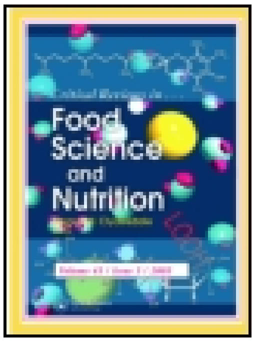

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Is a vegetarian diet safe to follow during pregnancy? A systematic review and meta-analysis of observational studies

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Abstract

Background: Whether a vegetarian diet is appropriate for pregnancy remains unclear.

Objective: This study aimed to determine the association between vegetarian diet during pregnancy and various maternal–fetal outcomes.

Method: PubMed-Medline, EMBASE, and Cochrane Library databases were searched for relevant articles published by August 30, 2017. Quantitative data were analyzed by a random-effects model with pooled odds ratios or weighted mean difference (WMD) and 95% confidence interval as aggregate estimations.

Results: A total of 19 observational studies were identified for each of meta-analysis and narrative review. The overall estimated relation between vegetarian pregnancy and low birth weight (LBW) was marginally significant (1.27 (0.98, 1.65), P=0.07, I^2=0%). Asian (India/Nepal) vegetarian mothers exhibited increased risks to deliver a baby with LBW (1.33 (1.01, 1.76), P=0.04, I^2=0%). However, the *WMD* of neonatal birth weight in five studies suggested no difference between vegetarians and omnivores. Given the high heterogeneity of the included studies, lack of high-quality evidence, and limited studies included for each category, we failed to reach conclusive results regarding the risks of hypospadias, intrauterine growth retardation, maternal anemia, and gestational diabetes mellitus.

Conclusion: Asian vegetarian mothers presented increased risks to deliver babies with LBW than those of omnivores. Large-scale prospective studies focusing on pre- and/or early gestational nutrition will help clarify the correlation between vegetarian diet and various pregnancy outcomes.

Keywords: vegetarian diet; pregnancy outcome; hypospadias, low birth weight; anemia; gestational diabetes

Introduction

During pregnancy, dietary patterns not only affect the health of the mother but also the growth and development of the fetus, which consequently determine the health of the offspring. Vegan diets are free of all flesh food, eggs, dairy products, and even honey(Pawlak R. 2017). Vegetarian diets exclude any meat, fish, seafood, or animal by-product but include milk, cheese, and eggs(Craig and Mangels 2009). Although the Academy of Nutrition and Dietetics (AND) argued that “well-planned vegan, lacto-vegetarian, and lacto-ovo-vegetarian diets are appropriate for all stages of the life cycle, including pregnancy and lactation”(Melina et al. 2016), the German Nutrition Society (DGE) stated that adequate nutrients are difficult to obtain with a vegetarian/vegan diet and that a vegan diet should not be recommended for pregnant women, lactating women, infants, children, or adolescents(Richter M et al. 2016). In addition, Cofnas claimed that the AND provided evidence and pointed out that vegetarianism is associated with serious risks for fetuses(Cofnas 2018). Vegetarian/vegan diets have received increasing attention worldwide in the past decade due to health, animal welfare, and environmental concerns. In India, vegetarianism is practiced by nearly 50% of the population. In the United States, approximately 3.3% of adults are vegans, of which 5.3% are aged 18–34 years old(Stahler 2015).

No conclusive data have been obtained about the association between maternal vegetarian diet and various pregnancy outcomes. Some studies suggested maternal vegetarianism during pregnancy is a risk factor for the low birth weight

(LBW)(Shrestha et al. 2017) and hypospadias of offspring(North et al. 2000; Akre et al. 2008; Samtani et al. 2014), while some studies suggested it provides protective effects against intrauterine growth retardation (IUGR)(Fikree et al. 1994) and excessive gestational weight gain (GWG)(Stuebe et al. 2009). One review considered vegetarian diet safe during pregnancy(Piccoli et al. 2015), and numerous studies found no association between vegetarian diet during pregnancy and adverse outcomes(Ormond et al. 2009; Brouwers et al. 2010; Shekharyadav et al. 2011; Carmichael et al. 2012; Misra et al. 2015; Pawlak Roman 2015; Raje and Rao 2015). However, weak associations may have been neglected because of the low statistical power due to the small sampling size. Therefore, we conducted a systematic review and meta-analysis to investigate the association between maternal vegetarian diet during pregnancy and various adverse pregnancy outcomes.

Material and Method

We followed the preferred reporting items for a systematic review and meta-analysis to ensure accuracy and comprehensiveness (Moher et al. 2010).

Search strategy

Relevant articles were identified by searching the PubMed, EMBASE, and Cochrane Library databases for works published by August 30, 2017. The search strategy used the following keywords and medical subject headings: “pregnancy,” “pregnant,” “gravidity,” “gestation,” “maternal,” “vegan,” “veganism,” “vegetarian,” and "vegetarianism." Terms referring to pregnancy were combined with "OR", terms referring to vegetarian diet were combined with "OR", and terms referring to both were combined with the "AND" operator. We also manually searched the reference lists of identified relevant studies and previous reviews and meta-analyses (Figure 1)

Inclusion criteria and exclusion criteria

The titles, abstracts, and full texts of the retrieved articles were screened for the following predefined inclusion criteria: 1) exposure to vegan/vegetarian diet (vegetarian diet: no meat, seafood, or products containing these food; vegan diets: free of all flesh food, eggs, and dairy products; nonvegetarian diet: diet consuming all types of foods, including meat and meat products) during pregnancy; 2) pregnancy outcomes were reported; 3) original human observational study; and 4) published in English. If the same result was reported in multiple publications, then we selected the study with complete information.

Assessment of methodological quality

The quality of the included studies was independently evaluated by two authors in accordance with the Newcastle–Ottawa Scale (NOS).

The NOS assessment is consisted of eight items. The eight items for case-control studies are as follows: adequate definition of cases, representativeness of cases, selection of controls, definition of controls, control of important factor, ascertainment of exposure, same method for ascertaining cases and controls, and nonresponse rate. The eight items for cohort studies are as follows: representativeness of cohort, selection of nonexposed cohort, ascertainment of exposure, outcome lacking at the beginning, comparability of cohorts, outcome assessment, sufficient follow-up time, and follow up adequacy. The eight items were classified under three groups: selection of the study group, comparability of the groups, and ascertainment of either the exposure or outcome of interest for case control or cohort studies. Each item was graded with a maximum score of 1, with the exception of those related to comparability whose maximum score was 2. The overall scoring ranged from 0 (lowest) to 9 (highest) (Supplemental Table 1). Studies that obtained a score ≥6 were considered high quality, whereas those with scores <6 were considered low quality.

Data extraction

The following data were extracted:

1. Baseline data: author, publication year, study design, source of control, study location, ethnicity, and sample size;
2. Neonatal outcomes: hypospadias, birthweight, LBW, preterm delivery, IUGR, small for gestational age (SGA), and neural tube defect (NTD);
3. Maternal outcomes: maternal anemia, pregnancy-induced hypertension (PIH), and gestational diabetes mellitus (GDM);
4. Methods for assessing dietary patterns;
5. Supplements during pregnancy; and

6. Odds ratios (ORs) (95% confidence intervals (CIs)) and weighted mean difference (WMD) (95% CIs) for the association between vegetarian diet during pregnancy and pregnancy outcomes.

Statistical analysis

We evaluated the pregnancy outcomes of vegetarians and nonvegetarians during pregnancy. ORs (95% CIs) were combined for observational studies with a binary outcome. The *WMD*s were combined for individual studies with a continuous outcome.

Random-effects models were applied in all meta-analyses due to uncontrolled confounders in the retrieved studies. Heterogeneity was assessed using the I^2 values of 0%, 25%, 50%, and 75%, which represented no, low, moderate, and high heterogeneity, respectively.

Subgroup analyses were performed to identify the potential sources of heterogeneity.

Sensitivity analysis was conducted with one study removed at a time to assess the stability of the aggregated estimation. The robustness of the LBW analysis was evaluated by subgroup analyses and stratified by study design (cohort or case control), ethnicity (Asian or Caucasian), and study quality (high and low).

All reported probabilities (P values) were two sided with $P<0.05$ considered statistically significant.

Result

Characteristics of included studies

Our search strategy extracted 823 distinct citations. Additional 18 articles were identified from reference lists and manual searching. When the titles and abstracts were screened, 769 studies were excluded due to duplicates and other publication types (review, abstracts, or comments). Fifty-four full-text articles were assessed for eligibility. A total of 19 articles satisfied the criteria for meta-analysis(Campbell‐Brown et al. 1985; Ward et al. 1988; Lakin et al. 1998; North et al. 2000; Brouwers et al. 2007; Akre et al. 2008; Ormond et al. 2009; Brouwers et al. 2010; Shekharyadav et al. 2011; Carmichael et al. 2012; Gadgil et al. 2014; Narain and Prasad 2014; Samtani et al. 2014; Johnson et al. 2015; Koirala and Bhatta 2015; Misra et al. 2015; Pawlak Roman 2015; Raje and Rao 2015; Shrestha et al. 2017), and 19 studies were eligible for systematic review(Benny et al. 1980; Sharma DC et al. 1991; Fikree et al. 1994; Reddy et al. 1994; Sharma DCC 1994; Sharma JB et al. 2003; Shaheen et al. 2009; Stuebe et al. 2009; Jali et al. 2011; Kaur et al. 2012; Vemulapalli and Rao 2013; Larsen et al. 2014; Arora et al. 2015; Bedi et al. 2015; Hans et al. 2015; TOHEED et al. 2015; Gomez Roig et al. 2017) (Figure 1).

The characteristics (LBW, birth weight, and hypospadias) of the studies included in the meta-analysis are shown in Table 1. Table 2 summarizes the characteristics of the studies included in the systematic review. We compared vegetarian diet with omnivorous diet because the majority of the included studies involved vegetarian diet (only one study(Pawlak Roman 2015) included subjects with vegan diets).

All of the included studies were observational. Studies about LBW and birth weight were mainly retrospective cohort. Eight studies on hypospadias comprised seven case-control studies and one prospective cohort study.

With regard to geographical distribution, most of the studies on LBW, birth weight (six out of eight), and maternal anemia (all seven) were conducted in Asia. Three of them were carried out in the UK, and two were performed in the USA. Studies on hypospadias were mainly conducted in Europe (six out of eight).

Meta-analysis

Asian mothers with vegetarian diets during pregnancy were more likely to deliver a baby with LBW than women of Caucasian ethnicity

According to the retrieval and selection strategy, eight eligible studies (seven retrospective cohorts and one case control) that reported on the incidence of LBW were included in the meta-analysis. The pooled estimation showed that vegetarian diets during pregnancy slightly increased the risk of LBW incidence (1.27 (0.98, 1.65), P=0.07, I^2=0.0%) (Supplemental Figure 1.1). Subgroup analysis revealed that Asian women presented increased risks to deliver a baby with LBW if they consumed vegetarian diet during pregnancy 1.33 (1.01, 1.76), I^2=0%, P=0.04;although the study quality exerted no effect on such association (Supplemental Figures 1.2 and 1.3).

Vegetarian diets during pregnancy exerted no substantial effect on birth weight

Birth weight was provided in five studies (four retrospective cohorts and one case control). No significant association was found between vegetarian diets during pregnancy and neonatal birth weight (WMD: 61.71 (−24.65, 148.08), P=0.16, I^2=0%) (Supplemental Figure 2.1).

Maternal vegetarian diets during pregnancy and risk of hypospadias in the offspring

Among the eight studies that examined 3111 cases of hypospadias, five reported nonsignificant association, and three reported positive association between vegetarian diets during pregnancy and hypospadias. The overall estimation of hypospadias incidence was nonsignificant (OR= 1.39 (0.88, 2.21), P= 0.16) with a strong evidence of heterogeneity (I^2: 74%; P =0.0003). Subgroup analysis stratified by either quality score or location detected no association between maternal vegetarian diets and hypospadias (Table 5, supplemental Figure 3.1~3.4).

Sensitivity analysis

Sensitivity analysis, which removed one study at a time, showed stable pooled ORs for hypospadias, which ranged from 1.22 (0.79, 1.90) to 1.53 (0.93, 2.54). Heterogeneity was reduced from I^2 of 74% to 64% when a study that involved an Indian population (the remaining studies mainly involved Europeans) was excluded. Consequently, the effect estimate was changed from 1.39 (0.88, 2.21) to 1.22 (0.79, 1.90). Nevertheless, neither subgroup nor sensitivity analyses can identify the source of heterogeneity.

Pooled ORs for the incidence of LBW were similarly unchanging, with values ranging from 1.13 (0.86, 1.50) to 1.34 (1.02, 1.77). Similarly, the pooled WMDs of birth weight were also stable, with values ranging from 41.19 (−48.68, 131.05) to 72.56 (−19.30, 164.42). Additionally, I^2 changed from 0% to 7%.

Narrative review

Maternal outcomes

*Maternal Anemia during pregnancy.*Seven studies about maternal anemia are presented in Table 2. Among them, two studies showed that women with vegetarian diets present high risks of developing anemia(Bedi et al. 2015; TOHEED et al. 2015), and two other studies reported no significant association(Sharma JB et al. 2003; Hans et al. 2015). Two studies published in the 1990s identified a lower level of Hb among women with vegetarian diets than those in the controls(Sharma DC et al. 1991; Sharma DCC 1994), and one study in the 2000s found no difference between them(Sharma JB et al. 2003). Additionally, with regard to the incidence of anemia severity (mild, moderate, severe, and decompensated), no significant difference existed between vegetarians and controls(Sharma JB et al. 2003; Vemulapalli and Rao 2013; Hans et al. 2015).

*Other maternal outcomes.*Findings on GDM are controversial (Table 3). One study reported a higher proportion of GDM in nonvegetarians than that in vegetarians based on the WHO criteria 1999(Jali et al. 2011). A later study found that vegetarians display a higher prevalence of GDM than those of controls (P=0.04) according to the WHO

2013 criteria(Arora et al. 2015). However, nonvegetarians present a higher prevalence of GDM than those of controls when the WHO1999 criteria were applied (P=0.001)(Arora et al. 2015).

Vegetarian mothers presented higher fasting plasma (FPG) than those of nonvegetarian controls(Arora et al. 2015). Hindu vegetarian mothers showed higher levels of mean diurnal glucose than those of Caucasian omnivores(Benny et al. 1980).

Two studies reported about gestational weight gain (GWG); one of them indicated lower GWG in Hindu vegetarians (6.8 kg) than those in Caucasian omnivores (10.9 kg)(Benny et al. 1980). The other study found that vegetarian diet during the first trimester is inversely associated with excessive GWG(Stuebe et al. 2009).

A study also identified an increased risk of PIH and recurrent abortion in vegetarian women(Kaur et al. 2012).

Neonatal outcomes.

Two studies (Fikree et al. 1994; Kaur et al. 2012)reported that maternal vegetarianism increases the risk of IUGR (Table 4), whereas another study found no association between vegetarian diet and SGA(Gomez Roig et al. 2017).

Conflicting findings regarding NTD have also been reported. A study in Denmark found no association between vegetarian diet during pregnancy and NTD(Larsen et al. 2014), whereas a study in India indicated maternal vegetarian as a risk factor of NTD(Deb et al. 2011).

Discussion

To the best of our knowledge, this work is the first meta-analysis and systematic review that included 38 observational studies, which assessed the association between maternal vegetarian diet and pregnancy outcomes. A large number of included studies facilitated the pooling of data from many observations that are considerably small by themselves to ensure conclusions.

Our meta-analyses demonstrated that vegetarian diet during pregnancy marginally increases the risk of LBW, with Asian women more likely to deliver LBW infants than those of Caucasian ethnicity. A vegetarian diet is typically challenged with deficiency of nutrients(Pawlak R. 2017), such as vitamin B 12 (VB12)(Pawlak R. et al. 2013)and zinc(Foster et al. 2015). VB12 deficiency is positively associated with LBW(Rogne et al. 2017). In India, poor fetal growth is largely attributed to maternal malnutrition(Raje and Rao 2015). Notably, a study reported that a plant-based diet is associated with high birth weight among south Asian women living in Canada(Zulyniak et al. 2017). However, their study was conducted in a high-income country, where the dietary context differs substantially from that of low-income countries. In addition, the plant-based diet in this study included meat and fish, which was in contrast to a vegetarian diet. The cooking methods of South Asians significantly alter the food compositions and micronutrients(Lesser et al. 2014), which may modify the association between vegetarian diet and birth weight among pregnancies of India or Nepal oringin. The high degree of variability in the food that comprises a vegetarian diet across ethnic groups may also partially explain the difference. Therefore, the total energy intake adjustment or recovery biomarker (Naska et al. 2017) should reveal the actual associations between vegetarian diet and birth weight when considering the qualitative difference in definitions across ethnic groups.

The overall estimation of hypospadias incidence was nonsignificant. Nevertheless, eight studies on hypospadias were highly heterogeneous (I^2=74%). The discrepancies were probably due to the differences in study designs, time points of dietary data collection, methods for dietary assessment, and sample sizes of eligible studies. Only one prospective study collected maternal dietary intake during gestation. The remaining included studies assessed dietary information postnatally, which ranged from several months to 10 years after (Table 1). Despite the long-term reliability of adult recall in vegetarian dietary patterns(Teixeira Martins et al. 2015), the present findings achieved a low degree of generalizability due to the distinct lifestyle of Adventists. Moreover, appetite fluctuations and nausea during early pregnancy probably exerted influence on long-term diet. The control group in one case-control study consisted of children with ear ventilation tubes(Brouwers et al. 2010); in this study, the prevalence of birth defects in the control group was much higher than that in the general population (14% vs. 2%–3%), which may also underestimate the association. Given that most hypospadias cases are mild(Donaire and Mendez 2018), the included studies only considered moderate and severe cases of hypospadias(Ormond et al. 2009; Brouwers et al. 2010; Carmichael et al. 2012), thereby minimizing the association.

Conflicting results about the relationship between hypospadias and VB12 have also been reported. Kowal et al. observed symptoms of VB12 deficiencies and high propionylcarnitine (C3) in mothers of babies born with hypospadias(Kowal et al. 2013). By contrast, Sutton et al. reported that children of mothers with hypospadias present no low blood VB12(Sutton et al. 2011), which was measured during the early second trimester. Nonetheless, regardless of hypospadias risk, VB12 is not naturally produced by plant foods. To satisfy the nutrient requirements during pregnancy, vegetarian women should follow dietary and medical advices regarding fortified food and/or supplementation. Failure to do so can lead to severe inadequacy of VB12 during pregnancy, which is associated with several adverse health outcomes for mothers and infants(Molloy et al. 2008).

The association between pesticide and hypospadias risk is also inconclusive. A meta-analysis on nine studies indicated that maternal occupational exposure marginally increases the risk of hypospadias(Rocheleau et al. 2009). A large population-based prospective pregnancy cohort demonstrated that women who consumed organic food during pregnancy are significantly less likely to give birth to a boy with hypospadias(Brantsaeter et al. 2016). By contrast, a case-control study on 306 boys operated on hypospadias suggested that the overall organic choice of food items during pregnancy is unassociated with hypospadias in the offspring(Christensen et al. 2013).

North et al. reported that vegetarian mothers may give birth to babies with hypospadias due to their high consumption of soy protein(North et al. 2000), which contains phytoestrogens. However, two later studies found no significant association between maternal legume consumption(Giordano et al. 2008) or maternal intake of soy meal replacement (Brouwers et al. 2010)and hypospadias. A large-population-based case-control study also demonstrated that a high phytoestrogen intake is associated with reduced risks of delivering infants with hypospadias(Carmichael et al. 2013). In the present study, the hypospadias cases were of second and third degrees, and the mothers were likely non-Hispanic white, with higher education, older and nulliparous, and higher folic-acid-containing supplement intake than those of mothers in the control group(Carmichael et al. 2013).

Notably, among the included studies that presented a positive association between maternal vegetarian diet and hypospadias, one was funded by dairy companies(North et al. 2000), and another was funded by a chemical industry. Existing research indicated that publication results may favor the sponsor's product(Lexchin et al. 2003).

Recently, Ghosh reported that among 50 consecutive patients who were diagnosed with hypospadias in their pediatric surgery department, 43 of them were children of mothers who took vegetarian diet during gestational period(Ghosh et al. 2016). Rodent studies revealed that genistein, which can be found in many plant foods, disrupts urethral development in male and female mice(Vilela et al. 2007; Ross et al.

2011; Padilla-Banks et al. 2012). Therefore, an association between maternal vegetarian diet and risk of hypospadias in the offspring may exist.

We failed to observe a consistent association between vegetarian pregnancies and maternal anemia. All of the studies on anemia were conducted in India and Pakistan, where anemia is particularly prominent. In India, approximately 88% of pregnant women are affected with anemia. A study involving Indians reported that the prevalence of anemia among primigravidae is 78.1%(TOHEED et al. 2015). Moreover, data from the National Nutrition Monitoring Bureau surveys indicated that the iron and folic acid intake in India is insufficient in all age groups(Hans et al. 2015), which may contribute to the increase in anemic cases among vegetarian mothers. Although the use of dietary supplements can prevent vitamin and mineral deficiencies(Schüpbach et al. 2017), supplements during pregnancy were unadjusted in any of the included studies, which may be an additional source of bias. Finally, anemia in the included studies was diagnosed at different stages of pregnancy: two cases at delivery(Sharma DC et al. 1991; Sharma DCC 1994), one during the third trimester, and the remaining cases at various gestational stages(Bedi et al. 2015). These differences may result in different effects on infant outcomes.

Studies on GDM provided conflicting conclusions. According to the WHO 1999 criteria, nonvegetarians present a significantly higher prevalence of GDM than those of control(Jali et al. 2011), whereas vegetarians display a higher prevalence when the WHO 2013 criteria were applied(Arora et al. 2015). A shift from the 1999 criteria to the 2013 one resulted in the diagnosis of many GDM cases among Chinese women who experienced worse pregnancy outcomes than those of neglected cases(Pan et al. 2015), which supported the need for an omnivorous diet during pregnancy. However, vegetarian women display higher FPG than those of mixed diet controls, although linear regression found no association between maternal vegetarian and GDM(Arora et al. 2015). Thus, considerably well-designed studies are needed to clarify this issue.

Our study also presents potential limitations. First, all of the included studies were observational; we were unable to adjust potential confounders, which may lead to bias. For instance, we failed to eliminate the effects of genetic background on hypospadias. Second, all of the studies about birth weight were hospital-based, and selection bias may have occurred. Third, most of the included studies concerning LBW provided no maternal body mass index or GWG for either vegetarians or controls. Given that GWG is an essential factor that significantly affects birth weight, the lack of such information can potentially skew the outcomes. Finally, the majority of the included studies evaluated maternal dietary intake through a food frequency questionnaire, which is subject to the limitations of food list and possible misreporting due to cognitive challenge that can significantly affect the interpretation.

The rising pandemic of global obesity augments the demand for strategies to shift from current eating patterns to those that align with dietary guidelines. Plant-based diets provide protection against several pregnancy-related issues and decrease the risk of developing pediatric disease(Pistollato et al. 2015). Furthermore, epidemiological observations and experimental studies supported that nutrition in fetal life is a central stimulus for programming susceptibility to various diseases in adulthood(Harding 2001). Maternal vegetarian during pregnancy is also associated with increased likelihood of drug and alcohol abuse in 15-year-old offspring(Hibbeln et al. 2017). In view of these potential limitations, large-scale observational studies or randomized controlled trials may help clarify the association between dietary patterns and gestational outcomes and provide strategies for pregestational dietary planning.

In conclusion, our meta-analysis found that Asian women who consumed vegetarian diet during pregnancy are likely to deliver infants with LBW. Nevertheless, inconclusive findings were obtained regarding the risks of hypospadias, IUGR, maternal anemia, and GDM for vegetarian mothers due to the high heterogeneity of the included studies. Therefore, caution should be taken when selecting a vegetarian diet during pregnancy.

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Table 1: Characteristics of included studies for meta-analysis

	No. of studies	First author, publication year	Study design	Source of control	Study Location	Ethnicity	Vegetarian/Control				
							Sample Size	Gestational age (weeks)	Outcome Measures	Dietary Supplement	Method of Dietary assessment (at which time)
Incidence of Hypospadias(n,%)	8										
		North,K, 2000;	PC	PB	The UK	Caucasian	321/5975	NR	7(2.2%)/37(0.6%)	Partialy with iron	Dietary history (32

									gestational weeks)
Brouwers, 2007	CC	PB	The Netherland	Caucasian	17/817	NR	10(58.82%)/573(70.13%)	Some with folic acid and iron.	NR (5~15 year after delivery)
Akre, 2008;	CC	PB	Sweden and Denmark	Caucasian	22/696	NR	14(63.64%)/277(39.80%)	NR	NR (0~9 months after delivery)
Ormond, 2009;	CC	PB	The UK	Caucasian	168/784	NR	77(45.83%)/390(49.74%)	Partly with folate at first 3months	NR (3~6 years after delivery)
Brouwers, 2010;	CC	HB	The Netherland	Caucasian	18/916	NR	6(33.33%)/299(32.64%)	NR	NR (2~9 years after delivery)
Shekharyadav, 2011;	CC	PB	India	Asian	123/77	NR	52(42.48%)/28(36.36%)	NR	NR (NR)

		Carmichael, 2012;	CC	HB	The USA	Caucasian	43/4325	NR	10(23.26%)/1240(28.67%)	Partly with folate acid:	FFQ [12.9 months (cases), 8.8 months (controls) after delivery (median)]
		Samtani, 2014	CC	PB	India	Caucasian	105/116	NR	62(59.05%)/39(36.79%)	Partly with folate acid:	NR (4~10 years after delivery)
Incidence of LBW (n,%)	8										
		Campbell-Brown, 1985	RC	HB	the UK	Asian	59/33	38.6±1.5/38.6±2.2	13(22.03%) / 7 (21.21)	Iron: 100mg/d; Folic acid: 359ug/d (both groups)	24-h dietary recall
		Johnson, 2015	RC	HB	India	Asian	84/60	NR	30(35.71%) /19(31.67)	NR	24-h dietary recall

		Koirala, 2015	RC	HB	Nepal	Asian	25/230	NR	7(28%)/52(22.61%)	NR	Dietary history
		Misra, 2015	RC	HB	India	Asian	36/314	NR	10(22.73%)/ 23(29.11%)	NR	Semi-quant FFQ
		Narain, 2014	RC	HB	India	Asian	134/66	NR	29(21.64%)/11(16.67%)	NR	Dietary history
		Pawlak, 2015	CS	PB	the USA	Caucasian	199/350	NR	9(3.7%)/16(4.6%)	NR	NR
		Raje, 2015	RC	HB	India	Asian	92/192	NR	46(50%)/83(43.23.5)	NR	FFQ
		Shrestha, 2017	RC	HB	Nepal	Asian	36/314	NR	19(52.78%) /97(30.89%)	NR	NR
Birthweight (mean ± SD)	5										
		Campbell-Brown, 1985	RC	HB	the UK	Asian	59/33	38.6±1.5/38.6±2.2	2905±517/2926±635(g)	Iron: 100mg/d; Folic acid: 359ug/d (both groups)	24-h dietary recall

Gadgil, 2014	RC	HB	India	Asian	26/23	26.84±4.37/28.26±4.53	2.87±0.53/2.56±0.58(kg)	Folate acid: 5mg/d (both groups)	24-h dietary recall, FFQ
Lakin, 1998	RC	HB	the UK	the British	4/10	28±6/27±3	3770 ± 500/3673 ± 485 (g)	NR	semi-quant FFQ
Pawlak, 2015	CS	PB	the USA	Caucasian	199/350	NR	3.38±0.59/3.32±0.63(kg)	NR	NR
Ward,1988	RC	HB	India	Asian	49/13	NR	2885±547/2904±383(g);	NR	24-h dietary recall

PC: prospective cohort study; CC: case control study; RC: retrospective cohort study; CS: cross sectional study; PB: population based; HB: hospital based; NR: no report. FFQ: food frequent questionnaire.

Table2: Characteristics of included studies for qualitative analysis of maternal anemia

No. of studies	First author, publication	Study design	Source of control	Study Location	Ethnicity	Vegetarian/Control			
						Sample	Outcome Measures	Hb level(g/L)	Anotation

		year		l			Size			
Incidence of Anemia (n,%)	7									
		Sharma D, 1991	PC	NR	India	Asian	50/50	NR	9.3±1.3/9.7±1.0*	diagnosed at delivery
		Sharma D, 1994	PC	NR	India	Asian	21/25	NR	9.64±0.46/10.16±0.35*	diagnosed at delivery
		Sharma J, 2003	CS	NA	India	Asian	524/626	504(96.18%)/600(95.85%)	9.2±1.4/9.2±1.42	incidence according to severity:Mild:471/562; Severe:28/33; Decompensated:5/5; most diagnosed at second or third trimester;

Vemulapalli, 2013	CS	NA	India	Asian	40/946	40(100.0%) / 946(100.0%)	NR	incidence according to severity:Mild:29/491 Moderate:10/394 Severe:1/61 ,most diagnosed at 2nd trimester
Toheed ,2015	CS	NA	Pakistan	Asian	87/375	75(86.21%) / 286(76.27%)*	NR	diagnosed at various gestational ages
Hans 2015	CS	NA	India	Asian	1241/269	974(78.49%)/76(28.25 %)	NR	incidence according to severity: Mild:714/54 Moderate:212/18 Severe:48/4 diagnosed at various gestational ages
Bedi, 2015	CS	NA	India	Asian	791/299	711(89.89%)/284(94.98 %) *	NR	diagnosed at 3rd trimester

PC: prospective cohort study; CS: cross sectional study; NR: no report. NR: not reported.

*: significantly different between two groups

Table3 Characteristics of included studies for qualitative analysis of maternal outcomes other than anemia

First author, publication year	Study design	Study Location	Ethnicity	Vegetarian/Control		
				Sample Size	Main result	Other results
Jali. MV, 2011	CS	India	Asian	202/123	Incidence of GDM: 9.90% vs 26.02%,*	NR
Arora, G. P., 2015	CS	India	Asian	3048/2052	Incidence of GDM: WHO 2013 applied: 36.0% vs 33.2%*; WHO 1999 applied:7.9% vs 10.6%*;	NR
Benny, P. S., 1980	PC	the UK	Hindu vegetarian Caucasian omnivore	10/11	Mean diurnal glucose: 5.41±0.14 /4.78±0.15 mmol/l*;	Mean diurnal HPL :5.79±0.05 /6.11±0.05 mg/l*; 24-h oestriol excretion :103±12 /149±6, mmol/24h* GWG:6.8kg/10.9kg
Stuebe, A. M., 2009	CS	the USA	Asian,caucasian,other	152/1236	vegetarian at 1st trimester inversely associatied with excessive GWG [AOR: 0.45(0.27-0.76)]	NR

Kaur, Lovejeet,2012	CC	India	Asian	208/241	PIH: 77 (52 %) / 71 (48%)*;	RA : 43(34.2%) /66(74.8%)*, IUD: 27(40.29%) /40(59.7%)* IUGR: 42 (44.68%) /(52 (55.32 %)*
Reddy, S., 1994	PC	the UK	Asian vegetarians and Caucasian omnivores	49/98	Hypertension with Proteinuria: 4%/12%;	Early onset of labor: 10.4% /1.1%* ; Emergency caesarean 10.4%/ 2.2%*; Duration of gestation(mean and 95%CI): 38.7(38.1-39.3) /39.5(39.1-39.8)*; Head circumference (mean and 95%CI): 33.6(33.0-24.2) /34.7(34.3-35.0)*

CS: cross-sectional study; PC: prospective cohort study; CC: case control study.

GWG: gestational weight gain; AOR: adjusted odds ratio; HPL: human placental lactogen

RA: recurrent abortion; IUD: intrauterine death; IUGR: intrauterine growth retardation

Table4 Characteristics of included studies for qualitative analysis of other neonatal outcomes

First author,	**Study**	**Study**	**Ethnicity**	**Vegetarian/Control**

publication year	design	Location		Sample Size	Main result	Conclusion
Shaheen, S. O., 2009	CS	the UK	Caucasian	320/8566	no significant association with eczema 2y; wheezing at 3.5y and 7.5 y, transient infant wheeze; later onset wheeze, persistent wheeze; asthma at 7.5 y, atopy at 7 y.	vegetarian diet during pregnancy was not associated with respiratory and atopic outcomes
Larsen, P. S., 2014	PC	Denmark	Caucasian	988/79757	No difference of impaired neurodevelopment between groups.	vegetarian diet during pregnancy was not associated with impaired neurodevelopment
Deb, R., 2011	CC	India	Asian	87/246	incidence of NTD:36(41.38%)/75(30.49%)*; AOR:1.77 (1.02–3.05).	vegetarian diet during pregnancy was a risk factor of NTD
Fikree, F. F.,1994	PS	Pakistan	Asian	83/655	IUGR:9(10.84%)/171(26.11%) [AOR:2.7 (1.1, 6.1)]	vegetarian diet during pregnancy was a protective factor of IUGR
Gomez Roig, M. D. 2017	CC	Spain	Caucasian	5/122	vegetarian mothers were 4.4% among SGA cases and 3.8% among controls.	vegetarian diet during pregnancy was not associated with SGA

CS: cross-sectional study; PC: prospective cohort study; CC: case control study. PS: prospective study.

y: years old; SDQ (Strengths and Difficulties Questionnaire): NTD: neuro tube defects

*:(including 4 items: Head circumference, age at sitting, age at walking, SDQ score)

Table 5: Summary of Pooled estimation

	No. of Studies	OR(95% CI)	P value	Heterogeneity(%)	P for heterogeneity
Hypospadias					
Overall	8	1.39 [0.88, 2.21]	0.16	74	0.0003
Location					
Europe and USA	6	1.22 [0.71, 2.10]	0.46	70	0.006
Asia	2	1.92 [0.88, 4.20]	0.1	74	0.05
Quality Score(cc)					
High	5	1.53 [0.88, 2.65]	0.13	62	0.03
Low	2	0.84 [0.62, 1.13]	0.24	0	0.75
Study Design					
CC	7	1.23 [0.78, 1.93]	0.36	70	0.003
PC	1	3.58 [1.58, 8.09]	0.002	NA	NA
Low birth weight (n,%)					

Overall	8	1.27 [0.98, 1.65]	0.07	0	0.45
Ethnicity					
Asian	7	1.33 [1.01, 1.76]	0.04	0	0.49
Caucasian	1	0.79 [0.34, 1.82]	0..58	NA	NA
Geographical location					
Asia	6	1.35 [1.02, 1.79]	0.04	5%	0.39
Europe and North America	2	0.88 [0.46, 1.68]	0.71	0	0.68
Quality Score					
High	6	1.20 [0.60, 2.39]	0.61	0	0.74
Low	2	1.27 [0.98, 1.65]	0.17	25	0.25

	No. of studies	**WMD (95% CI)**	**P value**	**Heterogeneity(%)**	**P for heterogeneity**
Birthweight	5	61.71 [-24.65, 148.08]	0.16	0	0.52

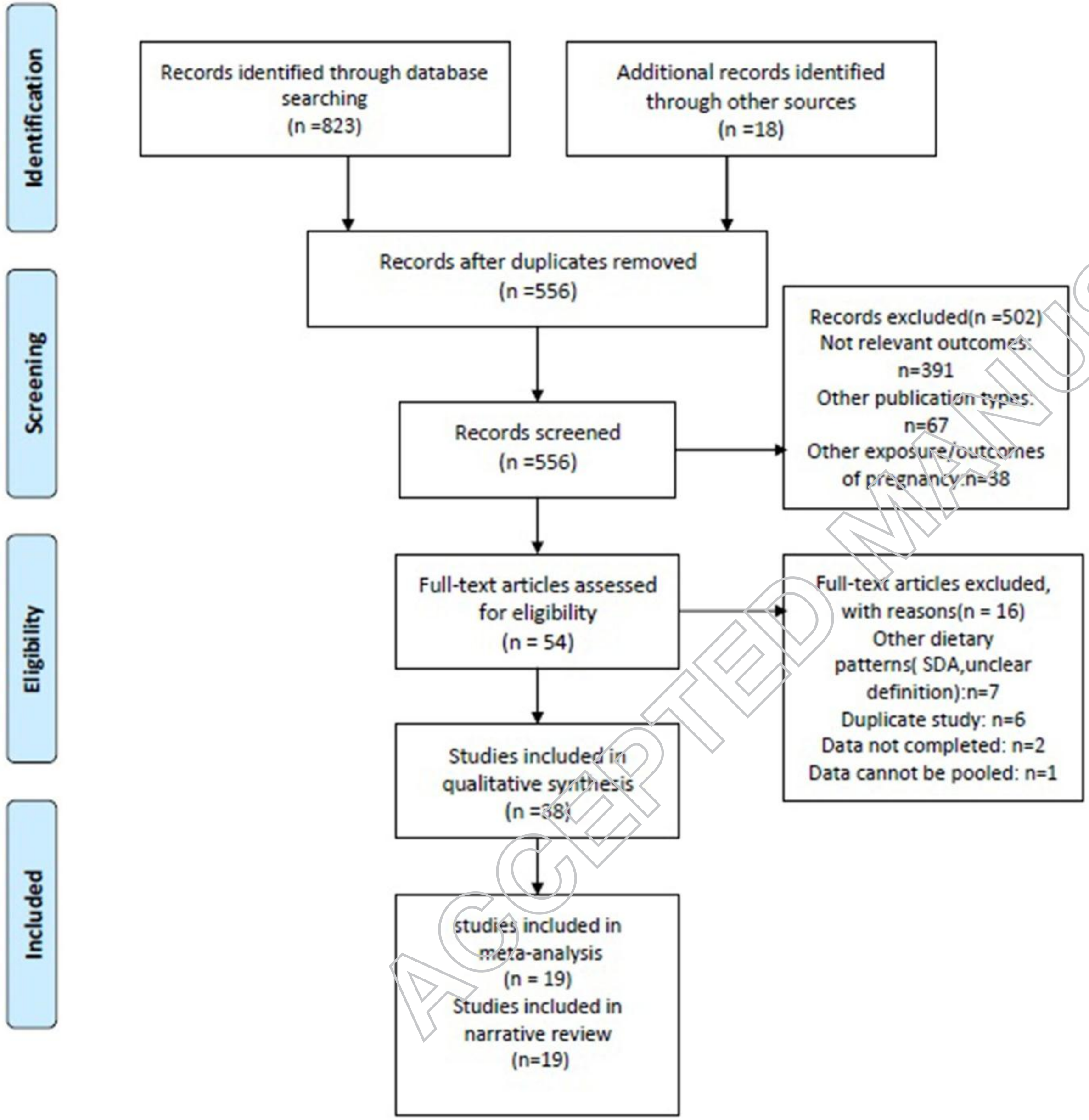
Identification
Screening
Eligibility
Included
Records identified through database searching
(n =823)
Additional records identified through other sources
(n =18)
Records after duplicates removed
(n =556)
Records screened
(n =556)
Records excluded(n =502)
Not relevant outcomes: n=391
Other publication types: n=67
Other exposure/outcomes of pregnancy:n=38
Full-text articles assessed for eligibility
(n = 54)
Full-text articles excluded, with reasons(n = 16)
Other dietary patterns(SDA,unclear definition):n=7
Duplicate study: n=6
Data not completed: n=2
Data cannot be pooled: n=1
Studies included in qualitative synthesis
(n =38)
studies included in meta-analysis
(n = 19)
Studies included in narrative review
(n=19)

Figure 1. XXX