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PERINATAL CONSEQUENCES OF MATERNAL CAFFEINE INTAKE DURING PREGNANCY: HOW MUCH IS SAFE?

A SYSTEMATIC REVIEW AND META- ANALYSIS

REVISÃO SISTEMÁTICA

ÁREA CIENTÍFICA DE OBSTETRÍCIA

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RESUMO

Introdução: A cafeína é um estimulante encontrado no café, chá, chocolate e até em alguns medicamentos, pelo que acaba por ser facilmente consumida em grande quantidade por gestantes.

A placenta é permeável à cafeína precocemente na gestação. No entanto, a principal enzima responsável pela metabolização da cafeína (citocromo P450 1A2) está ausente quer na placenta quer no feto. Devido à redução da atividade da enzima hepática que a metaboliza, bem como devido à redução da sua *clearance* durante a gravidez, a semi-vida da cafeína está significativamente aumentada no organismo de uma mulher grávida. Este facto combinado com a imaturidade hepática fetal que retarda a excreção deste metabolito, pois está dependente da metabolização materna, tornam prolongada a exposição do feto a este estimulante pelo que a probabilidade de existirem repercussões no desenvolvimento fetal aumenta.

Vários estudos observacionais associam o consumo materno de cafeina durante a gestação ao aumento do risco de aborto espontâneo, morte fetal, parto pré-termo, restrição do crescimento intrauterino, baixo peso ao nascimento, recém-nascido pequeno para a idade gestacional, anomalias congénitas, síndrome de morte súbita e diabetes gestacional. Os resultados da literatura divergem relativamente a esta temática e, como tal, atualmente existe ainda alguma ambiguidade quanto ao aconselhamento da grávida relativamente à quantidade de cafeína que é seguro consumir durante a gravidez.

Objetivo: O objetivo deste trabalho é rever a literatura publicada que relaciona o consumo materno de cafeína com as diferentes consequências a nível fetal, neonatal e na gestação e, consequentemente, estabelecer a quantidade segura de cafeína que a grávida pode consumir sem que o risco seja significativo.

Métodos e Resultados: Para cumprir o objetivo proposto, realizamos uma pesquisa sistemática de artigos nas bases de dados Pubmed, Web of Science e EMBASE que relacionam o consumo materno de cafeína com os eventos fetais, neonatais e gestacionais incluídos na revisão (aborto espontâneo, morte fetal, baixo peso ao nascimento, restrição do crescimento intrauterino, recém nascido pequeno para idade gestacional, parto pré-termo, anomalias congénitas, síndrome de morte súbita e diabetes gestacional). A pesquisa realizada incluiu os artigos publicados nos últimos 30 anos em inglês e português.

Após esta abordagem inicial, os artigos foram selecionados de acordo com a pertinência do título e do resumo, tendo sido excluídos aqueles que não se enquadravam no âmbito desta revisão. Posteriormente, procedeu-se a uma leitura integral dos artigos restantes. De 1002 artigos inicialmente identificados, 57 foram incluídos na revisão sistemática e apenas 46 na meta análise.

Realizamos uma meta análise usando um modelo de efeitos aleatórios, dado que é esperada elevada heterogeneidade entre os estudos (avaliada pelo I^2 de Higgins e Thompson), para cada um dos possíveis pontos de corte de consumo de cafeína tendo sido selecionado como resultado final o modelo

com maior significância estatística. Este procedimento foi repetido para cada um dos 9 eventos considerados.

De acordo com os resultados, o consumo materno de cafeína aparenta ter um efeito protetor na ocorrência de eventos, sendo que a ausência de consumo de cafeína parece aumentar o risco de ocorrência de aborto espontâneo (5 vezes), restrição do crescimento intrauterino (4 vezes), recém-nascido pequeno para a idade gestacional (11 vezes), parto pré-termo (6 vezes) ou anomalias congénitas (43 vezes).

Contudo, este efeito protetor não é independente do nível de consumo, uma vez que simultaneamente verificamos que um consumo materno de cafeína superior a 200 mg/dia parece potenciar o risco de restrição de crescimento intrauterino e anomalias congénitas, superior a 300 mg/dia parece aumentar o risco de aborto espontâneo e de um recém-nascido pequeno para a idade gestacional, e consumos de cafeína acima de 400 mg/dia parecem aumentar o risco de baixo peso ao nascimento e parto pré-termo em mais de 10 vezes (respetivamente 10,061 e 12,825).

Conclusão: De acordo com a metodologia utilizada, um consumo materno de cafeína até 200 mg/dia é seguro e parece ser simultaneamente protetor.

PALAVRAS-CHAVE: CAFEÍNA; CAFÉ; GRAVIDEZ; CONSEQUÊNCIAS PERINATAIS; CONSUMO MATERNO;

ABSTRACT

Introduction: Caffeine is a widely consumed stimulant that can be found in a range of beverages such as coffee, tea, chocolate, and even some medicine, which makes it easily ingested in considerable amounts during pregnancy.

This stimulant can freely transfer across all biological membranes, including the blood–placental barrier. The main enzyme involved in caffeine metabolism (cytochrome P450 1A2) is absent in both the placenta and the fetus. Therefore, the fetus depends on maternal caffeine metabolism. However, throughout gestation, there is a delayed maternal clearance of caffeine, and the rate of caffeine metabolism decreases progressively from the first to the third trimester. Consequently, the fetus is exposed to caffeine and its metabolites for a prolonged period, which can lead to caffeine accumulation in fetal tissues and leaves neonates at risk of adverse outcomes.

Several authors of observational studies established an association between maternal caffeine intake and adverse fetal, neonatal, and pregnancy outcomes. Nevertheless, conflicting results found in the literature make it difficult for health professionals to advise pregnant women about avoiding caffeine during pregnancy, since the precise level of intake above which the risk increases, remains unknown.

Aims: We aimed to systematically review the published literature on the effects of caffeine intake by mother on fetal, neonatal and pregnancy outcomes with the purpose to establish a safe quantity of caffeine that could be ingested during gestational period, without increasing the risk of adverse outcomes.

Methods and results: We systematically searched PubMed, EMBASE, and Web of Science on 27, 29, and 31 of January, respectively. The search was limited by language (English and Portuguese), type of subjects (human) and in time (since 1990, in the last 30 years). We searched for articles that related maternal caffeine consumption with fetal, neonatal and pregnancy outcomes under analyses (spontaneous abortion, stillbirth, low birth weight, intrauterine growth restriction, small for gestational age, preterm birth, congenital anomalies, SIDS and gestational diabetes mellitus). A total of 57 studies were included in the review; only 46 were included in the meta-analyses. We conducted a meta-analysis using a random-effects model (heterogeneity evaluated by Higgins e Thompson I^2) and selected as a final result the model that separated further cases and control groups, being the one who presented a lower p-value.

According to the results, the absence of caffeine consumption seems to increase the chance of occurrence of events such as spontaneous abortion (5 times), intrauterine growth restriction (4 times), small for gestational age (11 times), preterm birth (6 times) or congenital anomalies (43 times); therefore, we can infer that caffeine consumption may have a protective effect on the occurrence of those events in pregnant women and newborns. Additionally, we verified that a maternal caffeine intake higher than 200 mg/day seems to increase the risk of intrauterine growth restriction and congenital anomalies. A caffeine consumption above 300 mg/day also appears to enhance spontaneous abortion and small for gestational age events. Caffeine intake beyond 400 mg/day seems to increase the risk of low birth weight and preterm birth by more than ten times (10. 061 and 12. 825 on average, respectively).

Conclusion: According to these results, the ingestion of caffeine until 200 mg/day is secure and protective.

KEYWORDS: CAFFEINE; COFFEE; PREGNANCY; PERINATAL OUTCOME; MATERNAL CONSUMPTION;

ABBREVIATIONS

CA congenital anomalies
CVM Cardiovascular malformations
GDM Gestational Diabetes Mellitus
IUGR Intrauterine Growth Restriction
LBW Low Birth Weight
LD Limb Deficiencies
NTD neural tube defects (spina bifida)
PTB Preterm Birth
SAB Spontaneous Abortion
SGA Small for Gestational Age
SIDS sudden infant death syndrome

INTRODUCTION

Caffeine (1,3,7-trimethylxanthine) is a widely consumed stimulant that can be found in a range of beverages such as coffee, tea, chocolate, and even some medicines, which makes it easily ingested in considerable amounts during pregnancy. [1, 2]

Some authors of observational studies have associated maternal caffeine intake with intrauterine growth restriction [3, 4], low birth weight [4, 5], preterm birth [6-8], spontaneous abortion [9-25], or stillbirth [21]. There has also been hypothesized that maternal caffeine consumption during pregnancy might cause the infant to be more vulnerable to sudden infant death syndrome [26] and congenital anomalies [27-29] such as cardiovascular malformations[30] or neural tube defects [31, 32].

Throughout gestation, the rate of caffeine metabolism decreases progressively from the first to the third trimester. Therefore, the half-life of caffeine increases from an average of 3 hours for non-pregnant women to 10.5 hours during the last four weeks of pregnancy. [33, 34]

As a lipophilic substance, it is known that this stimulant can freely transfer across all biological membranes, including the blood–placental barrier. [35] The main enzyme involved in caffeine metabolism (cytochrome P450 1A2) is absent in both the placenta and the fetus [35, 36]. Therefore, the fetus depends on maternal caffeine metabolism. [5] Since there is a maternal delayed clearance of caffeine, the fetus is exposed to caffeine and its metabolites for a prolonged period, which can lead to caffeine accumulation in fetal tissues and leaves neonates at risk of adverse outcomes.

Furthermore, exposure to caffeine naturally induces an increase in catecholamine circulating concentrations (adrenaline, dopamine, and serotonin). It can lead to vasoconstriction in the uteroplacental circulation and increase of fetal heart rate, leading to impaired fetal oxygenation, which may, in turn, affect fetal growth and development of the fetus [37, 38].

Caffeine has been inversely related to levels of estradiol and progesterone during the luteal phase of the menstrual cycle and positively related to sex hormone-binding globulin [39, 40]. These alterations in endogenous hormone levels related to caffeine consumption could plausibly increase the risk of spontaneous abortion.[20]

Conflicting results found in the literature make it difficult for health professionals to advise pregnant women about avoiding caffeine during pregnancy, since the precise level of intake above which the risk increases remains unknown.

Having this in mind, we aimed to systematically review the published literature on the effects of caffeine intake by mother on fetal, neonatal and pregnancy outcomes with the purpose to establish a safe quantity of caffeine that could be ingested during gestation period without causing any repercussions.

MATERIALS AND METHODS

Protocol and registration

This study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Literature search

We systematically searched PubMed, EMBASE, and Web of Science on 27, 29, and 31 of January, respectively. The search equation used in all the databases was:

(coffee OR caffeine OR caffeine intake) AND (pregnancy OR pregnant) AND (miscarriage OR neonatal outcome OR spontaneous abortion OR stillbirth OR fetal loss OR low birth weight OR preterm birth OR premature delivery OR birth defects OR small for gestational age OR perinatal death OR fetal hypoxia OR fetal tachycardia OR fetal dysrhythmia OR gestational diabetes mellitus OR sudden infant death syndrome)

OR

("Infant, Premature"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Fetal Diseases"[Mesh])

AND

"Pregnancy"[Mesh] AND ("Coffee"[Mesh] OR "Caffeine"[Mesh])

The search was limited by language (English and Portuguese), type of subjects (human) and in time (since 1990, in the last 30 years).

Eligibility criteria

Studies were included if they met the following criteria: (i) Types of studies included were original and peer-reviewed. Review articles or meeting abstracts were excluded. Only studies performed on humans were included. (ii) Types of participants: Pregnant women of any age and parity. (iii) Types of

interventions: Caffeine intake and caffeine supplements (inclusive of all caffeinated beverages, such as tea and coffee, or non-beverages, such as chocolate and medications) during pregnancy versus limited use of caffeine. We only included studies that reported maternal caffeine consumption during pregnancy.

(iv) Types of outcome measures: The primary outcome is the safety of different levels of maternal caffeine consumption during pregnancy, and the secondary outcomes are:

1. Spontaneous abortion (natural or spontaneous end of a pregnancy at a stage where the embryo or the fetus is incapable of surviving, generally defined in humans at a gestation before 20 weeks) and stillbirth (fetal death after 20 gestational weeks).
2. Low birth weight, a fetus that weighs less than 2500 g regardless of gestational age (assessed at the time of birth).
3. Small-for-gestational age (a fetus whose birth weight lies below the 10^{th} percentile for that gestational age, assessed at the time of birth).
4. Intrauterine growth restriction (defined as $<10^{th}$ percentile of birth weight for gestational age)
5. Preterm birth (the birth of a baby before 37 weeks).
6. Congenital anomalies
7. Sudden infant death syndrome (a syndrome marked by the symptoms of a sudden and unexplained death of an apparently healthy infant aged one month to one year).
8. Gestational diabetes mellitus

Data collection and management

Two authors (MB and ALA) systematically screened titles and abstracts of publications retrieved using the search strategy, in order to select studies that met the inclusion criteria outlined above.

The full text of the eligible studies was, again, independently assessed for eligibility by the two review team members. One of the authors had a significant preponderance on the final decision, so any disagreement between them over the eligibility of particular studies was discussed, but the final word was from ALA. The inter-rater agreement was found to be very strong (Cohen's kappa = 0.845, $p < 0.001$).

Data extraction concerned: authors; year of publication; type of study; number of cases and controls or sample size; outcome-focused on the article; method of exposure assessment; the period of exposure assessment; types of containing beverages evaluated; and details of adjustment for potential confounding factors. For quantitative evaluation were additionally extracted the results regarding the level of maternal caffeine consumption during pregnancy.

We analyzed studies with multiple sequenced publications, ensuring no duplication of results and the collection of the most recent data.

Risk of bias assessment

Two authors (MB, ALA) independently assessed the risk of bias of the included articles, following ROBINS I, the Cochrane Collaboration's 'Risk of bias's tool recommended for observational studies.

Cohort and case-control studies were assessed as "low", "moderate", "critical", "serious" or "unclear" risk for the following biases: bias due to confounding, the bias in the selection of participants, the bias in the measurement of interventions, the bias due to departure from intended intervention, the bias due to missing data, the bias due to measurement of outcomes and the bias due to selection of the reported result.

Most studies were retrospective, which might have compromised the accuracy of the responses to the questionnaire. (Table 1, Appendix 1)

Statistical analysis

Data collected showed substantial variability in the way different studies reported caffeine intake. To combine the risk estimates from different categories we established six levels of caffeine consumption: (i) zero or no consumption (ii) low caffeine consumption (<200 mg/d); (iii) moderate-low caffeine consumption (200-300 mg/d); (iv) moderate-high caffeine consumption (300-400) (v) high caffeine consumption (400-600mg/d); and (vi) excessive caffeine consumption (≥600 mg/d).

To measure the risk of occurrence of events in the group of cases (exposed to a higher amount of caffeine intake per day) comparatively to the risk of occurrence of events in the control group (exposed to a lower amount of caffeine intake per day) we chose odds ratio as effect measure, in spite some of the studies where prospective cohorts. For this to be possible, we had to assembly the six categories of consumption in two groups. Thus, there are five possible models accordingly with previously considered cut-offs: model 1 considers "zero consumption" as control group versus "consumption"; model 2 considers "zero consumption" or "low consumption" versus "moderate-low" to "excessive consumption"; model 3 considers "zero consumption" till "moderate-low consumption" versus "moderate-high" till "excessive consumption"; model 4 considers "zero consumption" till "high consumption" versus "excessive consumption". Therefore, we conducted a meta-analysis using a random-effects model since potential sources of heterogeneity where expected between studies for the different possible cut-offs. Heterogeneity was assessed by the Higgins and Thompson I^2 statistic and assumed to be relevant if it exceeded 50%. We selected as a final result the model that separates more the cases and control groups, which is the one who presents a lower p-value.

This procedure was repeated for the nine events considered: SAB, LBW, IUGR, SGA, PTB, CA, SIDS, Stillbirth and GDM.

For each of the events considered it is presented global odds ratio value (OR_G), 95% confidence interval and the p-value that represents the comparison of this value with absence of effect (OR = 1). If OR > 1, this indicates that higher caffeine intake can increase the chance of occurrence of a certain event,

meanwhile OR < 1 means the increase of caffeine intake might have a protective effect on the occurrence of that same event.

The mean effect was considered significant if its 95% confidence interval did not include the zero value.

Additionally, for each analysis, we present a forest plot and a funnel plot. Analysis was conducted on RStudio, version 1.1.463 to access R application, version 3.5.3.

RESULTS

Search results

The literature search identified 1002 articles. After removal of duplicates, we excluded a total of 737 based on title and abstract evaluation, study type, study population, and outcomes evaluated. The full text of the remaining 110 studies was then screened, leading to the exclusion of 53 publications: 24 of the articles focused on outcomes that we did not consider, two did not provide quantitative or qualitative information about caffeine intake, one considered the impact of caffeine intake pre-pregnancy on the success rate of in vitro fertilization, 19 full texts could not be accessed, and 7 were reviews.

Finally, 57 publications met all the inclusion criteria for the qualitative review, and 46 of these were suitable for the quantitative synthesis with meta-analysis (Figure 1). Baseline characteristics of included studies are shown in table 2 (Appendix 2).

The process through the different phases of a systematic review is illustrated in the following PRISMA flowchart:

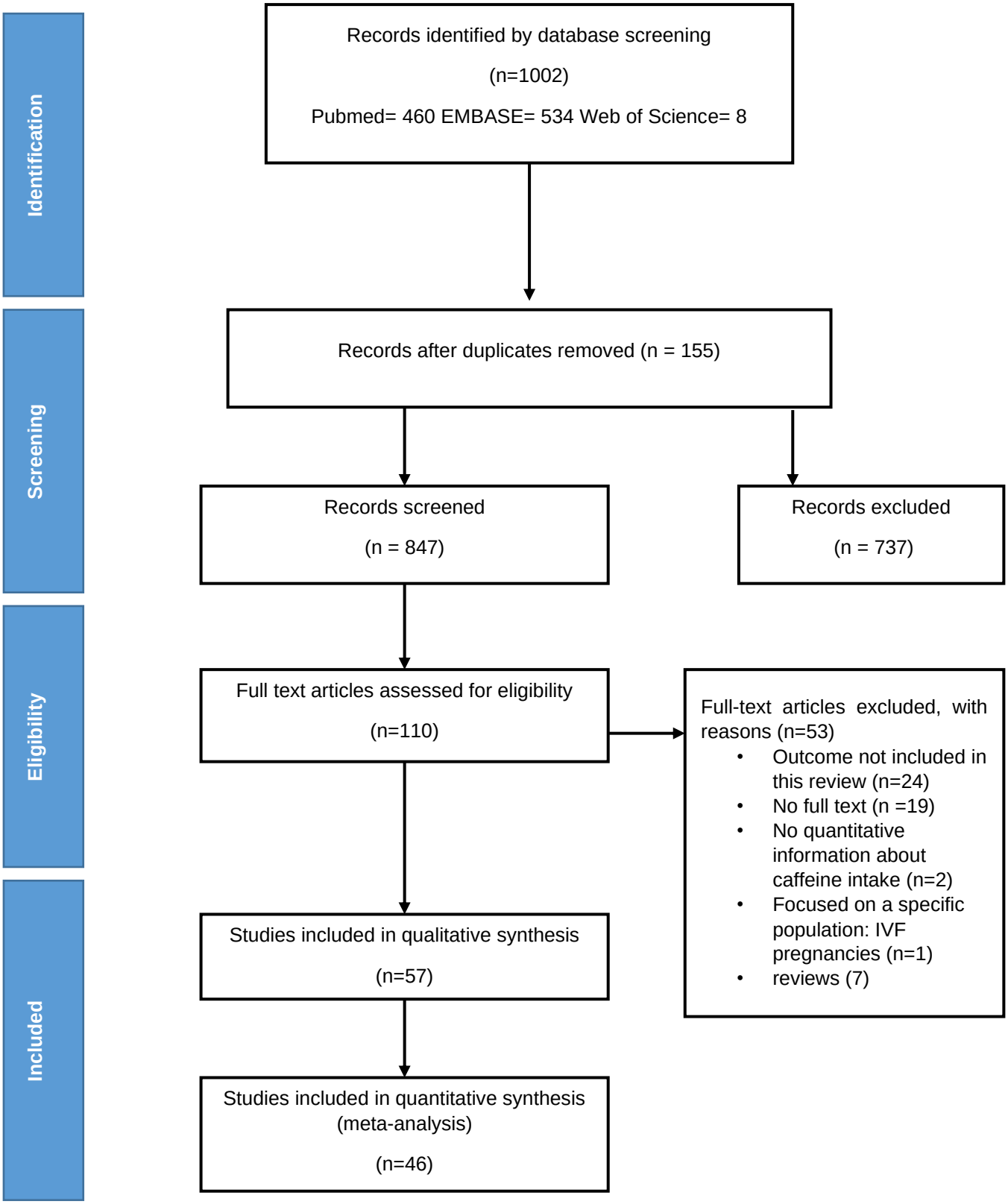

Figure 1 Flow diagram of literature search

SPONTANEOUS ABORTION

Overall, meta-analyses performed for this event for the different cut off points presented high variability, except model 5, where I^2 = 0.00% (Table 3, Figure 2). However, we have to point out that in this model, only two studies where included. This fact can be justified by the diversity of study designs involved in each of the models.

Table 3 Summary of values obtained by a meta-analysis of random effects for the SAB event, considering each possible cut-off point for caffeine consumption after variable dichotomization

Model	I^2	N Studies	OR	95%CI	*p value*
1	96.83%	5	0.197	0.092 – 0.421	< 0.001
2	99.34%	15	0.789	0.255 – 2.436	0.680
3	99.24%	13	5.974	1.798 – 19.852	0.004
4	99.17%	6	8.696	1.824 – 41.448	0.007
5	0.00%	2	22.481	17.723 – 28.516	< 0.001

Model 1: zero consumption versus consumption; Model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive; Model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption; Model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption; Model 5: zero consumption until high consumption(< 600mg/day) versus excessive consumption.

N studies – number of studies considered for the meta analyses; OR – odds ratio; 95% CI- confidence interval for odds ratio; p – statistical significance of model's odds ratio

It is observed that the consumption of caffeine in comparison to zero consumption appears to be protective of the occurrence of spontaneous abortion (OR = 0.197; p < 0.001), having pregnant women who consume caffeine a chance of having a spontaneous abortion by almost 80%.

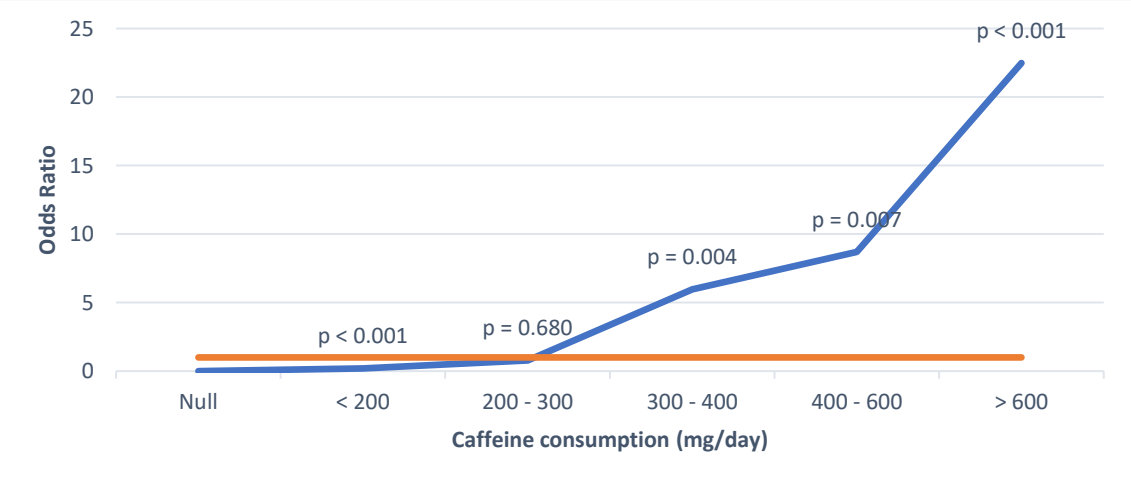

Figure 2 The black line represents the odds ratio observed by the change in caffeine consumption from the previous value to the corresponding or higher x value. The correspondent p value is presented on the dot label and the red line represents the value correspondent to the absence of risk (OR=1).

As it can be observed in table 3 and figure 2, there seems to be no observed impact of maternal caffeine consumption on the frequency of spontaneous abortion for the cut-off point of 200 mg/day (model 2) nonetheless, the risk of spontaneous abortion significantly increases from consumption of 300 mg/day to higher.

As it can be observed in figure 2, the increase in maternal daily consumption of caffeine appears to potentiate the occurrence of this type of event, being the chance of its occurrence almost six times more elevated in pregnant women who consume at least 300 mg/day of caffeine and increasing this chance to 22.5 when the consumption doubles. However, we only have two studies under analysis.

MODEL 1

The funnel plot correspondent to model 1 shows high heterogeneity, from five studies under analyses, only one is inside the confidence limits. According to the forest plot, all studies show a statistically significant effect in the sense that caffeine consumption has a protective effect on the occurrence of spontaneous abortion events when in comparison to zero consumption, being the global effect also statistically significant ($\ln(OR_G)$ = – 1.62; 95% CI: [-2.38, -0.87]),

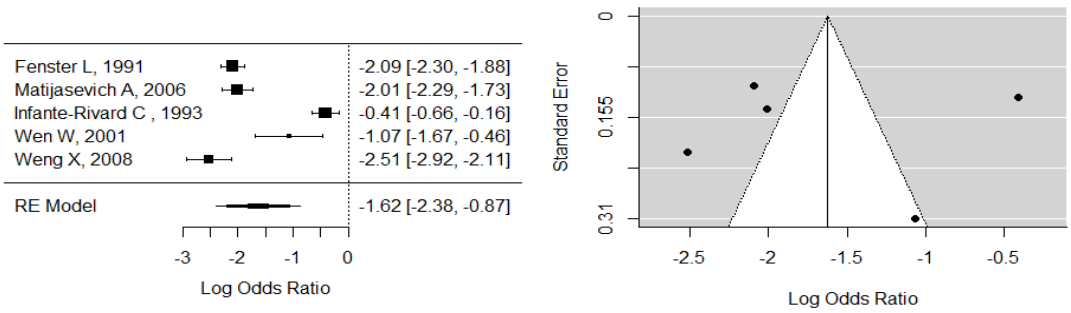

Figure 3 forest plot and funnel plot for *model 1: zero consumption versus consumption*

MODEL 2

For model 2, there was also high heterogeneity; only three of the fifteen studies included were inside the confidence limits. Five of the studies showed a statistically significant effect in the way that maternal caffeine consumption equal or superior to 200 mg per day could increase the risk of spontaneous abortion. Seven of the studies showed the opposite, also with a statistically significant effect. Three of the studies were inconclusive as to the summary measure, which was also inconclusive. Consequently, the global effect, for this cut-off point, does not present statistical significance ($\ln(OR_G)$ = -0.24; 95% CI: [-1.36, 0.89]).

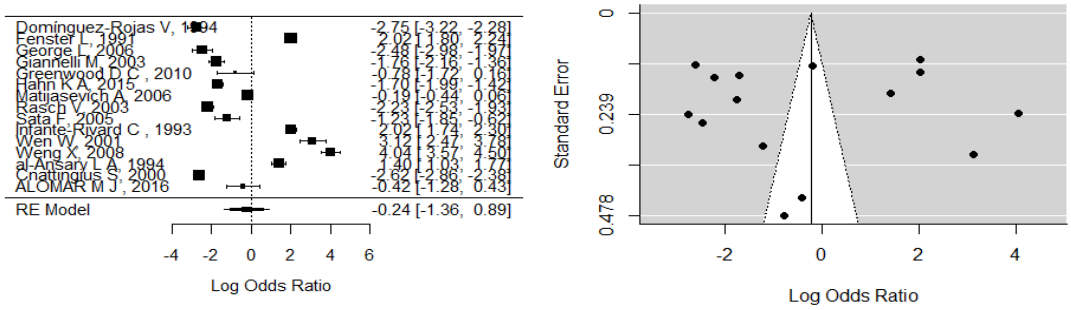

Figure 4 forest plot and funnel plot for *model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive*

MODEL 3

Model 3 also shows high heterogeneity, as we can see in the funnel plot, only one of the thirteen studies under analyses was inside de confidence limits. Eleven studies showed a statistically significant effect in the way that a consumption equal or superior to 300mg/day could increase the risk of spontaneous abortion. One study showed the opposite, also with a statistically significant effect. One study was inconclusive. The global effect, for this cut-off point, was statistically significant (ln (OR_G) = 1.79; 95%CI [0.59, 2.99]).

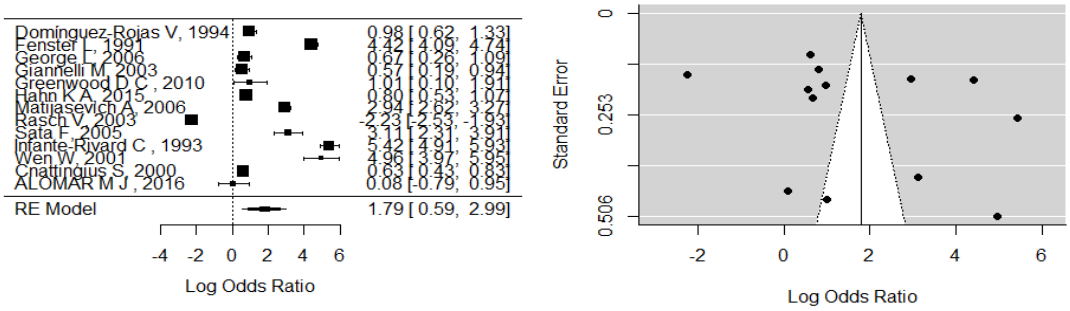

Figure 5 forest plot and funnel plot for *model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption*

MODEL 4

The funnel plot correspondent to model 4 also shows high heterogeneity; only 2 studies were between confidence limits. All studies show a statistically significant effect in the sense that a caffeine consumption high or excessive, equal, or superior to 400 mg/day has a potentiator effect

on the occurrence of spontaneous abortion being the overall effect also statistically significant (ln (OR_G) = 2.16 95%CI [0.60, 3.72]).

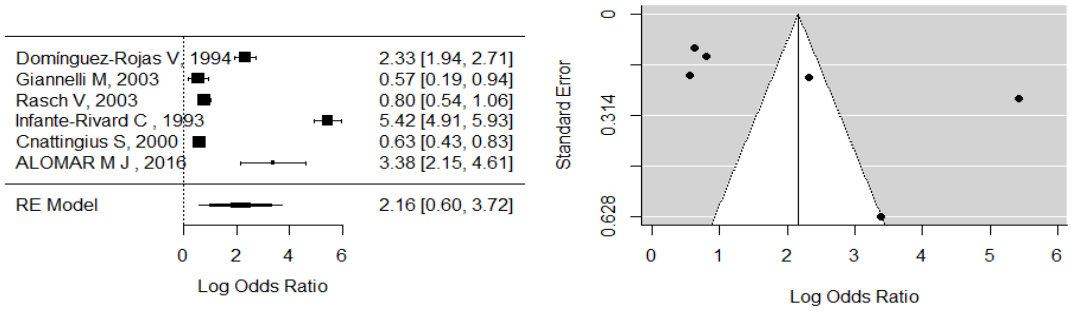

Figure 6 forest plot and funnel plot for *model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption;*

MODEL 5

As we can see in the correspondent funnel plot, model 5 was the only model that did not exhibit high heterogeneity. Both studies included presented a statistically significant effect (ln (OR_G) = 3.11 95% CI [2.87, 3.35]) in the sense that a maternal caffeine consumption higher than 600 mg/day increases the risk of spontaneous abortion exponentially.

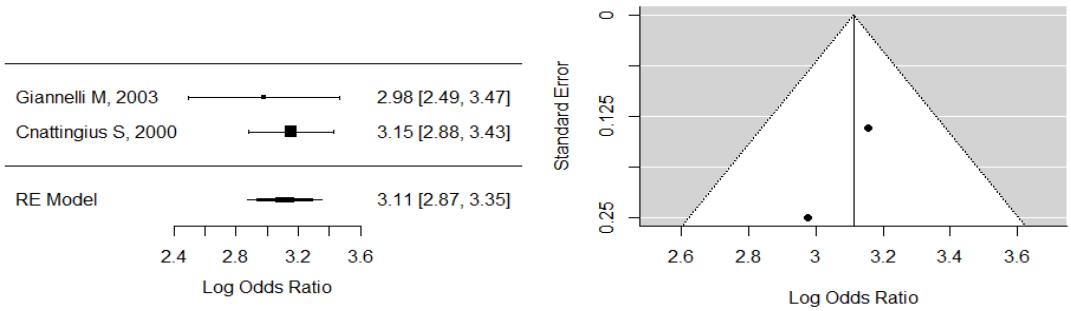

Figure 7 forest plot and funnel plot for *model 5: zero consumption until high consumption (< 600mg/day) versus excessive consumption.*

LOW BIRTH WEIGHT

Table 4 Summary of values obtained by meta-analysis of random effects for the LBW event, considering each possible cut-off point for caffeine consumption after variable dichotomization

Model	I^2	Nstudies	OR	95%CI	*p value*
1	95.46%	2	0.399	0.089 – 1.782	0.229
2	99.34%	4	3.511	0.191 – 64.618	0.398
3	99.81%	6	9.503	0.788 – 114.640	0.076
4	99.10%	3	10.061	1.172 – 86.388	0.035
5	98.61%	2	454.143	18.290 – 11276.371	< 0.001

Model 1: zero consumption versus consumption; Model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive; Model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption; Model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption; Model 5: zero consumption until high consumption(< 600mg/day) versus excessive consumption.

N studies – number of studies considered for the meta analyses; OR – odds ratio; 95% CI- confidence interval for odds ratio; p – statistical significance of model's odds ratio

Our analyses showed that the risk of low birth weight increases for maternal caffeine consumption equal or superior to 400mg/day (Table 4, Figure 8).

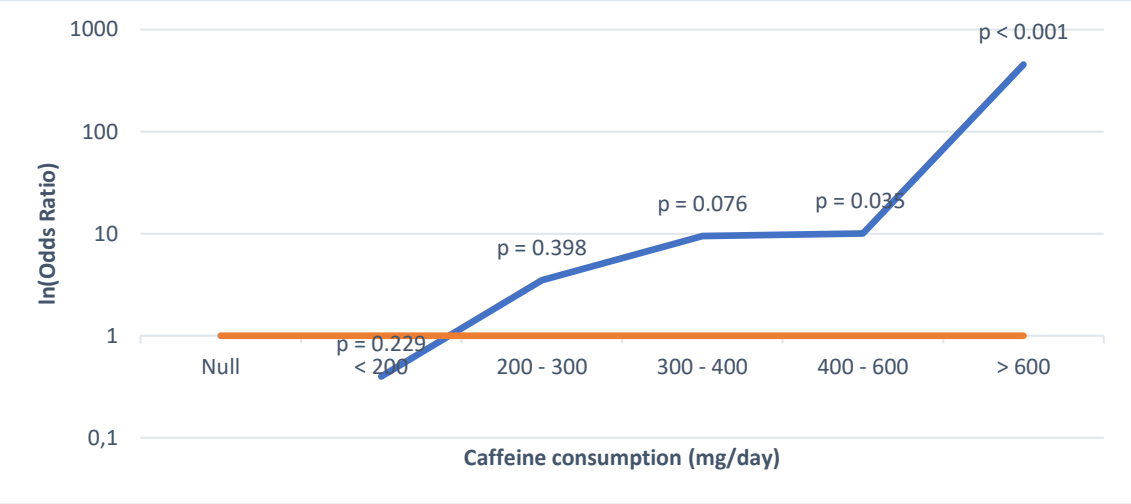

Figure 8 The blue line represents the ln (OR) observed by the change in caffeine consumption from the previous value to the corresponding or higher x value. The correspondent p-value is on the dot label, and the orange line represents the value correspondent to the absence of risk (OR=1).

MODEL 1

Only two studies were included in model 1 and according to the funnel plot none of them were between limits of confidence. One of the studies showed a statistically significant effect in the way that caffeine consumption was protective to the ocurrence of low birth weight and the other one

was inconclusive. Consequently, the global effect measure, for this cut-off point, does not present statistical significance (ln (OR_G) = -0.92; 95%CI [-2.42, 0.58]).

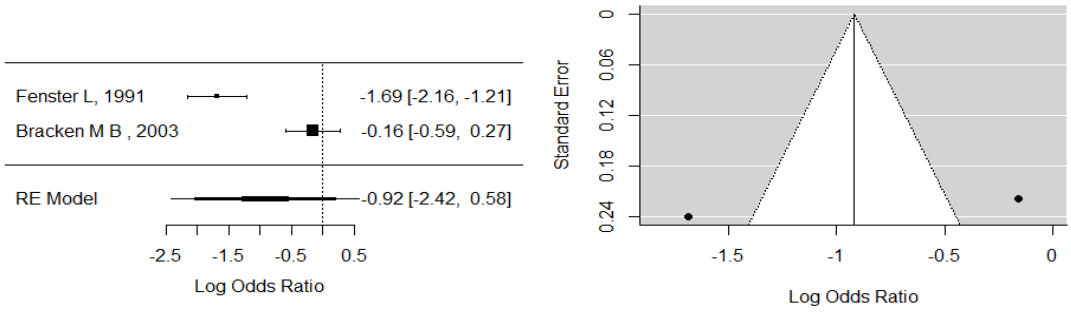

Figure 9 forest plot and funnel plot for *model 1: zero consumption versus consumption*

MODEL 2

Funnel plot regarding model 2, showed high heterogeneity; none of the studies were inside the confidence limits. Three of the studies showed a statistically significant effect in the way that a maternal caffeine consumption ≥ 200 mg/day increases the risk of low birth weight. One study showed the opposite and another was inconclusive as to the summary measure, which was also inconclusive. Consequently, the global effect, for this cut-off point, does not present statistical significance (ln (OR_G) = 1.26; 95%CI [-1.66, 4.17]).

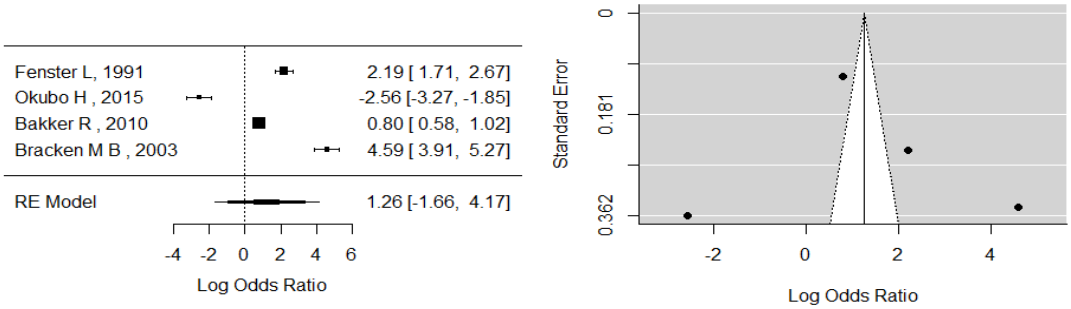

Figure 10 forest plot and funnel plot for *model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive*

MODEL 3

Model 3 also shows high heterogeneity, as we can see in the funnel plot, none of the six studies under analyses was inside de confidence limits. Four studies showed a statistically significant effect in the way that a consumption equal or superior to 300mg/day, could increase the risk of low birth weight. The other two studies were inconclusive. The global (overall) effect, for this cut-off point does not shows statistical significance (ln (OR_G) = 2.25; 95%CI [-0.24, 4.74]).

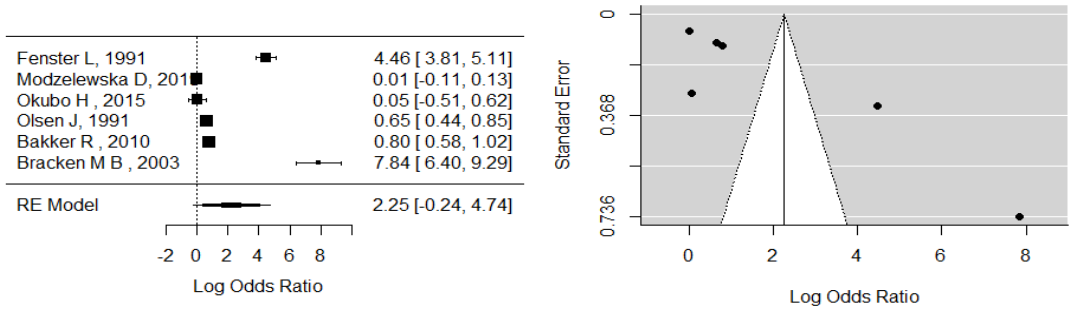

Figure 11 forest plot and funnel plot for *model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption*

MODEL 4

The Funnel plot correspondent to model 4 also shows high heterogeneity, only one of three studies under analysis was included in confidence limits. All studies show a statistically significant effect in the sense that a caffeine consumption equal or superior to 400 mg/day increases the risk of low birth weight. The global effect is also statistically significant (ln (OR_G) = 2.31; 95% CI [0.16, 4.46]).

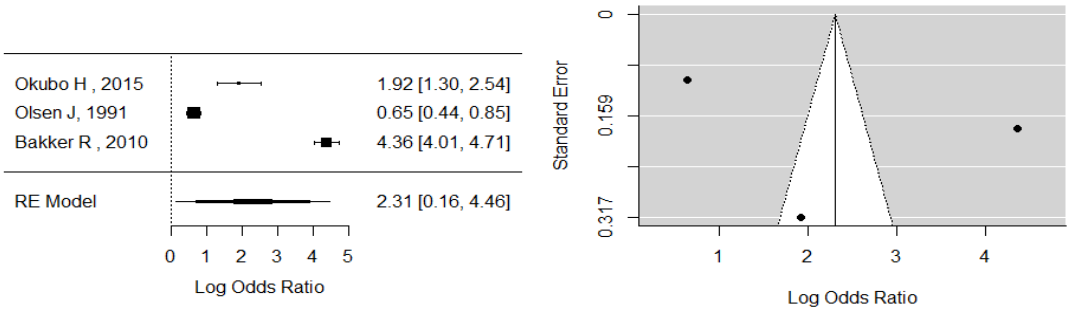

Figure 12 forest plot and funnel plot for *model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption;*

MODEL 5

As we can see in the correspondent funnel plot, model 5 also showed high heterogeneity. As we can see in the forest plot, both studies included showed a statistically significant effect in the sense that a maternal caffeine consumption higher than 600 mg/day increases significatively the risk of lower birth weight. The global effect is also statistically significant (ln (OR_G) = 6.12; 95%CI [2.91,9.33]).

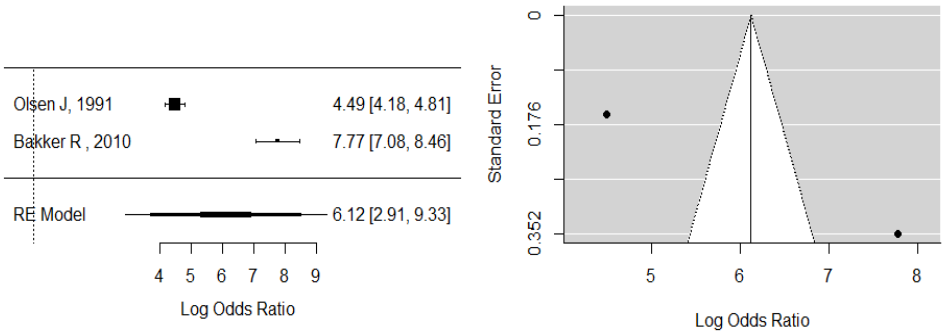

Figure 13 forest plot and funnel plot for *model 5: zero consumption until high consumption (< 600mg/day) versus excessive consumption.*

SMALL FOR GESTATIONAL AGE

Table 5 Summary of values obtained by meta-analysis of random effects for the SGA event, considering each possible cut-off point for caffeine consumption after variable dichotomization

Model	I^2	Nstudies	OR	95% CI	*p value*
1	99.27%	4	0.091	0.032 – 0.257	< 0.001
2	99.85%	8	2.215	0.520 – 9.430	0.282
3	99.74%	6	12.825	3.119 – 52.731	< 0.001
4	99.27%	3	38.263	3.033 – 482.762	0.005
5	-	1	-	-	-

Model 1: zero consumption versus consumption; Model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive; Model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption; Model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption; Model 5: zero consumption until high consumption(< 600mg/day) versus excessive consumption.

N studies – number of studies considered for the meta analyses; OR – odds ratio; 95% CI- confidence interval for odds ratio; p – statistical significance of model's odds ratio

In this analyses, we can infer that there is an increase in the risk of occurrence of SGA events for a consumption equal or superior to 300 mg/day (table 5, figure 14) although we also observe that moderate maternal consumption of caffeine can be protective to the occurrence of events when compared to no consumption (p< 0.001).

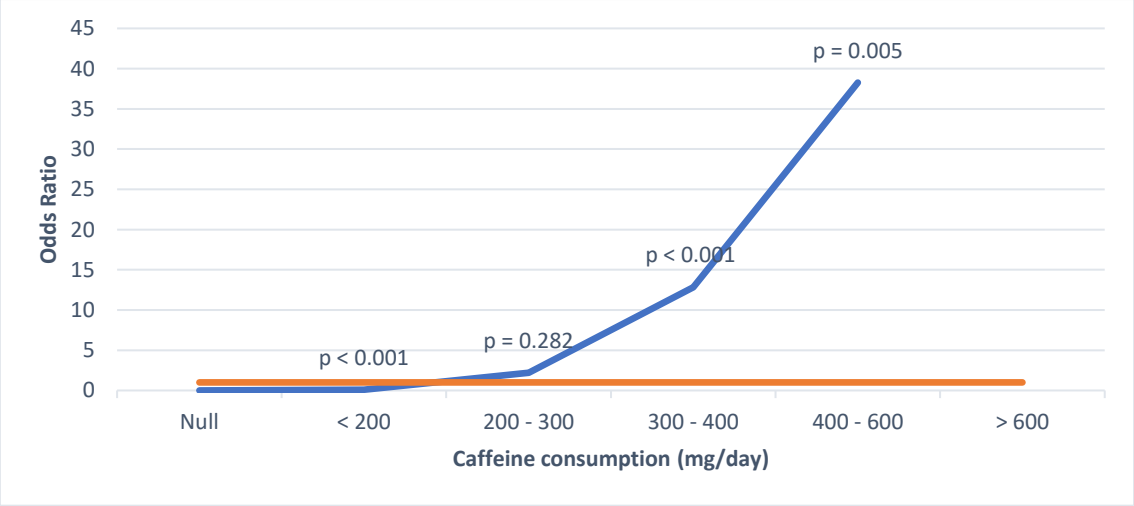

Figure 14 The blue line represents the odds ratio *observed by the change in caffeine consumption from the previous value to the corresponding or higher x value. The correspondent p-value is on the dot label, and the orange line represents the value correspondent to the absence of risk (OR=1).*

MODEL 1

The funnel plot correspondent to model 1 shows high heterogeneity: of four studies only one is between confidence limits. The forest plot shows a statistically significant effect in the sense that caffeine consumption has a protective effect on the occurrence of low birth weight when in comparison to no consumption, being the global effect also statistically significant (ln (OR_G) = -2.39; 95%CI [-3.43, -1.36]).

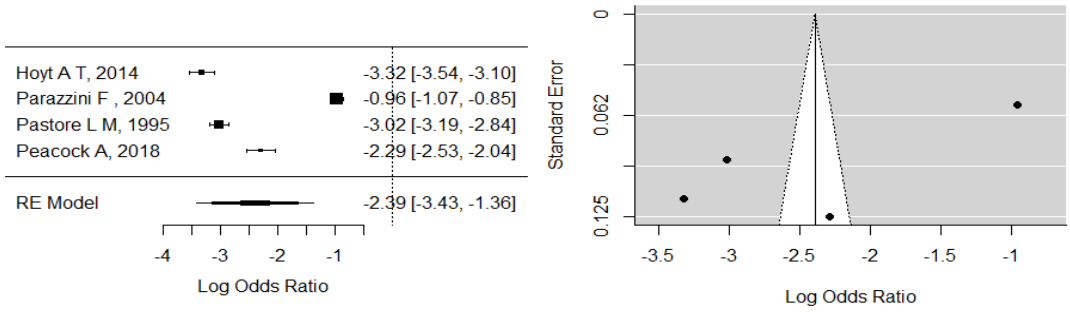

Figure 15 forest plot and funnel plot for *model 1: zero consumption versus consumption*

MODEL 2

The funnel plot regarding model 2, showed high heterogeneity, none of the eight studies included was between the confidence limits.Three of the studies showed a statistically significant effect in the way that a maternal caffeine intake until 200 mg/day could be protective for the fetus to be small for gestional age. Four of the studies showed the opposite, also with a statistically significant effect. One study was inconclusive as the summary measure, which was also inconclusive. Consequently, the global effect, for this cut-off point, does not present statistical significance (ln (OR_G) = 0.80; 95%CI [-0.65; 2.24]).

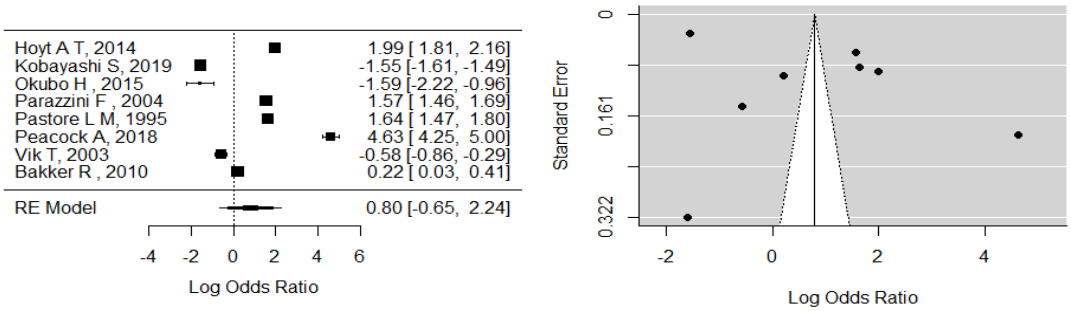

Figure 16 forest plot and funnel plot for *model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive*

MODEL 3

The funnel plot designed for model 3 also shows high heterogeneity, as we can see in the funnel plot, none of the studies under analyses was inside de confidence limits. Five studies showed a statistically significant effect in the way that a consumption equal or superior to 300mg/day, could increase the risk of the fetus being small for gestational age. One study was inconclusive. The global effect, for this cut-off point was statistical significant, (ln (OR_G) = 2.55; 95%CI [1.14, 3.97]).

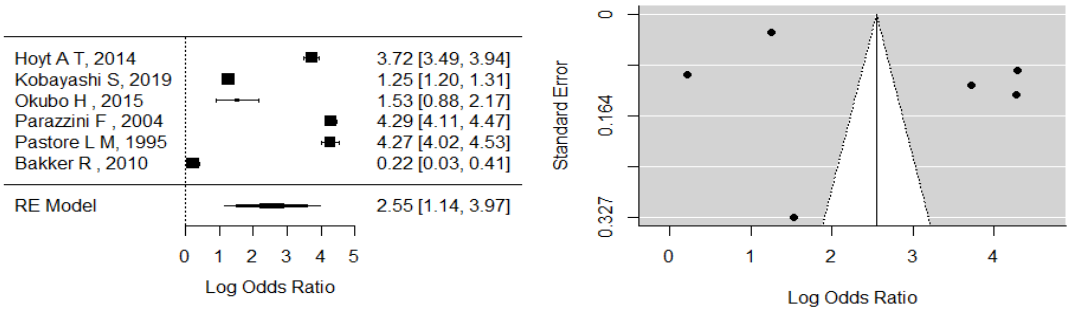

Figure 17 forest plot and funnel plot for *model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption;*

MODEL 4

The funnel plot correspondent to model 4 shows high heterogeneity, none of studies was included in confidence limits. All studies show a statistically significant effect in the sense that a caffeine consumption “high” or “excessive”, equal or superior to 400 mg/day has a potentiator effect on the occurrence of this event being the global effect also statistically significant, (ln(OR_G) = 3.64; 95%CI [1.11, 6.18]).

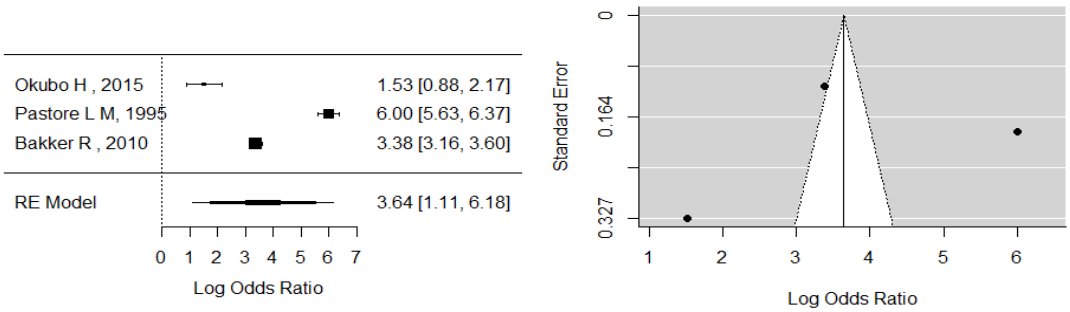

Figure 18 forest plot and funnel plot for *model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption;*

MODEL 5

There was only one study (Bakker R, 2010 (41) under analyses, which presented an *odds ratio* of 3968.893; 95%CI [1835.152, 8583.543] ($p < 0.001$), so the meta-analysis was not performed for model 5.

INTRAUTERINE GROWTH RESTRICTION

For this event, as for spontaneous abortion and small for gestational age, we could also see that a low consumption could be protective of the occurrence of IUGR events when compared to no consumption, but the cut-off for which the risk of intrauterine growth restriction increases was inferior to the events previously described since it was equal or superior to 200 mg/day (table 6, figure 19).

Table 6 Summary of values obtained by meta-analysis of random effects for the IUGR event, considering each possible cut-off point for caffeine consumption after variable dichotomization

Model	I^2	Nstudies	OR	95%CI	*p value*
1	95.59%	3	0.276	0.112 – 0.678	0.005
2	93.90%	3	21.302	8.644 – 52.484	< 0.001
3	97.08%	4	107.300	28.406 – 405.316	< 0.001

Model 1: zero consumption versus consumption; Model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive; Model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption; Model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption; Model 5: zero consumption until high consumption(< 600mg/day) versus excessive consumption.

N studies – number of studies considered for the meta analyses; OR – odds ratio; 95% CI- confidence interval for odds ratio; p – statistical significance of model's odds ratio

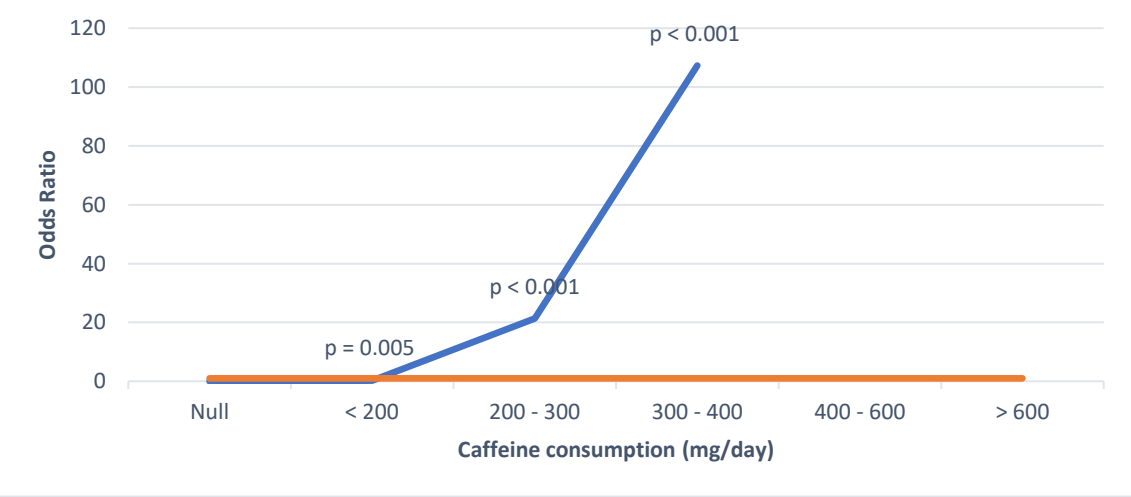

Figure 19 The blue line represents the odds ratio *observed by the change in caffeine consumption from the previous value to the corresponding or higher x value. The correspondent p-value is on the dot label, and the orange line represents the value correspondent to the absence of risk (OR=1).*

MODEL 1

The funnel plot correspondent to model 1 shows high heterogeneity: 3 studies were included, and only one was inside confidence limits. All studies show a statistically significant effect in the sense

that caffeine consumption has a protective effect on the occurrence of intrauterine growth restriction when in comparison to zero consumption (forest plot), being the global effect also statistically significant (ln (OR_G) = -1.29; 95%CI [-2.19, -0.39].

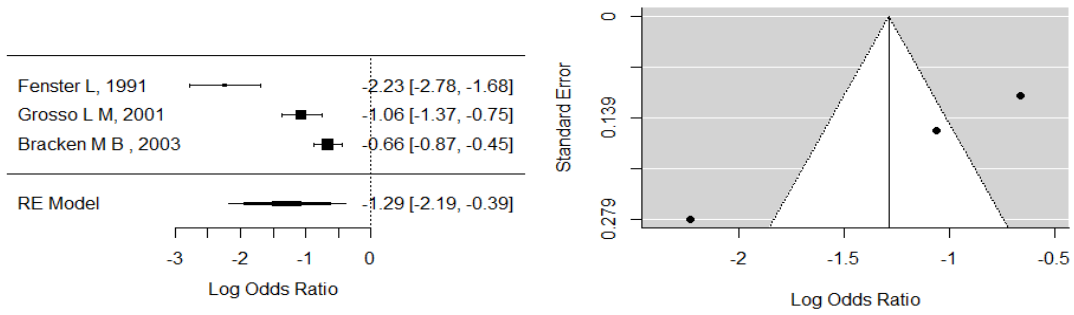

Figure 20 forest plot and funnel plot for *model 1: zero consumption versus consumption*

MODEL 2

For model 2, there was also high heterogeneity; from three of the studies under analyses only one was inside the confidence limits. All of the studies showed a statistically significant effect in the way that a "low-moderate" and higher consumption could increase the risk of intrauterine growth restriction. The global effect, for this cut-off point, shows a sigificative statistical meaning (ln (OR_G) = 3.06; 95%CI [2.16, 3.96].

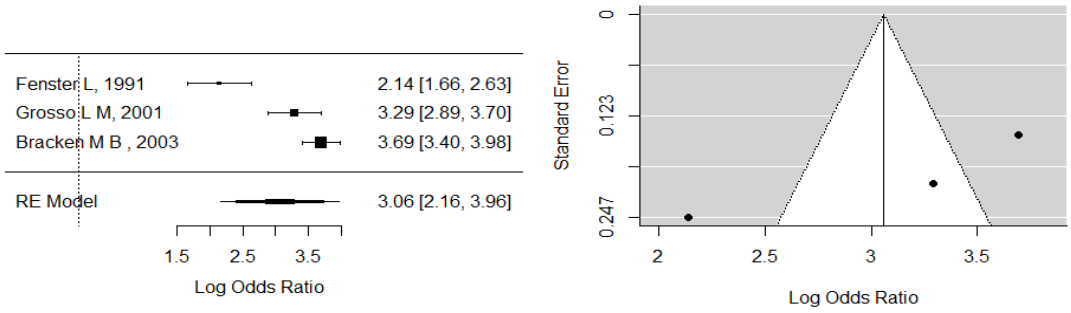

Figure 21 forest plot and funnel plot for *model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive*

MODEL 3

Funnel plot regarding model 3 also shows high heterogeneity, only one of the four studies under analyses was inside de confidence limits. All studies presented a statistically significant effect in

the way that a consumption equal or superior to 300mg/day, could increase the risk of intrauterine growth restriction.. The global effect, for this cut-off point was statistical significant (ln (OR_G) = 4.68; 95%CI [3,35, 6.00]).

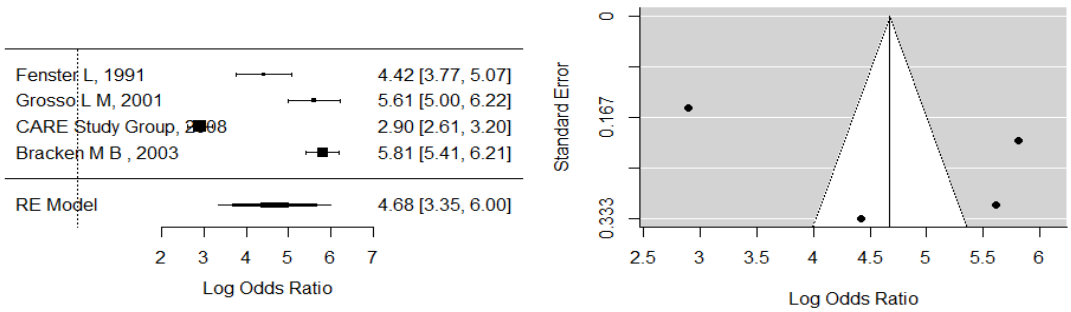

Figure 22 forest plot and funnel plot for *model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption*

There were no studies to perform meta-analysis for model 4 and 5.

PRETERM BIRTH

Table 7 ***Summary of values obtained by meta-analysis of random effects for the PTB event, considering each possible cut-off point for caffeine consumption*** **after variable dichotomization**

Model	I^2	Nstudies	OR	95%*CI*	*p value*
1	99-38%	3	0.170	0.047 – 0.223	0.007
2	99.81%	5	1.635	0.202 – 13.266	0.645
3	99.83%	5	6.417	0.605 – 68.094	0.123
4	99.09%	3	11.299	1.028 – 124.200	0.047
5	98.25%	2	574.521	23.153 – 14256.358	< 0.001

Model 1: zero consumption versus consumption; Model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive; Model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption; Model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption; Model 5: zero consumption until high consumption(< 600mg/day) versus excessive consumption.

N studies – number of studies considered for the meta analyses; OR – odds ratio; CI 95% confidence interval for odds ratio; p – statistical significance of model's odds ratio

For this event, we observed that zero consumption was also a risk factor for the occurrence of preterm birth since the chance of occurrence becomes 5.9 times higher. As for the risk associated with the consumption, it verified for a maternal consumption of 400 mg/day (table 7, figure 23).

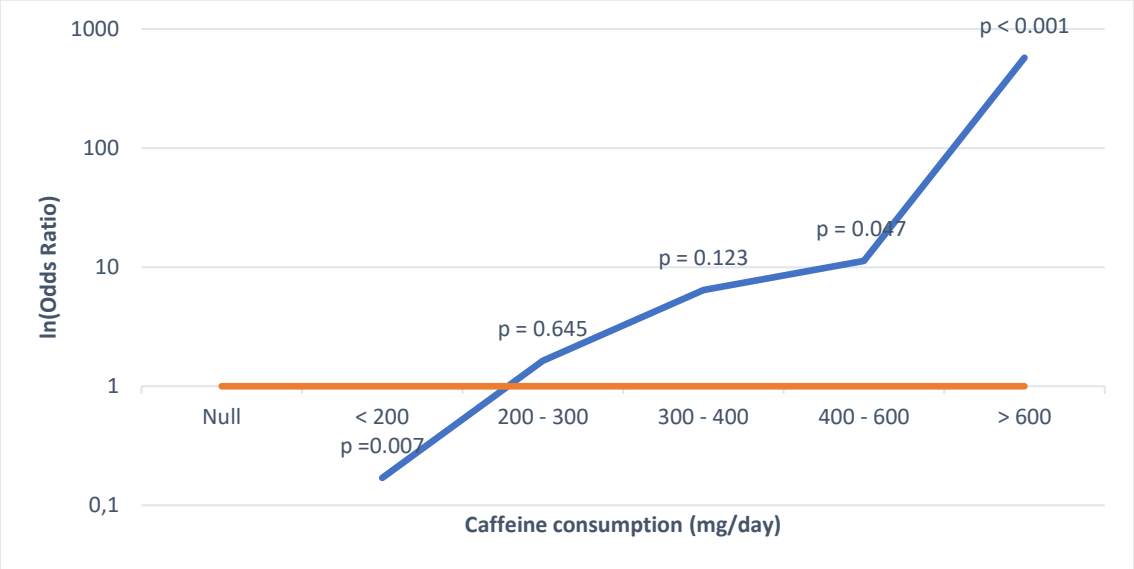

Figure 23 The blue line represents the ln (OR) *observed by the change in caffeine consumption from the previous value to the corresponding or higher x value. The correspondent p-value is on the dot label, and the orange line represents the value correspondent to the absence of risk (OR=1).*

MODEL 1

The funnel plot correspondent to model 1 shows high heterogeneity: Of the three studies under analyses none was inside the confidence limits. All studies show a statistically significant effect in the sense that caffeine consumption has a protective effect on the occurrence of preterm birth when in comparison to zero consumption (forest plot), being the overall effect also statistically significant (ln (OR_G) = -1.77; 95%CI [-3.07, -0.47]).

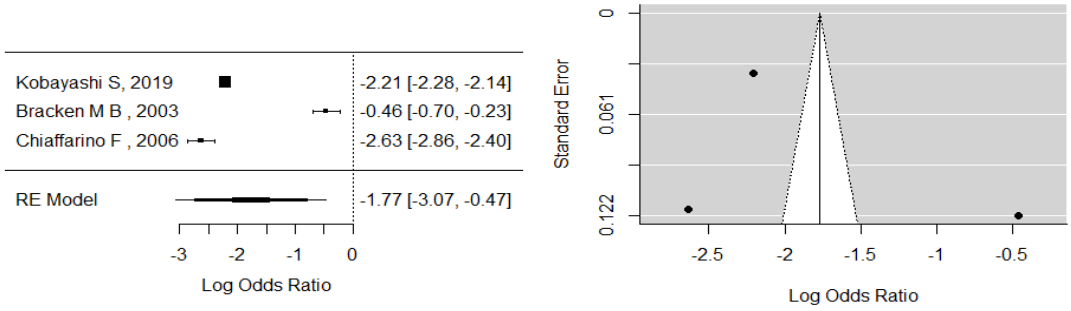

Figure 24 forest plot and funnel plot for *model 1 (zero consumption versus consumption)*

MODEL 2

For model 2, there was also high heterogeneity; from three of the studies only two were between the confidence limits. Three of the studies showed a statistically significant effect in the way that a maternal caffeine consumption equal or above 200 mg/day could increase the risk of preterm birth. One showed the opposite, also with a statistically significant effect. One of the studies was inconclusive as the summary measure, which was also inconclusive. Consequently, the global (overall) effect, for this cut-off point, does not present statistical significance (ln (OR_G) = 0.49; 95%CI [-1.60, 2.59].

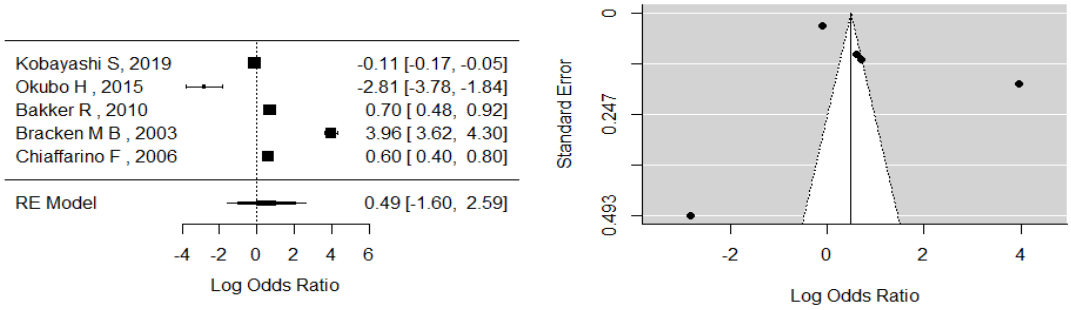

Figure 25 forest plot and funnel plot for *model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive*

MODEL 3

Model 3 also shows high heterogeneity, as we can see in the funnel plot, none of the five studies under analyses was inside de confidence limits. Four studies showed a statistically significant effect in the way that a maternal caffeine consumption equal or superior to 300mg/day, could increase the risk of preterm birth. One study showed the opposite, also with a statistically significant effect. Consequently, the global (overall) effect, for this cut-off point was not statistical significant (ln (OR_G) = 1.86; 95%CI [-0.50, 4.22]).

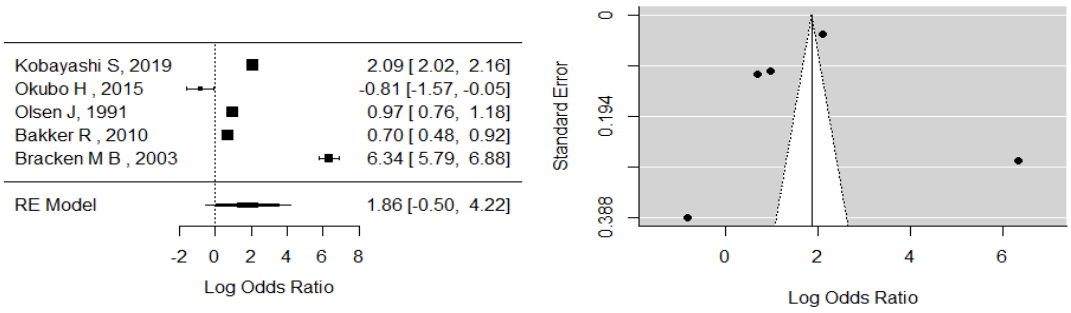

Figure 26 forest plot and funnel plot for *model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption*

MODEL 4

The funnel plot correspondent to model 4 shows high heterogeneity, none of the three studies included were between in confidence limits. All studies showed a statistically significant effect in the sense that a maternal caffeine consumption equal or superior to 400 mg/day is a potentiator effect on the occurrence of preterm birth, being the overall effect also statistically significant (ln (OR_G) = 2.42; 95%CI [0.03, 4.82]).

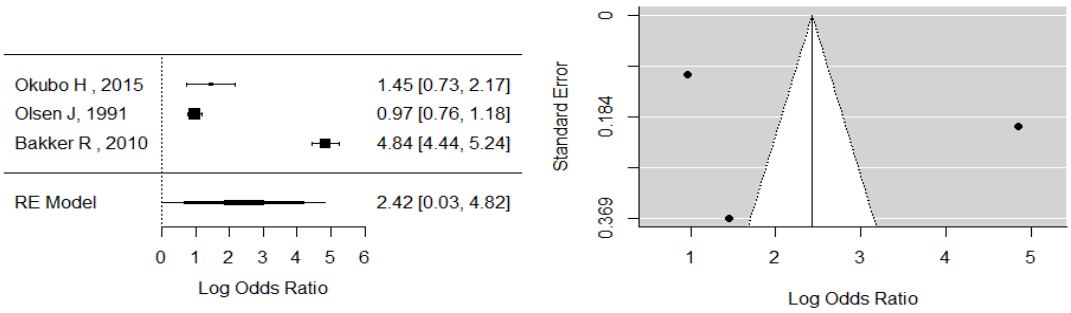

Figure 27 forest plot and funnel plot for *model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption;*

MODEL 5

As we can see in the correspondent funnel plot, model 5 showed high heterogeneity. Both studies included showed a statistically significant effect in the sense that a maternal caffeine consumption higher than 600 mg/day increases significatively the risk of preterm birth (ln (OR_G) = 6.35 95%CI [3.14, 9.56]).

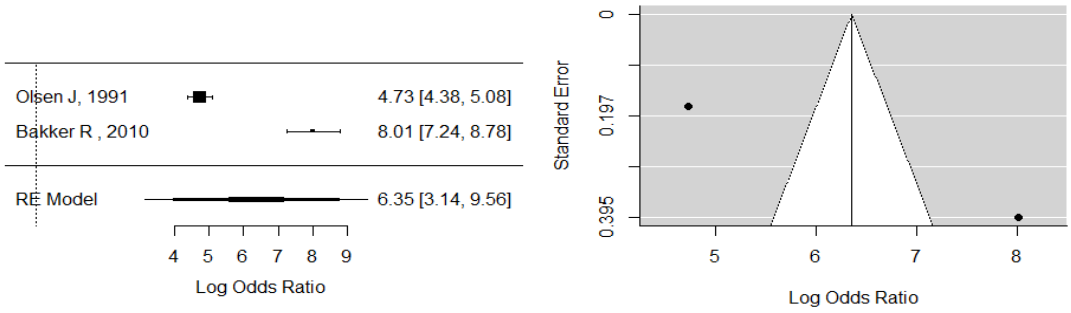

Figure 28 forest plot and funnel plot for *model 5: zero consumption until high consumption (< 600mg/day) versus excessive consumption.*

CONGENITAL ANOMALIES

Through this meta-analysis, it is observed that the risk of occurrence of congenital anomalies increases with maternal consumption of caffeine in moderate-low quantity equivalent or superior to 200 mg/day with an increased chance of event occurrence of 6.555 times, on average (table x). As for other previously described outcomes, the absence of caffeine consumption also appears to translate into an increased risk of congenital disabilities in about 43.478 times (=1/0.023). (table 8, figure 29)

Table 8 Summary of values obtained by meta-analysis of random effects for the CA event, considering each possible cut-off point for caffeine consumption after variable dichotomization

Model	I^2	NStudies	OR	CI95%	*p value*
1	0.00%	2	0.023	0.020 – 0.027	< 0.001
2	0.00%	2	6.555	5.784 – 7.429	< 0.001
3	99.35%	3	16.782	3.101 – 90.819	0.001
4	-	1	-	-	-
5	-	1	-	-	-

Model 1: zero consumption versus consumption; Model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive; Model 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption; Model 4: zero consumption until high-moderate (< 400mg/day) versus high or excessive consumption; Model 5: zero consumption until high consumption(< 600mg/day) versus excessive consumption.

N studies – number of studies considered for the meta analyses; OR – odds ratio; 95% CI- confidence interval for odds ratio; p – statistical significance of model's odds ratio

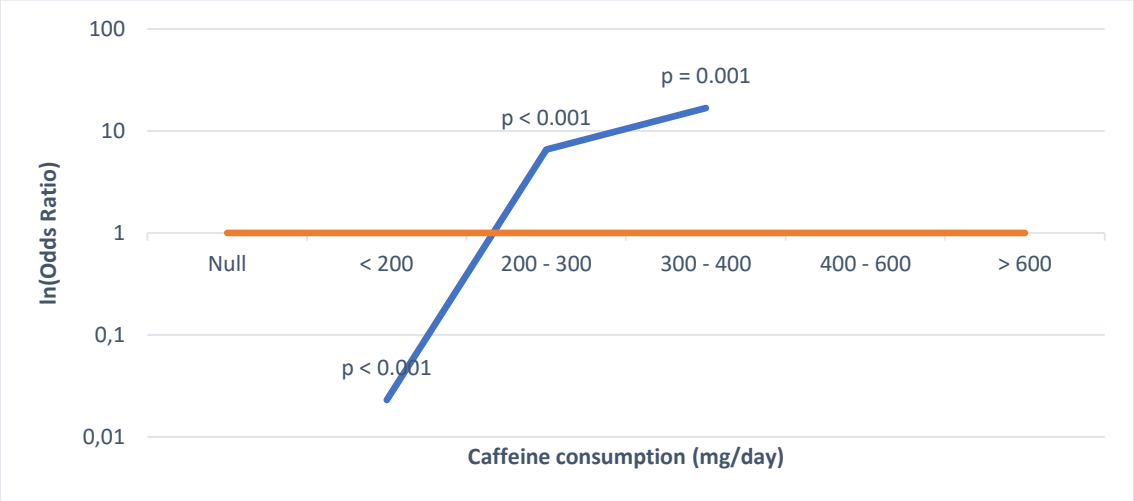

Figure 29 The blue line represents the ln (OR) observed by the change in caffeine consumption from the previous value to the corresponding or higher x value. The correspondent p-value is on the dot label, and the orange line represents the value correspondent to the absence of risk (OR=1).

MODEL 1

The funnel plot correspondent to model 1 shows low heterogeneity, although there are only two studies under analyses both are inside the confidence limits. All studies show a statistically significant effect in the sense that caffeine consumption has a protective effect on the occurrence of congenital anomalies when in comparison to zero consumption (forest plot), being the overall effect also statistically significant (ln (OR_G) = -3.76; 95%CI [-3.93, -3.60].

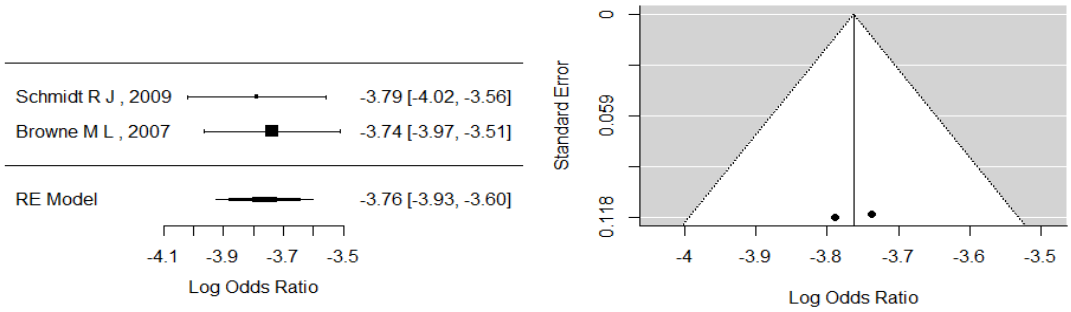

Figure 30 forest plot and funnel plot for *model 1: zero consumption versus consumption*

MODEL 2

The funnel plot for model 2, shows low heterogeineity, although only two studies were under analyses. Both studies showed a statistically significant effect in the way that a maternal caffeine consumption above 200 mg per day could increase the risk of congenital anomalies (forest plot). The global effect, for this cut-off point, showed statistical significance (ln (OR_G) = 1.88 [1.76, 2.01]).

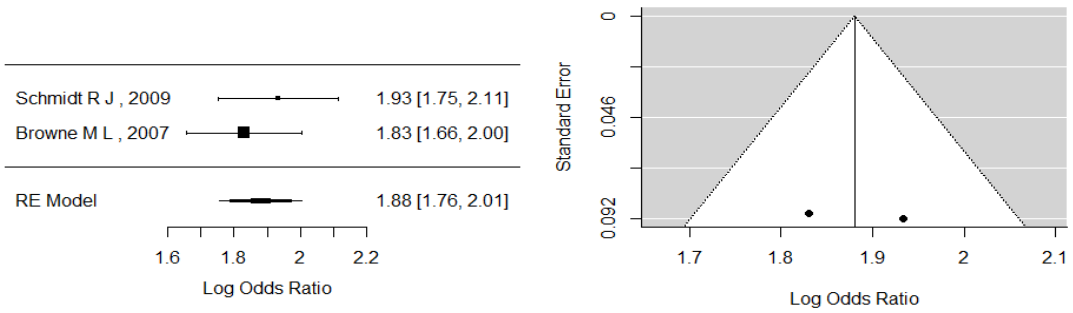

Figure 31 forest plot and funnel plot for *model 2: zero consumption or low consumption (< 200mg/day) versus low-moderate consumption until excessive*

MODEL 3

Model 3 also shows high heterogeneity, as we can see in the funnel plot, none of the studies under analyses was inside de confidence limits. All three studies included showed a statistically significant effect in the way that a maternal consumption equal or superior 300mg/day, could increase the risk of congenital anomalies. The global effect, for this cut-off point was statistical significant (ln (OR_G) = 2.82; 95%CI [1.13, 4.51]).

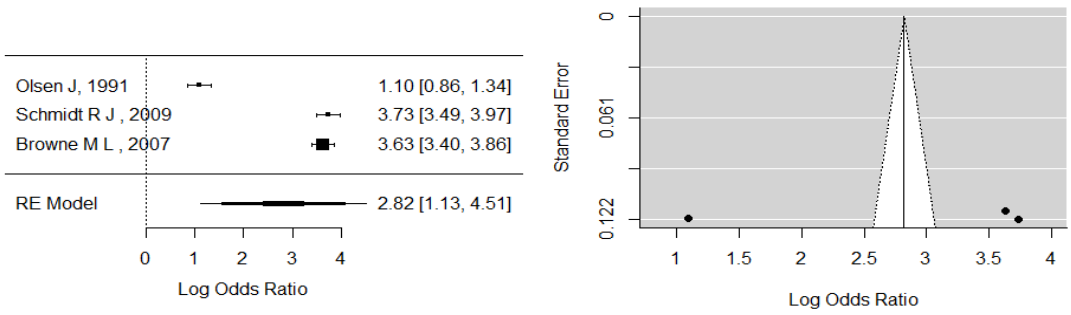

Figure 32 forest plot and funnel plot for m*odel 3: zero consumption until low-moderate consumption (< 300mg/day) versus high-moderate until excessive consumption*

For model 4 and model 5 there was only one study under analysis so meta-analysis wasn't performed for both models. Model 4 presents an OR= 2.998; 95%CI [2.363 a 3.805] ($p < 0.001$) and model 5 presents an OR= 134.157 95%CI [88.542 a 203.271] ($p < 0.001$).

SIDS, STILLBIRTH AND GESTATIONAL DIABETES MELLITUS

The number of studies reporting stillbirth, SIDS, or GDM events was not sufficient to perform a meta-analysis.

DISCUSSION AND LIMITATIONS

According to our meta-analysis, in general, the absence of caffeine consumption seems to increase the chance of occurrence of events such as SAB (5 times), IUGR (4 times), SGA (11 times), PTB (6 times) or congenital anomalies (43 times) therefore we can infer that caffeine consumption may have a protective effect on the occurrence of those events in pregnant women and newborns.

However, this does not mean that it is beneficial for pregnant women to ingest caffeine at any level. According to the results, we verified that a maternal caffeine intake higher than 200 mg/day seems to increase the risk of IUGR and birth defects events. A caffeine consumption above 300 mg/day also appears to enhance SAB and SGA events. Caffeine intake beyond 400 mg/day seems to increase the risk of LBW and PTB by more than ten times (10. 061 and 12, 825 on average, respectively). (Table 9, Figure 33)

This further supports the *American College of Obstetrics and Gynecology* guidelines that recommends a moderate consumption of caffeine, without surpassing 200 mg/day, since, although relationship of caffeine to IUGR still remains undetermined, it was not considered to be a major contributing factor in an increased risk of fetal loss or PTB.[42]

In Portugal, according to the World Health Organization and also supported by *Graça et al.* [43], the recommendation is that pregnant women can consume until 2-3 cups/day of coffee without exceeding the consumption of 300 mg/day.

Table 9 Odds ratio, and respective p-value, for the chance of events for higher levels of caffeine consumption after dichotomization of this variable according to the cut-off value registered (in mg/day)

Model	Cut-off (mg/d)	SAB	LBW	RCIU	SGA	PPT	CA
0	Null	0	0	0	0	0	0
1	< 200	0.197 (< 0.001)	*0.399 (0.229)*	*0.276 (0.005)*	*0.091 (< 0.001)*	*0.170 (0.007)*	*0.023 (< 0.001)*
2	200 - 300	0.789 (0.680)	*3.511 (0.398)*	*21.302 (< 0.001)*	*2.215 (0.282)*	*1.635 (0.645)*	*6.555 (< 0.001)*
3	300 - 400	5.974 (0.004)	*9.503 (0.076)*	*107.300 (< 0.001)*	*12.825 (< 0.001)*	*6.417 (0.123)*	*16.782 (0.001)*
4	400 - 600	8.696 (0.007)	*10.061 (0.035)*		*38.263 (0.005)*	*11.299 (0.047)*	
5	> 600	22.481 (< 0.001)	*454.143 (< 0.001)*			*574.521 (< 0.001)*	

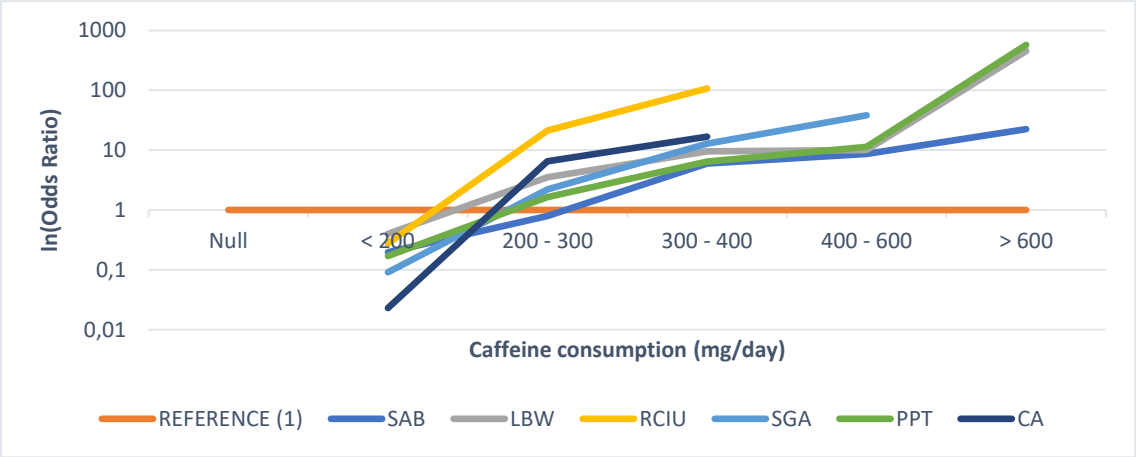

Figure 33 Logarithmic scale for each type of event according to the cut-offs considered for caffeine consumption after variable dichotomization

Spontaneous abortion

After reviewing the literature, we found fourteen studies [9-25] that strongly relate high maternal caffeine consumption, with SAB. On the contrary, three [44-46] studies found no evidence that moderate caffeine consumption increased the risk of such events.

Generally, studies describe an increase in the risk of SAB directly proportional to the level of caffeine [10, 14, 25] [21]. *Infante-Rivard C et al.*[14] declared that there was a strong association of caffeine intake during pregnancy and fetal loss, compatible with a linear trend on the logistic scale in which ORs increased by a factor of 1.22 (95%CI [1.10 to 1.34]) for each 100 mg of caffeine ingested daily during pregnancy. Results quantified an OR=1.95 (95% CI [1.29, 2.93]) for consumption between 163 and 321 mg and an OR= 2.62 (95%CI [1.38 to 5.01]) for more than 321 mg.

These results were supported by *Cnattingius S et al.* [10] who reported that the increase in risk was related to the amount ingested, describing a significant effect for a consumption equal or superior to 500 mg/day, OR= 2.2 (95% CI [1.3, 3.8])

Matijasevich A et al. [18], also published that a mean caffeine intake through pregnancy superior to 300 mg/day showed a significantly increased risk of fetal death (OR= 2.33; 95%CI [1.23; 4.41]) when compared with no caffeine consumption during pregnancy.[22] *Wen W et al.* [13] demonstrated a 2.5-fold increase in the risk of SAB among women who consumed 300 or more mg/day of caffeine during pregnancy compared with women who consumed <20 mg (HR: 2.5; 95%CI [1.0, 6.4]).

Weng X et al. [12], compared zero caffeine consumption with a consumption until 200 (OR= 1.42; 95% CI [0.93- 2.15]) and superior to 200 mg/day. (OR=2.23; 95%CI [1.34 -3.69]), and his results also support this hypothesis.

Our results corroborate the information previously published. There is no observed impact of maternal caffeine consumption on the frequency of SAB for the cut-off point of 200 mg/day. However, the risk of SAB significantly increases from consumption of 300 mg/day. The increase in maternal daily consumption of caffeine appears to potentiate the occurrence of this type of event, being the chance of occurrence almost six times more elevated in pregnant women who consume at least 300 mg/day of caffeine and increasing this chance to 22.5 when the consumption doubles.

The underlying mechanisms hypothesized for LBW, IUGR, and SGA are that, as a consequence of caffeine intake, an increase of catecholamines in the circulation can lead to vasoconstriction in the uteroplacental circulation and fetal hypoxia, which may eventually affect fetal growth and development.[37] It was reported a 25% reduction in intervillous placental blood flow after maternal consumption of 200 mg of caffeine. [37] Another potential hypothesis concerns the increased cellular concentration of cyclic adenosine monophosphate (cAMP) following caffeine consumption through inhibition of phosphodiesterase (an enzyme responsible for the breakdown of cAMP). The accumulation of cAMP may then affect fetal growth by its influence on cell division or through catecholamine-mediated vasoconstriction. [47]

The fourth to eighth month, the period between the last month of the first trimester and the first month of the third trimester, of gestation, represents the critical window of maternal exposure to chemicals leading to LBW. Fetal growth accelerates through the third trimester of gestation with an average increase of 240-g/wk.[8]

Low Birth Weight

The results of the literature divide, eight [3, 7, 41, 45, 48-51] studies report that there is no association between caffeine consumption and LBW.

Some authors assign the absence of association to the fact that caffeine does not reduce fetal growth robustly enough to shift the birth weight of some neonates from the upper to the lower side of the 2,500-g cutoff point. [3] *Del Castillo N et al.* [51] reported a significant association ($p < 0.05$) with decreased birth weight (-87.7; 95% CI -159.8, -15.6 g) for caffeine consumption in the fourth quartile (115.01-650 mg/day). Pregnant women with a higher caffeine intake than 115 mg/day had a decreased fetal weight of 87.7 g compared with no consumption. However, although significant, this result does not seem to be clinically relevant.

This finding matches the results of *Bracken M B et al.* [49] who also reported a decrease in fetal weight of 28 g per cup of coffee daily in pregnant women that, despite being statistically significant, did not appear to have clinical significance since it only applies for women who ingest more than 600 mg of caffeine.

Some studies describe a moderate association between LBW and the maternal ingestion of caffeine [8, 27]. According to *Fenster L et al.* [4], results suggest an effect of caffeine consumption of greater than 300 mg/daily on IUGR and LBW. A dose-response effect with increasing consumption of caffeine was observed (X^2 trend = 4.03, p = 0.05). Women who reduced their heavy caffeine consumption had a lower risk of delivering a LBW infant (OR = 0.65; 95%CI [0.20, 2.11]) than those women who continued to drink this amount (OR = 3.05; 95%CI [1.09, 8.51]). Their recommendation is in that women should be counselled early in pregnancy about reducing caffeine intake to below 300 mg daily.

Chen L W et al. [47] concluded that higher maternal caffeine intake, even at a level lower than that of the current recommended cutoffs (<200 mg/d by the American College of Obstetricians and Gynecologists, and <300 mg/d by the World Health Organization) is in general associated with suboptimal birth outcomes, especially with LBW.

Our analyses showed that the risk of LBW increases for maternal caffeine consumption equal or superior to 400mg/day.

Small for gestational age

Our results show an association between caffeine and an increase in the risk of occurrence of SGA events for a consumption equal or superior to 300 mg/day. We also concluded that moderate maternal consumption of caffeine seems to be protective of the occurrence of events when compared to no consumption.

These results were corroborated by *Hoyt A T et al*.[52], which also observed an increase in SGA births for mothers with higher caffeine intake, particularly for those consuming >300 mg of caffeine per day. *Kobayashi S et al.* [8] established that the risk of SGA increases in a dose-dependent manner with increasing caffeine consumption during pregnancy, mentioning that risk begins at low levels of caffeine exposure.

Two meta-analyses described a dose-response relationship between caffeine intake and SGA, even though the effects were modest. [5, 53] These findings can be justified by the fact that this association was only significant for excessive consumption of caffeine, as supported by *Bech B H et al.* [54] and *Bakker R et al.* [41], the first described a significant association between caffeine consumption and SGA events only for women who consumed more than 8 cups of coffee per day (OR = 1.51; 95% CI [1.21–1.88]) and the second established a cut-off for increased risk of SGA at birth at maternal consumption of 600 mg/day.

Klebanoff M A et al.[55] evaluated serum paraxanthine and concluded that maternal third-trimester serum paraxanthine concentration, which reflects caffeine consumption, was associated with a higher risk of reduced fetal growth, particularly among women who smoked.[55]

Vik T et al.[56] supported that this association was more prevalent through third-trimester consumption. The risk of SGA birth was approximately doubled if the mother had a high rather than a low caffeine intake in the third trimester (OR=1.8; 95% CI [1.2- 2.5])

Still, from the studies under analyses, three [7, 51, 57] did not observe evident relationships between total caffeine intake and risk of SGA.

Intrauterine growth restriction

According to the results of our meta-analyses for this event, as for SAB and SGA, it was described that low caffeine consumption, when compared to no consumption, could be protective of the occurrence of IUGR events. The cut-off for which the risk of IUGR increases was equal or superior to 200 mg/day.

From the studies included in this review, only two [3, 4] of six articles, that studied the association between caffeine consumption and IUGR, concluded that caffeine consumption was associated with an increased risk of IUGR

Fortier E et al. [3]., described that the risk increases gradually with the amount ingested. According to the results, for women whose average daily caffeine consumption was 0-10, 11-150, 151-300, or >300 mg, the adjusted odds ratios for delivering a newborn with growth retardation were 1.00, 1.28 (95%Cl [1.04-1.59]), 1.42 (95%Cl [1.07-1.87]), and 1.57 (95% Cl [1.05-2.33]), respectively. *Fenster L. et al.* [4] also corroborated this hypothesis, considering that women who reduced their caffeine intake from greater than 300 mg/day to less than that early in pregnancy had lower risks of delivering infants with IUGR than women who continued to consume that amount.

The other four [45, 48, 49, 58] studies under analyses found no caffeine effect on IUGR and none of them reported a protective association.

Preterm birth

We observed that either zero consumption, either a maternal consumption of 400 mg/day, were risk factors for the occurrence of preterm birth.

According to the literature included in the systematic review, most studies did not find an association between caffeine consumption and PTB [3, 41, 49, 51, 59-62]. *Chiaffarino F et al.* [60] affirm that the principal reason could have been the low pattern of consumption of the population in their study. *Kobayashi S et al.* [8], *Okubo H et al.* [7] and *Eskenazi B et al.* [6] describe a moderate association.

Congenital anomalies

For the meta-analyses to be possible concerning the event congenital anomalies, we decided to assemble all the studies selected for the review that could be included in this group. Therefore, we combined articles results that focused on CVM, NTD (spina bifida), LD, CA (in general), and oral clefts. We observed that the risk of occurrence of congenital anomalies increases with maternal consumption of caffeine equivalent or superior to 200 mg/day. The absence of caffeine consumption also appeared to translate into an increased risk.

Two of the studies report little evidence regarding an association between caffeine consumption and CA.[27, 28] *Chen L et al.*[29] described a weak increased risk of congenital LDs associated with maternal dietary caffeine consumption.

Positive associations were recognized between spina bifida and total caffeine consumption (OR 1.4; 95% CI: [1.1–1.9]). Associations with modestly increased risk of NTDs and encephalocele were also observed. The association between caffeine consumption and anencephaly differed by maternal race/ethnicity. No dose effects were found [63]. These results were supported by *De Marco P et al* [31]., who also reported an increase in the risk for spina bifida for > 300 mg/day (OR=10.82; 95% CI [3.78–31]).

Browne M L et al. [30] found no evidence for an appreciable teratogenic effect of caffeine concerning CVMs. However, for tetralogy of Fallot, nonsignificant elevations in risk were observed for moderate (but not high) caffeine intake overall and among nonsmokers (ORs of 1.3 to 1.5). It was also described an inverse trend between coffee intake and risk of an atrial septal defect; authors interpreted this single significant pattern of association as a chance finding.

SIDS, Stillbirth and Gestational Diabetes Mellitus

The number of studies reporting stillbirth, SIDS, or GDM events was not sufficient to perform a meta-analysis.

According to *Ford P K et al* [26], a heavy maternal caffeine consumption, superior to 400 mg/day, throughout pregnancy was strongly associated with an increased relative risk for SIDS (OR 1.65) after adjustment for confounders.

For the secondary outcome stillbirth, *Greenwood D C et al.* [21] stated that, even though there were insufficient events to present late miscarriage and stillbirth separately, there was a strong association between caffeine intake in the first trimester and subsequent late miscarriage between 12 and 24 weeks or stillbirth after 24 weeks. Compared to those consuming less than 100 mg/day, the *odds ratio* for late miscarriage or stillbirth increased to 2.2 (95% CI [0.7–7.1]) for intakes between 100 and 199 mg/day, to 1.7 (95%CI [0.4–7.1]) for those taking between 200 and 299 mg/day and to 5.1 (95%CI [1.6–16.4]) for those consuming over 300 mg/day (*p = 0.004).*

A retrospective cohort study [64] that focused on the potential combined effects of maternal smoking and coffee intake on fetal death, authors concluded smoking and coffee intake during pregnancy elevate the risk of an adverse pregnancy outcome, a reduction in either or both of these evitable exposures could reduce the risk of fetal death. Results suggested that the combined effect of smoking and coffee intake during pregnancy on the risk of fetal death is coffee-dose dependent. [9] It further stated that smokers, regardless of coffee consumption, have a higher risk of fetal death than non-smokers. Nonetheless, this risk among smokers of >10 cigarettes/day may be reduced by low (up to 300 mg/day) coffee intake.

Additionally, *Bech B H et al.* [38] observed that women who drank eight or more cups of coffee per day had twice the risk of fetal death of women who did not drink coffee. There was no statistically

significant interaction between coffee consumption and fetal death during specific periods of gestation (p= 0.45). The analysis of causes of stillbirth described that the risk due to placental dysfunction increased among consumers of > 400 mg of coffee per day (OR=2.27, 95%CI [1.21, 4.28]).

Regarding gestational diabetes mellitus, there were two studies included in this review that stated that first trimester coffee and tea intake of <8 cups/day was not associated with an increased risk for GDM and possibly may have a protective effect. According to *Adeney K L et al* [65] , women who reported moderate pre pregnancy caffeinated coffee intake had a significantly reduced risk of GDM (OR 0.50; 95% CI [0.29, 0.85]) when compared with non-consumers and no risk reduction was associated with decaffeinated coffee intake.

This meta-analysis is extremely valuable in daily practice since it allows to advise pregnant women on the level of caffeine that is safe to ingest during pregnancy. According to the results, it is secure and protective the ingestion of caffeine until 200 mg/day. Nevertheless, we have to remember that caffeine is present in a vast number of beverages, food, and medications. Assuming one coffee has between 80-100 mg of caffeine, according to the reported data of studies included, the consumption of two cups might be a risk of surpassing the quantity recommended.

Through the results of our meta-analyses, emerged a protective effect of reduced caffeine consumption (until 200 mg per day). After reviewing the literature, we found only two [30, 65] studies that mention a protective effect of caffeine, however the reasons have not been clarified.

Nevertheless, caffeine is used in premature newborns to treat symptoms related to apnea of prematurity and to facilitate extubation, due to its pharmacologic effects since caffeine improves lung function by increasing central respiratory drive and diaphragmatic activity, as well as by inducing diuresis and bronchodilation. There is evidence that caffeine also has beneficial cardiovascular effects, for example, on the closure of patent ductus arteriosus by enhancing diuresis and antagonizing prostaglandin activity, and neuroprotective effects presumably by up-regulating adenosine A1 receptors and attenuating the effects of intermittent hypoxia. [66] These results are described in premature newborns, even though the immaturity of the hepatic enzymes limits caffeine metabolism.

We think it is relevant to conduct more investigation to realize in which ways maternal caffeine consumption could have potential benefits.

LIMITATIONS

Our study has a few limitations that we have to consider in the interpretation of our findings. First and foremost, the articles included were all observational, which enhances the risk of bias and therefore limits the strength of our results.

In general, the models presented high heterogeneity, and consequently, the global effect measure determined using a random effect model, grants little accuracy. Nevertheless, it was determined even for situations in which the number of studies was only two.

The difference in methodologies used both in terms of study design and methods of measuring daily caffeine intake, as well as the previous adjustment of this consumption into the six categories, are all reasons that justify this excessive heterogeneity represented in the funnel plots.

Overall, the method of maternal caffeine intake assessment was through a questionnaire. Therefore, a measurement error in the assessment of caffeine intake may have affected the results. In most studies, an interviewer-administered questionnaire was used, which may have improved the completeness of their data collection. Nevertheless, we have to consider that the presence of the evaluator might have conditioned the response.

Misclassification of exposure is a particular concern considering that different questionnaires were used between studies, and consequently, the period of evaluation of the exposure, type of beverages, caffeine concentrations, and volume of beverages varied. All this, coupled with the mother's memory recall of consumption rates, suggests that caffeine dose can only be approximately ascertained.

Even though in the majority of studies, results were adjusted for the most relevant confounding factors, residual confounding by unmeasured or imperfectly measured covariates should be considered as a potential limitation of our meta-analysis.

Smoking and nausea are two of the confounders that potentially can have an effect modification on caffeine metabolism. Genetic interindividual differences in caffeine metabolism also represent a source of error in measuring caffeine exposure and not easy to circumvent. CYP1A2 is the enzyme primarily responsible for caffeine metabolism, responsible for the conversion of caffeine into its metabolites (paraxanthine).

Signorello L B et al. [67], concluded that high CYP1A2 activity might increase the risk of SAB, independently or by modifying the effect of caffeine. Specifically, their findings suggest that women with high CYP1A2 activity and possibly women who are slow acetylators have an augmented risk. Women with high inducible genotype for CYP1A2 have an increased risk of harmful reproductive outcomes. [68].

Cigarette smoking nearly doubles the rate of caffeine metabolism because cigarettes contain polycyclic aromatic hydrocarbons known to increase liver CYP1A2 enzyme activity[69-71] . One study observed that, within each category of reported consumption, smokers had lower serum

caffeine concentrations than nonsmokers. [69, 72]These findings suggest that there may be adverse effects of the caffeine metabolite paraxanthine, rather than of caffeine itself.
Despite the adjustments made, residual confounding still cannot be completely ruled out in observational studies.

Previous studies pointed out that while nausea is likely to reduce caffeine consumption during pregnancy, it is also an indicator of a viable pregnancy [73]. Considering pregnancy symptoms like nausea, vomiting, and aversions to smells and taste, are more prevalent in healthy pregnancies. Women with healthy pregnancies are more likely to decrease their caffeine consumption in response to pregnancy symptoms [74], and there is a suggestion that pregnancy symptoms can partly account for the relationship of caffeine intake and adverse pregnancy outcomes.

Our study limited the research to the last thirty years, and additionally, we had to exclude nineteen of the studies because we could not have access to the full article. These facts can represent another limitation even though we do not think that it might have impacted the results of this meta-analyses. However, we have to have it under consideration.

CONCLUSION

This systematic review concerning the safe quantity of caffeine that could be ingested during gestation leads us to conclude that maternal caffeine ingestion until 200 mg/day is secure. Our meta analyses also indicates that a consumption of caffeine below 200 mg per day may also be protective of the occurrence of events.

IMPACT ON DAILY PRACTICE

This systematic review with meta-analysis is extremely valuable in daily practice since it allows to advise pregnant women on the level of caffeine that is safe to ingest during pregnancy. According to the results, it is secure and protective the ingestion of caffeine until 200 mg/day. Nevertheless, we have to remember that caffeine is present in a vast number of beverages, food, and medications. Assuming one coffee has between 80-100 mg of caffeine, according to the reported data of studies included, the consumption of two cups might be a risk of surpassing the quantity recommended.

FUNDING

No funding was provided for this research.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests that could prejudice the impartiality of this review.

APPENDIX 1

Study		Pre-intervention	At intervention		Post-intervention			
First author	Publication	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departure from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Domínguez-Rojas V [25]	1994	moderate risk	moderate risk	moderate risk	low risk	low	moderate risk	moderate risk
Fenster L [4]	1991	moderate risk	low risk	moderate risk	low risk	low	low risk	moderate risk
Fenster L [24]	1991	moderate risk	moderate risk	moderate risk	low risk	moderate risk	low risk	low risk
Ford R P K [26]	1998	moderate risk	low risk	moderate risk	low risk	low risk	serious risk	low risk
Fortier I [3]	1993	moderate risk	moderate risk	moderate risk	low risk	low risk	low risk	low risk
George L [23]	2006	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Giannelli M [22]	2003	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Greenwood D C [21]	2010	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Grosso L M [58]	2001	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Hahn K A [20]	2015	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Del Castillo N [51]	2015	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Hinkle S N [75]	2014	moderate risk	moderate risk	moderate risk	low risk	low risk	moderate risk	low risk
Hoyt A T [52]	2013	moderate risk	low risk	moderate risk	low risk	moderate risk	low risk	low risk
Jarosz M [62]	2011	moderate risk	low risk	moderate risk	low risk	critical risk	low risk	serious risk
Johansen A M W [28]	2009	moderate risk	moderate risk	moderate risk	low risk	low risk	low risk	low risk
Klebanoff M A [19]	1999	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Klebanoff M A [55]	2002	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Kline J [46]	1991	moderate risk	serious risk	moderate risk	low risk	low risk	low risk	low risk
Kobayashi S [8]	2019	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Matijasevich A [18]	2006	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Mills J L [45]	1993	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Modzelewska D [76]	2019	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk

Morales-Suárez-Varela M [64]	2017	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Okubo H [7]	2015	moderate risk	moderate risk	moderate risk	low risk	low risk	low risk	low risk
Olsen J [27]	1991	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Parazzini F [57]	2005	moderate risk	moderate risk	low risk	low risk	low risk	low risk	low risk
Pastore L M [61]	1995	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Peacock A [77]	2018	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Pollack A Z [44]	2010	moderate risk	moderate risk	low risk	low risk	moderate risk	low risk	low risk
Rasch V [17]	2003	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Sata F [16]	2005	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Schmidt R J [32]	2009	moderate risk	low risk	moderate risk	low risk	moderate risk	low risk	low risk
Shu X O [50]	1995	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Stefanidou E M [15]	2011	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Vik T [56]	2003	moderate risk	low risk	moderate risk	low risk	low risk	low risk	low risk
Infante-Rivard C [14]	1993	moderate risk	low risk	serious risk	low risk	low risk	low risk	low risk
Wen W [13]	2001	moderate risk	moderate risk	low risk	low risk	low risk	low risk	low risk
Weng X [12]	2008	moderate risk	moderate risk	low risk	low risk	low risk	low risk	low risk
CARE Study Group [35]	2008	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Adeney K L [65]	2007	moderate risk	low risk	low risk	low risk	moderate risk	low risk	low risk
al-Ansary L A [11]	1994	moderate risk	serious risk	low risk	low risk	moderate risk	low risk	low risk
Bakker R [41]	2010	moderate risk	serious risk	low risk	low risk	moderate risk	low risk	low risk
Bech B H [38]	2005	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Bracken M B [49]	2003	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Browne M L [30]	2007	moderate risk	low risk	moderate risk	low risk	low risk	moderate risk	low risk
Chen L W [47]	2018	serious risk	low risk	serious risk	low risk	low risk	moderate risk	low risk
Chiaffarino F [60]	2006	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Clausson B [48]	2002	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
Cnattingius S [10]	2000	moderate risk	low risk	low risk	low risk	low risk	low risk	low risk
De Marco P [31]	2011	moderate risk	low risk	low risk	low risk	moderate risk	low risk	low risk

ALOMAR M J [9]	2016	no information	serious risk	no information	low risk	serious risk	low risk	low risk
Bech B H [54]	2015	moderate risk	moderate	moderate risk	low risk	low risk	low risk	low risk
Chen L [29]	2012	moderate risk	low risk	serious risk	low risk	low risk	low risk	low risk
Eskenazi B [6]	1999	moderate risk	low risk	low risk	low risk	moderate risk	moderate risk	low risk
Godel J C [78]	1992	moderate risk	low risk	low risk	low risk	moderate risk	serious risk	low risk
Vitti F P [59]	2018	moderate risk	moderate risk	moderate risk	low risk	low risk	low risk	low risk

Table 1 RISK OF BIAS ANALYSES ACCORDING TO ROBBINS I

APPENDIX 2

Author	Publication	Study design	No. of cases	Total no. of participants	Outcome	Method of exposure assessment	Period of exposure assessment	Exposure	Adjustments
Domínguez-Rojas V (25)	1994	retrospective cohort study		711	SAB	personal interview	during pregnancy	coffee	maternal age, menarcheal age, marital status and previous spontaneous abortions.
Fenster L (4)	1991	retrospective case control study	LBW: 87; IUGR: 84	1230	LBW, IUGR	telephone interviews	during pregnancy	caffeinated coffee, tea and soft drinks	maternal age, parity, race, hypertension during pregnancy, cigarettes smoked and alcohol consumed.
Fenster L (24)	1991	retrospective case-control study		1891	SAB	telephone interviews	1ºT	caffeinated coffee, tea and soda	maternal age, gravidity, pregnancy history, illnesses, diagnostic procedures, occupation during pregnancy, exposure to solvents at work and home, other occupational exposures, previous spontaneous abortion, previous therapeutic abortions, previous stillbirths, race, education, marital status, insurance coverage, employment, nausea, smoking, alcohol, water intake.
Ford R P K (26)	1998	retrospective case-control study	393	1985	SIDS	interview based questionnaire	1º e 3º T	tea, caffeinated coffee, and cola drinks	no information
Fortier I (3)	1993	retrospective cohort study		7025	LBW, IUGR, PTB	telephone interviews	two periods: the first 16 weeks and the rest of pregnancy.	caffeinated coffee, tea, colas, and chocolate	age, education, marital status, family income, obstetric history, weight before pregnancy, height, weight gain during pregnancy, passive smoking, alcohol intake, occupational factors, physical factors and physical activity.
George L (23)	2006	retrospective case-control study	108	562	SAB	in-person interviews	during pregnancy	coffee (brewed, boiled, instant and decaffeinated), tea (loose tea, tea bags and herbal tea), cocoa, chocolate, soft drinks and caffeine containing medications	maternal age, previous pregnancy history, induced abortions, myoma, time to conceive, marital status, plasma folate levels, smoking, caffeine and alcohol intake.
Giannelli M (22)	2003	case-control study	159	474	SAB	interview	during pregnancy	coffee, tea, cola	maternal age, severity of nausea and gestational age.
Greenwood D C (21)	2010	prospective cohort study	28	2 635	SAB, stillbirth	questionnaire	1º,2º,3º T	all potential dietary sources of caffeine, both food and drink, and over the counter medications	maternal age, parity, amount smoked and alcohol intake.

Grosso L M (58)	2001	prospective cohort study	190	2 714	IUGR	questionnaire	3ºT	coffee, tea, and soda, chocolate foods and drinks	smoking, height, antenatal weight gain, preeclampsia during index pregnancy, parity and bleeding during the third trimester.
Hahn K A (20)	2015	prospective cohort study	732	5132	SAB	questionnaire	during pregnancy	caffeinated and decaffeinated coffee, tea (green and black), regular and diet cola	age, smoking status, alcohol consumption, prior SAB, physical activity, vocational training/education), parity, BMI.
Del Castillo N (51)	2015	prospective cohort study	LBW-61; PTB- 64; SGA- 127	1 175	PTB, LBW, SGA	questionnaire		cola, diet caffeinated cola, coffee, decaffeinated coffee, chocolate, and chocolate biscuits	confounding factors such as tobacco and alcohol.
Hinkle S N (75)	2014	prospective cohort study	912	71239	GDM	interview	beginning of pregnancy	coffee, tea	maternal age at delivery, parity, smoking status, cola intake, pre-pregnancy body mass index, calculated from self-reported height and pre-pregnancy weight, and socio-occupational status.
Hoyt A T (52)	2013	case control study	648	7943	SGA	interview	during pregnancy	coffee, tea, and soda	age at delivery, parity, race/ethnicity, education, pre-pregnancy BMI, total caloric intake, high blood pressure during the index pregnancy, folic acid-containing supplement use, smoking and alcohol use, infant sex and mother's state of residence at the time of the infant's birth.
Jarosz M (62)	2011	retrospective cohort study	22	509	PTB	in person interview	during pregnancy	coffee, chocolate, tea, soda coffee, cola drinks, energy drinks, plain chocolate	no information
Johansen A M W (28)	2009	case-control study	573	1336	oral clefts	questionnaire	1ºT	coffee, tea, and soft drinks	demographic characteristics, reproductive history, and exposures during pregnancy (including smoking, alcohol consumption, coffee intake, medication use, and occupational and household exposures)
Klebanoff M A (19)	1999	prospective case control study	487	3149	SAB	Serum caffeine and paraxanthine samples high-performance liquid chromatography	3ºT	caffeine	maternal age, smoking status, and race or ethnic group
Klebanoff M A (55)	2002	prospective cohort study	222	2515	SGA	Serum caffeine and paraxanthine samples high-performance liquid chromatography	3ºT	caffeine	maternal age, ethnicity, parity, education, prepregnant weight, and (among smokers) the daily number of cigarettes smoked

Kline J (46)	1991	prospective case control study	899	1423	SAB	interview	pre and during pregnancy	coffee (caffeinated and decaffeinated), cocoa and other chocolate drinks, regular or diet colas, specific caffeinated noncola sodas, and several beverages without caffeine.	payment group and maternal age
Kobayashi S (8)	2019	prospective cohort study	SGA:7252 PTB:4281	94 876	SGA, PTB, LBW	Self-administered questionnaire	during pregnancy and the year prior to pregnancy	tea and coffee	maternal age, maternal body mass index (BMI) before pregnancy, maternal smoking during pregnancy, maternal drinking during pregnancy, maternal education level, annual household income, total energy intake, parity, infant sex, and gestational age.
Matijasevich A (18)	2006	case control study	382	1174	SAB	Interview	during pregnancy	coffee	maternal and partner's education, history of abortions and/or fetal deaths, vomiting/nausea during the first trimester and attendance for prenatal care.
Mills J L (45)	1993	prospective cohort study		431	IUGR, SAB, LBW	Interview	during pregnancy	regular coffee, decaffeinated coffee, hot tea, cocoa, iced tea, regular cola drinks, diet cola drinks or other diet drinks	maternal age, income, education, pre pregnancy weight, height, race, parity, smoking, and alcohol use
Modzelewska D (76)	2019	prospective cohort study		67 569	SGA	Questionnaire	during pregnancy	coffee, tea, soft drinks and chocolate	maternal pre-pregnancy body mass index, household income, maternal education, marital status, parity, maternal age at delivery, smoking status, presence of nausea, folic acid supplementation, planned pregnancy, baby's sex and total energy intake. When studying different caffeine sources, analyses were mutually adjusted for caffeine sources.
Morales-Suárez-Varela M (64)	2017	retrospective cohort study	1178	90 086	Stillbirth	telephone interviews	1ºT	coffee and smoking	mother's age, parity, pre-pregnancy BMI, drinking alcohol, practicing exercise and socio-economic status
Okubo H (7)	2015	prospective cohort study		858	PTB, LBW, SGA	self-administered questionnaire	during pregnancy	tea, coffee, black tea, cola, sports drinks, hot chocolate, diet cola, non–energy containing soft drinks, and confectionaries (mainly chocolate)	maternal age, gestational age at enrollment, height, body mass index, 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 pre pregnancy, energy intake, and baby's sex.

Olsen J (27)	1991	prospective cohort study		11 858	LBW, PTB, CA	self-administered questionnaire	during pregnancy	coffee and tea	social group, smoking, parity alcohol intake
Parazzini F (57)	2005	retrospective case control study	555	2521	SGA	no information	during pregnancy	coffee, tea, cola and decaffeinated coffee	age, education, parity, smoking during the third trimester of pregnancy, gestational hypertension and history of SGA birth.
Pastore L M (61)	1995	case control study	408	898	PTB	telephone interview	1ºT	caffeinated coffee, tea, cola soft drinks, and non-cola caffeinated soft drinks	race, hospital of delivery, parity, alcohol use, and smoking.
Peacock A (77)	2018	prospective cohort study	125	1232	SGA	interview (telephone or in person)	1º,2º,3ºT	no information	mother socio-demographic and infant covariates: mother age at birth, SES, country of birth, tertiary qualification completed, living with partner, and sex of child, planned pregnancy, parity, fertility treatment, illicit drug use during pregnancy, smoked tobacco during pregnancy, used alcohol during pregnancy, body mass index pre-pregnancy
Pollack A Z (44)	2010	prospective cohort study	14	113	SAB	Interview		coffee, tea, caffeinated soft drinks	standardized cigarette smoking age, history of prior spontaneous pregnancy loss, standardized alcohol consumption;
Rasch V (17)	2003	case control study	330	1498	SAB	self-administered questionnaire	during pregnancy	coffee, tea, chocolate and cola	age, parity, occupation, cigarette, alcohol and caffeine consumption;
Sata F (16)	2005	case control study	58	205	SAB	self-administered questionnaire	during pregnancy	coffee (caffeinated and decaffeinated), green tea, black tea, oolong tea and cola	age and smoking status during pregnancy;
Schmidt R J (32)	2009	retrospective case control study	768	4911	NTDs	in person interview	one year before and during pregnancy	coffee, tea, soda, and chocolate and medications containing caffeine	maternal alcohol consumption one month before through the third month of pregnancy, maternal education, maternal pre pregnancy obesity (BMI >30 kg/cm2), study center and household income.
Shu X O (50)	1995	prospective cohort study		712	LBW	telephone interview	1º, 2º e 3ºT	caffeinated coffee, tea, and caffeinated soft drinks	gestational age, parity, smoking;
Stefanidou E M (15)	2011	retrospective case-control study	52	312	SAB	interview in person	2 periods: 1 month before their LMP and through the last GW before miscarriage or delivery.	coffee (caffeinated or decaffeinated), tea, cocoa, chocolate and cola.	no information

Vik T (56)	2003	prospective case control study	111	858	SGA	interview in person	2 e 3ºT	chocolate, coffee, tea, cola	total population, and stratified by gender, smoking at pregnancy, prepregnancy weight, low education and previous SGA birth
Infante-Rivard C (14)	1993	prospective case-control study	331	1324	SAB	Interview in person	one month before and during pregnancy	coffee, tea, and cola	adjusted for period of pregnancy, age, educational level, smoking and alcohol use during pregnancy, uterine abnormality, and work schedule.
Wen W (13)	2001	prospective cohort study	75	650	SAB	self-administered questionnaire	during pregnancy	regular coffee, tea, cola, hot chocolate and caffeinated diet soda and caffeine content of products that contain chocolate (for example: brownies and chocolate syrup)	no information
Weng X (12)	2008	prospective cohort study.		1063	SAB	interview in person	1ºT	coffee (caffeinated or decaffeinated), tea (caffeinated or decaffeinated), caffeinated soda (including 17 brands, such as Coca-Cola, Big Red, and Pepsi-Cola, etc.), and hot chocolate.	adjusted for maternal age, race, education, family income, marital status, previous miscarriage, nausea and vomiting since LMP, smoking status, alcohol drinking, Jacuzzi use, and exposure to MFs.
CARE Study Group (35)	2008	Prospective cohort study		2635	IUGR	interview questionnaire	1º, 2º,3ºT	No information	alcohol intake and smoking status
Adeney K L (65)	2007	prospective cohort study	75	1744	GDM	interview	during pregnancy	coffee	maternal age, smoking during pregnancy, and regular alcohol use before pregnancy, maternal race, pre-pregnancy BMI and chronic hypertension, average daily caloric intake
al-Ansary L A (11)	1994	prospective case control study	226	452	SAB	interview in person	during pregnancy	instant coffee, tea, colas and Arabic coffee	no information
Bakker R (41)	2010	prospective cohort study	LBW-329; PTB- 337; SGA- 354	7346	LBW, SGA, PTB	self-administered questionnaire	during pregnancy	coffee or tea	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 (pregnancy-induced hypertension, preeclampsia, and gestational diabetes), and fetal sex.
Bech B H (38)	2005	prospective cohort study.	1102	88482	SAB and stillbirth	telephone interview	during pregnancy	coffee	age, parity, socio-occupational status, body mass index, smoking, and alcohol consumption, pre pregnancy body mass index;
Bracken M B (49)	2003	prospective cohort study	IUGR: 191; LBW:	2291	LBW, PTB, IUGR	Interview	1º e 2º T	coffee, tea, and soda consumption	age, parity, no. of prior pregnancies, marital status, race, education, height, smoking during the third trimester, and weight;

			108; PTB: 160						
Browne M L (30)	2007	retrospective case control study	4 196	8153	cardiovascular malformations	telephone interview	during pregnancy	caffeinated coffee, tea, soda, and chocolate	Adjusted for race/ethnicity; mother's state of residence at the time of birth;
Chen L W (47)	2018	prospective cohort study		941	LBW, SGA	interview questionnaire	during the first 12 -16 wk. of pregnancy	coffee, tea, soft drinks, and chocolate-containing food and beverages	maternal socioeconomic status, education attainment, cigarette smoking and alcohol consumption during pregnancy, age at recruitment, parity, prepregnancy BMI, and child gender; regressions for different caffeine sources were additionally mutually adjusted for each other
Chiaffarino F (60)	2006	retrospective case-control study	502	2468	PTB	interview face to face	during pregnancy	coffee, tea, cola and decaffeinated coffee	age, education, parity, smoking during the first trimester of pregnancy, gestational hypertension and history of preterm births;
Clausson B (48)	2002	prospective cohort study		873	LBW, IUGR	in-person interview	1º e 3ºT	coffee, tea, cocoa, chocolate, soft drinks, and caffeine containing medications.	age, height, body mass index, country of birth, parity, previous low birth weight infant (<2,500 g), education, work, nausea, vomiting, fatigue, diabetes, hypertensive disorders;
Cnattingius S (10)	2000	case control study	562	1515	SAB	interview questionnaire	during pregnancy	coffee (brewed, boiled, instant, and decaffeinated), tea, cocoa, chocolate, soft drinks, and caffeine-containing medications	age, number of previous pregnancies, history of spontaneous abortion, consumption of alcohol during pregnancy, presence or absence of nausea, vomiting and fatigue as symptoms of pregnancy.
De Marco P (31)	2011	prospective case control study	133	406	spina bifida (NTD)	interview questionnaire	3 months before and during 1ºT	coffee	no information
ALOMAR M J (9)	2016	retrospective cohort study	42	97	SAB, stillbirth	no information	no information	coffee, tea, soft drinks	no information
Bech B H (54)	2015	prospective cohort study		89539	LBW, SGA	Interview	2ºT	no information	maternal age, smoking, parity, alcohol, height, pre-pregnancy BMI, nausea, infant sex, socio-occupational status and gestational age;
Chen L (29)	2012	retrospective case control study	844	8913	congenital limb deficiencies	telephone interview	during pregnancy	coffee, tea, soda and chocolate	education, alcohol intake 1 month before pregnancy and through the first trimester, maternal exposure to environmental smoking and active smoking during 1 month before pregnancy through the first trimester
Eskenazi B (6)	1999	cohort study		7855	SGA, PTB, LBW	self-administered questionnaire	during pregnancy	tea, coffee, cola	age, parity, race, height, education, third trimester smoking and tea and cola consumption

Godel J C (78)	1992	cohort study		162	LBW	self-administered questionnaire	during pregnancy	coffee, tea and colas	gestational age
Vitti F P (59)	2018	retrospective cohort study		7607	LBW, PTB	questionnaire	1, 2, 3º T	coffee	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;

Table 2 Characteristics of included studies

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