Association of E-Cigarette Use during Pregnancy with Adverse Birth Outcomes: A Meta-Analysis

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Abstract - With the increasing growth of the global e-cigarette market, more and more pregnant women use e-cigarettes as a safe alternative to traditional cigarettes. However, several studies have shown that e-cigarettes damage the human respiratory and cardiovascular systems and that nicotine is a risk factor for fetal development. To determine the association between e-cigarette use during pregnancy and adverse birth outcomes in pregnant women, we conducted a meta-analysis to assess the present evidence's strength. 735 studies were screened through PubMed, Web of Science, and Scopus databases. A total of nine articles met the inclusion criteria of this paper, and six articles were conducted for a meta-analysis after excluding studies with high heterogeneity. The six studies were further divided into two subgroups based on their differences in study types and population samples: one subgroup was three national case-control studies based on the United State Pregnancy Risk Assessment Monitor System (PRAMS) database, and the other included three small-scale regional studies. The small for gestational age (SGA) was identified as the indicator for assessing the association between e-cigarette use and adverse birth outcomes in pregnant women. We found a significant association of pregnant women using e-cigarettes during pregnancy with SGA (OR = 1.32, 95%CI = 1.03, 1.69). Low heterogeneity of multiple studies (I²=32%) and low publication bias as indicated by funnel plots. Our research proves that the risks of e-cigarette use during pregnancy to the unborn child are evident. Therefore, pregnant women need to be advocated to reduce their use of e-cigarettes during pregnancy.

Keywords: E-cigarette; Pregnant women; Small for gestational age; Meta-analysis

1. Introduction
E-cigarettes, also known as electronic nicotine delivery systems (ENDS), are a type of inhalation handheld atomizer that has emerged in the last decade. ENDS generally consist of a battery, a heating module, and a container of liquid that can be atomized. The main components of the nebulizing liquid are (1) carrier solvent: typically, propylene glycol and glycerin; (2) flavoring agents: ethyl maltol, vanillin, menthol; (3) nicotine [1]. Since the introduction of e-cigarettes, various types of e-cigarette manufacturers have been emerging around the world. In the United States alone, the prevalence of e-cigarettes among high school students increased from 1.5% in 2011 to 16% in 2015. As of 2018, 20.8% of U.S. high school students use e-cigarettes [2].

Curiosity is the most common reason driving young people to start trying e-cigarettes [3]. In addition, many people believe that e-cigarettes are safer than traditional cigarettes [4][5]. They tend to use e-cigarettes to help with smoking cessation because e-cigarettes do not produce carcinogens such as tar and polycyclic aromatic hydrocarbons (PAHs) found in tobacco. And the use of electronic cigarettes compared to traditional cigarettes is more “hidden,” such as not producing odor, and can be used anywhere, anytime. This is more convenient than traditional cigarettes. Similar to the general population, studies have shown that pregnant women generally believe that e-cigarettes are less harmful and can help them quit smoking. To reduce the risk of miscarriage and premature birth caused by smoking, pregnant women use e-cigarettes as an alternative to traditional cigarettes before or during pregnancy [6][7]. The prevalence of e-cigarettes among pregnant women is increasing and is approaching the prevalence of traditional cigarettes [8].

However, there has been a gradual increase in research on the harmful effects of e-cigarettes on humans. For the respiratory system, e-cigarette users have a higher prevalence of chronic obstructive pulmonary disease (COPD), asthma, and chronic bronchitis compared to non-smokers [9]. E-cigarettes are a significant risk for cardiovascular damage for the cardiovascular system, similar to traditional...
cigarettes. Compounds such as propylene glycol and glycerin in the atomizing fluid react with the flavoring agent in the e-cigarette when heated at high temperatures to produce carbonyl compounds. These carbonyl compounds can cause damage to cardiovascular tissue, which can lead to health problems such as endothelial dysfunction, vascular damage, platelet activation, and atherosclerosis [10].

Most of these studies were conducted based on the general population, and studies on vulnerable populations such as pregnant women are inadequate. Papers published before 2018 on the association between adverse pregnancy birth outcomes and pregnant women's e-cigarette use were largely based on animal and cellular experiments or extrapolated through the harm of nicotine to pregnant women. These studies do not give enough evidence about the health risks of e-cigarette use in pregnant women [11]. Therefore, our study aims to explore the relationship between e-cigarette exposure and adverse birth outcomes through a meta-analysis. By bringing together the latest research findings, we hope to provide sufficient evidence for the harm of e-cigarette use during pregnancy and to raise awareness of e-cigarette among the pregnant population. We also hope to engage more researchers in this topic.

2. Method
2.1. Search for literature
We searched PubMed, Web of Science, and Scopus for studies published. Two authors (Zhilin and Yi) participated in the literature search. Study selection and data extraction, and discrepancies were resolved through discussion. The search strategy was divided into two directions: (1) through the combination of different keywords for e-cigarettes with the study population; (2) by using e-cigarette keywords in combination with adverse birth outcomes. The specific search formula is as follows: (((TS=(electronic cigarette)) OR TS=(Electronic Nicotine Delivery Systems)) OR TS=(vaping)) OR TS=(E-Cigarette Vapor)) AND (((TS=(Pregnancy)) OR TS=(Pregnant women)) OR TS=(birth outcome)). The search years are 2014-2022. The language of the literature is restricted to English. Bilateral verification was used to assure the quality of the included literature. One author (Zhilin) reviewed the studies for compliance with the inclusion criteria. The study population and sample recruitment method were reviewed. The confounding factors involved in the article and the adjustment method were recorded in detail. The accuracy was checked by another author (Yi).

2.2. Inclusion and exclusion criteria
A study was considered eligible for inclusion if the following criteria were met: (1) the study was based on a population of pregnant women; (2) the purpose of the study focused on the association between e-cigarette smoking and adverse birth outcomes; (3) the study clearly grouped pregnant women based on smoking behavior during pregnancy; (4) the study provides the prevalence or number of adverse birth outcomes among different subgroups of pregnant women; (5) the characteristics of the study population were described. Only abstracts and unpublished results are not included. As such, a total of 9 published articles (Figure 1) were included in our analysis.
2.3. Quality Assessment

In this paper, the Cochrane bias assessment scale was used to assess the quality of the included studies (figure 2).

The assessment of allocation concealment selection bias examined whether the study validated or adjusted for self-reported smoking behavior among pregnant women to ensure fidelity in the subgroups of pregnant women who used e-cigarettes only and who did not smoke. The item on incomplete outcome data examines whether the study's treatment of the missing and incomplete sample data was reasonable. Other biases examined the way these studies treated confounding factors such as maternal age, income, and physical condition during pregnancy. No problems were found with selective reporting in these 9 studies, and therefore the items were all at low risk of bias. In addition, the studies we chose were 2 cohort studies and 7 case-control studies, with no clinical randomized controlled study involved. Therefore, the items of blinding of participants, random sequence, and blinding of outcome assessment were identified as "unclear".
2.4. Data abstraction

Two authors extracted the following information from articles: first author’s name, year of publication, source of study population, sample size (or weighted sample size), definition and number of pregnant women who smoked e-cigarettes only, definition and number of pregnant women who did not smoke at all, prevalence or number with adverse birth outcomes, and preconception smoking status. Two authors carefully confirmed the extracted data, and controversial parts were discussed jointly among the three authors (Table 1).

<table>
<thead>
<tr>
<th>First author</th>
<th>Published</th>
<th>Sample Sources</th>
<th>N (Unweighted)</th>
<th>EC users* (n)</th>
<th>A of EC users (n)</th>
<th>No-smokers* (n)</th>
<th>SGA of Non-smokers (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shittu et al</td>
<td>202</td>
<td>PRA (2016~2018)</td>
<td>108,1</td>
<td>10</td>
<td>57,04</td>
<td>66</td>
<td>51, 6981</td>
</tr>
<tr>
<td>Haws et al</td>
<td>202</td>
<td>MS (2016)</td>
<td>57,06</td>
<td>6</td>
<td>10,02</td>
<td>18</td>
<td>22, 89</td>
</tr>
<tr>
<td>Regan &amp; Pereira</td>
<td>1</td>
<td>MS (2016~2018)</td>
<td>2</td>
<td>9</td>
<td>232</td>
<td>2</td>
<td>64, 5</td>
</tr>
<tr>
<td>Cardeñas et al</td>
<td>9</td>
<td>Arkansas Little Rock (2016~2017)</td>
<td>620</td>
<td>21</td>
<td>31,97</td>
<td>24</td>
<td>10, 10</td>
</tr>
</tbody>
</table>
| McDo
nell et al | 202       | Dublin, Ireland (2016) | 6            | 8            | 31,97            | 24              | 10, 10               |
| Wang et al  | 202       | PRA (2016)      | 3,197         | 6            | 79,17            | 31              | 57, 9118             |
| Regan et al | 1         | MS (2016~2018)  | 6             | 6            | 55,25            | 33              | 51, 6981             |
| Kim et al   | 0         | MS (2016~2018)  | 1             | 7            | 79,17            | 31              | 57, 9118             |
| Cardeñas et al | 202       | PRA (2016~2018) | 1594          | 12           | 55,25            | 33              | 51, 6981             |

Note: *EC users: Indicates people who use only e-cigarettes during pregnancy.
*Non-smokers: Indicates those who do not use both e-cigarettes and traditional cigarettes during pregnancy.
*/: The study’s findings were presented as weighted numbers, and no raw data were provided.

The definition of maternal smoking varies between studies due to the different types of studies and the fact that the data on maternal smoking provided by PRAMS does not cover the complete pregnancy cycle. The PRAMS survey is an observational cross-sectional study and is not sufficiently precise in collecting data on smoking behavior among pregnant women. The PRAMS questionnaire only asks about smoking behavior in the last trimester of pregnancy and prenatal smoking, and information on e-cigarette use in early pregnancy is not available. Moreover, information on smoking behavior was obtained from self-reports of pregnant women, so there may be misreporting or underreporting. This limitation was present in all but 2 of the cohort studies and in the other 7 case-control studies. Therefore, these 7 studies established their own criteria for e-cigarette-only users and nonsmokers (Table 2). We followed the criteria for each one to extract the data, and the common characteristic for e-cigarette-only users was the use of e-cigarettes only during the last trimester of pregnancy. The common characteristic for non-smoking pregnant women was the complete absence of e-cigarettes and traditional cigarettes in the last trimester of pregnancy.
Table 2 Definitions of pregnant women who used only e-cigarettes during pregnancy and those who did not smoke in different studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Published</th>
<th>EC-only users</th>
<th>Non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shittu et al</td>
<td>2021</td>
<td>Pre-pregnancy trimester and last trimester e-cigarette only [12]</td>
<td>No traditional cigarettes or e-cigarettes in the pre-pregnancy trimester and last trimester</td>
</tr>
<tr>
<td>Hawkins et al</td>
<td>2021</td>
<td>Used e-cigarettes for the past two years and for the last trimester of pregnancy [13]</td>
<td>Used e-cigarettes for the past two years, no e-cigarettes and traditional cigarettes in the last trimester of pregnancy</td>
</tr>
<tr>
<td>Regan &amp; Pereira</td>
<td>2021</td>
<td>Smoked traditional cigarettes for the past two years, and only smoked e-cigarettes in the last trimester of pregnancy [14]</td>
<td>Smoked traditional cigarettes for the past two years, but no traditional cigarettes or e-cigarettes in the last trimester of pregnancy</td>
</tr>
<tr>
<td>Cardenas et al</td>
<td>2019</td>
<td>Cohort study: E-cigarette-only smoking during pregnancy [15]</td>
<td>Not exposed to any tobacco products at all</td>
</tr>
<tr>
<td>McDonnell et al</td>
<td>2020</td>
<td>Cohort study: e-cigarette only in the first and second trimesters, no data in the third trimester [16]</td>
<td>Not used any cigarettes at all during pregnancy</td>
</tr>
<tr>
<td>Wang et al</td>
<td>2020</td>
<td>Smoking only e-cigarettes in the last trimester of pregnancy [17]</td>
<td>No e-cigarettes or traditional cigarettes in the last trimester of pregnancy</td>
</tr>
<tr>
<td>Regan et al</td>
<td>2021</td>
<td>Smoking only e-cigarettes in the last trimester of pregnancy [18]</td>
<td>No e-cigarettes or traditional cigarettes in the last trimester of pregnancy</td>
</tr>
<tr>
<td>Kim et al</td>
<td>2020</td>
<td>Smoking only e-cigarettes in the last trimester of pregnancy [19]</td>
<td>No e-cigarettes or traditional cigarettes in the last trimester of pregnancy</td>
</tr>
<tr>
<td>Cardenas et al</td>
<td>2020</td>
<td>Pre-pregnancy trimester and last trimester e-cigarette only [20]</td>
<td>No traditional cigarettes or e-cigarettes in pre-pregnancy</td>
</tr>
</tbody>
</table>

2.5. Data Analysis

Based on the description of the data extraction method described above. As the weighting formula varies from article to article, we extracted raw data from pregnant women using e-cigarettes only and from non-smoking pregnant women. The Shittu study was therefore finally excluded due to lack of raw data. The group of pregnant women who smoked e-cigarettes only was the exposed group, the non-smoking pregnant women were the control group, and SGA was the outcome.

To assess the heterogeneity of the included studies, a Cochran’s Q test was performed for testing the p-value and the I² value. We included only raw data on the number of people, and because of gaps in the sample size and population characteristics of these studies, we used random effects to analyze the results in order to make the average effects more balanced and the results closer to the real situation. Odds ratio as a measure of risk associated with e-cigarette exposure and adverse birth outcomes. Publication bias was assessed using funnel plots. The above data analysis was carried out by RevMan 5.4 software.

3. Results

3.1. Meta-Analysis of Association between E-cigarettes use and adverse birth outcomes

The pooled analysis found that E-cigarette smoking significantly increased the risk of small for gestational age birth outcomes in pregnant women (OR = 1.31, 95% CI: 1.00, 1.72; Figure 3), but the formal test for heterogeneity gave a significant result (I² = 59%)
To explore possible reasons for the high heterogeneity, we used the case-by-case exclusion method and subgroup analysis. Subgroups were national studies based on PRAMS data, and regional studies. The PRAMS-based study, which included data from pregnant women in at least 32 states and New York City, is a more representative study of the association between overall pregnancy outcomes and e-cigarette use among pregnant women in the United States. The regional studies were an Arkansas cohort study and a case-control study, and a Dublin, Ireland cohort study. These three studies were more regionally representative, such as Arkansas being the state with the highest rate of e-cigarette use among pregnant women in the United States. By a case-by-case exclusion method, we found that Wang’s and Hawkins’ articles led to a high level of heterogeneity. The possible reason for this analysis is that Wang’s article used data from the 2016 PRAMS questionnaire, the first year PRAMS added the e-cigarette question to the questionnaire for pregnant women [17]. Considering the increasing prevalence of e-cigarette smoking among pregnant women, there may be a large difference from the subsequent two years of data. Hawkins’ study included e-cigarette use habits prior to two years of pregnancy when grouping pregnant women, which may account for the heterogeneity [13].

The results of the subgroup analysis are shown in Figure 4. The test for the overall effect of multiple studies was statistically significant (z=2.21; p=0.03) and the heterogeneity ($I^2=32\%$) of the two subgroups aggregated was low. Thus, the overall OR (1.32; 95% CI 1.03, 1.69) of the two subgroups indicates that e-cigarette smoking increases the risk of SGA birth outcomes in pregnant women. The subgroup heterogeneity ($I^2=0\%$) of the PRAMS-based all-U.S. show that these three studies are homogeneous. The three articles in the regional studies subgroup had high heterogeneity ($I^2=61\%$) and their conclusion was contradictory. It is speculated that the reason may be due to population characteristics differences and the small sample size of e-cigarette users. Differences between the two subgroups were associated with different types of studies and sources of the sample. Meanwhile, in contrast to case-control studies with large samples, the 2 cohort studies in the regional study were good at excluding bias due to misreporting of their smoking habits by pregnant women.
3.2. Publication bias

We used funnel plots to assess publication bias. According to Figure 2, it can be seen that the funnel points basically show a symmetrical distribution, which indicates a small publication bias. There was a slightly uneven distribution of funnel points, suggesting that the findings of different studies are controversial, which may be related to the study population and sample size. After all, the percentage of pregnant women who use e-cigarettes is relatively low in the overall pregnant population. However, in general, the analysis results have good stability and reliability (figure 5).

![Funnel plot of e-cigarette use and adverse birth outcomes in pregnant women](image)

**Figure 5** Funnel plot of e-cigarette use and adverse birth outcomes in pregnant women

4. Discussion

Our finding shows that the use of e-cigarettes during pregnancy (especially in the last trimester) significantly increases the risk of SGA birth outcomes in pregnant women. The conclusion confirms that e-cigarettes are not a safe alternative to traditional cigarettes and that past perception of the low risk of e-cigarettes among pregnant women needs to be changed. Preterm birth and low birth weight are equally poor birth outcomes that have similar points to small for gestational age, and they are both manifestations of fetal developmental problems. Although we did not conduct a meta-analysis of these two birth outcomes, it was concluded in some of the articles we included that e-cigarette use during pregnancy also resulted in an increased risk of preterm birth and low birth weight. Therefore, pregnant women still need to do their best to avoid using any cigarettes or e-cigarette products.

In addition to analyzing the association between e-cigarette use and adverse birth outcomes, two other questions in this area need to be addressed. The first is the policy aspect. Active government regulation is also necessary to reduce e-cigarette use among pregnant women. However, developing these regulatory policies is a complex political process because of the wide variety of e-cigarettes and the varying national policies governing nicotine products. Current regulations and policy development are lagging significantly behind the pace of e-cigarette iterations and market expansion [21]. The lack of effective industry regulation will lead to a growing group of e-cigarette users. Secondly, we do not yet know the physiological mechanisms by which e-cigarettes contribute to poor fertility outcomes. At this stage, research on the chemical composition of e-cigarettes is more focused on cellular experiments and animal experiments. This does not provide an adequate prediction of the hazards of e-cigarette use in humans. Events of E-cigarette or vaping product use-associated lung injury (EVALI) in the United States in 2019 is the first case of death explicitly due to e-cigarettes since the beginning of the massive e-cigarette epidemic and has created a huge public outcry. Subsequent studies attributed the etiology primarily to the addition of vitamin E acetate to the nebulizer solution [22]. This event highlights the complexity of e-cigarette hazard research because of the wide variety of secondary reaction products in atomized liquids after high-temperature atomization, including benzene aromatic compounds, carbonyl compounds, and some heavy metal inorganics [23]. These problems have limited the progress of research related to e-cigarettes. Therefore, e-cigarettes, a public health problem, still requires more research and concerted efforts from all sectors of society to address.

There are some limitations to our study. One is that we included a small number of studies and the sample population was mainly the US population of pregnant women. Given that e-cigarette use among pregnant women is a global issue, we provide limited representativeness of the evidence. Another limitation is that we set the criterion for the e-cigarette-only exposure group as e-cigarette-only in the last trimester of pregnancy in order to extract data. This criterion prevented us from correcting the effect of pre-pregnancy smoking behavior on outcomes. We, therefore, need to complement this with more cohort studies that document in detail the smoking behavior of pregnant women during their complete pregnancy.
Our study also has some strengths. Firstly, our study is innovative, and no similar meta-analysis has been published before. Our article can be a reference for subsequent analyses. Secondly, we provide more convincing evidence that e-cigarettes are harmful to pregnant women, which can make more pregnant women concerned about their health and that of their fetuses. Finally, our study will help more researchers to pay attention to and participate in the study of e-cigarettes and contribute to this public health issue.

5. Conclusion
As e-cigarettes have become the most popular product on the market, more and more pregnant women are inclined to use e-cigarettes as an alternative to traditional cigarettes. Most of them are unaware of several major risk factors associated with e-cigarette use. Our study demonstrates that there are clear harms associated with the use of e-cigarettes during pregnancy. It may lead to small for gestational age. In addition, studies on the teratogenicity of e-cigarettes on the fetus, preterm birth, and other adverse birth outcomes are inadequate. They need to be brought to the attention of researchers. Thus, complete cessation of smoking and avoidance of exposure to secondhand smoke can genuinely reduce the likelihood of adverse birth outcomes. More and longer-term clinical studies on the prenatal and postnatal risks of e-cigarette use in pregnant women are needed to provide more robust conclusions in this area.

Acknowledgments
Not Applicable.

References


