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Association between Caffeine Intake and Anemia Risk in Pregnant Women: A Systematic Review and Meta-Analysis of Observational Studies

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Abstract

Background: Although many studies have linked caffeine to the risk of anemia in pregnant women, but in many of them contradictory results have been reported. The aim of this study was to investigate association between caffeine intake and anemia risk in pregnant women.

Methods: Related papers were found by searching through PubMed/Medline, Scopus, and Google Scholar up to 14/09/2020. Prospective cohort studies examined the association between relationship between caffeine intake and anemia risk in pregnant women, were included. The random-effects model was used to pool the reported relative risks (RR).

Results: Six prospective studies, including 4910 participants were included. Based on overall pooled results, we found a significantly higher risk (Pooled risk estimate: 1.57; 95% CI; 1.07 to 2.32, P=0.022). The association between anemia and caffeine was significant in studies which conducted in the middle east countries (pooled risk estimate: 1.41, 95% CI: 1.18–1.69, P< 0.001), participants used coffee as a source of caffeine (pooled risk estimate: 1.50, 95% CI: 1.21–1.86, P< 0.001), more than 3 times a week (pooled risk estimate: 1.76, 95% CI: 1.28–2.42, P< 0.001).

Conclusion: Our found a positive association between caffeine consumption and the risk of anemia in pregnant women. Longer studies with more control over future factors provide clearer information on caffeine consumption in the development of anemia during pregnancy.

Keywords: Caffeine; Anemia; Pregnant women

Introduction

Anemia is one of the most common nutritional deficiencies worldwide. Although nutritional anemia can occur in both sexes and all age groups [1] it is more common in women and high maternal caffeine intake in pregnancy may lead to a miscarriage, premature birth, or low-birth neonatal weight but, despite extensive research, the evidence remains inconclusive [2]. Infant low birth weight, defined as a birth weight smaller than 2,500 g, is a well-established risk factor associated with several adult diseases, such as hypertension and diabetes mellitus, and obesity [3].

In contrast, a recent Cochrane review of caffeine intervention studies concluded that insufficient evidence to confirm or refute the effectiveness of caffeine avoidance on birth weight or other pregnancy outcomes [4]. The main cause of anemia is iron deficiency, but other factors such as lack of nutrients such as vitamins A, C, B2, B12 and folic acid, low intake of fruits and vegetables daily, low consumption of red meat, caffeine consumption (including coffee and tea) eating is one of the most important factors in anemia [5]. The World Health Organization (WHO) defines anemia in pregnancy as a decrease in the concentration of hemoglobin to less than 11 grams per deciliter, which reduces the oxygen-carrying capacity of the blood [6]. It is estimated that nutritional anemia accounts for approximately two-thirds of pregnant women in developing countries, so global access to antenatal care is a priority in developed and developing countries. The Centers for Disease Control and Prevention (CDC) recommends screening for anemia in pregnant women and universal iron supplementation to meet the iron needs of pregnancy, except in certain cases of genetic disorder such as hemochromatosis. The recommended daily amount of iron during pregnancy is 27 ml [7]. Pregnant women have slower caffeine metabolism, with 1.5 to 3.5 times longer half-life needed to eliminate caffeine, compared to non-pregnant woman. Caffeine has been detected in the amniotic fluid, umbilical cord, urine, and plasma of fetuses, which suggests that caffeine, is easily transmitted across the placenta [3]. Caffeine and its metabolites easily cross the placental barrier, and caffeine excretion is delayed due to the immaturity of the fetal liver [8]. Coffee, tea, soda, and chocolate are the main sources of caffeine consumption among pregnant women [9]. The half-life of caffeine increases between the first and third trimester, resulting in increased foetal exposure [10]. Various organizations have established guidelines recommending caffeine consumption of no more than 200 mg/day (equivalent to approximately two ground coffees) for women who are pregnant [11].

Recently, several studies have examined the effect of caffeine consumption on anemia during pregnancy; however, the results of studies in this field are variable. The advantage of meta-analysis studies over review studies is the ability to obtain results with less bias. Therefore, the aim of this study was to summarize information, the link of between caffeine consumption and anemia in pregnant women and a meta-analysis in this area.

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Methods

The present analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [12].

Search strategy

All articles were gathered by further analyzing through PubMed, Scopus and Google Scholar up to August 2020 to identify relevant articles. Mesh and non-Mesh keywords were incorporated in this research. The following terms were used in the electronic search: (caffeine (tiab) OR caffeine (MESH) OR coffee(tiab) OR coffee (MESH) OR tea (tiab) OR tea (MeSH) AND ("Hemoglobins"(Mesh) OR Hemoglobin (tiab) OR Eryhem (tiab) OR "Ferrous Hemoglobin"(tiab) OR "Hemoglobin, Ferrous"(tiab) OR "anemia"(tiab) OR "Anemia"(Mesh) OR "anaemia"(tiab) OR "iron deficiency anaemia"(tiab) OR "Anemia, Iron-Deficiency"(Mesh) OR "iron deficiency anemia"(tiab) OR "iron-deficiency anaemia"(tiab) OR "iron deficiency anemia"(tiab)

We were not faced with date and language limitations. To avoid missing any study, the reference list of all included studies was manually reviewed. Furthermore, the reference list of obtained articles was manually reviewed as well. Unpublished data and grey literature, including congress abstracts, thesis, dissertations and patent were not encompassed (Table 1).

Eligibility criteria

Studies in meta-analysis take into account the following inclusion criteria: (1) Observational studies. (2) Consumption of caffeine (3) the study population (pregnant women) (4) reported the data as odds ratio (OR), relative risks (RRs) or hazard ratio (HR) with 95% CI for The relationship between caffeine consumption and Risk of anemia in pregnant women; (5) were published in English defined. Anemia in pregnancy as a decrease in the concentration of hemoglobin to less than 11 grams per deciliter.

Interventional studies, book chapters, conference abstracts, letters, gray literature as well as ecological and unpublished studies and those with unusable information and abstracts were excluded. In addition, studies that were conducted on children, adolescents and populations with preexisting health conditions were not included.

Study selection

Titles and abstracts of all arrived articles in the primary search were evaluated independently by 2 reviewers (FT and AM). Articles that did not meet the competency criteria were excluded using a screen form with a hierarchical approach based on study design, population or intervention or outcome. Then, full-texts of eligible articles were retrieved and subjected to a second evaluation by the same reviewers. Any disagreements were discussed and resolved by consensus.

Authors(year)	Country	Kind of study	Sample Size	Gestational Age	Tea/Coffeine	Estimate(95%CI)*	Adjusted variable in Analysis	Quality assessment
FARUK AHMED (2011)	Kuwaiti	cross-sectional	465	4-39 weeks	(never consumed) Tea/coffee 1–6 times/week >7 times/week	2.21(1.28-3.79) 2.62(1.24-5.52	age,education and employment status,parity and birth space from last pregnancy,gestational age food frequency (questionnaire,source of iron and foods that are known to enhance fiber, phytates and tannins)	7
Niguse Obse (2 012)	Ethiopia	cross-sectional	374	8-38weeks	tea intake:Always after every meal tea intake:Once or less per day coffee intake: Always after meal coffee intake: Once or less per day	7.79(1.6-37.89) 1.77(0.504-6.25)	age,sex.cross- sectional,Family sizes, third trimester, meat consumption and pica Having five or more children intake of vegetables and fruits less than once per day.intake of tea always after meal, and recurrence of illness during pregnancy	8
Naila Baig-Ansari (2014)	Pakistan	cross-sectional	1366	20-26weeks	Never or < 1×/day 1–3×/day > 3×/day	1.9(1.01-3.7) 3.2(1.03-8)	blood sample, hemoglobin levels nutritional knowledge, attitudes, and practice and dietary history regarding usual food intake before and during pregnancy	8
Gemechu Kumera (2018)	Ethiopia	cross-sectional	234	24.2±9.2 weeks	< 3 coffee cups (< 210ml) > 3 coffee cups (>210ml)	4.03(1.89-9.95)	sociodemographic factors,environmental and sanitation factors, Reproductive factors, and nutrition related characteristic structured questionnaire. Hemoglobin level, The stool sample	7
Kidanemaryam Berhe (2019)	Ethiopia	case-control	All third trimester 150(case) 450(control)	with/ immediately Caffeine intake Never Caffeine intake: Daily Caffeine intake: weekly Caffeine intake : occasionally	after meals daily : YES with/immediately after meals daily : NO	13.4(8.5-21.1) 0.91(0.6-1.37) 2.08(0.86-5.03) 2.36(1.42-3.93)	intestinal parasites, confidence interval, farmer occupation, unprotected sources of drinking water, drinking coffee/tea with or immediately after meal daily and diet diversity score	6

Table 1: Characteristics of studies that reported the relationship between caffeine consumption and anemia in pregnant women.

*CI: confidence interval

Anemia in pregnancy in all articles: Haemoglobin level below 11g/dl during pregnancy

Pregnant woman in all articles: A woman whose pregnancy is confirmed by HCG test or abdominal examination and fetoscope at the study health centre

Data extraction

Two independent reviewers (FT and AM) separately extracted data from the included publications using a standard data extraction form. Data collected from each study included:

(1) first author's name (2) the type of study (3) year of study (4) country of study (5) number of participants in the study (6) type of substance studied (caffeine, coffee, tea) (7) caffeine consumption assessment methods (8) reported risk estimates related caffeine consumption to risk of anemia in pregnant woman (including ORs, RRs, and HRs and 95% confidence intervals).

Quality assessment for individual studies

The scale assesses aspects of methodology in observational studies related to study quality, including nine items grouped into three major categories: selection (four items, one star for each), comparability (one item, up to two stars), and outcomes (three items, one star for each). The maximum score was nine stars and six stars or more were regarded as high quality for cross-sectional studies; we applied an adapted form of the Newcastle-Ottawa Scale (NOS) [13]. The maximum score was ten, and seven points were used to identify studies with high quality. Two reviewers (FT, LS) worked independently, and any disagreement was resolved by discussion.

Statistical analysis

The reported RRs and 95% CIs in the original studies were considered as the effect size. We examined heterogeneity between studies by the Cochran's Q test and I2 statistics to test the robustness of the findings and investigate the between-study heterogeneity; we conducted subgroup analyses to find the possible sources of heterogeneity. These analyses were performed based on race (in the Middle East countries) source of caffeine (coffee as a source of caffeine) and frequency of use (more than 3 times a week). Visual inspection of the funnel plot and the results of the Egger's test were used to examine publication bias. All statistical analyses were accomplished using STATA software, version 14.

Results

Study selection

We initially obtained a total of 2121 potential articles, including the publications identified via screening of references cited with in encountered articles. We retained 126 articles after excluding 401 duplicate and 1594 irrelevant articles based on the title or abstract. Following the revision of the full texts, 120 articles were excluded. Of these 120 publications, 59 were non-observational studies, 7 were review articles, 12 reported irrelevant outcomes, 25 did not report findings as risk estimates with 95% confidence intervals, 10 reported insufficient data, and 7 combined exposure with other outcomes. Ultimately, 6 articles were included in this study. The flow diagram of the literature search and exclusion process is depicted in Figure 1.

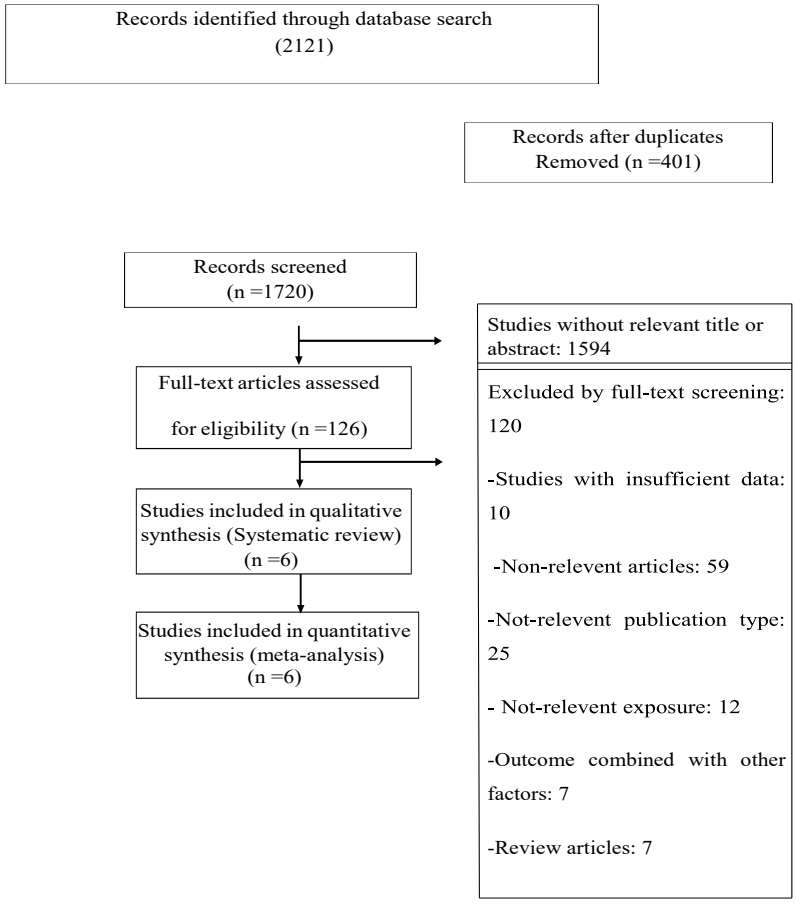

Figure 1: Flow Diagram of the literature search and exclusion process is depicted.

Study characteristics

The 6 included studies were published between 2011 and 2019 that involved a total of 4910 participants with a gestational age range between 4-39 weeks. Four studies were conducted in Ethiopia while the remaining was performed in Kuwaiti and Pakistan. Five were cross-sectional studies, while one was a cohort study.

Findings from the meta-analysis

Examining the association of coffee consumption with risk of anemia during pregnancy in six publications, that involved a total of 4910 participants, we found a significantly higher risk (Pooled risk estimate: 1.57; 95% CI: 1.07 to 2.32, P= 0.022), with significant heterogeneity among the studies (I2 =93.5 %; P< 0.001) (Figure 2).

Subgroup analysis

To test the robustness of the findings and investigate the between-study heterogeneity, we conducted subgroup analyses to find the possible sources of heterogeneity. These analyses were performed based on race, source of caffeine and frequency of use Table 2 presents findings for the different subgroups. The association between anemia and caffeine was significant in studies which conducted in the middle east countries (pooled risk estimate: 1.41, 95% CI: 1.18–1.69, P< 0.001), participants used coffee as a source of caffeine (pooled risk estimate: 1.50, 95% CI: 1.21–1.86, P< 0.001), more than 3 times a week (pooled risk estimate: 1.76, 95% CI: 1.28–2.42, P< 0.001).

Sensitivity analysis

Findings of the sensitivity analysis showed that the association between caffeine consumption during pregnancy with the risk of anemia did not rely on a single or a few publications (Figure 3).

Publication bias

Visual inspection of the funnel plot and the results of the Egger's test were used to examine publication bias (Figure 4). No evidence of publication bias was observed regarding the association between caffeine consumption and the risk of anemia (P= 0.851). Moreover, Egger's statistic demonstrated no significant publication bias regarding the association between caffeine consumption and the risk of anemia (P=0.731).

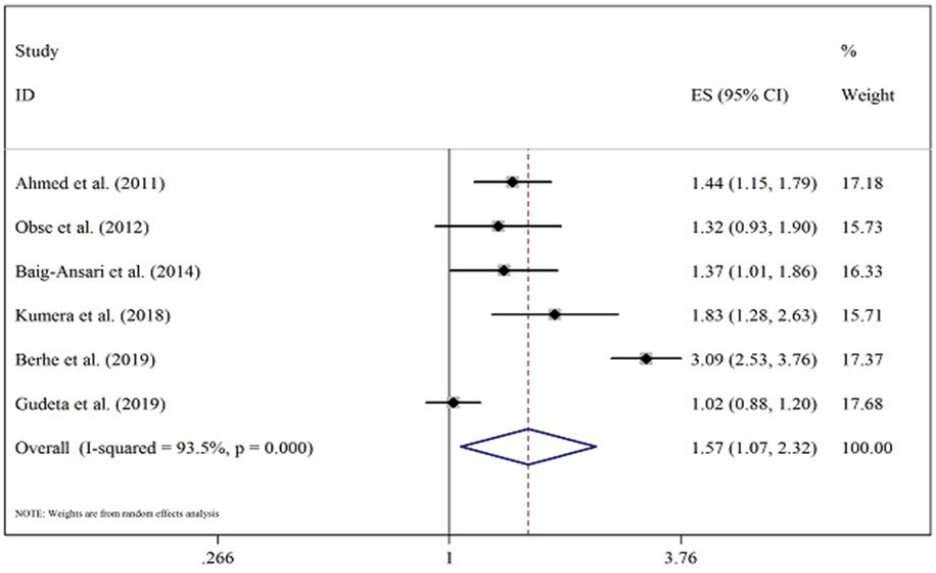

Figure 2: Forest plot of the association between Caffeine intake and anaemia in pregnant women.

Subgroup	Effect sizes (n)	Effect sizes (95% CI)	I^2 (%)	*P* Heterogeneity	*P* Within
Overall	6	1.57 (1.05, 2.35)	93.5%	<0.0001	0.022
Caffeine source					
Tea/coffee	3	1.65 (0.85, 3.22)	97.3%	<0.0001	0.139
Coffee	3	1.04(0.93, 1.16)	84.5%	0.398	<0.0001
Frequency					
1-3 times/day	3	1.20 (0.94, 1.55)	71.5%	0.030	0.145
> 3 times/day	3	1.76 (1.28, 2.42)	85.7%	<0.0001	0.001
Continent					
Middle east	2	1.41 (1.18, 1.69)	0.0%	0.796	<0.0001
African	4	1.67 (0.91, 3.05)	96.0%	<0.0001	0.099

Table 2: Subgroup analysis for the association between Caffeine intake and Anaemia risk in Pregnant Women. (Odds ratios and 95% confidence intervals).

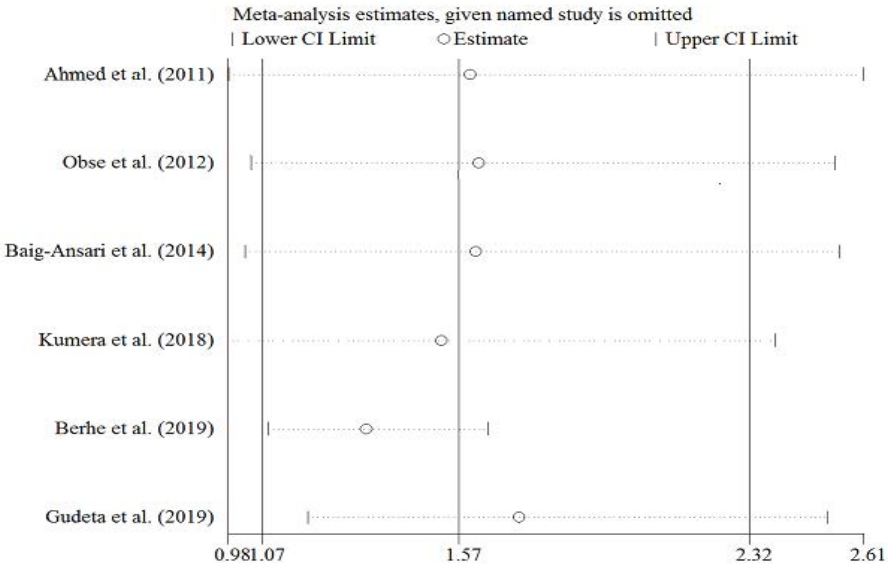

Figure 3: Analysis of the association between Caffeine intake and anaemia in pregnant women. (Sensitivity analysis).

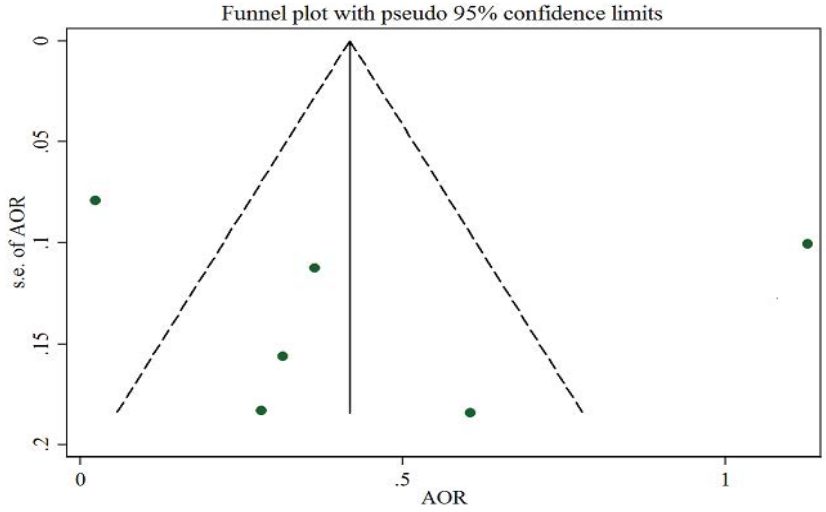

Figure 4: Funnel plots for publications bias.

Discussion

We found that increasing coffee consumption, as a caffeine source, to about more than 3 times a week in pregnant women that mostly live in middle-east region, results to a higher risk of developing anemia. To the best of our knowledge, this is the first meta-analysis of observational studies assessing the effect of caffeine intake on risk of anemia among pregnant women.

One study demonstrated that pregnant women who occasionally used coffee and tea were two and two & half respectively times more likely developed anemia as compared to mothers never used and as well as those were under nourished were more susceptible to anemia compared to women were well nourished [14]. Ahmed et al. found Hb concentration of the pregnant women was negatively associated with frequency of intake of tea as a source of caffeine. These researchers also stated that consumption of tea or coffees at least once a week were important predictors of iron deficiency in these women [5]. A study examining the prevalence of anemia in women has been reported that about 98% of Ethiopian women drink tea before and after meals, and 59.5% of them consume tea more than two times a day [15]. Obse et al. showed that Women who consume coffee and tea more frequently are more likely to develop anemia compared to those who consume these substance less. The results of this study showed that participants who drink tea after meal were found to be more anemic than those who take tea once or none per day [6]. Berhe et al. suggested that one of the main risk factors for anemia development over the pregnancy in Eastern Zone of Tigray is coffee or tea drinking immediately after or with meals [16]. Similar results were found from studies conducted in Pakistan [1] and Oromia region [6]. Another study investigated that anemia was more common in tea drinking pregnant women [17]. A study indicated that there is a negative correlation between coffee intake and pregnancy and maternal anemia that it was different results from other studies and previous study performed in Costa Rica also supported its finding [18]. Tea and coffee tend to reduce iron absorption by 60% and

50% respectively. Coffee in some beverages due to its tannin content is considered to be an inhibitor of iron absorption in the body and consuming more than the recommended amount of coffee can reduce the bioavailability of iron [19,20]. Tea (especially black tea) and coffee, contains polyphenolic compounds, that act as antioxidants, but it has undergone oxidation which can bind minerals such as iron, Zinc, and Calcium, so inhibit non-hem iron absorption [21,22]. In other words, by consuming caffeinated beverages, iron-tannate complex is formed and non-heme iron becomes insoluble and thus its absorption rate decreases. So by reduction in iron concentration over the body red blood cell (RBC) production is reduced which can lead to anemia [6]. It can also be mentioned that caffeine can cross the placenta into the amniotic fluid and fetus and results in adverse pregnancy outcomes. The American Pregnancy Association and March of Dimes recommends that a pregnant woman should not take more than 200mg caffeine per day, which is around 355 milliliters coffee [23]. The effects of caffeine on cell cycle are as follows: caffeine is a compound known to inhibit post replication repair of deoxyribonucleic acid (DNA) and also this component can potentiates the lethal effects of a variety of DNA damaging agents such as irradiation. Caffeine increases cytotoxicity by affecting of S phase and DNA replication over the cell cycle. So caffeine can be considered as a compound that exacerbates the condition of some types of anemia, such as fanconi anemia (FA) [24,25].

Due to the increasing consumption of caffeinated compounds in recent years and the various effects that these compounds have on society health and also because pregnant women are considered as a part of sensitive groups in society and growing the prevalence of anemia over the societies especially in this population, this study has clinical and social implications to prevent or reduce anemia among pregnant women. So far, many observational studies have been published worldwide about the effect of increasing caffeine consumption on anemia and this makes meta-analysis of their results possible. However, several limitations of the current meta-analysis should also be mentioned; in this meta-analysis study we just included observational study and as we know observational studies cannot reach a causal relationship; therefore, to detect causal effects, randomized clinical trial (RCT) s are the most appropriate study and meta-analysis of their results can be considered more reasonable. Therefore, in this study, we could not determine the exact amount of caffeine or caffeinated beverages that lead to anemia and also in this meta-analysis study, we included studies that examined caffeinated beverages and did not examine other caffeinated compounds such as cola drinks, chocolate, cocoa, and medicines. It must be kept in mind that most studies have been conducted in Middle-East countries and do not include other parts of the world. Some studies included in the current meta-analysis had small sample sizes and the possibility of bias induced by the exclusion of some studies is another explanation.

Conclusion

Our meta-analysis on observational studies indicated that increasing caffeine consumption may lead to a higher risk of anemia development among pregnant women. Although further large prospective and RCT studies are recommended to confirm the observed relationship of the present study.

Abbreviations

LBW: Low-birth weight; RBC: Red blood cell; FA: Fanconi anemia; DNA: Deoxy ribonucleic acid; CI: Confidence interval; OR: Odds ratio; RRs: Relative risks; HR: Hazard ratio; HB: Hemoglobin; MOOS: Meta-analyses of observational studies in epidemiology

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Author Contributions

F.T, AM and K.M. contributed to the study concept and design; F.T and AT designed search strategy and screened papers; S.M. performed statistical analysis; F.T wrote the first draft of manuscript; all authors read and approved the final manuscript.

Availability of data and materials

Not applicable

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