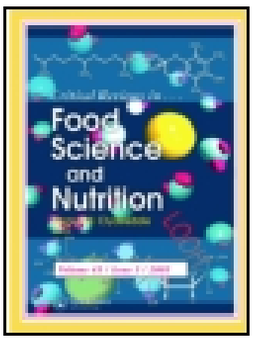

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Maternal caffeine consumption during pregnancy and risk of low birth weight: a dose–response meta-analysis of cohort studies

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REVIEW

Maternal caffeine consumption during pregnancy and risk of low birth weight: a dose–response meta-analysis of cohort studies

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ABSTRACT

Background & Objectives: Earlier published studies on maternal caffeine intake during pregnancy in relation to the risk of low birth weight (LBW) (birth weight <2500 g) have indicated conflicting findings. Therefore, the present systematic review and meta-analysis was conducted to examine the association between maternal caffeine intake and risk of LBW.

Methods: We searched for relevant articles published up to Jan 2021 through PubMed and Scopus. For this purpose, we used MESH (Medical Subject Heading) and non-MESH keywords. Cohort studies that considered maternal caffeine intake as the exposure variable and LBW as the main outcome variable were included in the systematic review. Finally, seven cohort studies were considered in this systematic review and meta-analysis.

Results: Combining seven effect sizes, we found a significant positive association between maternal caffeine intake and risk of LBW (RR: 1.70; 95% CI: 1.19–2.43). We also found that each additional 100-mg per day of maternal caffeine intake was significantly associated with an increased risk of LBW (RR: 1.12; 95% CI: 1.03–1.22; $P_{heterogeneity} = 0.020$). In addition, nonlinear dose–response analysis showed a significant relationship ($P_{nonlinearity} < 0.001$) between maternal caffeine intake and risk of LBW.

Conclusions: In this systematic review and meta-analysis, we found a significant positive association between maternal caffeine intake and risk of LBW.

KEYWORDS
Caffeine; low birth weight; meta-analysis; pregnancy; systematic review

Introduction

Low birth weight (LBW, birth weight <2500 g) is a prevalent adverse gestational outcome that contributes to infant morbidity and mortality (Lawani et al. 2016; Petrou 2003). LBW annually affects about 7–15% of all live births around the world (UNICEF). LBW children are more prone to a variety of adverse health outcomes such as asthma, cognitive disorder, diabetes, hypertension and overweight/obesity (Shenkin, Starr, and Deary 2004; Mu et al. 2012; Hirschler et al. 2008; Wei et al. 2003; Mu et al. 2014). A shorter gestational period (prematurity), fetal growth restriction or a combination of both may cause LBW (Kramer 1987).

Several factors including social, economic, genetic, psychological and lifestyle factors, either before or during pregnancy, may affect LBW birth (Kramer 1987). Dietary intakes of pregnant women has also been given a major role in this regard (Chia et al. 2019). Among other dietary factors, maternal caffeine intake has received great attention. Caffeine (1,3,7-trimethylxanthine), as a component of many popular beverages such as coffee and tea, is widely used by pregnant women (Sengpiel et al. 2013; Temple et al. 2017). High maternal caffeine intake during pregnancy was associated with a greater risk of growth restriction, cardiovascular and skeletal abnormalities in offsprings (Golding 1995). The potential harmful effects of caffeine might be attributed to its easily passing the placental barrier and entering the uterine secretions and amniotic fluid (Soyka 1981; Goldstein and Warren. 1962). Given the low capacity of the placenta and the fetus for caffeine metabolism (Aldridge, Aranda, and Neims 1979; Group 2008; Sengpiel et al. 2013), its harmful effects are intensified in pregnancy.

Although several earlier studies investigated the association between maternal caffeine intake and risk of LBW, findings are inconsistent. Some studies revealed that maternal caffeine intake during pregnancy increased the risk of LBW (Martin and Bracken 1987; Bakker et al. 2010), but others found no significant association between maternal caffeine intake and risk of LBW (Fortier, Marcoux, and

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Beaulac-Baillargeon 1993; Bracken et al. 2003; Okubo et al. 2015; Chen et al. 2018; Vitti et al. 2018). Several previous meta-analyses reported a significant positive association between maternal caffeine intake and risk of LBW (Chen et al. 2014; Rhee et al. 2015; Greenwood et al. 2014); however, there are some limitations in these documents. For instance, Chen et al. have combined several outcomes with each other. They considered low birth weight and small for gestational age and intra-uterine growth retardation as a single outcome (Chen et al. 2014). In a most recent meta-analysis, Jin et al. found that maternal caffeine intake during pregnancy was directly associated with a higher risk of LBW (Jin and Qiao. 2020). However, findings of that meta-analysis might be misleading due to inaccuracies in data extraction (Soltani et al. 2021). Therefore, it seems that an updated comprehensive meta-analysis, considering the limitation of previously published studies, is required in this regard. This study was therefore done to systematically review the available evidence on the association between maternal caffeine intake and LBW and to perform a meta-analysis summarizing earlier findings in this regard.

Methods

This study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al. 2009).

Search strategy: We searched for relevant articles published up to Jan 2021 through PubMed and Scopus. For this purpose, we used MESH (Medical Subject Heading) and non-MESH keywords including the following keywords: ("Coffee" OR "Caffeine") AND ("Pregnancy" OR "Pregnancy outcome" OR "Perinatal" OR "Maternal" OR "Birth weight" OR "Infant" OR "Low birth weight"). In addition, reference lists of all available studies, including review articles, were also examined to avoid missing any publication. Unpublished data and gray literature, including congress abstracts, dissertations, and patents, were not included in this meta-analysis. Moreover, duplicate citations were removed.

Inclusion criteria: In this meta-analysis, eligible publications were included based on the following criteria: (1) all cohort studies; (2) that evaluated the association of the maternal caffeine intake and LBW; and (3) reported odds ratio (ORs) or relative risks (RRs) or hazard ratios (HRs) along with 95% confidence intervals.

Exclusion criteria: Letters, comments, short communications, reviews, meta-analyses, ecological studies and animal studies were excluded. In our initial search, we found 6959 articles. After removing duplicate papers, 5234 articles remained. Based on initial screening for title and abstracts, we excluded 5219 studies. In addition, out of 15 remaining articles, eight were excluded for the following reasons: the relevant exposure of interest was not reported ($n = 4$), studies other than cohort investigations including cross-sectional ($n = 1$) and case-control studies ($n = 3$). Therefore, 7 studies (Martin and Bracken 1987; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Bracken et al. 2003; Bakker et al. 2010; Okubo et al. 2015; Chen et al. 2018; Vitti et al. 2018) were finally remained for the current investigation (Figure 1).

Data extraction: Study selection and data extraction from each eligible study were done independently by two investigators (SS and MA), and any disagreements were resolved by a third investigator (AE). In the present study, caffeine consumption during pregnancy was the key exposure variable and incidence of LBW was the key outcome variable. Any reported ORs or RRs for LBW among individuals in the highest category of maternal caffeine consumption compared with those in the lowest category, were extracted. For one study (Bracken et al. 2003) that had provided effect sizes separately for the first and third trimesters, we combined the effect sizes using a fixed-effects model and then, included in the meta-analysis.

Statistical analysis

First, we converted all reported estimates in the included studies to estimates involving the top versus bottom tertile of caffeine intake, using previously suggested standard methods (Chêne and Thompson 1996; Greenland and Longnecker 1992). The formula suggested for these conversions were also applied for computing standard errors. All reported ORs and RRs and their 95% CIs for the risk of LBW were used to calculate the log RRs and their SEs. Using a random effects model with consideration of between-study heterogeneity, the overall ES was calculated. Between-study heterogeneity was examined using Cochrane's Q test and I^2. We also performed a linear dose–response meta-analysis per 100-mg/d increment of caffeine intake using generalized least squares trend estimation. These methods require the number of cases or person-years and total number of subjects for at least three quantitative exposure categories. The generalized least squares trend estimation also requires a mean intake for each level of the exposure. When the range of caffeine intake was available, rather than mean intake, the midpoint of the upper and lower limits in each category was chosen as the assigned dose. In cases for which the higher category was open-ended, we assumed it to have the same amplitude as the previous category. When the lower limit of the lowest category was open-ended, we considered it to be zero. Next, a two-stage random-effects dose–response meta-analysis was conducted to examine the linear trends between caffeine intake and risk of LBW. First, the methods of Greenland and Longnecker (1992) and Orsini, Bellocco, and Greenland (2006) were used to calculate the correlation within each study. Second, the study-specific estimates were combined using a random-effects meta-analysis. To examine the nonlinear dose–response relationship between caffeine intake and risk of LBW, restricted cubic splines with four knots at 5%, 35%, 65%, and 95% percentiles of the distribution were used (Orsini et al. 2012). A sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or group of studies. Publication bias was assessed by visual inspection

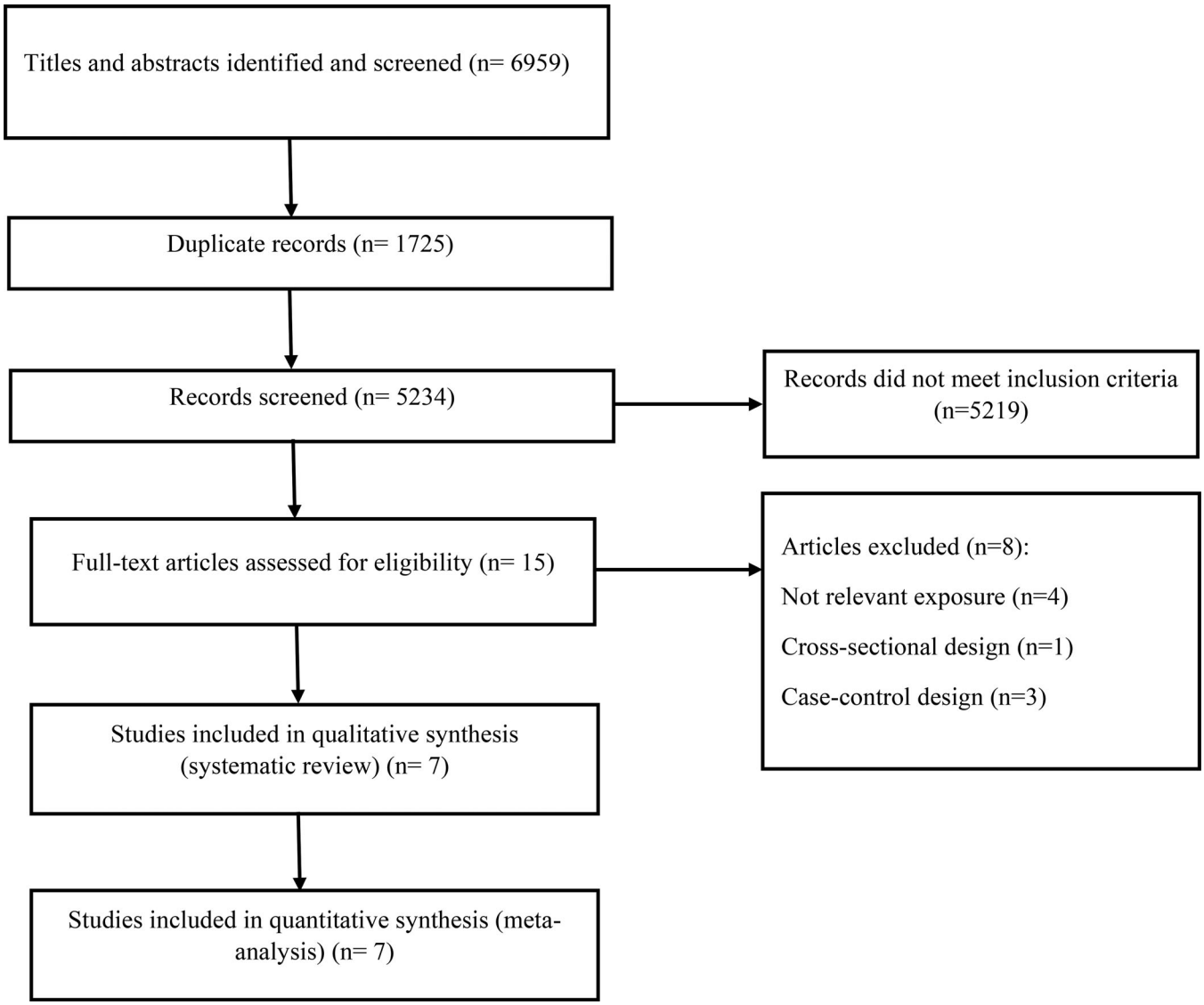

Figure 1. Flow diagram of study selection.

of funnel plots. Formal statistical assessment of funnel plot asymmetry was performed using Egger's regression asymmetry test. Statistical analyses were performed in Stata, version 14.2 (StataCorp). *P*-values were considered significant at the level of <0.05.

Results

Findings from systematic review: In the current systematic review, 7 cohort studies were included (Martin and Bracken 1987; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Bracken et al. 2003; Bakker et al. 2010; Okubo et al. 2015; Chen et al. 2018; Vitti et al. 2018). Characteristics of these studies are briefly presented in Table 1. The sample size of included studies ranged from 858 to 7607 individuals, and in total, 29,168 individuals were included. These studies were published from 1987 to 2018; two were from the United States (Martin and Bracken 1987; Bracken et al. 2003), two from Europe (Bakker et al. 2010; Chen et al. 2018), one from Canada (Fortier, Marcoux, and Beaulac-Baillargeon 1993), one from Asia (Okubo et al. 2015), and one from the Brazil (Vitti et al. 2018). Four studies had assessed maternal caffeine intake in the entire pregnancy (Martin and Bracken 1987; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Okubo et al. 2015; Vitti et al. 2018), one in the first trimester (Chen et al. 2018), one in the first and third trimesters (Bracken et al. 2003) and one in the third trimester (Bakker et al. 2010). Number and type of potential confounders used for statistical adjustment were different across studies. Most studies had controlled for age, parity, education, smoking and alcohol consumption. Several studies had done further adjustments for previous stillbirth, spontaneous abortion (Martin and Bracken 1987; Vitti et al. 2018), marital status (Bracken et al. 2003; Vitti et al. 2018), ethnicity (Martin and Bracken 1987; Bakker et al. 2010) and BMI (Martin and Bracken 1987; Bakker et al. 2010; Okubo et al. 2015; Chen et al. 2018). The majority of included studies used a questionnaire to assess maternal dietary intake. One study used a diet history questionnaire (DHQ) (Okubo et al. 2015), and one study used a self-completed 149-item semi-quantitative food frequency questionnaire (Chen et al. 2018). All 7 studies had considered coffee as their main

Table 1. Main characteristics of studies examining association between maternal caffeine intake and LBW.

Authors (Year)	Country	Trimester considered	Sample size	Exposure (Caffeine from)	Exposure assessment	Outcome assessment	Comparison	OR, RR or HR (95% CI)	Adjustments
Martin and Bracken (1987)	USA	Throughout pregnancy	Cases: 70 Total: 3654	Coffee, tea, colas, drugs	Questionnaire (interview)	Medical chart	0 mg/d 1–150 mg/d 151–300 mg/d ≥ 300 mg/d	OR: 1 1.4 (0.70–3.00) 2.3 (1.10–5.20) 4.6 (2.00–10.50)	Age, marriage, ethnicity, education, cigarettes, alcohol, marijuana use, parity, previous spontaneous abortion, previous induced abortion, previous stillbirth, weight gain, BMI
Fortier, Marcoux, and Beaulac-Baillargeon (1993)	Canada	Throughout pregnancy	Cases: 321 Total: 6733	Coffee, tea, caffeinated cola, chocolate	Questionnaire (interview by phone)	Obtained from the birth certificate	0–10 mg/d 11–150 mg/d 151–300 mg/d ≥ 300 mg/d	OR: 1 1.27 (0.91–1.76) 1.25 (0.81–1.93) 0.99 (0.52–1.87)	Cigarette consumption, number of previous low birth weight newborns, family income, and parity
Bracken et al. (2003)	USA	First and third	Cases: 108 Total: 2292	Coffee, tea, soda	Questionnaire (interview)	Obstetric records	0 mg/d 1–149 mg/d 150–299 mg/d > 300 mg/d	OR: 1 1.21 (0.85–1.71) 1.37 (0.74–2.55) 1.14 (0.46–2.79)	Age, parity, no. of prior pregnancies, marital status, race, education, height, smoking during third trimester, prepregnancy weight
Bakker et al. (2010)	Netherlands	Third	Cases: 329 Total: 7083	Coffee or tea (caffeinated and decaffeinated)	Self-administered questionnaire (postal)	Obtained from medical records	< 2 unit/d 2–3.9 unit/d 4–5.9 unit/d > 6 unit/d	**OR:** 1 1.08 (0.84–1.40) 1.19 (0.73–1.95) 2.58 (1.26–5.30)	Gestational age at visit, maternal age, educational level, ethnicity, parity, smoking habits, alcohol consumption, height, BMI at intake, nutritional intake, folic acid supplement use, maternal pregnancy complications, and fetal sex.
Okubo et al. (2015)	Japan	Throughout pregnancy	Cases: 51 Total: 858	Japanese and Chinese tea, coffee, black tea, soft drinks	Self-administered dietary history questionnaire (DHQ)	Self-administered questionnaire	< 175 mg/d 175- mg/d 258- mg/d ≥ 373 mg/d	**OR:** 1 2.07 (0.87- 4.89) 0.89 (0.33- 2.36) 1.85 (0.74- 4.59)	Age, gestational age at enrollment, height, BMI, education, employment, family structure, parity, smoking status during pregnancy, alcohol intake, folic acid and vitamin B supplement usage, medical problem during pregnancy, dietary change in the preceding month compared with prepregnancy, energy intake, and baby's sex.
Chen (2018)	Ireland	First	Cases: 35 Total: 941	coffee, tea, soft drinks, cocoa-containing	Self-completed149-item food	Hospital records	< 50 mg/d 50 to < 100 mg/d	**OR:** 1 1.55 (0.45- 5.3)	Maternal socioeconomic status, education attainment, cigarette

				foods and beverages	frequency questionnaire		100 to < 200 mg/d ≥ 200 mg/d	3.15 (1.01–9.84) 3.16 (0.82–12.28)	smoking and alcohol consumption during pregnancy, age at recruitment, parity, prepregnancy BMI, and child gender
Vitti (2018)	Brazil	Throughout pregnancy	Cases: 662 Total: 7607	Coffee	Self-reported Questionnaire	Medical records	Not consumed < 300 mg/day ≥ 300 mg/day	**RR:** 1 1.10 (0.92–1.32) 1.42 (0.85–2.38)	Maternal age, education and skin color, marital status, and occupation of the head of the family, parity, previous preterm birth, abortion, and stillbirth, gestational hypertension and diabetes, threatened abortion and preterm delivery, alcohol consumption, maternal smoking, and urinary tract infection

Abbreviations: LBW, low birth weight; DHQ, dietary history questionnaire; BMI, body mass index.

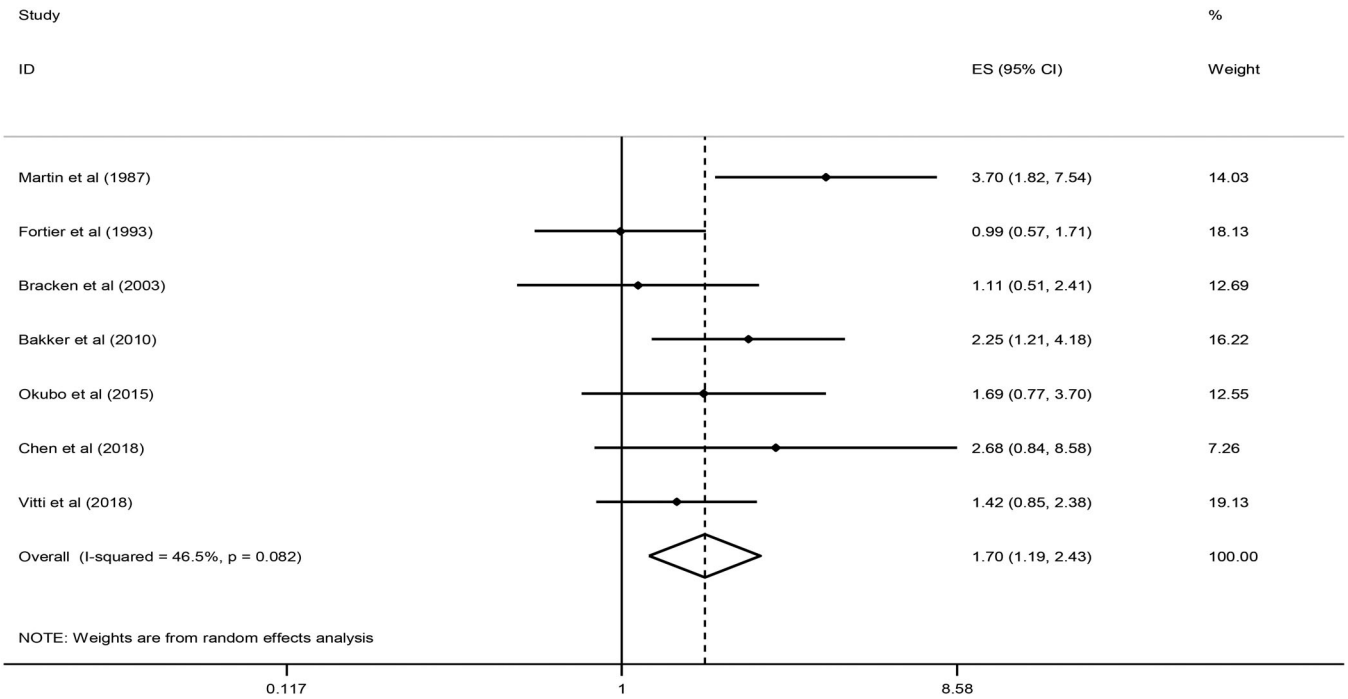

Figure 2. Forest plot for the association between maternal caffeine intake and risk of low birth weight using a random-effects model.

exposure, six studies had examined tea (Martin and Bracken 1987; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Bracken et al. 2003; Bakker et al. 2010; Okubo et al. 2015; Chen et al. 2018) and five studies had considered soft drinks (colas and soda) (Martin and Bracken 1987; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Bracken et al. 2003; Okubo et al. 2015; Chen et al. 2018). In addition drugs (Martin and Bracken 1987), Japanese and Chinese tea (Okubo et al. 2015), chocolate (Fortier, Marcoux, and Beaulac-Baillargeon 1993), and cocoa-containing foods and beverages (Chen et al. 2018) were also considered in other studies. In all included studies, LBW was defined as birth weight less than 2500 g, which obtained from medical records, except for one study in which self-administered questionnaire was used to collect information on neonatal anthropometric measurements at birth (Okubo et al. 2015). Among 7 studies that classified individuals based on maternal caffeine intake, 6 reported the risk of LBW across quartiles of maternal caffeine intake (Martin and Bracken 1987; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Bracken et al. 2003; Bakker et al. 2010; Okubo et al. 2015; Chen et al. 2018) and one remained study assessed this risk across tertiles of maternal caffeine intake (Vitti et al. 2018). In addition, in one prospective study, the risk of LBW was also reported for each 100 mg/d increment in total maternal caffeine intake (Chen et al. 2018). In the current systematic review, 2 out of 7 included studies showed a significant positive association between maternal caffeine intake and risk of LBW (Martin and Bracken 1987; Bakker et al. 2010). All other included studies reported no significant association between maternal caffeine intake and risk of LBW (Fortier, Marcoux, and Beaulac-Baillargeon 1993; Bracken et al. 2003; Okubo et al. 2015; Chen et al. 2018; Vitti et al. 2018).

Meta-analysis on maternal caffeine intake and the risk of LBW

Seven studies examined the association between maternal caffeine intake and risk of LBW (Martin and Bracken 1987; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Bracken et al. 2003; Bakker et al. 2010; Okubo et al. 2015; Chen et al. 2018; Vitti et al. 2018). Combining these seven effect sizes, we found a significant positive association between maternal caffeine intake and risk of LBW; such that those with the highest caffeine intake had 70% higher risk of having a LBW infant (RR: 1.70; 95% CI: 1.19–2.43; Figure 2). No significant between-study heterogeneity was found (I^2= 46.5%; $P_{\text{heterogeneity}} = 0.082$).

All seven studies were included in the present linear dose–response meta-analysis on maternal caffeine intake and risk of LBW (Martin and Bracken 1987; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Bracken et al. 2003; Bakker et al. 2010; Okubo et al. 2015; Chen et al. 2018; Vitti et al. 2018). We found that each additional 100-mg per day of maternal caffeine intake was significantly associated with an increased risk of LBW (RR: 1.12; 95% CI: 1.03–1.22; $P_{\text{heterogeneity}} = 0.020$) (Figure 3). Nonlinear dose–response analysis showed a significant relationship ($P_{\text{nonlinearity}} < 0.001$) between maternal caffeine intake and risk of LBW. So that, the risk of LBW was significantly increased with caffeine intake of 0-100 mg/day. Then, the risk was remained constant by the consumption of 100–250 mg/day. An increasing trend in the risk of LBW was also observed after 250 mg/day intake (Figure 4).

In the present analysis, no evidence of publication bias was found based on the visual inspection of funnel plot (Figure 5) as well as according to results of Egger's test ($P = 0.35$). In sensitivity analysis, we found that our main

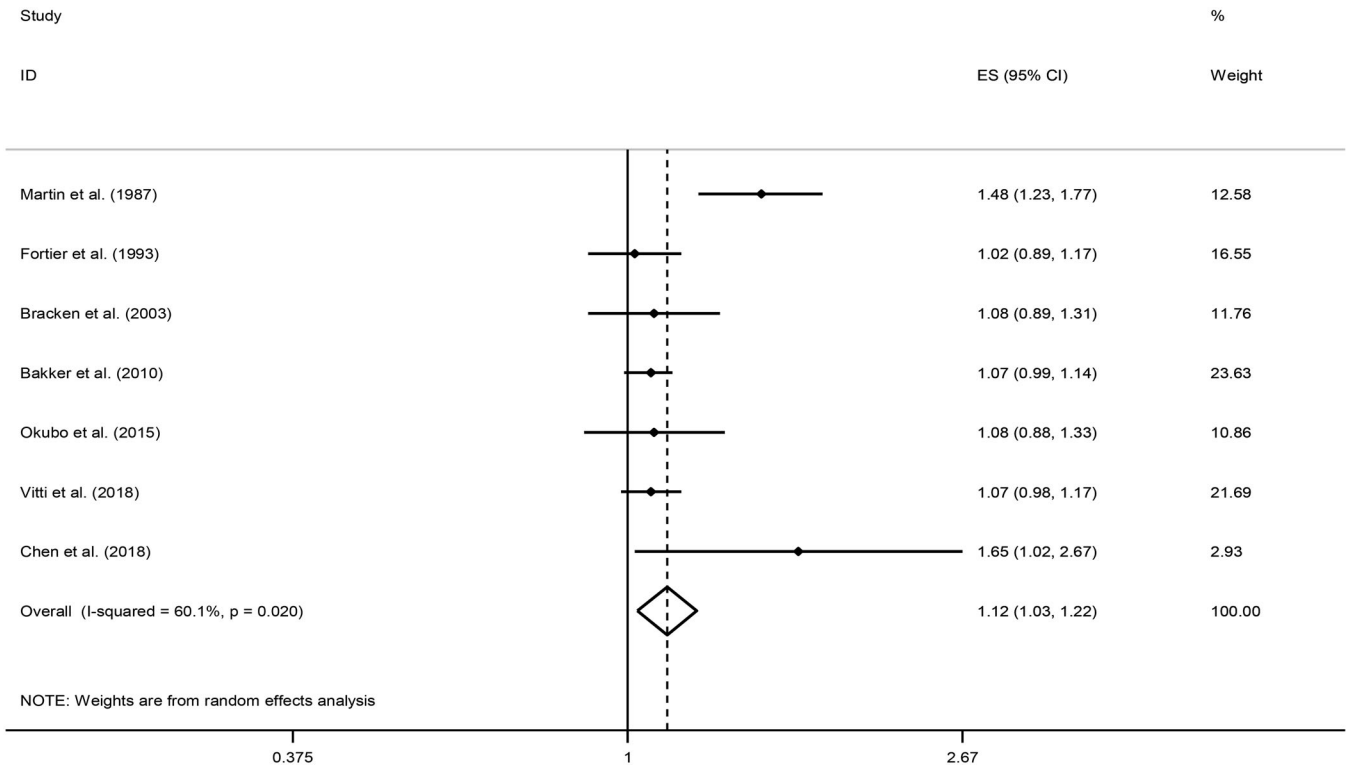

Figure 3. Linear dose–response relationship between maternal caffeine intake and risk of low birth weight.

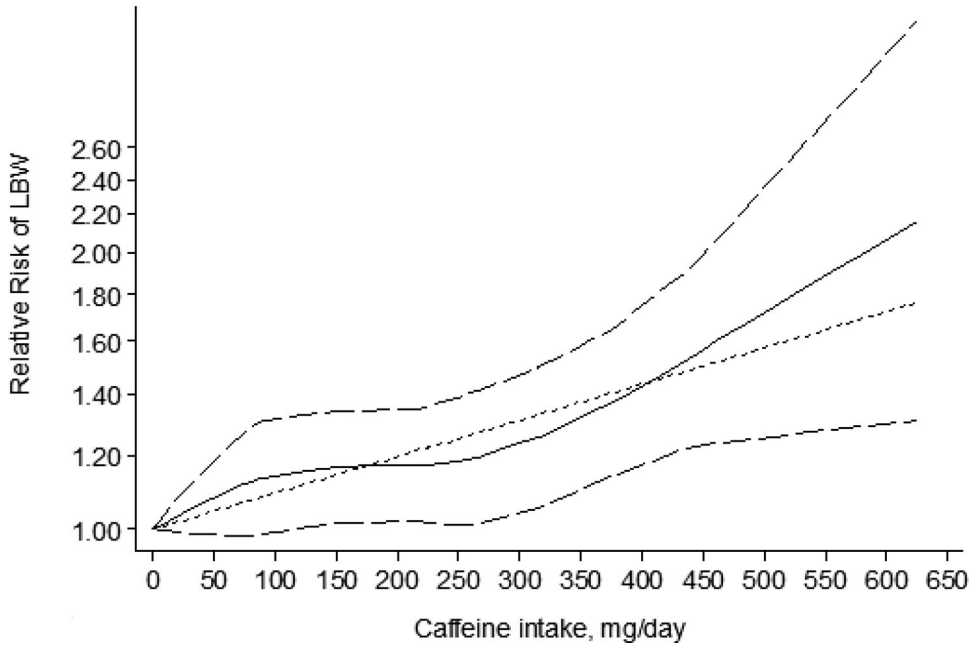

Figure 4. Nonlinear dose–response relationship between maternal caffeine intake and risk of low birth weight.

result was not influenced by a particular study or group of studies assessing the association between maternal caffeine intake and LBW.

Discussion

In the present systematic review and meta-analysis, pooled analyses of seven prospective cohort studies, we observed a significant positive association between maternal caffeine intake and risk of LBW. There was an evidence of non-linear association between maternal caffeine intake and risk of LBW. Moreover, consumption of each additional 100-mg per day of maternal caffeine intake was significantly associated with an increased risk of LBW.

LBW is a well-known cause of infant mortality and morbidity (UNICEF; Lawn et al. 2005). A considerable number of studies have focused on the association between maternal caffeine intake during pregnancy and birth weight; however, the results are controversial (Martin and Bracken 1987; Linn

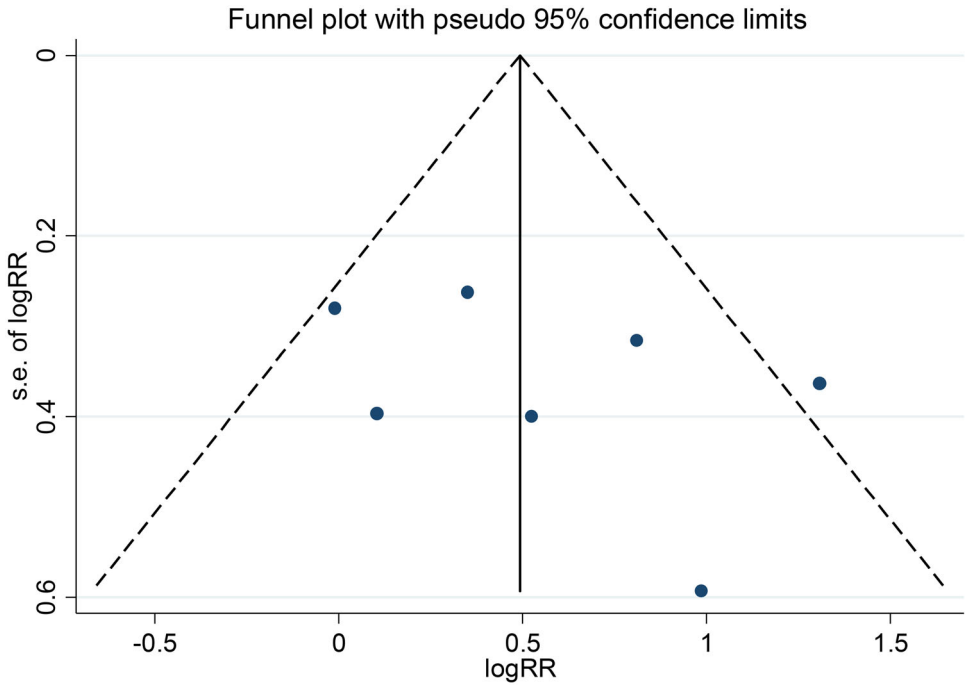

Figure 5. Funnel plot of maternal caffeine intake and risk of low birth weight.

et al. 1982; Fenster et al. 1991; Fortier, Marcoux, and Beaulac-Baillargeon 1993; Cook et al. 1996; Eskenazi et al. 1999; Bech et al. 2007; Larroque et al. 1993; Shu et al. 1995). To our knowledge, only one randomized controlled trial has investigated the effect of reducing caffeine intake (by replacing caffeinated coffee with a decaffeinated one) on birth weight. This Danish study randomly assigned 1207 pregnant women to caffeinated or decaffeinated instant coffee during the second half of pregnancy and reported no significant differences in birth weight between the newborns of women in the caffeinated and decaffeinated groups (Bech et al. 2007).

To date, several qualitative and quantitative reviews have been published to summarize and evaluate the available evidence on maternal caffeine intake and risk of low birth weight. Quantitative reviews in this regard considered studies published up to June 2019. In all previous meta-analyses, maternal caffeine intake was positively associated with LBW (Rhee et al. 2015; Chen et al. 2014; Greenwood et al. 2014). The most recent meta-analysis conducted by Jin and Qiao (2020) showed a significant 7% increase in risk of LBW with 100-mg/d maternal caffeine intake. However, they failed to detect nonlinearity dose–response association. The results of the present meta-analysis indicated that the risk of LBW increased by 12% for every 100-mg/day increment in maternal caffeine intake. We further observed a significant nonlinear relationship between maternal caffeine intake and risk of LBW. It should be noted that findings from Jin and Qiao' meta-analysis might be misleading due to some inaccuracies in data extraction, as we explained them in a letter (Soltani et al. 2021).

Although, the exact mechanism by which caffeine could alter fetal growth is poorly understood, there are several hypothesis. In pregnant women, caffeine freely crosses the placenta into the fetus, where the half-life of caffeine is protracted due to a lack of metabolic enzyme CYP1A2 (Fredholm 1995; Browne 2006; Aldridge, Aranda, and Neims 1979). Caffeine has been shown to inhibit cyclic adenosine monophosphate (cAMP)–phosphodiesterase activity and consequential rise in intracellular cAMP concentrations (Weathersbee and Lodge 1977), which in turn may interfere with fetal cell growth and development (Bistoletti, Fredholm, and Lagercrantz 1981; Soyka 1979). Moreover, caffeine consumption during pregnancy is associated with reduced placental blood flow and hypoxia that result from the blockage of adenosine receptors, as well as from increased epinephrine concentrations in the mother and in the fetus (Kirkinen et al. 1983; Käar et al. 1980; Daly 2000).

The present study has some strengths and limitations. Most included studies had prospective cohort designs that could minimize the possibility of recall or selection bias. Moreover, reported risk estimates from the included studies were harmonized using standard and well-established reliable methods and this provided solid estimates of the nature and magnitude of the association between maternal caffeine intake and the risk of LBW. Despite these strengths, some limitations should be taken into account when interpreting our findings. As our meta-analysis was solely based on observational studies, causal inference cannot be inferred between maternal caffeine intake and LBW. Moreover, for most included studies, maternal caffeine intake was assessed using a questionnaire. Therefore, measurement error in terms of exposure remains a concern. As the current study was conducted on relatively healthy pregnant women with singleton pregnancies, the results can only be generalized to a population with similar characteristics. Finally, publication bias is another potentially important limitation which can affect the results of meta-analyses. In the present meta-analysis, Egger test and visual inspection of the funnel plot did

not indicate publication bias; however, this type of bias cannot be completely ruled out.

Conclusion

This systematic review and updated meta-analysis revealed a significant positive association between maternal caffeine intake and risk of LBW when cohort studies were analyzed. In addition, both linear and non-linear dose–response analyses showed a significant positive association between maternal caffeine intake and risk of LBW.

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The authors' responsibilities were as follows— SS, LA, BL and AE: designed the research; SS and MA: conducted the research; SS, ASM and PS: analyzed the data; SS and AE: wrote the manuscript; AE: had primary responsibility for the final content; and all authors read and approved the final manuscript.

Disclosure statement

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