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Relationship between caffeine or coffee consumption and Miscarriage: Findings from systematic review and meta-analysis

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Abstract

Background: There is growing evidence that fetal development is affected by maternal lifestyle and can increase the risk of complications of pregnancy and disease later in life. Obesity, smoking, alcohol, and coffee use are just a few of the lifestyle factors that have been related to an increased probability of spontaneous abortion. The link between caffeine usage and pregnancy has been researched, although the results have been mixed. Several research on the link between caffeine/coffee consumption and miscarriage have been conducted, but the evidence has not been synthesized. As a result, we conducted this review to update the evidence and combine data from a variety of observational studies that present and elucidate information on the relationship between caffeine consumption and spontaneous miscarriage.

Methods: Preferred Reporting Items for Systematic Reviews (PRISMA) criteria were followed to undertake this systematic review and meta-analysis. Using databases such as PubMed/Medline and Scopus, a systematic search of published publications was conducted using the keywords ("Caffeine or Coffee") and ("Miscarriage or Spontaneous Abortion or Pregnancy loss or Stillbirth or fetal loss"). Only articles written in English were included in the search. For all observational studies, quality assessment was done using Newcastle–Ottawa Scales.

Results: A total of 15 studies meet the inclusion criteria and were included in the analysis. In comparison to the women with no or low coffee consumption, the pooled RR for women with high coffee consumption was 1.65 (95 % CI 1.46–1.87) in the caffeine-exposed group (>150 mg caffeine/day). The I^2 statistics was 51%, suggesting a clear heterogeneity between-studies with Q = 28.44 (P = 0.01). The funnel plot suggested a possibility of existing publication bias.

Conclusion: High caffeine intake (300 mg or more per day) was linked to a considerably higher chance of spontaneous abortion, according to our data. Given the biological plausibility of negative impacts on the fetus and evidence of the effects of maternal caffeine consumption on fetal development, pregnant women need to remain cautious and limit their caffeine intake to moderate levels during pregnancy.

Keywords: Caffeine intake, Miscarriage, systematic review, Meta-analysis

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1. Introduction

Spontaneous miscarriage is one of the widespread adverse outcomes during pregnancy(1). Almost 10% to 15% of clinically diagnosed pregnancies end up in miscarriage across the globe (2-5), and about 17–22% of cases of spontaneous abortion occur at a very early stage of pregnancy when a woman is not even aware of her pregnancy (6). The reported annual prevalence of miscarriage in the United Kingdom is about 125,000, resulting in 42,000 hospital admissions(7). Whereas, the occurrence of first-trimester miscarriage in France is between 12% and 25% (8). The corresponding figures appear to be lower in some developing countries(9). The prevalence of spontaneous abortion in the Middle East and North Africa ranged from 12.9 to 17.5 per 1000 births(10). For several women, sudden and unanticipated loss of pregnancy may be traumatic and distressing. Previous research has found that the miscarriage causes a considerable number of women to meet the criteria for mental disorders such as depression (27%) and anxiety (28–41%) (11-13). These symptoms gradually fade, reaching levels comparable to the non-pregnant women almost after a year (14). Similarly, 41 % of women reported substantial levels of anxiety, whereas 22 % reported significant levels of depression 7-14 days following miscarriage as reported by one study (15). Although psychological impact after miscarriage recovers within a few months of loss, psychiatric morbidity can linger for several months(16).

Furthermore, we may discover that there are many linked risk factors that we can explore and study when examining the cause and risk factors of spontaneous miscarriage throughout history. Chromosomal anomalies are the most prevalent cause of miscarriage in the first trimester, with 50–60% of tissue specimens from spontaneous miscarriages showing indications of chromosomal problems(17, 18). Rarer, miscarriages are causes by hereditary uterine abnormalities (19) and thrombophilias (antithrombin deficiency, protein C, and protein S deficiency, factor V Leiden mutation, mild hyperhomocysteinemia) (20). There is growing evidence that that maternal lifestyle affects fetal development and can raise the risk of pregnancy problems and disease later in life(21). Several factors such as obesity, smoking cigarettes, alcohol consumption, use of drugs, and caffeine-containing beverages have been identified to increase the incidence of spontaneous miscarriage (22, 23). For example, smoker women have an increased risk of recurrent abortion of around 40% compared to non-smokers, and the risk has increased with the number of cigarettes smoked each day (24). Similarly, a case-control study undertaken in the USA found an elevated risk of spontaneous miscarriages in women drinking alcoholic beverages twice a week or more (25). A population-based cohort study found that the use of NSAIDs (painkillers) by pregnant women raised the danger of miscarriage by 80% (26). Moreover, at least small amounts of coffee and other caffeine-containing beverages and foods are consumed frequently by most

pregnant women or those planning to conceive(27), 82% of whom in the USA(28) and 91% in France are reported to consume caffeine on a regular basis(29).

Since the 1980s, the impact of caffeine on fetal growth and development and survival has been of great concern(30). The biological rationale for this interest stems from caffeine's capability to cross the placenta and be easily absorbed from the gastrointestinal tract and spread across all of the organism's tissues during pregnancy (31), exposing the fetus to drug concentrations comparable to the mother's systemic levels (32). Overall, the relationship between coffee intake during pregnancy has been explored with conflicting results(33), partly due to difficulties in measuring caffeine consumption, but also due to other clinical effects on fetal development and birth outcomes(34, 35). Several research on the association between caffeine/coffee intake and miscarriage have been conducted due to the potential associations with miscarriage and stillbirth in humans. However, it appears that the most recent meta-analysis study was completed in 2015. As a result, the aim of this review is aggregate data from a variety of observational studies that present and elucidate information on the relationship between caffeine and spontaneous miscarriage.

2. Subjects and Methods

This study used a systematic procedure to identify research papers, assess their quality, and synthesize the results to reach evidence for a potential causal relationship between coffee intake and the chance of spontaneous abortion. All published information on the potential causal relationship between caffeine and the risk of miscarriage was retrieved, evaluated, and summarized. Following that, a meta-analysis was used to synthesize the findings of those investigations and measure the pooled interpretation estimate of the connection based on the findings of these research. Preferred Reporting Items for Systematic Reviews (PRISMA) criteria were followed to conduct this systematic review and meta-analysis (36).

2.1 Inclusion and Exclusion Criteria

Except for reviews, case reports, letters, editorials, and suggestions, all observational research (Cohort and Case-control designs) were included. Throughout the search procedure, we followed the PRISMA standards (Fig. 1) for publishing systemic reviews and meta-analyses. The only articles that were considered for inclusion in relation to the exposure were those that considered coffee/caffeine as the primary cause of miscarriage. Only studies with a formal diagnosis of pregnancy miscarriage met our inclusion criteria for the outcome. Recurrent miscarriage, pre-pregnancy caffeine intake, and coffee/caffeine doses less than 200 mg/day were also excluded from the study.

2.2 Sources of information and strategy for searching the relevant articles

Researches of interest were identified by searches of the PubMed and Scopus databases from 1986 until 2015 using key words (Caffeine or Coffee) and (Miscarriage or Spontaneous Abortion or Pregnancy loss or Stillbirth or fetal loss). Only articles written in English were included in the search. Boolean operators (OR and AND) were utilized to discover published primary research that particularly investigated this research issue. We also employed truncation (*) with the same root term to find more research publications. To avoid missing any relevant articles, we employed truncation to ensure that all possible permutations of search phrases were retrieved. In addition to keyword searches, MeSH phrases were used to discover all publications related to our study issue in PubMed and Scopus. Following the electronic database scan, the reference lists of the identified publications were evaluated to see if there were any more research not found through the PubMed and Scopus searches. To include eligible studies in the search, we used language (English) search constraints or filters, as well as publication era, age group, and kind of intervention restrictions.

2.3 Data abstraction

We imported all relevant research papers into the reference manager software (EndnoteTM) file, where each research article was reviewed, and we also used this software to scan titles for duplicates. Full texts were not read for abstracts that did not clearly investigate the study purpose. Finally, we collected the full-text articles of the leftover relevant research articles and studied them. The articles that met the eligibility requirements were then abstracted and summarized using a standardized proforma. As a result, we removed papers that were outside the scope of this review based on inclusion criteria after removing duplicates, title, and abstract screening. In addition, the bibliographies of the remaining research were checked and confirmed to ensure that no useful studies were overlooked. The reviewers conducted their own searches of the publications, and their judgements and extracted summaries were compared to find differences and resolve them appropriately.

Independent reviewers retrieved study characteristics from eligible research publications using a standardized data extraction form. Before beginning the data extraction process, the reviewers examined the data extraction tables to ensure that they included the critical results of the eligible studies. Any disagreements between the two reviewers were resolved through mutual agreement. The study name, publication year, sample size or population, study design, exposure and outcome evaluation, and effect magnitude were among the abstracted data.

2.4 Quality assessment

The quality assessment and risk of bias assessment of eligible full-text article was undertaken for all observational studies with the help of Newcastle–Ottawa Scales (37). Selection, comparability, and outcome ascertainment are the three key categories to be assessed according to the scale for observational studies. The highest score for selection is 5, which is based on the study sample's representativeness, sample size and justification, response rate, and exposure ascertainment. Similarly, the highest score for comparability is 2, which is based on the advanced analysis' correction of potential confounders and other factors. Finally, the outcome's maximum score is 3, which is based on the outcome's assessment technique and a statistical test to examine the data. The overall score for all these territories is 10, and each eligible study was given a score that represents its quality. A score between 7 and 10 points was assigned to the studies with good quality, a score between 5 and 6 points was assigned to studies with satisfactory quality, and bad studies were given a score between 0 and 4 points.

2.5 Statistical Analysis

The meta-analysis includes papers that calculated an effect size (odds ratio or relative risk) for coffee/caffeine consumption and miscarriage. In each of the trials, age adjustment was a minimal criterion. We decided to do a random-effects meta-analysis because the results of a random-effects model are generally more conservative than fixed-effects model. To determine heterogeneity, the Cochran's chi-squared (Q-test) and statistic were utilized. Any variance in the conclusions of studies on the link between coffee and miscarriage is referred to as heterogeneity. Significant heterogeneity suggests that the variance is not due to chance only. The I2 statistic represents the proportion of total variance across research studies that is not due to chance and has a range of values from 0% to 100%. I2 statistic of 25%, 50%, and 75% represent small, moderate, and high heterogeneity respectively. Meta-regression was used to see if study-level factors explain the heterogeneity. To calculate individual and pooled effects of coffee/caffeine consumption on miscarriage and analyze statistical heterogeneity, forest plots were created. In addition, funnel plots were utilized to investigate the issue of publication bias. The presence of publication bias may result into asymmetrical funnel plot. Three statistical techniques (the rank correlation method (Begg's test),18 regression analysis (Egger's test), and the trim-and-fill method) were used to measure funnel plot asymmetry. To achieve the modified pooled estimates, fixed-effect model for trimming and the random-effects model for filling in the trim-and-fill method were employed. For cross-sectional and cohort studies, as well as each pregnancy miscarriage outcome, we measured publishing bias. Meta-analysis was undertaken using Rev-man software, version 5.0.

3. Results

3.1 Conclusions of the search strategy

The chosen articles were primarily screened by titles and abstracts. This was followed by assessment of full-text articles. Our preliminary search identified 154 records in two databases, however, 35 records were removed due to duplicates. After screening 119 records, were excluded 41 as their titles and abstracts were not relevant. Of the remaining 78 eligible abstract, we found full texts of 59 articles that were assessed for eligibility. Finally, we included 15 articles for qualitative synthesis as a part of the systematic review, and the same number was included in the quantitative synthesis as shown in the PRISMA flow diagram for screening the studies (Figure 1). A total of 15 studies were found to be eligible based on inclusion criteria and were incorporated in the analysis (Figure 1, Table 1).

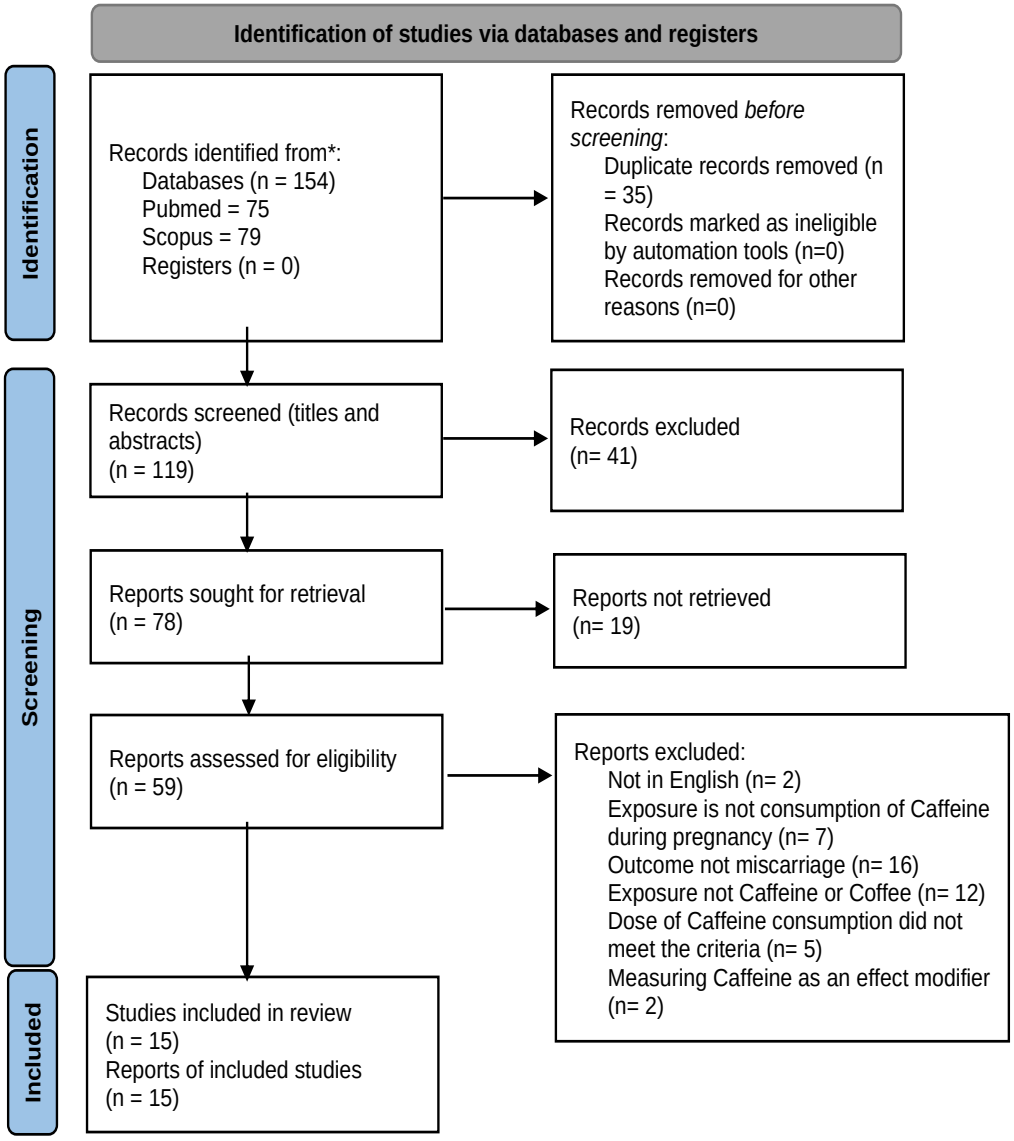

Figure (1) Flow diagram of study selection for systematic review and meta-analysis

3.2 Characteristics of the eligible studies

Concerning the study design, 6 studies were case control, whereas 9 were cohort studies. The studies were performed in countries such as the United States of America (USA) (n=8), Uruguay (n=1), Denmark (n=2), and Sweden (n=1). One study was conducted each in 1986, 1991, 1994, and 1999, 2 in 2000 and 2003 each, one each in 2005, 2006, 2007, 2010, and 2015 as illustrated in Table 1. The total sample size of all eligible studies was between 88 to 5132. Exposure assessment was done using different methods such as Questionnaire and interviews, and Monthly food frequency questionnaire, and structured questionnaire. Whereas outcome assessment was done using electronic maternity databases, reviewing National Hospital Discharge Register and Medical records, and physicians, hospital labor and delivery logs, birth records, and postpartum interviews (Table 1).

Table 1: Characteristics of eligible studies included in systematic review and meta-analysis (n=15)

Author, Year	Country	Sample Size	Exposure Assessment	Outcome Assessment	Study Design	Effect Size (95% CI)
Domínguez-Rojas et al., 1994	Spain	711	Personal interview	Clinical histories registered at the preventive Medicine Service.	Retrospective cohort	281-420 mg/day OR= 4.81 CI (2.28-10.14).
Matijasevich et al., 2006	Uruguay	382 cases, 792 controls	Questionnaire tested in a previous study.	Medically confirmed diagnosis of Spontaneous Abortion (SA) in the maternity hospitals.	Case-control	300 mg or more/day OR= 2.33 CI (1.23-4.41).
Klebanoff et al., 1999	United States	487 cases, 2087 controls	A biologic marker (serum paraxanthine) was used to measure the dose of caffeine.	The original study records were reviewed to identify women who had SA.	Nested-Case-control	Serum paraxanthine concentrations more than 1845 ng/milliliter OR= 1.9 CI (1.2-2.8).
Fenster et al., 1991	United States	607 cases, 1284 controls	Computer-assisted telephone interviews.	Pathology report files were reviewed for SA.	Case-control	300 mg or more/day crude OR= 1.55 CI (1.04-2.31), adjusted OR= 1.22 CI (0.80-1.87).
Srisuphan et al., 1986	United States	3135	In person interview with the use of standardized schedule.	SA's identified from medical records.	Prospective cohort	>150 mg /day crude RR= 1.69 CI (1.04-2.71), adjusted RR=1.73
Wisborg et al., 2003	Denmark	18,478	Questionnaire.	SA data were collected at Aarhus University Hospital and from the Danish medical birth registry.	Prospective cohort	8 or more cups of coffee/day OR= 3.0 CI (1.5-5.9).
Vibeke Rasch, 2003	Denmark	330 cases, 1168 controls	Questionnaire.	Medically confirmed diagnosis of SA at Odense University Hospital.	Case-control	375 mg or more/day adjusted OR= 2.21 CI (1.53-3.18)
Greenwood	United	2643	Questionnaire.	Electronic maternity	Prospective	300 mg or more/day

et al., 2010	Kingdom			databases.	cohort	OR= 5.1 CI (1.6-16.4)
Hahn et al., 2015	United States	5132	Questionnaire.	The Danish National Registry of Patients and the Danish Medical Birth Registry.	Prospective cohort	300 mg or more/day HR= 1.23 CI (0.61-2.46)
Bech et al., 2005	United States	88.482	Interviews.	National Hospital Discharge Register and Medical records.	Prospective cohort	4 to 7 cups of coffee/day HR= 1.33 CI (1.08-1.63).
Giannelli et al., 2003	United Kingdom	160 cases, 314 controls	Questionnaire and interviews.	Clinically confirmed either by a GP or in hospital.	Case-control	301-500 mg/day adjusted OR= 1.94 CI (1.04-3.63),
Wen et al., 2000	United States	968	Monthly food frequency questionnaire.	Medical records abstractions.	Prospective cohort	300 mg or more/day RR= 2.5 CI (1.0-6.4)
Cnattingius., 2000	Sweden	562 cases, 953 controls	In-person interviews and questionnaire.	Medically confirmed diagnosis of SA at Uppsala University Hospital.	Case-control	300-499 mg/day OR= 1.4 CI (0.9-2.0), 500 mg or more/day OR= 2.2 CI (1.3-3.8)
Weng et al., 2007	United States	1063	Interviews.	Kaiser Permanente Medical Care program. Medical records. contacting participants.	Prospective cohort	200 mg or more/day HR= 2.23 CI (1.34-3.69)
Dlugosz et al., 1995	United States	2967	Interviewed using a structured questionnaire.	Physicians, hospital labor and delivery logs, birth records, and postpartum interviews.	Prospective cohort	>300 mg/day adjusted OR= 1.75 CI (0.88-3.47), 3 or more cups/day OR= 2.63 CI (1.29-5.34).

3.3 Findings regarding the pooled estimate for primary outcome

Table 1 shows the effect size for spontaneous abortion in separate research studies. The forest plot in figure 2 shows the pooled risk ratio (RR) for the relationship between caffeine consumption during pregnancy and miscarriage. In comparison to the women with no or low coffee consumption, the pooled RR for women with high coffee consumption was 1.65 (95 % CI 1.46–1.87) in the caffeine-exposed group (>150 mg caffeine/day). The I^2 statistics was 51%, suggesting a clear heterogeneity between-studies with Q = 28.44 (P = 0.01).

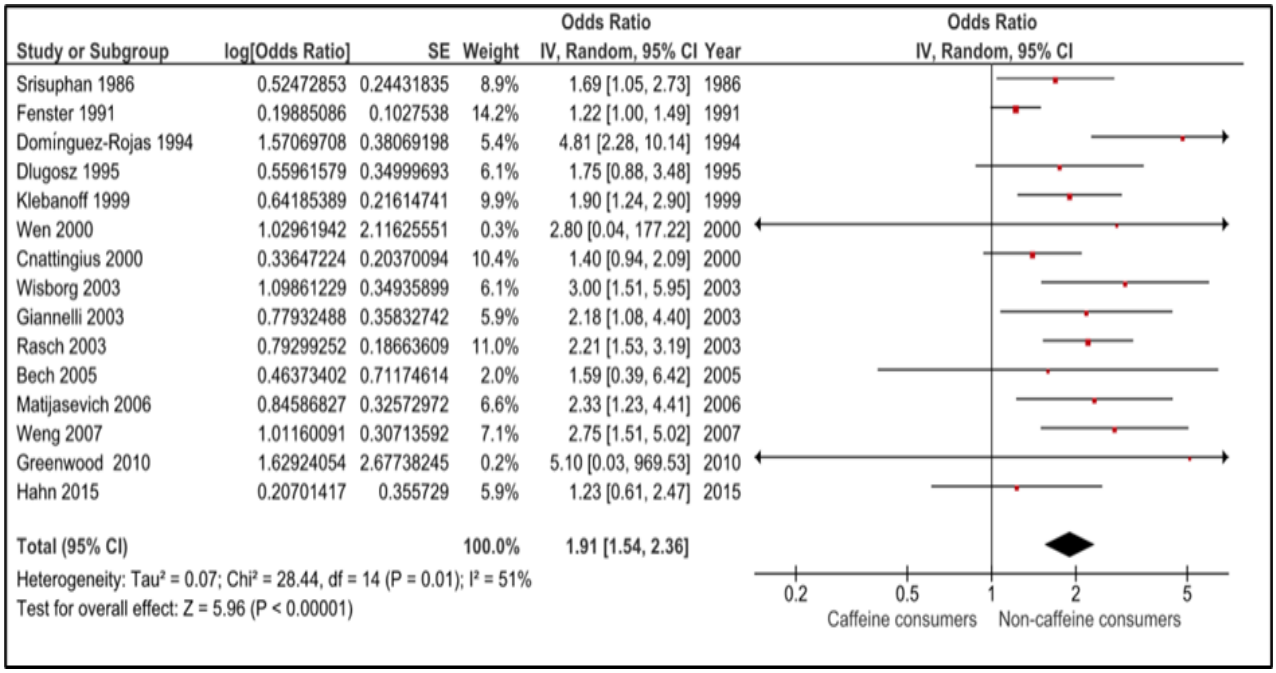

Figure (2) Forest plot of the association between miscarriage and caffeine consumption and coffee consumption.

3.4 Risk of bias and publication bias assessment

Included studies scored between 6 to 9 using New-castle-Ottawa Scale (higher scores reflects better study quality; table 2). Almost all included studies were of good quality as their scores ranged between 7 to 9 except one case-control study that scored 6 thus did not met the criteria for adequate quality. Some of the quality domains that were deducted may have been met, but they were not scored because the publication lacked adequate information for scoring. The asymmetrical funnel plot (Fig. 3) suggests that there is a possibility of existing publication bias.

Table 2: Findings of quality assessment using modified New-castle Ottawa Quality assessment scale (n=15)

Study/Domain	Study groups	Attrition	Exposure Measure	Outcome Measure	Investigators Blinded	Confounders Identified	Statistical Adjustment	Funding Source
Domínguez-Rojas et al., 1994	Y	Y	Y	Y	Y	Y	Y	Y
Matijasevich et al., 2006	N	N	Y	Y	Y	Y	Y	Y
Klebanoff et al., 1999	Y	N	Y	Y	Y	Y	Y	Y
Fenster et al., 1991	Y	N	Y	Y	Y	Y	Y	Y
Srisuphan et al., 1986	Y	N	Y	Y	Y	Y	Y	Y
Wisborg et al., 2003	Y	Y	N	Y	Y	Y	Y	Y
Vibeke Rasch, 2003	Y	N	N	Y	Y	Y	Y	Y

Parazzini et al., 1998	Y	Y	Y	Y	Y	Y	Y	Y
Greenwood et al., 2010	Y	N	Y	N	Y	Y	Y	Y
Hahn et al., 2015	Y	N	N	Y	Y	Y	Y	Y
Bech et al., 2005	Y	Y	Y	Y	Y	Y	Y	Y
Giannelli et al., 2003	Y	Y	Y	Y	Y	Y	Y	Y
Wen et al., 2000	Y	N	Y	Y	Y	Y	Y	Y
Cnattingius., 2000	Y	N	Y	Y	Y	Y	Y	Y
Weng et al., 2007	Y	N	Y	Y	Y	Y	Y	Y
Dlugosz et al., 1995	Y	N	Y	Y	Y	Y	Y	Y

Table 3. Quality assessment using New-castle Ottawa Quality Assessment Scale (n=15)

First author, year	Study design	Selection	Comparability	Exposure/Outcome	Total scores
Domínguez-Rojas et al., 1994	Cohort	★★★★	★	★★★	8
Matijasevich et al., 2006	Case-control	★★★	★★	★★★	8
Klebanoff et al., 1999	Case-control	★★★	★	★★★	7
Fenster et al., 1991	Case-control	★★★★	★★	★★★	9
Srisuphan et al., 1986	Cohort	★★★★	★★	★★★	9
Wisborg et al., 2003	Cohort	★★★★	★	★★★	8
Vibeke Rasch, 2003	Case-control	★★	★	★★★	6
Dlugosz et al., 1995	Cohort	★★★★	★	★★★	8
Greenwood et al., 2010	Cohort	★★★	★	★★★	7
Hahn et al., 2015	Cohort	★★★★	★	★★★	8
Bech et al., 2005	Cohort	★★★	★	★★★	7
Giannelli et al., 2003	Case-control	★★	★★	★★★	7
Wen et al., 2000	Cohort	★★★	★★	★★	7
Cnattingius., 2000	Case-control	★★★★	★★	★★	8

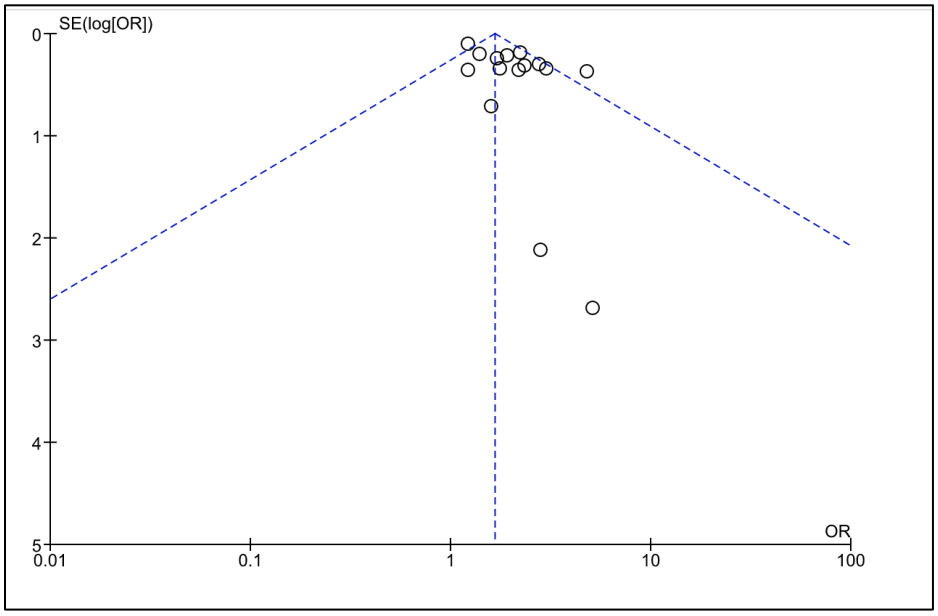

Figure (3) Funnel plot for maternal caffeine intake and pregnancy loss. There was a suggestion of publication bias.

4. Discussion

The aim of this meta-analysis was to investigate the relationship between maternal coffee consumption and spontaneous abortion. A modest but substantial association between moderate to excessive caffeine use during pregnancy and the incidence of miscarriage was discovered in this meta-analysis. To assess the implications of these findings in a realistic manner, the findings of subgroup and sensitivity analyses, as well as the limitations of the included studies, must be considered. In this study, defining a relevant reference group, for example, was difficult. Most studies failed to differentiate between low- and no-exposure groups. The reference group (0 to 150 mg caffeine/day) was chosen since it has been used in a significant number of studies as "light" caffeine users (0 to 150 mg caffeine/day). Caffeine usage and the probability of spontaneous abortion were investigated by Srisuphan et al.(38). They proposed a caffeine "threshold impact" of roughly 150 mg/day, claiming that caffeine intake below this level would have no effect on the baby's cell development or division. The study by Dominguez-Rojas et al. (39) was recognized as an outlier by assessing its contribution to the variance of Q for homogeneity. The summary effect size was reduced to 1.60, the statistics for heterogeneity were no longer significant (Q= 20.36, P = 0.09), and the I2 statistics were reduced to 36% after removing this study from analysis. The results of the study were investigated to determine if there was a cause for the discrepancies. Espresso coffee was identified as the most common source of caffeine intake in the study, which was done in Madrid, Spain. Espresso coffee contains about 140 milligrams of caffeine per cup, which is roughly twofold as much as a cup of coffee ingested in North America(40). When the data of pregnant women

who drank more than 420 mg of caffeine per day were investigated, it was shown that 61 of 87 pregnancies (71 percent) terminated in miscarriage. It's possible that short-term consumption of high-concentrated caffeine drinks has a higher impact on fetal growth than standard consumption, or that there are other unmeasured components in espresso coffee that are impacting the results. These theories should be considered in future research.

The exact mechanism through which caffeine increases the risk of miscarriage is unknown. Caffeine increases catecholamine release, which can cause vasoconstriction of the uteroplacental circulation and fetal hypoxia, impairing fetal development and growth(41). When the mother consumes only 200 mg of coffee, the intervillous placental blood flow is decreased by 25%(42). Another theory is that coffee directly affects the fetal cardiovascular system, producing tachycardia via raising fetal heart rate accelerations(43, 44). As previously noted, there may be differences in the causes of spontaneous abortion and stillbirth. Caffeine may impact these outcomes by vascular dysfunction or through several channels, but there isn't enough evidence to speculate more. If caffeine consumption during pregnancy is causally linked to spontaneous abortion, the metabolites of caffeine may also play a role. Klebanoff et al. discovered a link between serum paraxanthine levels, a main caffeine metabolite, and spontaneous miscarriage(45). Compared with serum paraxanthine levels in controls, those women whose pregnancies ended in spontaneous abortion were higher ($p < 0.001$). These may have significant repercussions because extensive inter-individual difference in metabolism of caffeine has been observed owing to either genetic variation (or lifestyle factors such as smoking(46). To offer a more comprehensive portrait of caffeine metabolism, imminent research should include assaying for circulating caffeine, its metabolites, and genetic information in addition to well-scheduled caffeine use and lifestyle factor assessments.

The findings of previous studies on maternal caffeine use and spontaneous abortion were mixed. The most recent meta-analysis, conducted by Keiji Kuroda in 2018, looked at the effects of a variety of lifestyle choices on pregnancy loss(47). According to the study, the relationship between coffee consumption and miscarriage is uncertain. However, there is grounds for concern because this meta-analysis only included four publications. While high maternal caffeine consumption was consistently linked to a higher incidence of spontaneous abortion, results for moderate and low caffeine consumption were mixed, owing to measurement constraints as well as differences in research locations and participants. Similarly, in the other meta-analysis, Chen et al. reviewed the effect of maternal caffeine intake and probability of abortion(48). However, some reports of pre-pregnancy exposure assessments were included in that study. As a result, this study centered on the impacts of caffeine consumption on miscarriage during pregnancy and incorporated additional data because it comprised 15 research and

pooled the effect estimates.

4.1. Strengths and Limitations

Several methodological concerns remain, and the study's limitations must be acknowledged. First, as shown in (Fig. 3), publication bias could be an issue because this meta-analysis was conducted solely using PubMed and Scopus, limiting the number of articles included in the study. Furthermore, residual confounding from unmeasured or poorly measured covariates exists in all observational studies. Besides, case-control studies are typically subject to recall bias, which cannot be addressed at the analysis stage. Even though acceptable studies controlled for confounders such as age, concurrent smoking, and alcohol consumption, it is impossible to exclude out all possible confounding factors such as pregnancy history or nausea. Pregnancy symptoms such as nausea and vomiting may alter our knowledge of the link between coffee and pregnancy loss in two ways. To begin with, pregnant symptoms are linked to both pregnancy loss and mother coffee intake, suggesting that they could be a confounder. Second, fetal viability loss (which occurs before the actual diagnosis of pregnancy loss) can lead to a decrease in pregnant symptoms and, as a result, an increase in caffeine consumption; this is an example of reverse causality. If pregnant symptoms obfuscate the caffeine-pregnancy loss link, the influence of these symptoms can be studied by correcting or stratifying for them. Wen et al. discovered a link between caffeine consumption measured after nausea start and the risk of misscarraige among nauseated women, but not in women who were not nauseated(49). Klebanoff et al., on the other hand, found comparable relationships among women who did or did not experience vomiting(45). As a result, assessing relevant pregnant symptoms are less likely to be free from errors, and lingering confounding by symptoms indicating fetal viability cannot be ruled out entirely. Finally, because coffee consumption was assessed based on the quantity of cups drunk in some studies, and the size of a cup can vary, misclassification of coffee intake is unavoidable. The key methodological issue in the analysis of the studies was shown to be this incorrect exposure assessment.

The current meta-analysis has several strengths, including the fact that it used a systematic and quantitative approach to determine whether there is a link between pregnancy loss and caffeine or coffee consumption during pregnancy. The use of a quality assessment scoring system (New-castle-Ottawa Scale) to qualify the articles was helpful in establishing that the methodological quality of the bulk of the investigations was not significantly different. Furthermore, in order to optimize the completeness of the research identification, appropriate key terms were used to search the databases. Another aspect of this study is the analysis of the dose-response relationship; by collecting information on intermediate categories, we are able to include all information on exposure consequence, making the study more successful than the traditional highest vs lowest approach.

5. Conclusion

The premise that increased maternal caffeine consumption is linked to a higher incidence of spontaneous miscarriage was supported by this review. Caffeine consumption of < 300 mg (three cups of coffee) per day is presently recommended by the WHO. High caffeine consumption (300 mg or more per day) was linked to a higher chance of spontaneous abortion, according to our data. Our findings are not free from publication bias and residual confounding from smoking or pregnancy symptoms. Nonetheless, given the biological plausibility of negative effects on the fetus and proof of the impacts of maternal caffeine consumption on fetal development, one should adhere to public recommendations and limit caffeine intake during pregnancy to no more than two cups per day.

6. Declarations

6.1 Conflict of Interest Statement

The authors have no conflict of interests to declare.

6.2 Funding Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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