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Review

Maternal dietary nitrate intake and risk of neural tube defects: A systematic review and dose-response meta-analysis

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ABSTRACT

Despite growing evidence for the potential teratogenicity of nitrate, knowledge about the dose-response relationship of dietary nitrate intake and risk of specific birth defects such as neural tube defects (NTDs) is limited. Therefore, the aim of this meta-analysis was to synthesize the knowledge about the dose-response relation between maternal dietary nitrate intake and the risk of NTDs. We conducted a systematic search in PubMed, ISI Web of Science and Scopus up to February 2018 for observational studies. Risk ratios (RRs) and 95% confidence intervals (95% CI) were calculated using a random-effects model for highest versus lowest intake categories. The linear and non-linear relationships between nitrate intake and risk of NTDs were also investigated. Overall, 5 studies were included in the meta-analyses. No association was observed between nitrate intake and NTDs risk in high versus low intake (RR: 1.33; 95% CI: 0.89–1.99, $p = 0.158$) and linear dose-response (RR: 1.03; 95% CI: 0.99–1.07, $p = 0.141$) meta-analysis. However, there were positive relationships between nitrate intake and risk of NTDs in non-linear ($p_{non\text{-}linearity} < 0.05$) model. Findings from this dose-response meta-analysis indicate that maternal nitrate intake higher than ~3 mg/day is positively associated with NTDs risk.

1. Introduction

Nitrates are naturally occurring compounds in drinking water and foods, especially vegetables and plant foods, and are also used as food additives to delay pathogenic bacteria growth and spoilage (Bryan et al., 2012). Vegetables are the most important sources of dietary nitrate intake <)80–95%((Hord et al., 2009).

Drinking-water contains different concentrations of nitrate. The World Health Organization defined the acceptable concentrations of nitrate and nitrite in drinking water < 50 mg/l and 3 mg/l, respectively (Ghasemi and Zahediasl, 2011; Edition, 2011). Furthermore, the acceptable daily intakes of nitrate and nitrite from food sources by the Scientific Committee on Food (SCF), have been defined to be 3.7 and 0.06 mg/kg body weight respectively and confirmed by the Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additive (JECFA) (Alexander et al., 2008).

Birth defects are the main cause of infant mortality in the first year of life, and, for infants who survive there is an increased risk for long-term disabilities (Flores et al., 2014). Several epidemiologic studies have shown an association between prenatal exposure to nitrates in drinking water and birth defects, including neural tube defects (NTDs) (Brender et al., 2004; Dorsch et al., 1984). NTDs are serious birth defects of the brain (anencephaly) and spine (spina bifida), that finally will form a baby's brain and spine, fails to close properly. NTDs, although largely preventable, are an important cause of death and lifelong disability worldwide (Christianson et al., 2006). Spina bifida as an example NTD, is due to the incomplete closure of the tissue and bone surrounding the spinal cord, which can occur anywhere along the spine and causes a range of lifelong disabilities (Shaer et al., 1995; Little and Elwood, 1992). There are approximately 300,000 babies born with NTDs every year in worldwide. The global prevalence of NTD is highly variable, ranging from 1 to 11 per 1000 births in various populations (Busby et al., 2005; Castilla et al., 1985; Rankin et al., 2000; Tuncbilek et al., 1999). The lifelong cost of care for one child born with neural

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Table 1
Characteristics of studies included in the meta-analysis of nitrate intake and risk of NTDs.

Authors (year)	Design	Country	Cases (n)	Controls (n)	Age range	Exposure	Exposure assessment	Outcome	Outcome assessment	Comparison	OR, RR or HR (95%CI)	Matching factors	Adjustment for confounding variables
Weyer et al. 2014	Case-control	USA	150	660	–	Nitrate	Drinking water	NTDs	Medical record	T3 vs. T1	1.25 (0.76–2.06)	–	maternal race/ethnicity, education, folic acid supplementation, study center
Huber et al., 2013	Case-control	USA	658	6698	< 18 – > 49	Nitrate	Dietary intake	NTDs	Medical record	Q4 vs. Q1	0.87 (0.7–1.08)	–	energy intake, maternal race/ethnicity, dietary folate intake, folic acid supplementation, dietary fat intake
Brender et al., 2013	Case-control	USA	227	1101	< 18 – > 34	Nitrate	Drinking Water	NTDs	Medical record	T3 vs. T1	1.43 (1.1–2.04)	–	maternal race/ ethnicity, education, study center, folic acid supplementation
Li et al., 2011	Case-control	China	519	694	< 20 - ≥35	Nitrate	Pickled vegetables	NTDs	Medical record	Q4 vs. Q1	3.6 (1.9–6.9)	county, sex, maternal ethnic group, date of conception	maternal education, history of pregnancy affected by birth defects, multiparity, and consumption of meat, egg or milk, fresh vegetables, fresh fruit, legumes
Croen et al., 2001	Case-control	USA	454	462	≤19 - ≥35	Nitrate	Drinking Water	NTDs	Medical record	Q4 vs. Q1	1.01 (0.62–1.6)	actual dates, season, year of residence	maternal age, race/ethnicity, body mass index, education, income, vitamin use, dietary folate, zinc, protein

AbbreviationsNTDs: Neural tube defects, OR: Odds ratio, RR: Relative risk, HR: Hazard ratio.

tube defect in the United States is estimated to be $768,000 (Grosse et al., 2016). There also are major emotional and social costs for children with NTDs and their families (Little and Elwood, 1992). NTDs can be due to different reasons, such as unclear genetic and environmental interactions (Copp et al., 1990).

The several epidemiological studies have shown that maternal exposure to nitrates, nitrites from drinking water and diet is associated with an increased risk of NTDs in offspring (Brender et al., 2004; Brender et al., 2013a; Li et al., 2011). Although other studies have shown that exposure to nitrate and nitrite were not associated with an increased risk of NTDs (Weyer et al., 2014; Huber et al., 2013a; Croen et al., 2001).

In this study, we did a comprehensive literature research, on the basis of a quantitative meta-analysis, with an attempt to find the association between dietary nitrates and risks for neural tube defect.

2. Materials and methods

2.1. Protocol

We conducted this systematic review and meta-analysis with the guidelines outlined in Cochrane Handbook for Systematic Reviews and were reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (Liberati et al., 2009).

2.2. Search strategy

In this investigation, the ISI Web of Science, Scopus and PubMed was used to identify eligible studies published in English up to February 2018. The following search keywords were used: (nitrate* OR nitrite* OR nitrosamine* OR N-nitrosodimethylamine* OR NDMA) AND ("spina bifida" OR "Neural Tube Defects" OR "Spinal Dysraphism" OR NTDs OR anencephaly OR encephaloceles OR hydranencephaly OR iniencephaly OR schizencephaly OR meningocele OR myelomeningocele OR Arnold-Chiari Malformation).

At first, title and abstract were screened and relevant articles retrieved. Then, full texts were screened for eligibility. The search strategy was completed by screening the reference lists of selected articles. Literature search was conducted by two authors (NR and HN). Any disagreement concerning study selection was settled according to the principal investigator opinion (MP).

2.3. Inclusion and exclusion criteria

Eligibility criteria for all included study were determined by two reviewers (NR and MP). all studies included in this systematic review and meta-analysis met the following inclusion criteria: 1. Full-text papers published in English, 2. The exposure of interest was maternal dietary nitrate intake, while the outcome of interest was risk of NTDs in offspring, 3. Observational studies, including case-control, cross-sectional, and cohort studies carried out on human subjects, 4. Effect size data (RRs/ORs/HRs and 95%CI) were reported for the association between maternal dietary nitrate intake and risk of NTDs in offspring. Animal studies, genetic researches, ecological studies, case reports, theses, books, review articles, and those unrelated to the subject of the review were excluded.

2.4. Study selection

Observational studies addressing the relation between maternal dietary nitrate intake and risk of NTDs in offspring were chosen to be examined in this systematic review and dose-response meta-analysis.

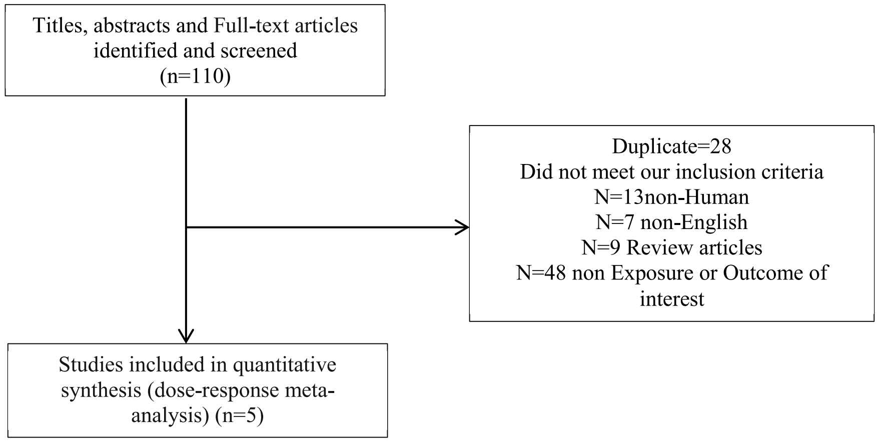

Fig. 1. Flow chart of study selection.

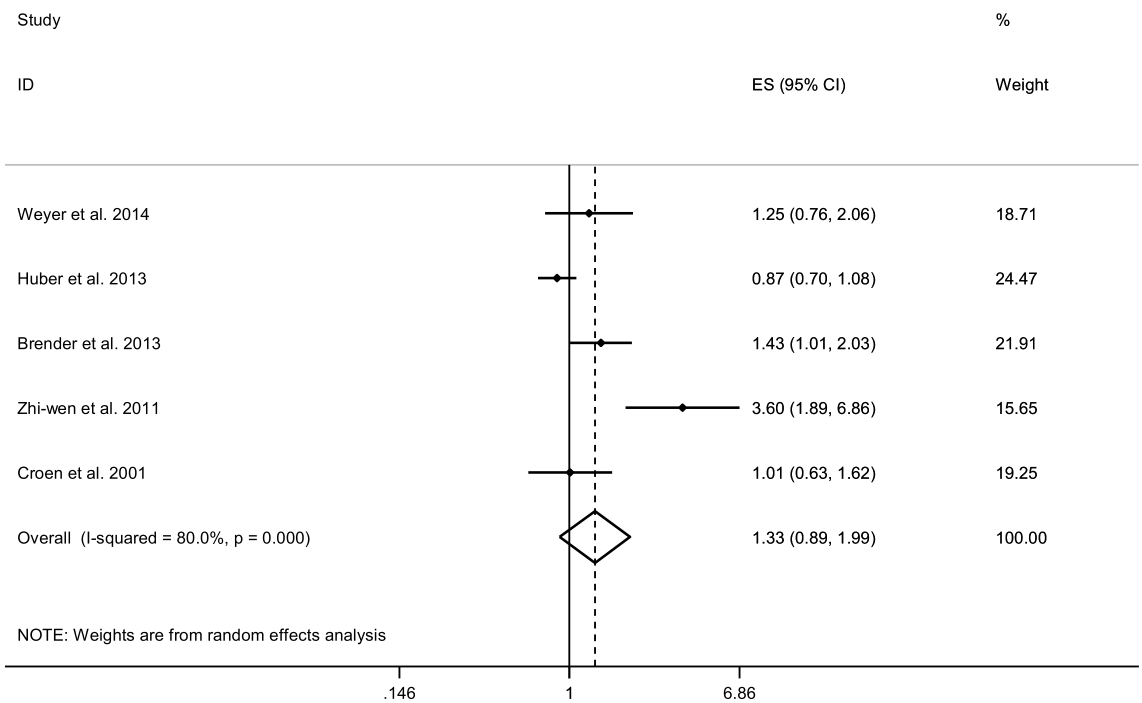

Fig. 2. Forest plot of case-control studies of NTDs for the highest versus lowest category of nitrate intake, using a random-effects model.

2.5. Data extraction and assessment for study quality

Two authors (AHS and AH) extracted the following characteristics: the first author's name, publication year, study design, number of participants and cases, age of participants, exposure (dietary nitrate intake), outcome (risk of NTDs), exposure and outcome assessment, most adjusted risk estimate with their corresponding 95% confidence intervals and adjusted confounding variables.

To assess the quality of included studies Newcastle–Ottawa Scale (NOS) was used based on the following three major components: selection of the study group, quality of the adjustment for confounding variables and assessment of outcome (Stang, 2010). A higher NOS score represents better methodological quality.

2.6. Statistical analysis

The odds ratio (OR) and 95% CIs were considered as the effect size of all studies. For high versus low, linear and nonlinear dose-response meta-analyses, fixed-effects or the random-effects model was used to calculate summary risk estimate and 95% CIs for the associations between maternal dietary nitrate intake, and risk of NTDs (DerSimonian and Laird, 1986). To explore heterogeneity between studies, we performed the Chi-square test (with $I^2 > 50\%$ considered to be heterogeneity) (Higgins and Green, 2011). The method of Greenland and Longnecker was applied for the linear dose-response meta-analysis (Greenland and Longnecker, 1992; Berlin et al., 1993; Orsini et al., 2006). The unit of exposure (maternal dietary nitrate intake) was defined as 0.5 mg/day. Distribution of participants, cases and adjusted odds ratio across different categories of dietary nitrate intake is needed for this method. Using random effect model, study specific results were combined. The median point in each category of dietary nitrate intake was assigned. If medians were not reported, we estimated approximate medians by using the midpoint of the lower and upper bounds. If the highest category was open-ended, we considered it to have the same widths as the closest category. The lower bound was considered as equal to zero if the lowest category was open-ended. For those

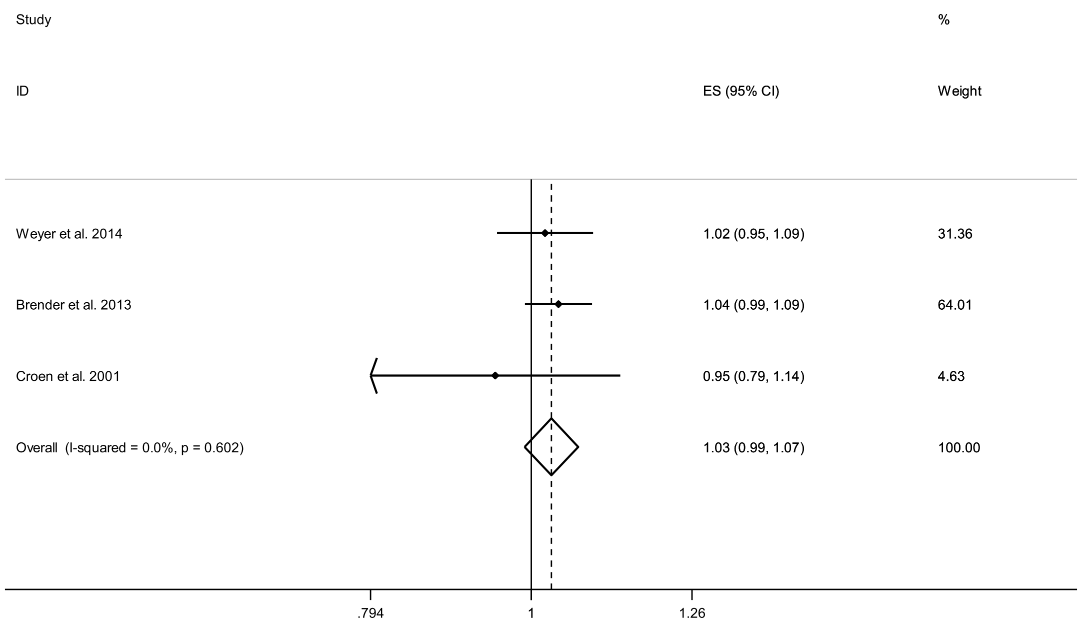

Fig. 3. Linear dose-response relationship between nitrate intake and risk of NTDs.

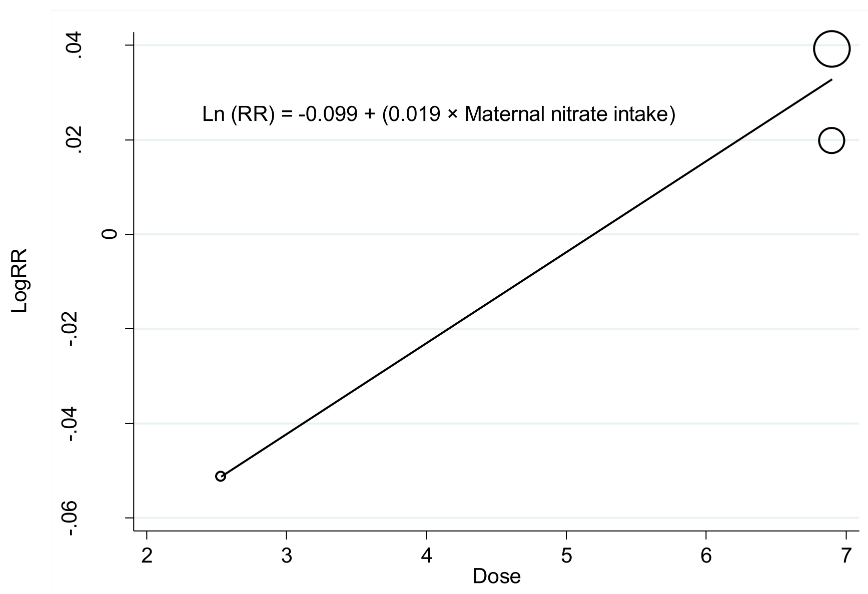

Fig. 4. Dose-response meta-regression analysis to examine the association between maternal dietary nitrate intake and risk of NTDs (b = 0.019, $p > 0.05$).

categories that mean of each category was reported, we considered mean as the same as median.

The non-linear relationships between maternal dietary nitrate intake and risk of NTDs were examined non-parametrically with stepwise restricted cubic splines at fixed percentiles (5, 35, 65, and 95%) of the distribution (Durrleman and Simon, 1989). Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis (Jackson et al., 2010). A P-value for nonlinearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. Furthermore, we performed sensitivity analyses to investigate the impact of each study on the overall results. The potential effects of publication bias were explored using Egger's test (Egger et al., 1997). All statistical analyses were performed with Stata 14.0 for Windows software (StataCorp, College Station, TX).

3. Results

3.1. Search results

The search strategy retrieved 110 articles. Of these, 28 duplicates, 13 non-human, 7 non-English, 9 reviews and 48 studies that did not

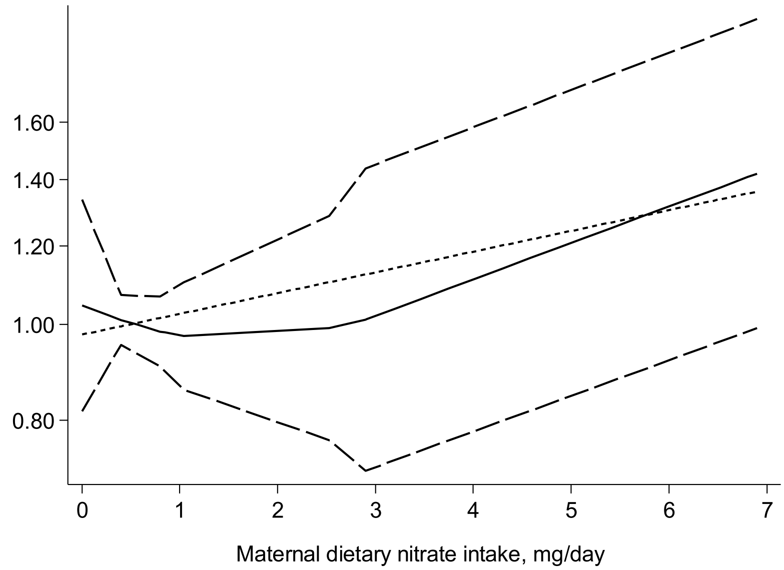

Fig. 5. Non-linear dose-response relationship between nitrate intake and risk of NTDs (pnon-linearity < 0.05, n = 3).

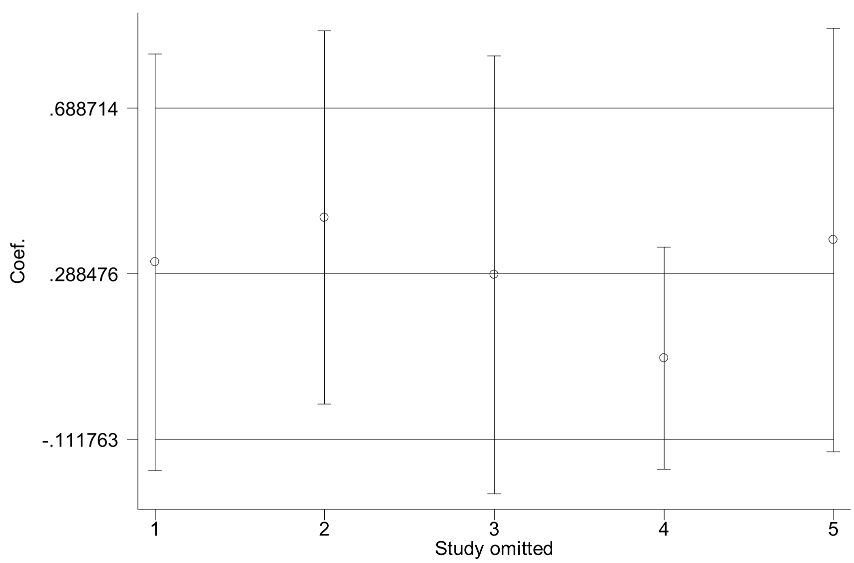

Fig. 6. Sensitivity analysis graph for included case-control studies.

fulfill our inclusion criteria were identified and eliminated. Finally, 5 papers met eligibility and included in the systematic review and meta-analysis (Table 1). The outline of search strategy is summarized in Fig. 1.

3.2. Study characteristics

All of the included articles used case-control design. Four studies were conducted in the United State (Brender et al., 2013a; Weyer et al., 2014; Huber et al., 2013a; Croen et al., 2001) and one study was conducted in China (Li et al., 2011). The sample size of studies varied from 810 to 7356. Maternal nitrate intake was assessed in drinking water (Brender et al., 2013a; Weyer et al., 2014; Croen et al., 2001), dietary intake (Huber et al., 2013a; Croen et al., 2001) and pickled vegetables (Li et al., 2011). In all studies, the risk of NTDs was assessed by medical records. All studies provided adjusted odds ratio with 95% CIs. The overall quality scores ranged from 6 to 9.

3.3. Maternal nitrate intake and risk of NTDs in offspring

Five studies with 2008 cases were included in the high versus low intake meta-analysis. Comparing the highest to the lowest categories of nitrate intake, no association between maternal nitrate intake and risk of NTDs (RR: 1.33; 95% CI 0.89 to 1.99, $I^2 = 80\%$, $p_{heterogeneity} = 0 < 001$) was observed (Fig. 2).

Each additional daily 0.5 mg of maternal nitrate intake were not associated with risk of NTDs in linear dose-response analysis (RR: 1.03; 95% CI: 0.99 to 1.07, p = 0.141, $I^2 = 0\%$, $p_{heterogeneity} = 0.602$, n = 3) (Fig. 3). Meta-regression of included observational studies revealed no significant linear association between maternal nitrate intake and risk of NTDs (b = 0.019, p > 0.05) (Fig. 4).

There was evidence of a non-linear dose-response association for

NTDs ($p_{non-linearity} < 0.05$, n = 3). The risk of NTDs increased with increasing intake of maternal dietary nitrate above ~3 mg/day (Fig. 5).

3.4. Sensitivity analysis and publication bias

The results of the influence analyses showed that none of the studies significantly affected the pooled RRs and 95% CIs (Fig. 6). We used Egger's test to check for potential publication bias, which showed no evidence of publication bias for the associations between maternal dietary nitrate intake and risk of NTDs (P value for Egger's test, 0.108).

4. Discussion

The associations between maternal nitrate intake and risk of NTDs in offspring were systematically assessed in this dose-response meta-analysis through comparison of the highest to the lowest categories, linear and non-linear analyses. In the high versus low intake comparison, no association was present for NTDs risk.

Insufficient evidence from previous studies suggest a positive association between maternal dietary nitrates intake (including vegetables and drinking water) and risk of NTDs (Brender et al., 2013b; Li et al., 2011). Weyer et al. (2014) and croen et al. (Croen et al., 2001) did not find any significant association between nitrate intake and risk of NTDs; however, Huber et al. (2013b) found that higher levels of nitrite consumption from plant sources reduced the risk of NTDs when compared to the women with the lowest level of plant nitrite intake. This protective effect may be due to other nutrients and vitamins such as folic acid contained within vegetables, fruit and grain products. Furthermore, a large portion of dietary nitrite intake comes from grains, which are often fortified with vitamins and minerals.

In the linear dose-response meta-analysis, no association was present for risk of NTDs. There was clear indication for non-linearity between maternal nitrate intake and risk of NTDs.

Our findings are partially in agreement with previous narrative review (Brender and Weyer, 2016), conducted on agricultural contaminants such as nitrate, arsenic and atrazine in drinking water and risk of birth defects; however, they fail to investigate the relationship between maternal nitrate intake and risk of NTDs in dose-dependent manner. To our knowledge, this is the first systematic review and dose-response meta-analysis of published studies to evaluate the association between dietary nitrate intake and risk of NTDs in offspring.

Referring to NTDs in offspring, we observed heterogeneity in subgroups stratified for country (United State versus China) showing a positive association in one study conducted in China. The subgroup analysis was based on a limited number of studies (5 studies). In linear dose-response analysis we did not observe significant increase in NTDs risk by each additional daily 0.5 mg of maternal nitrate intake. In nonlinear analysis we observed increased risk of NTDs in doses higher than ~3 mg/day. The potential teratogenic effects of nitrate on embryos are thought to be related to their roles in the formation of N-nitroso compounds, which may induce abnormalities through DNA alkylation of target organs (Jablonowski et al., 2011). These cytotoxic, mutagenic, carcinogenic and teratogenic effects of N-nitroso compounds have been shown in various animal models (Joshi et al., 2013; Bochert et al., 1985; Platzek et al., 1983).

This meta-analysis has several strengths. The dose-response meta-analysis offers advantages over the conventional methodology. A large number of cases (2008 offspring with NTDs) enhanced the statistical power of this dose-response meta-analysis.

Our study contains some limitations. Misclassification of nitrate intake could be a great concern. One study assessed dietary nitrate intake based on self-administered food frequency questionnaire, one study based on pickled vegetables consumption and two studies used an indirect approach to estimate maternal exposure to nitrate in drinking water. The results of subgroup analysis were based on limited number of studies.

5. Conclusions

Findings from this dose-response meta-analysis indicate that maternal nitrate intake higher than ~3 mg/day is positively associated with NTDs risk.

Conflicts of interest

The authors declare no conflict of interest.

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Transparency document

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