MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 1788-1799
DOI: 10.12659/MSM.914621

Received: 2018.12.14
Accepted: 2019.01.22
Published: 2019.03.09

Association Between Nitrite and Nitrate Intake and Risk of Gastric Cancer: A Systematic Review and Meta-Analysis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Source of support: Funding was provided by the National Natural Science Foundation of China (81460370)

Background: Studies have shown inconsistent associations of nitrite and nitrate intake with the risk of gastric cancer or its associated mortality. We performed a meta-analysis of observational studies to evaluate the correlation of nitrite and nitrate intake with the risk of gastric cancer.

Material/Methods: We searched for studies reporting effect estimates and 95% confidence intervals (CIs) of gastric cancer in PubMed, EMBASE, and the Cochrane Library through November 2018. The summary results of the included studies were pooled using a random-effects model.

Results: Eighteen case-control and 6 prospective cohort studies recruiting 800 321 participants were included in this study. The summary results indicated that the highest (odds ratio [OR], 1.27; 95%CI, 1.03–1.55; P=0.022) or moderate (OR: 1.12; 95%CI, 1.01–1.26; P=0.037) nitrite intake were associated with a higher risk of gastric cancer. However, we noted that high (OR, 0.81; 95%CI, 0.68–0.97; P=0.021) or moderate (OR, 0.86; 95%CI, 0.75–0.99; P=0.036) nitrate intakes were associated with a reduced risk of gastric cancer. These associations differed when stratified by publication year, study design, country, the percentage of male participants, assessment of exposure, adjusted model, and study quality.

Conclusions: High or moderate nitrite intake was associated with higher risk of gastric cancer, whereas high or moderate nitrate intake was correlated with lower risk of gastric cancer.

MeSH Keywords: Amyl Nitrite • Meta-Analysis • Nitrates • Stomach Neoplasms

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914621

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Background

Gastric cancer (GC) is the sixth most common form of cancer and the second most common in terms of mortality worldwide [1]. The pathology of GC can be divided into 2 groups: cardia and non-cardia adenocarcinoma. Diagnostic and treatment strategies are advancing, yet the prognosis for GC patients remains poor [2]. Since there is an increasing trend of the disease burden, more research is needed on identify the risk factors for GC. Numerous studies have already demonstrated that obesity, smoking, gastroesophageal reflux disease, and *Helicobacter pylori* infection are significantly associated with the risk of GC [3–7]. Moreover, fruit and vegetable consumption was associated with a reduced risk of GC, irrespective of the subsite or histologic type. An explanation for this could be that the high contents of antioxidants, phytosterols, and other substances in fruits and vegetables could inhibit carcinogenesis by free-radical quenching or blocking N-nitroso compound formation [8–10].

Ingested nitrate can convert to nitrite through the bacterial flora in the mouth and digestive tract. Moreover, nitrite levels can affect the formation of N-nitroso compounds. Endogenous nitrosation accounts for an estimated 45–75% of total N-nitroso compounds exposure [11], and the acceptable daily intake values should be explored in the general population. Moreover, the potential impacts of nitrite and nitrate intake and subsequent risk of GC remain controversial. Therefore, we performed a comprehensive search of the available observational studies to assess the association between nitrite or nitrate intake and the risk of GC. We also assessed whether these relationships differed according to study or participant characteristics.

Material and Methods

Data sources, search strategy, and selection criteria

This meta-analysis was according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement, which published in 2009 [12]. The study investigated the associations of nitrite or nitrate intake with the risk of GC, and no restrictions were placed on language or status of eligible publications. The PubMed, EMBASE, and the Cochrane Library databases were systematically searched in the timeframe from their inception to November 2018 for potentially eligible publications. The core search terms of (nitrate OR nitrite OR N-nitroso compounds) AND (cancer OR neoplasm OR carcinoma OR tumor) AND (gastric OR stomach) were used. The reference lists from the retrieved studies were manually searched to identify any new eligible studies. The PICOS criteria were used to identify any potential studies.

The study selection process was conducted by 2 authors, and any disagreement was resolved by the corresponding author. The inclusion criteria of this meta-analysis were as follows: (1) study designed as case-control or prospective cohort; (2) the study reported the relationship between nitrite or nitrate intake and the risk of GC incidence or mortality; and (3) the study reporting effect estimates and 95% confidence intervals (CIs) for comparisons of various categories and the lowest nitrite or nitrate intake.

Data collection and quality assessment

Data collection and quality assessment processes were performed by 2 authors and any disagreement was settled by group discussion and by an additional author referring to the original study. The collected information included the first author's surname, publication year, study design, country, sample size, age, the percentage of male patients, assessment of exposure, GC incidence or mortality, and adjusted factors. The Newcastle-Ottawa Scale (NOS), based on selection (4 stars), comparability (2 stars), and outcome (3 stars), was used to evaluate study quality, and the "star system" range was 0–9 for evaluating the quality of included studies [13].

Statistical analysis

The relationship between nitrite or nitrate intake and the risk of GC were examined based on the effect estimate (odds ratio [OR], relative risk [RR], or hazard ratio [HR]) and corresponding 95% CIs in each study. The multiple categories of nitrite or nitrate intake within a single study were summarized into high or moderate nitrite/nitrate intake using a fixed-effects model, while the pooled results across included studies were evaluated using a random-effects model [14,15]. Heterogeneity test was performed using the I-square and Q statistic, and significant heterogeneity was defined as $P<0.010$ [16,17]. Sensitivity analyses were conducted to assess the stability of the pooled results [18]. Subgroup analyses for high or moderate nitrite/nitrate intake and the risk of GC were conducted based on publication year, study design, country, the percentage of male patients, assessment of exposure, adjusted model, and study quality. The interaction tests between subgroups were also performed to compare whether these associations differed according to study or participant characteristics [19]. Publication biases for high or moderate nitrite/nitrate intake and the risk of GC were evaluated using funnel plots, Egger test [20], and Begg [21] test. The inspective levels for pooled results are 2-sided, and p values less than 0.05 were regarded as statistically significant. Stata software was employed for all statistical analyses (version 10.0; Stata Corporation, College Station, TX, USA).

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Results

Literature search and study characteristics

The initial searches of the electronic databases produced 831 articles; of these, 769 were discarded due to duplication or irrelevance. The remaining 62 studies underwent full-text evaluations; 38 of these were excluded for not assigning nitrite or nitrate as exposure markers (n=21), for reporting the sample population (n=12), or for being a systematic review (n=5). Ultimately, 18 case-control studies and 6 cohort studies were included in the final quantitative meta-analysis [22–45]. No additional eligible studies were found in the manual search of the references of retrieved studies. Details of the study selection process are presented in Figure 1, while the baseline characteristics of the patients included in the examined studies are shown in Table 1.

A total of 24 studies that recruited a total of 800 321 individuals were included in this study; the publication dates ranged from 1985 to 2017. The sample sizes ranged from 220 to 494 979, and the percentage of male patients ranged from 20.0% to 78.1%. Thirteen studies were conducted in Europe, while the rest were conducted in Canada, the USA, Mexico, Korea, and India. Eighteen studies used a food-frequency questionnaire (FFQ) to assess exposure, while the remaining 6 studies used an interviewer-administered questionnaire (IAQ) to evaluate exposure. The association between nitrite intake and the risk of GC was reported in 19 studies, and the impact of nitrate intake was reported in 17 studies. NOS was used for evaluation of study quality and is shown in Table 1. Six studies had 8 stars, 13 studies had 7 stars, and the remaining 5 studies had 6 stars.

Nitrite intake and gastric cancer

The association between high nitrite intake and the risk of GC was reported in 19 studies. A high nitrite intake was associated with an increased risk of GC (OR, 1.27; 95%CI, 1.03–1.55; P=0.022; Figure 2), and significant heterogeneity across included studies (I-square, 89.6%; P<0.001). A sensitivity analysis indicated that the conclusion was not altered by excluding any particular study (data not shown). Subgroup analyses suggested the significantly increased GC risk mainly included pooled studies published in or after 2000 (OR, 1.28; 95%CI, 1.09–1.51; P=0.003), studies designed as case-control (OR, 1.38; 95%CI, 1.02–1.85; P=0.034), studies conducted in other countries (OR, 1.56; 95%CI, 1.32–1.84; P<0.001), studies with a percentage of male patients <60.0% (OR, 1.18; 95%CI, 1.01–1.37; P=0.032), studies using an IAQ to assess exposure (OR, 1.73; 95%CI, 1.22–2.44; P=0.002), studies with partial adjustment (OR, 1.47; 95%CI, 1.20–1.79; P<0.001), and studies of high quality (OR, 1.36; 95%CI, 1.18–1.56; P<0.001). Moreover,

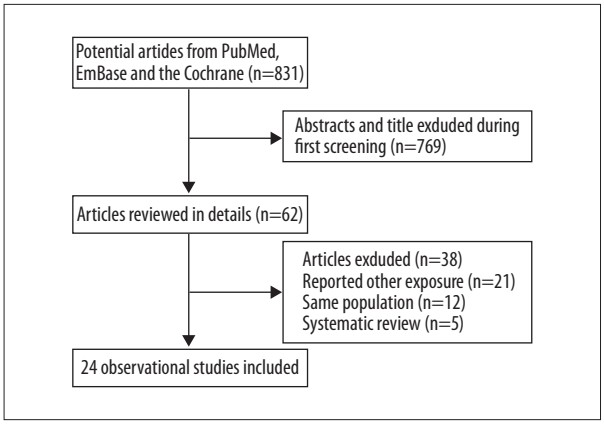

Figure 1. Flow diagram of the literature search and studies selection process.

we assessed whether publication year, country, the percentage of male patients, assessment of exposure, adjusted extent, and study quality could bias the correlation between high nitrite intake and the risk of GC (Table 2). We found no significant publication bias for high nitrite intake and GC risk (P for Egger=0.061; P for Begg=0.576).

An association between moderate nitrite intake and the risk of GC was reported in 15 studies. The pooled OR indicated that moderate nitrite intake produced additional risk for GC risk by 12% (OR, 1.12; 95%CI, 1.01–1.26; P=0.037; Figure 3), and significant heterogeneity was detected (I-square, 63.9%; P<0.001). Sensitivity analyses indicated that the pooled results changed after the exclusion of several studies due to marginal 95%CI (data not shown). The subgroup analysis upon pooling of the case-control studies (OR, 1.23; 95%CI, 1.07–1.43; P=0.005), the studies conducted in other countries (OR, 1.30; 95%CI, 1.01–1.67; P=0.045), studies with a percentage of male patients ≥60.0% (OR, 1.43; 95%CI, 1.16–1.77; P=0.001), studies using IAQ to assess exposure (OR, 1.56; 95%CI, 1.27–1.93; P<0.001), studies with partial adjustment (OR, 1.20; 95%CI, 1.02–1.40; P=0.025), and studies of high quality (OR, 1.13; 95%CI, 1.00–1.27; P=0.044) indicated that moderate nitrite intake increases the risk of GC. Study design, country, the percentage of male patients, and assessment of exposure played an important role in the correlation between moderate nitrite intake and GC risk (Table 2). No significant publication bias was observed (P for Egger, 0.115; P for Begg, 0.692).

Nitrate intake and gastric cancer

The association between high nitrate intake and the risk of GC was reported in 17 studies. The summary OR indicated that a high nitrate intake plays a protective role on the progression of GC (OR, 0.81; 95%CI, 0.68–0.97; P=0.021; Figure 4), and showed significant heterogeneity across the included studies (I-square, 76.3%; P<0.001). A sensitivity analysis found the

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Table 1. Baseline characteristic of studies included in the systematic review and meta-analysis.

Study	Publication year	Study design	Country	Sample size	Age (years)	Percentage male (%)	Assessment of exposure	Reported outcomes	Adjusted factors	NOS score
Risch [22]	1985	Case-control	Canada	492	35–79	66.3	FFQ	Nitrite and nitrate	Age, sex, and area of residence	7
Buiatti [23]	1990	Case-control	Italy	1,782	<75	NA	FFQ	Nitrite and nitrate	Non-dietary variables and kilocalorie	7
Boeing [24]	1991	Case-control	Germany	722	32–80	20.0-30.0	IAQ	Nitrate	Age, sex and hospital	6
Hansson [25]	1994	Case-control	Sweden	1,017	40–79	64.4	FFQ	Nitrate	Age, gender, ascorbic acid, β-carotene, α-tocopherol	7
La Vecchia [26]	1994	Case-control	Italy	2,747	19–74	59.4	FFQ	Nitrite and nitrate	age, sex, education, family history of gastric cancer, BMI, TEI	8
Pobel [27]	1995	Case-control	France	220	66.5	69.5	FFQ	Nitrite and nitrate	Age, sex, occupation and total calorie intake	6
La Vecchia [28]	1997	Case-control	Italy	2,799	19–74	59.4	FFQ	Nitrite	Sex, age, and education	7
van Loon [29]	1998	Prospective cohort	The Netherlands	120,852	55–69	48.2	FFQ	Nitrite and nitrate	Age, sex, smoking, education, coffee consumption, intake of vitamin C and beta-carotene, family history of stomach cancer, prevalence of stomach disorders, use of refrigerator and use of freezer	8
Galanis [30]	1998	Prospective cohort	USA	11 907	>18.0	47.1	FFQ	Nitrate	Age, education, Japanese place of birth, and gender. Analyses among men were also adjusted for cigarette and alcohol	7
De Stefani [31]	1998	Case-control	France	1038	25–84	65.8	FFQ	Nitrite	Age, sex, residence, urban/rural status, smoking duration, alcohol consumption, and „mate" consumption	6
Knekt [32]	1999	Prospective cohort	Finland	9985	15–99	52.8	FFQ	Nitrite and nitrate	Sex, age, municipality, smoking and TEI	7
Palli [33]	2001	Case-control	Italy	943	All stages	60.1	FFQ	Nitrite and nitrate	Age, sex, social class, family history of gastric cancer, area of rural residence, BMI, total energy and each nutrient of interest	7
Mayne [34]	2001	Case-control	USA	1294	30–79	78.1	IAQ	Nitrite	Sex, site, age; race, proxy status, income, education, BMI, cigarettes/day, years of consuming beer, wine, and liquor, and TEI	7

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Table 1 continued. Baseline characteristic of studies included in the systematic review and meta-analysis.

Study	Publication year	Study design	Country	Sample size	Age (years)	Percentage male (%)	Assessment of exposure	Reported outcomes	Adjusted factors	NOS score
De Stefani [35]	2001	Case-control	France	405	30–89	65.2	FFQ	Nitrite and nitrate	Age, gender, residence, urban/rural status, and education	6
Engel [36]	2003	Case-control	USA	1324	30–79	77.9	IAQ	Nitrite	Geographic center, age, sex, race, income, respondent type, TEI	7
Lopez-Carrillo [37]	2004	Case-control	Mexico	665	>20	56.7	FFQ	Nitrite	Age, gender, residence, TEI, education, Hp/CagA status and ascorbic acid	8
Kim [38]	2007	Case-control	Korea	272	57.2	68.4	FFQ	Nitrate	Age, sex, socioeconomic status, refrigerator use, *H. pylori* infection, and foods	7
Ward [39]	2008	Case-control	USA	400	>21	NA	IAQ	Nitrite and nitrate	Year of birth, gender, education, smoking, alcohol, TEI, vitamin C, fiber, carbohydrate	6
Hernández-Ramírez [40]	2009	Case-control	Mexico	735	>20	54.0	FFQ	Nitrite and nitrate	Energy, age, gender, *H. pylori* CagA status, schooling and consumptions of salt, chili and alcohol	7
Loh [41]	2011	Prospective cohort	UK	23 363	40–79	46.2	FFQ	Nitrite	Age, sex, BMI, cigarette smoking status, alcohol intake, TEI, PI, educational, and menopausal status	8
Cross [42]	2011	Prospective cohort	France	494 979	50–71	59.7	FFQ	Nitrite and nitrate	Age, sex, BMI, education, ethnicity, tobacco smoking, alcohol drinking, PI, vigorous physical activity, and the daily intake of fruit, vegetables, saturated fat, and TEI	8
Navarro Silvera [43]	2011	Case-control	USA	1294	30–79	NA	IAQ	Nitrite	Gender, age, site, race, income, education, proxy status, TEI, and mutual adjustment for other principle components	7
Keszei [44]	2013	Prospective cohort	The Netherlands	120 852	55–69	48.2	FFQ	Nitrite and nitrate	Age, smoking status, TEI, BMI, alcoholic intake, vegetable intake, fruit intake, education, and PI	8
Taneja [45]	2017	Case-control	India	234	All stages	67.1	IAQ	Nitrate	Age, gender, and tobacco consumption	7

BMI – body mass index; FFQ – food-frequency questionnaire; IAQ – interviewer-administered questionnaire; PI – physical activity; TEI – total energy intake.

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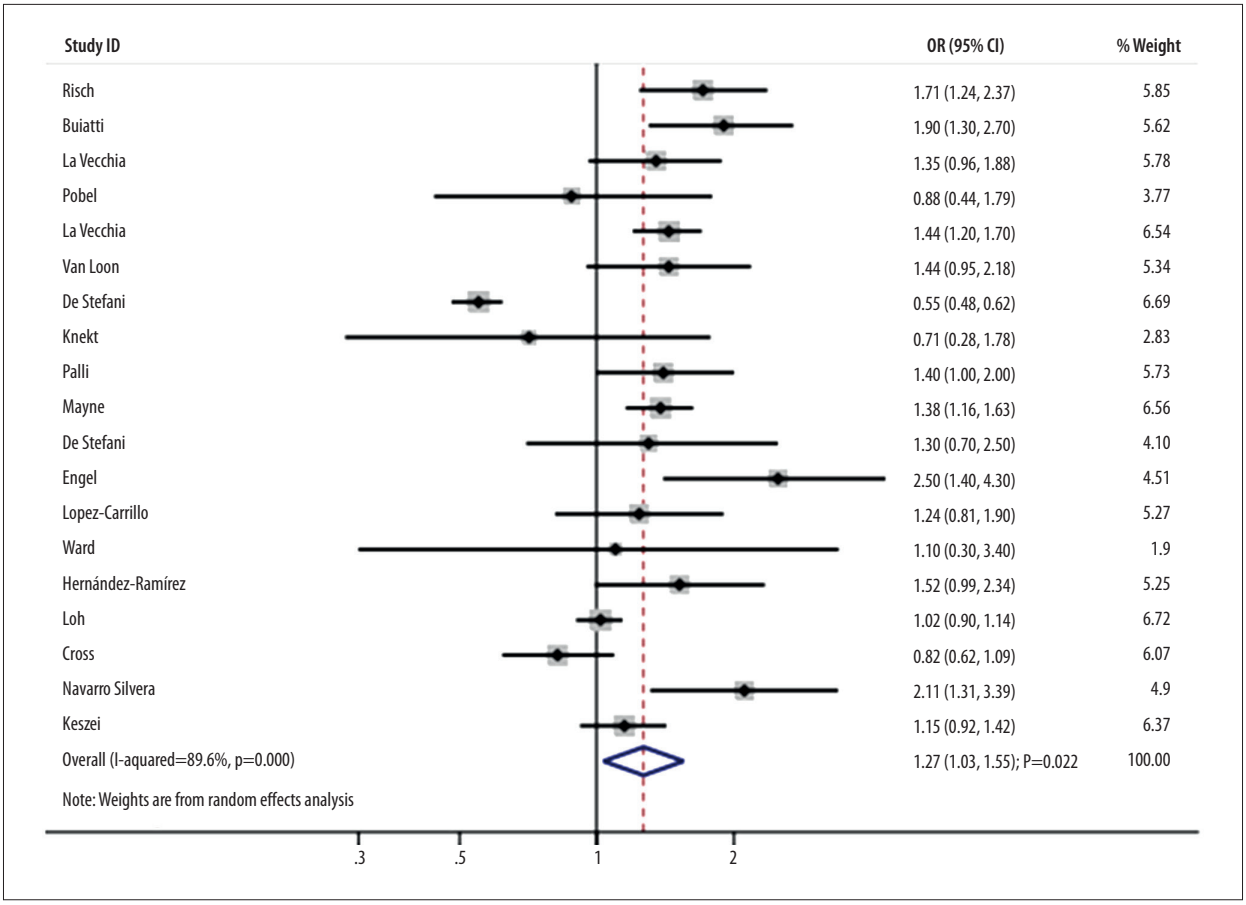

Figure 2. Association between high nitrite intake and the risk of gastric cancer.

conclusion was stable and not changed by excluding individual studies (data not shown). Subgroup analyses indicated that high nitrate intake was associated with decreased risk of GC in studies published before 2000 (OR, 0.75; 95%CI, 0.60–0.93; P=0.010), those conducted in Europe (OR, 0.78; 95%CI, 0.64–0.95; P=0.015), those that used FFQ to assess exposure (OR, 0.75; 95%CI, 0.64–0.88; P<0.001), and those of high quality (OR, 0.75; 95%CI, 0.63–0.89; P=0.001). Moreover, publication year, country, the percentage of male patients, assessment of exposure, adjustment extent, and study quality could bias the correlation between high nitrate intake and GC (Table 2). There was no publication bias among included studies (P for Egger, 0.054; P for Begg, 0.343).

The association between moderate nitrate intake and the risk of GC was reported in 15 studies. We noted that a moderate nitrate intake was associated with a decreased risk of GC (OR, 0.86; 95%CI, 0.75–0.99; P=0.036; Figure 5), and significant heterogeneity was noted (I-square, 67.6%; P<0.001). The pooled results were variable after the sequential exclusion of individual studies due to marginal 95%CI (data not shown). The subgroup analyses indicated that the risk of GC was decreased in the moderate versus the lowest nitrate intake when studies were conducted before 2000 (OR, 0.80; 95%CI, 0.65–0.98; P=0.032), studies had a case-control design (OR, 0.80; 95%CI, 0.66–0.96; P=0.018), studies conducted in Europe (OR, 0.81; 95%CI, 0.70–0.94; P=0.006), studies that used FFQ to assess exposure (OR, 0.85; 95%CI, 0.74–0.99; P=0.037), and studies with partial adjustment (OR, 0.83; 95%CI, 0.74–0.93; P=0.002). Moreover, publication year, study design, and country played an important role in the correlation between moderate nitrate intake and the risk of GC (Table 2). No evidence of publication bias was observed by using Egger and Begg tests (P for Egger, 0.323; P for Begg, 0.921).

Discussion

This comprehensive quantitative meta-analysis aimed to assess any potential associations between nitrite or nitrate intake and subsequent GC risk based on all available observational studies. The current study included 800 321 individuals from 18 case-control and 6 cohort studies with a wide range of participant characteristics. Overall, a high or moderate nitrite intake was associated with an increased risk of GC. Conversely, a high or moderate nitrate intake provides a protective effect

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against GC. The summary results for moderate nitrite or nitrate intake on the risk of GC were variable and therefore require further large-scale studies for verification. Moreover, these associations differed when stratified by publication year, study design, country, the percentage of male patients, assessment of exposure, adjusted model, and study quality.

The study conducted by Xie et al. contained 62 observational studies and found dietary nitrate intake was inversely associated with the risk of GC, whereas dietary nitrite intake did not yield a significant association with the risk of GC [46]. However, the study compared only the highest versus lowest dietary nitrate or nitrite intake, while the effect estimates at various medium exposures were not included; this may result

Table 2. Subgroup analyses for nitrite and nitrate intake and the risk of gastric cancer.

Outcomes	Factor	Groups	Number of studies	OR and 95% CI	P value	Hetero-geneity (%)	P value for heterogeneity	P value between subgroups
High versus low nitrite intake	Publication year	2000 or after	11	1.28 (1.09–1.51)	0.003	67.2	0.001	<0.001
		Before 2000	8	1.18 (0.76–1.83)	0.462	94.5	<0.001	
	Study design	Case-control	14	1.38 (1.02–1.85)	0.034	92.2	<0.001	0.588
		Cohort	5	1.04 (0.89–1.21)	0.633	39.8	0.156	
	Country	Europe	12	1.11 (0.87–1.43)	0.402	91.2	<0.001	<0.001
		Other	7	1.56 (1.32–1.84)	<0.001	22.4	0.259	
	Percent male	≥60.0	7	1.25 (0.78–2.02)	0.353	94.8	<0.001	<0.001
		<60.0	9	1.18 (1.01–1.37)	0.032	61.2	0.008	
	Assessment of exposure	FFQ	15	1.18 (0.94–1.48)	0.150	90.2	<0.001	<0.001
		IAQ	4	1.73 (1.22–2.44)	0.002	52.7	0.096	
	Adjusted extent	Fully	13	1.23 (0.97–1.57)	0.091	91.1	<0.001	<0.001
		Partial	6	1.47 (1.20–1.79)	<0.001	31.9	0.196	
	Study quality	High	15	1.36 (1.18–1.56)	<0.001	70.1	<0.001	<0.001
		Low	4	0.83 (0.50–1.38)	0.466	67.6	0.026	
Moderate versus low nitrite intake	Publication year	2000 or after	10	1.14 (0.97–1.34)	0.104	74.1	<0.001	0.265
		Before 2000	5	1.11 (0.99–1.23)	0.070	0.0	0.593	
	Study design	Case-control	10	1.23 (1.07–1.43)	0.005	46.9	0.049	<0.001
		Cohort	5	0.98 (0.88–1.10)	0.744	42.7	0.137	
	Country	Europe	10	1.04 (0.95–1.14)	0.375	43.5	0.068	<0.001
		Other	5	1.30 (1.01–1.67)	0.045	53.5	0.072	
	Percent male	≥ 60.0	4	1.43 (1.16–1.77)	0.001	0.0	0.407	<0.001
		<60.0	8	0.99 (0.92–1.05)	0.672	7.1	0.376	
	Assessment of exposure	FFQ	12	1.03 (0.95–1.12)	0.414	31.6	0.139	<0.001
		IAQ	3	1.56 (1.27–1.93)	<0.001	14.6	0.310	
	Adjusted extent	Fully	11	1.11 (0.97–1.26)	0.127	69.9	<0.001	0.078
		Partial	4	1.20 (1.02–1.40)	0.025	0.0	0.479	
	Study quality	High	12	1.13 (1.00–1.27)	0.044	70.1	<0.001	0.759
		Low	3	1.11 (0.76–1.61)	0.583	0.0	0.375	

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Table 2 continued. Subgroup analyses for nitrite and nitrate intake and the risk of gastric cancer.

Outcomes	Factor	Groups	Number of studies	OR and 95% CI	P value	Hetero-geneity (%)	P value for heterogeneity	P value between subgroups
High versus low nitrate intake	Publication year	2000 or after	8	0.89 (0.73–1.09)	0.268	61.3	0.011	<0.001
		Before 2000	9	0.75 (0.60–0.93)	0.010	59.1	0.012	
	Study design	Case-control	12	0.79 (0.63–1.01)	0.058	83.1	<0.001	0.599
		Cohort	5	0.92 (0.77–1.09)	0.321	0.0	0.745	
	Country	Europe	11	0.78 (0.64–0.95)	0.015	59.3	0.006	<0.001
		Other	6	0.88 (0.65–1.21)	0.444	82.2	<0.001	
	Percent male	≥60.0	7	0.81 (0.61–1.08)	0.148	80.3	<0.001	0.002
		<60.0	8	0.77 (0.58–1.01)	0.055	68.6	0.002	
	Assessment of exposure	FFQ	14	0.75 (0.64–0.88)	<0.001	51.3	0.014	<0.001
		IAQ	3	1.10 (1.03–1.19)	0.008	0.0	0.633	
	Adjusted extent	Fully	9	0.78 (0.61–1.02)	0.065	68.0	0.002	<0.001
		Partial	8	0.85 (0.68–1.08)	0.179	74.6	<0.001	
	Study quality	High	12	0.75 (0.63–0.89)	0.001	58.7	0.005	<0.001
		Low	5	1.07 (0.94–1.23)	0.304	6.2	0.371	
Moderate versus low nitrate intake	Publication year	2000 or after	7	0.94 (0.84–1.05)	0.294	0.0	0.486	0.003
		Before 2000	8	0.80 (0.65–0.98)	0.032	75.8	<0.001	
	Study design	Case-control	10	0.80 (0.66–0.96)	0.018	66.8	0.001	<0.001
		Cohort	5	0.96 (0.86–1.08)	0.512	0.0	0.517	
	Country	Europe	11	0.81 (0.70–0.94)	0.006	71.2	<0.001	0.008
		Other	4	1.13 (0.89–1.45)	0.324	0.0	0.671	
	Percent male	≥60.0	5	0.82 (0.67–1.02)	0.069	10.8	0.344	0.679
		<60.0	8	0.86 (0.70–1.07)	0.170	80.2	<0.001	
	Assessment of exposure	FFQ	13	0.85 (0.74–0.99)	0.037	69.8	<0.001	0.587
		IAQ	2	0.95 (0.54–1.67)	0.853	69.2	0.072	
	Adjusted extent	Fully	9	0.91 (0.73–1.13)	0.387	79.9	<0.001	0.883
		Partial	6	0.83 (0.74–0.93)	0.002	0.0	0.632	
	Study quality	High	11	0.86 (0.74–1.01)	0.065	73.1	<0.001	0.786
		Low	4	0.85 (0.59–1.23)	0.389	49.5	0.115	

CI – confidence interval; FFQ – food-frequency questionnaire; IAQ – interviewer-administered questionnaire; OR – odds ratio.

in the oversight of several important datapoints for these associations. Moreover, several additional studies should be updated in this study. Therefore, the current study aimed to systematically evaluate the potential role of nitrite and nitrate intake in the risk of GC.

The summary results indicated that a high or moderate nitrite intake was associated with an increased risk of GC. Most of the included studies reported a positive trend between high or moderate nitrite intake and the risk of GC, while several studies reported reverse trend. Pobel et al. indicated that nitrite and nitrate intakes were not correlated with the risk of GC, and

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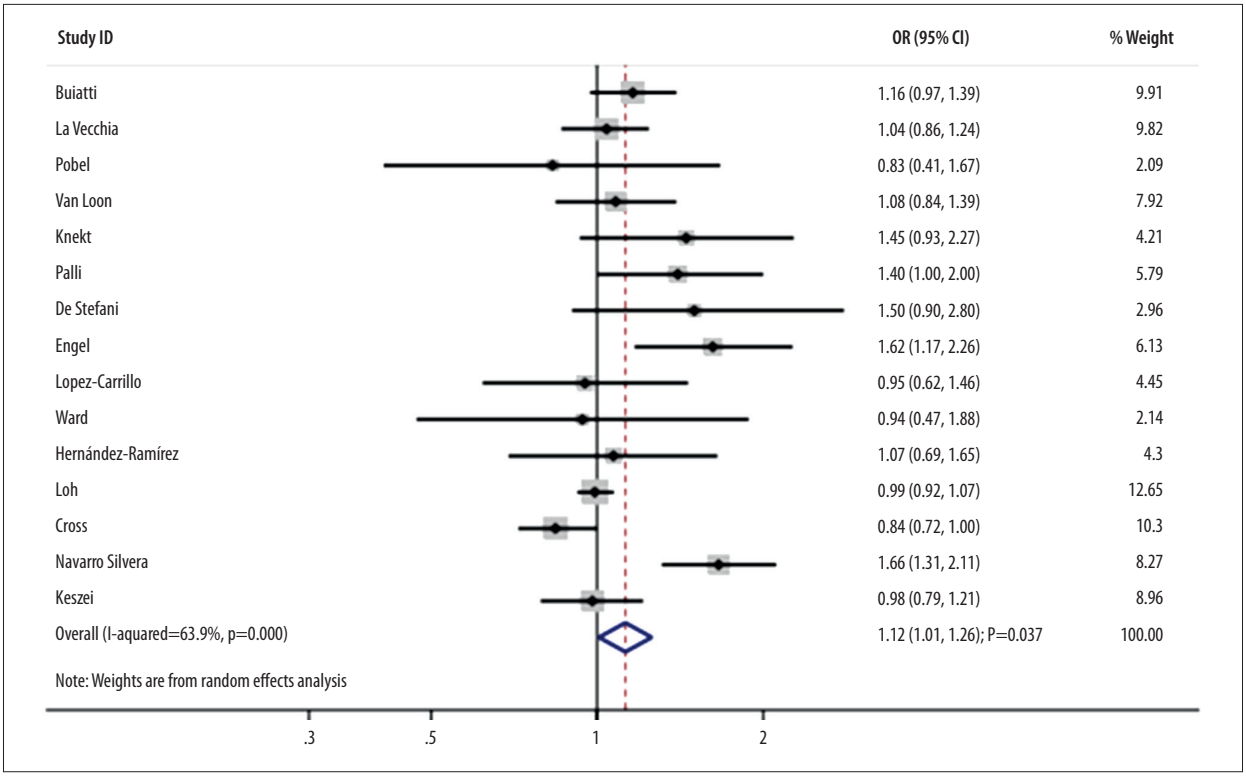

Figure 3. Association between moderate nitrite intake and the risk of gastric cancer.

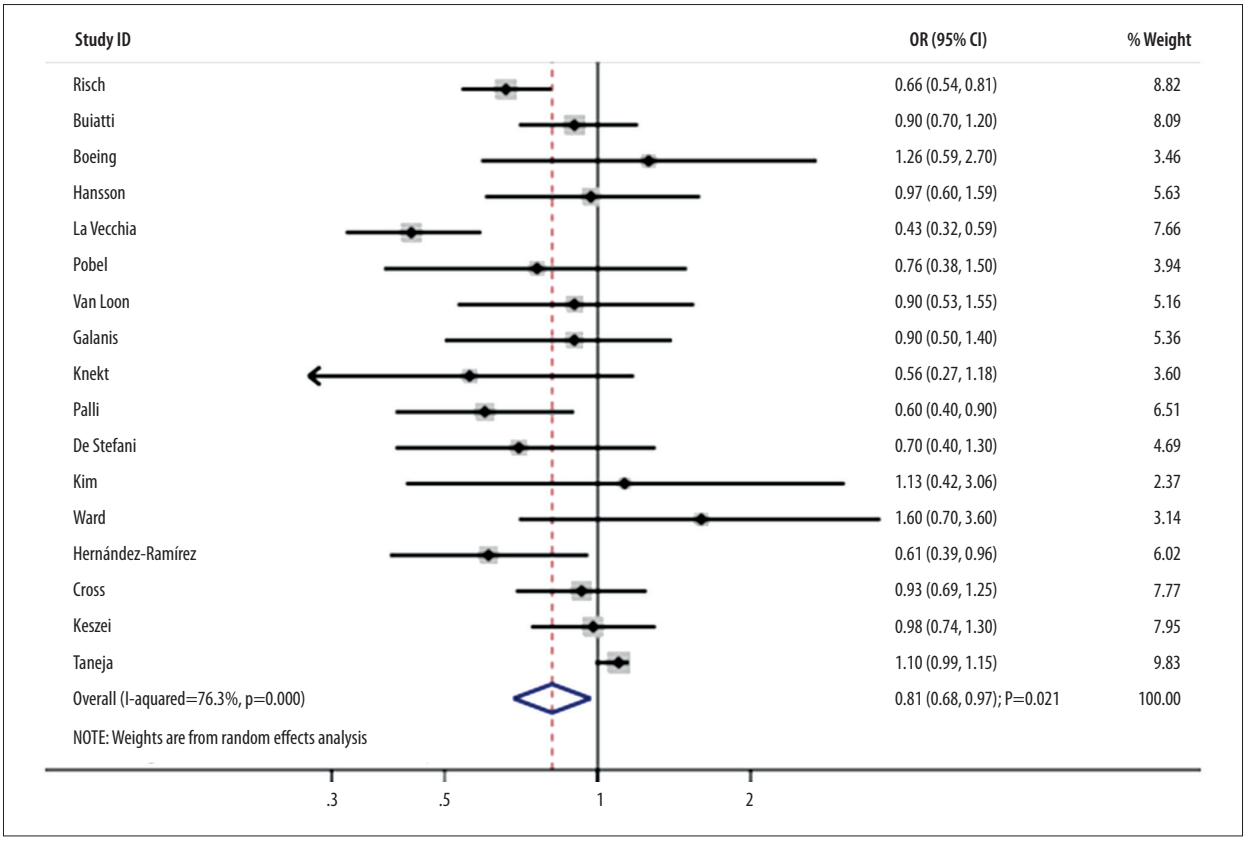

Figure 4. Association between high nitrate intake and the risk of gastric cancer.

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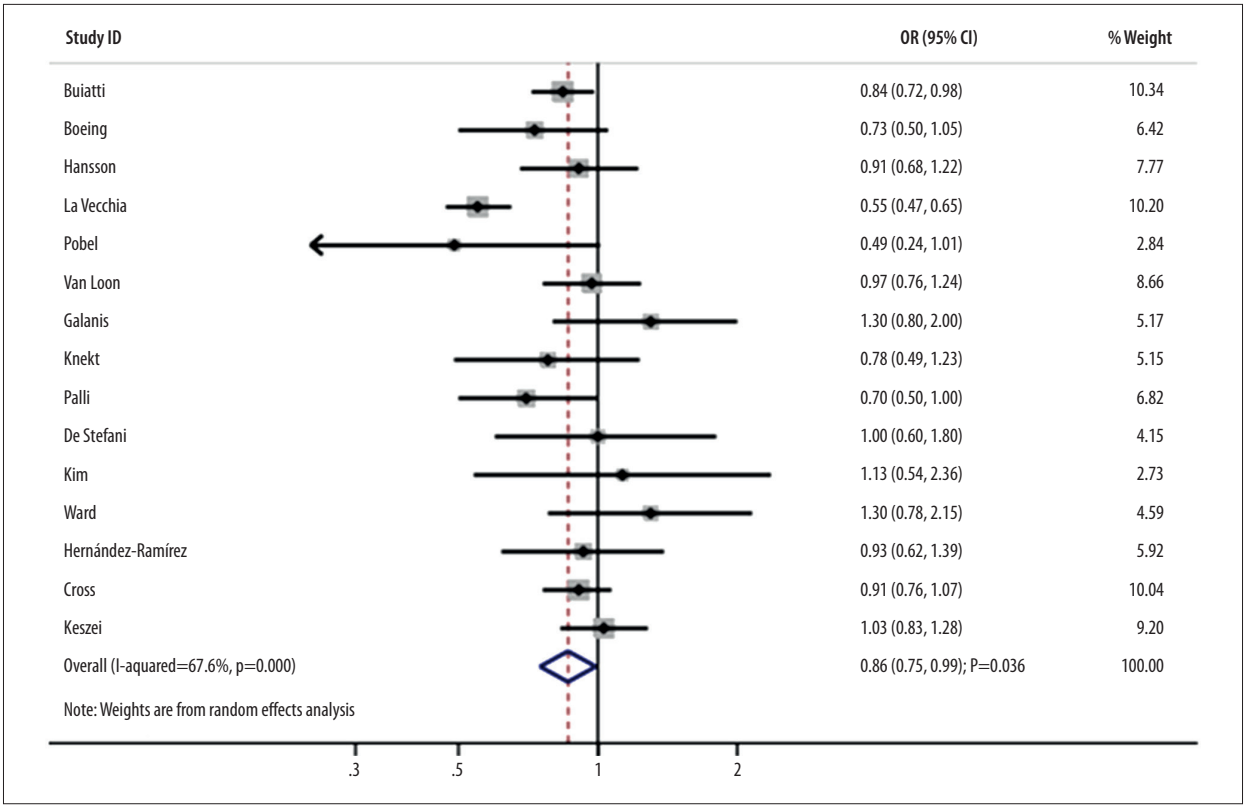

Figure 5. Association between moderate nitrate intake and the risk of gastric cancer.

speculated that this could be due to the contribution of vegetables and fruits to dietary nitrite [27]. De Stefani et al. found that high nitrite intake produced a protective effect on GC risk, which could be due to exogenous N-nitroso compounds contributing to a similar role in the risk of GC [31]. This study indicated that a high or moderate nitrite intake was correlated with a higher risk of GC; the reason for this was correlated with the sources of nitrite intake, and nitrite from animal products play an important role on endogenous nitrosation [47].

We noted that high or moderate nitrate intakes are correlated with a reduced risk of GC than the lowest nitrate intake. Taneja et al. indicated that the intake of >45 mg/L nitrate via drinking water produced an additional GC risk [45]. The potential reason for this could be the source of nitrate. In this study, the nitrate source in most of the included studies was vegetables that contain nutrients that inhibit the N-nitrosation in food, and the beneficial effects of nitrate intake could be affected by vitamin C and other antioxidants [48]. Vitamins C and E could inhibit endogenous nitrosation and hinder the formation of nitrosation compounds [49].

Subgroup analyses indicated that publication year, study design, country, the percentage of male patients, assessment of exposure, adjusted model, and study quality could bias the correlation between nitrite or nitrate intake and the risk of GC. First, the diagnosing strategy and timing were developed through the study publication year. Second, the current study included case-control and cohort studies, which associated with the evidence level. Third, the percentage of male patients contributed to the heterogeneity of the associations, possibly due to the different prevalence of GC between men and women. Fourth, the assessment of exposure was correlated with the accuracy of data collection. Fifth, the extent of adjustment could affect the intrinsic association of nitrite or nitrate intake with the risk of GC. Sixth, the quality of the included studies reflects the reliability of the conclusions made therein.

We were aware of several limitations of this meta-analysis. First, most of the included studies were retrospective case-control studies, which might have introduced potential selection and recall biases. Second, the cutoff values of nitrite and nitrate intakes differed among the included studies, which could have affected the comparability between exposure and control. Third, the significant heterogeneity could not be fully interpreted in the sensitivity and subgroup analyses. Fourth, the adjusted factors differed among the included studies, and these factors may have played an important role in the progression of GC. Fifth, publication bias is inevitable since this study was based on published articles.

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Conclusions

This study concluded that a high or moderate nitrite intake increases the risk of GC, whereas a high or moderate nitrate intake was associated with a decreased risk of GC. These associations are variable according to several characteristics of study or patients. Further large-scale prospective cohort studies are required to evaluate the correlation between nitrite or nitrate intake from various sources and the risk of GC.

Conflicts of interest

None.

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