Pregnancy and Low Birth Weight

Four studies with sample sizes larger than 40 000 that were included in the systematic review were excluded from the meta-analysis.[34,36,37,39] Thirty studies were included in the meta-analysis, resulting in a sample of 60 048 pregnant women who smoked tobacco during pregnancy. Low birth weight was associated with maternal active smoking during pregnancy with an *OR* of 2.00 (95% CI: 1.77–2.26; Figure 2).

Sensitivity Analysis and Publication Bias

The combined measure of association when the four studies with sample sizes larger than 40 000 were included was an *OR* of 1.86 (95% CI: 1.42–2.45; I^2 = 98.9%, $p < .001$). When the meta-analysis was performed without these studies an *OR* of 2.00 (95% CI: 1.77–2.26; I^2 = 66.3%, $p < .001$) was revealed. As the CIs of both *OR*s overlap, the differences between the measures were not statistically significant. However, as the heterogeneity (I^2) diminished, we decided to exclude the four studies from the meta-analysis. In the sensitivity analysis, studies with outlier *OR*s[33,35,40,50,58] showed that there were no changes in directionality and significance of the combined measure in the meta-analysis.

The Egger's test ($p = .14$) and the funnel plot indicated no publication bias among the studies included in the meta-analysis. No publication bias was found in the subgroup analyses (Egger's Test $p > .05$).

Heterogeneity and Subgroup Analysis

A high level of between-study heterogeneity was observed (I^2 = 66.3%, $p < .001$). The meta-regression revealed that sample size ($p = .66$), study quality ($p = .77$) and the number of confounders ($p = .43$) had no influence on the heterogeneity.

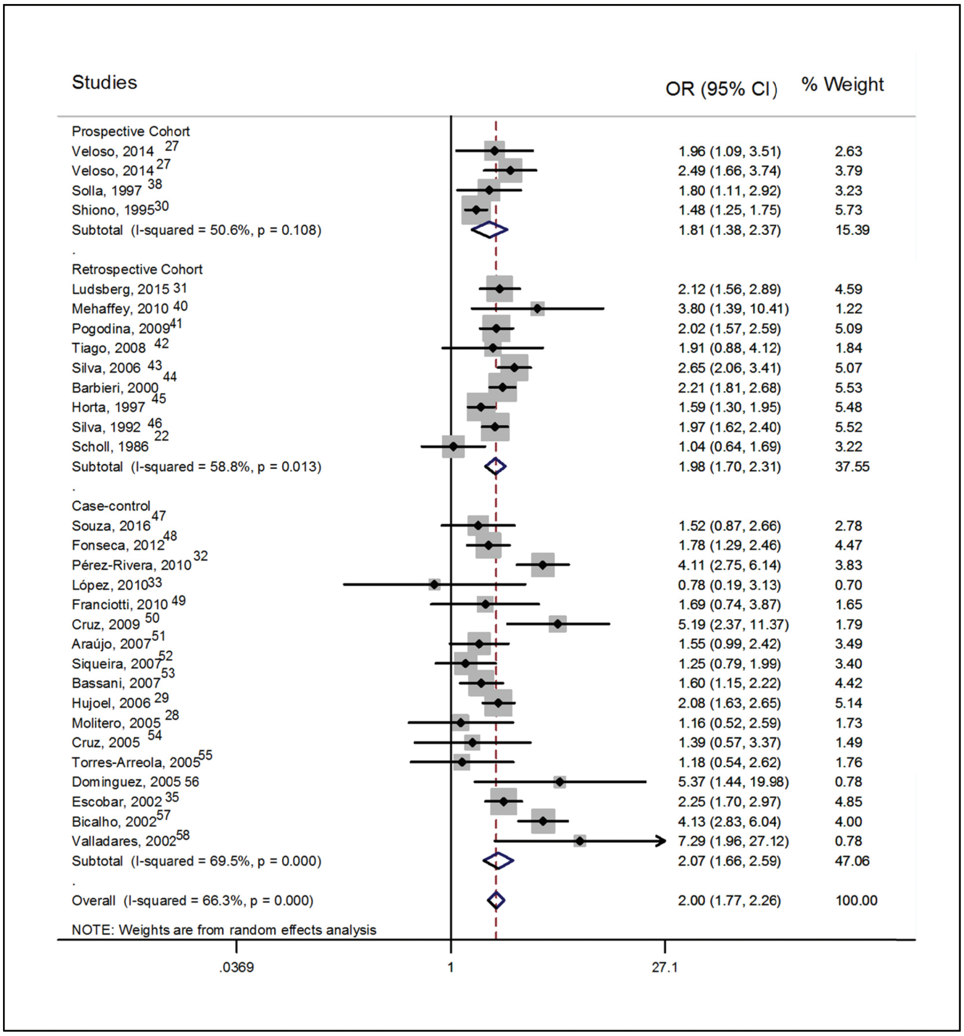

Figure 2. Effect of maternal active smoking during pregnancy on low birth weight.

Table 2. Subgroup Analysis of the Effect of Maternal Active Smoking During Pregnancy on Low Birth Weight

Variable	Groups	*N* of studies/ participants	*OR* (95% CI)	I^2	χ^2 *p* value
Sample size	<1000	16/ 8353	2.10 (1.54–2.87)	73.1%	.001
	≥1000	14/ 51 695	1.94 (1.74–2.16)	54.1%	.008
Study design	Prospective cohort	4/ 15 959	1.81 (1.38–2.37)	50,6%	.108
	Retrospective cohort	9/ 29 426	1.98 (1.70–2.31)	58.8%	.013
	Case-control	17/ 14 663	2.07 (1.66–2.59)	69.5%	.001
Methodologic quality	Moderate	14/ 12 042	2.16 (1.68–2.77)	63.3%	.001
	High	16/ 48 006	1.94 (1.68–2.24)	69.6%	.001
Region of the Americas	South	18/ 35 987	1.97 (1.70–2.28)	60.3%	.001
	North	7/ 20 836	1.75 (1.42–2.10)	62.9%	.013
	Central	5/ 3225	3.07 (1.80–5.25)	67.1%	.016

CI = confidence interval; *OR* = odds ratio.

In the subgroup analysis (Table 2), maternal active smoking during pregnancy remained associated with low birth weight even when the studies were grouped and compared by sample size (fewer or more than 1000 participants), study design (prospective cohort, retrospective cohort or case-control), study quality (moderate or high quality), and region of the Americas (South, Central or North).

The level of heterogeneity in the subgroups was also classified as high ($I^2 > 50\%$ and $\chi 2 < 0.10$). It is worth noting that the category of prospective cohort studies (in the study type subgroup) presented an I^2 of 50.6% indicating a high level of heterogeneity, even though it has presented a borderline value in the chi-square test ($p = .108$).

Discussion

The seminal study about the effect of smoking on birth weight was conducted by Simpson in 1957 in California.[59] Currently, there seems to be evidence that maternal active smoking during pregnancy contributes to a decrease in birth weight. However, the discussion on the topic is still important, given that the negative effects vary in magnitude among different populations.[60]

In this review, maternal active smoking during pregnancy was associated with low birth weight because low birth weight infants were twice as likely to be born to pregnant smokers compared to those born to nonsmokers.

In the subgroup analysis, this association remained unchanged, and there were no significant group differences in the *OR*s when measured by sample size, type of study, methodological quality, and regions of the Americas. Based on the results of meta-regressions and subgroup analyses, we kept in the meta-analysis the studies assessed as moderate methodological quality because they did not change the summarized association measure.

Both the meta-analysis and the subgroup analysis showed high levels of between-study heterogeneity. Overall, this heterogeneity occurs because of clinical differences inherent to population characteristics or due to study methodological issues.[61] The results of the meta-regression indicated that sample size, quality of study, and number of confounders did not explain the observed heterogeneity. It is likely that the heterogeneity between studies is related to specific population differences, such as genetics, socioeconomic level, nutritional and educational status, cultural and anthropometric parameters, and differences in access to health care during pregnancy and childbirth. However, this variety in population characteristics were not enough to account for significant differences in the association measure when subgroups were compared by region of the Americas.

No systematic review regarding active maternal smoking and low birth weight was found in the electronic database searches. A systematic review of six studies conducted in India and Bangladesh found that smokeless tobacco use during pregnancy increases the risk of low birth weight.[62] An integrative review of the literature published in 2014 also found higher rates of low birth weight among infants of mothers exposed to smokeless tobacco during pregnancy when compared with infants of mothers without similar exposure.[63] Another systematic review of two cohorts and one case-control study conducted in three Asian countries revealed an association between inhaled flavored tobacco, also known as shisha (water-pipe tobacco smoking), and low birth weight.[64] The association between maternal passive exposure to cigarette smoke and low birth weight was shown in two previous systematic reviews. However, in both studies, the summary estimates were very close to unity, warranting caution when interpreting the results.[65,66]

Study Limitations

In this review, active smoking was self-reported. However, it is known that many women may not reveal their true smoking status during pregnancy when they are facing the possibility of adverse fetal outcome. Information bias has been previously acknowledged as a cause of underestimated risk measures in self-reported studies.[66]

Studies show that differences in the type of consumption during pregnancy impact on the magnitude of the risk measure for low birth weight.[67–69] Information on the number and frequency of smoked cigarettes and the gestational age have not been analyzed in this review due to the lack of information available from the included studies. Only one study presented continuous data on birth weight in relation to the number of consumed cigarettes.[40] The information about the number of smoked cigarettes per day was categorized in seven studies[34,37,39,40,43,45,56] however, due to different ways of categorization, it was not possible to stratify the meta-analysis by type of consumption.

Out of the 34 studies included in this systematic review, only 14 have adjusted their association measure for confounding variables. Even though it is important, the variable second hand smoke exposure during pregnancy was considered by only one study.[57] Similarly, the use of alcohol and illicit drugs was adjusted in few studies.[28,30,37,39,45] Some other potential confounders that are highly complicated to be measured, for example, maternal stress and nutrition are not often considered in the analysis between active maternal smoking during pregnancy and low birth weight.[37]

Strengths of the Study

An extensive search for studies was carried out in the main literature sources, the grey literature, and the reference lists of the eligible articles. We contacted authors of studies when we needed to obtain extra data to carry out the meta-analysis. This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) tool guide, and the included studies were of high methodological quality, according to Newcastle-Ottawa criteria.

Conclusion

This systematic review reinforces the evidence that low birth weight is associated with smoking during pregnancy. Meta-regressions and subgroup analyses showed this association regardless of region of the Americas or methodological aspects such as sample size, study type, publication year, and number of confounders in the primary studies.

Maternal smoking during pregnancy is one of the most important modifiable risk factors that negatively impacts fetal growth and development. As relevant directions for future research, meta-analysis should be used to clarify the relationship between cigarettes consumption during pregnancy and other outcomes such as congenital malformations, cognitive development, behavioral development childhood cancer, risk of acute respiratory infections, ear problems, and more severe asthma.

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Declaration of Interests

None declared.

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