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REVIEW

Dietary vitamin B intake and the risk of esophageal cancer: a meta-analysis

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Jun-Li Ma[1]
Yan Zhao[1]
Chen-Yang Guo[1]
Hong-Tao Hu[1]
Lin Zheng[1]
Er-Jiang Zhao[2]
Hai-Liang Li[1]

[1]Department of Radiology Intervention, Affiliated Tumor Hospital of Zhengzhou University, Zhengzhou 450003, China; [2]Department of Epidemiology and Biostatistics, Affiliated Tumor Hospital of Zhengzhou University, Zhengzhou 450003, China

Background: Several epidemiology studies have explored the association between dietary B vitamins' intake and the risk of esophageal cancer (EC). However, the results remain inconclusive. Thus, we conducted a systematic review with meta-analysis to evaluate such association.

Methods: Literature retrieval was performed using PubMed (Medline), ScienceDirect, and Cochrane Library electronic databases for all studies published from database inception to December 2017.

Results: The meta-analysis included 19 studies and showed an overall decreased risk of EC (OR=0.77, 95% CI: 0.68–0.87) in association with multivitamin B (ie, B1, B2, B3, B5, B6, B9, and B12) dietary intake. In a subgroup analysis based on vitamin B subclass, B1, B3, B6, and B9 vitamins were associated with decreased EC risk (vitamin B1: OR=0.68, 95% CI: 0.56–0.82; vitamin B3: OR=0.70, 95% CI: 0.53–0.94; vitamin B6: OR=0.64, 95% CI: 0.49–0.83; and vitamin B9: OR=0.69, 95% CI: 0.55–0.86). By contrast, no association was detected between dietary vitamin B2 and vitamin B5 intake and EC risk (vitamin B2: OR=0.86, 95% CI: 0.64–1.16; vitamin B5: OR=0.49, 95% CI: 0.20–1.20), whereas a potential non-linear dose–response association was found between dietary vitamin B12 intake and EC risk. A statistically significant, inverse association was observed for an increase of 100 μg/day in supplemental vitamin B6 and B9 and EC risk (vitamin B6: OR=0.98, 95% CI: 0.98–0.99; vitamin B9: OR= 0.89; 95% CI: 0.86–0.94).

Conclusion: These findings support that vitamin B may have an influence on carcinogenesis of the esophagus. Vitamin B1, B3, B6, B9 showed a decreased risk of EC, and vitamin B12 showed an increased risk of EC.

Keywords: B vitamins, esophageal cancer, meta-analysis

Introduction

Esophageal cancer (EC) has been ranked as the eighth most common cancer and the sixth leading cause of cancer-related deaths worldwide.[1] Its epidemiology varies widely, particularly in incidence rates among geographic regions.[2] The latest epidemiological studies indicated the highest rate of EC located on the "esophageal cancer belt" ie, China, South Africa, and France.[3,4] Possible risk factors for EC include alcohol drinking, hot-temperature food items, cigarette smoking, chronic mucosal irritation, and a family history of cancers.[5–7] Deficiency of nutrients, such as vitamins and microelements, was also found to be associated with an increased risk of EC, whereas a high intake of fruit and vegetables has been considered to be effective in prevention.[6] Several previous research studies have evaluated the effect of beta-carotene, vitamin A, C, and E on EC.[8–17] Regarding multivitamin B, most studies only examined folate

Correspondence: Hai-Liang Li
Department of Radiology Intervention, Affiliated Tumor Hospital of Zhengzhou University, 127 Dongming Road, Zhengzhou 450003, China
Email hlli2016@163.com

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intake and EC risk, and no relevant pooled analyses have been performed. Thus, we conducted a meta-analysis of the current epidemiological articles to better characterize the association between multivitamin B intake and EC risk.

Materials and methods

Search strategy

We conducted a systematic search for published articles and abstracts that evaluated the relationships between B vitamins (B1, B2, B3, B5, B6, B9, B12) and the risk of esophageal carcinoma in humans.

We conducted systemic searches of PubMed (Medline), ScienceDirect, and Cochrane Library electronic databases (from database inception to December 2017). The searches were performed using ((((cohort studies) OR case–control studies)) AND ((((((((((((vitamin B) OR vitamin B1) OR vitamin B2) OR vitamin B3) OR vitamin B5) OR vitamin B6) OR vitamin B9) OR vitamin B12) OR thiamin) OR riboflavin) OR pyridoxal) OR folate) OR cyanocobalamin)) AND (((((cancer) OR neoplasm) OR carcinoma)) AND Esophag*) in all fields. In addition, we scrutinized references from relevant original reports, review articles, and meta-analyses to identify other appropriate studies.

Inclusion criteria

In order to be included, the following criteria were needed: 1) the study was designed as a cohort, nested case–control or case–control study; 2) the study reported vitamin B and any kind of B vitamin group intake and the risk of EC; 3) the results reported effect estimates (RR, OR) and 95% CIs for comparisons between high and low dietary vitamin B intake. When multiple levels of vitamin B intake were presented, the ratio comparing the highest intake vs the lowest intake was chosen. When data from several publications were overlapping, we selected the articles with the most comprehensive data for inclusion in this meta-analysis.

Data extraction and quality assessment

Two researchers independently reviewed titles and abstracts of potentially eligible research identified by the search strategy and extracted the date using a standard extraction form from each included publication: the first author's name, publication year, source of control, study design, country where the study was performed, type of cancer, specific vitamin measured, number of cases, number of controls or cohort size, total sample size, lowest vitamin B level, highest vitamin B level, difference between the highest and lowest vitamin B levels, and the risk estimates on EC and corresponding 95% CIs for the highest vs lowest categories of vitamin B intake or for each category, factors adjusted for. Adjusted ratios were extracted in preference to non-adjusted ratios.

Two authors independently assessed the quality of included studies using the Newcastle–Ottawa Scale (NOS), which is a validated scale for assessing the quality of non-randomized studies in meta-analyses.[18,19] This scale awards a maximum of 9 points to each study: 4 for selection of participants and measurement of exposure, 2 for comparability of cohorts on the basis of the design or analysis, and 3 for evaluation of methodological quality outcomes. We assigned scores of 7 or higher to high-quality studies.[20,21]

Statistical analyses

In this meta-analysis, we calculated effect estimates (RR or OR) and 95% CIs in each study to evaluate the relationship between vitamin B intake and the risk of EC. We used a fixed effects model (Mantel–Haenszel method) when heterogeneity was negligible, and a random effects model (DerSimonian and Laird method) when heterogeneity was significant. Heterogeneity was assessed using I^2 statistic. Significant heterogeneity was indicated if I^2 values were greater than 50%.[22,23] We also performed a sensitivity analysis by removing individual studies from the meta-analysis when statistically significant heterogeneity was detected. We also used Egger's and Begg's tests to assess publication bias.[24,25] All tests were two-sided and results were regarded as statistically significant if $P<0.05$. All statistical analyses were done by using STATA software (version 12.0; StataCorp LP, College Station, TX, USA).

Results

Literature search

Figure 1 shows the literature search results and screening of this study. We identified 390 observational studies from PubMed (Medline), ScienceDirect, and Cochrane Library. A total of 332 articles were assessed after eliminating 58 duplicate papers. A total of 268 articles were excluded owing to reported irrelevant results after reviewing the title and abstract. In addition, three additional studies were found by a manual search of the reference lists. In total, full text of 67 articles was reviewed. Among them, 13 studies did not show the association of vitamin B and EC risk, because these 13 articles explored the relationship between nutrient intervention or mineral compound vitamin B or all the nutrient intake and risk of EC or precancerous lesions. Four articles did not report sufficient data for estimation of OR/RR, three articles did not separately report the 95% CI, nine articles were

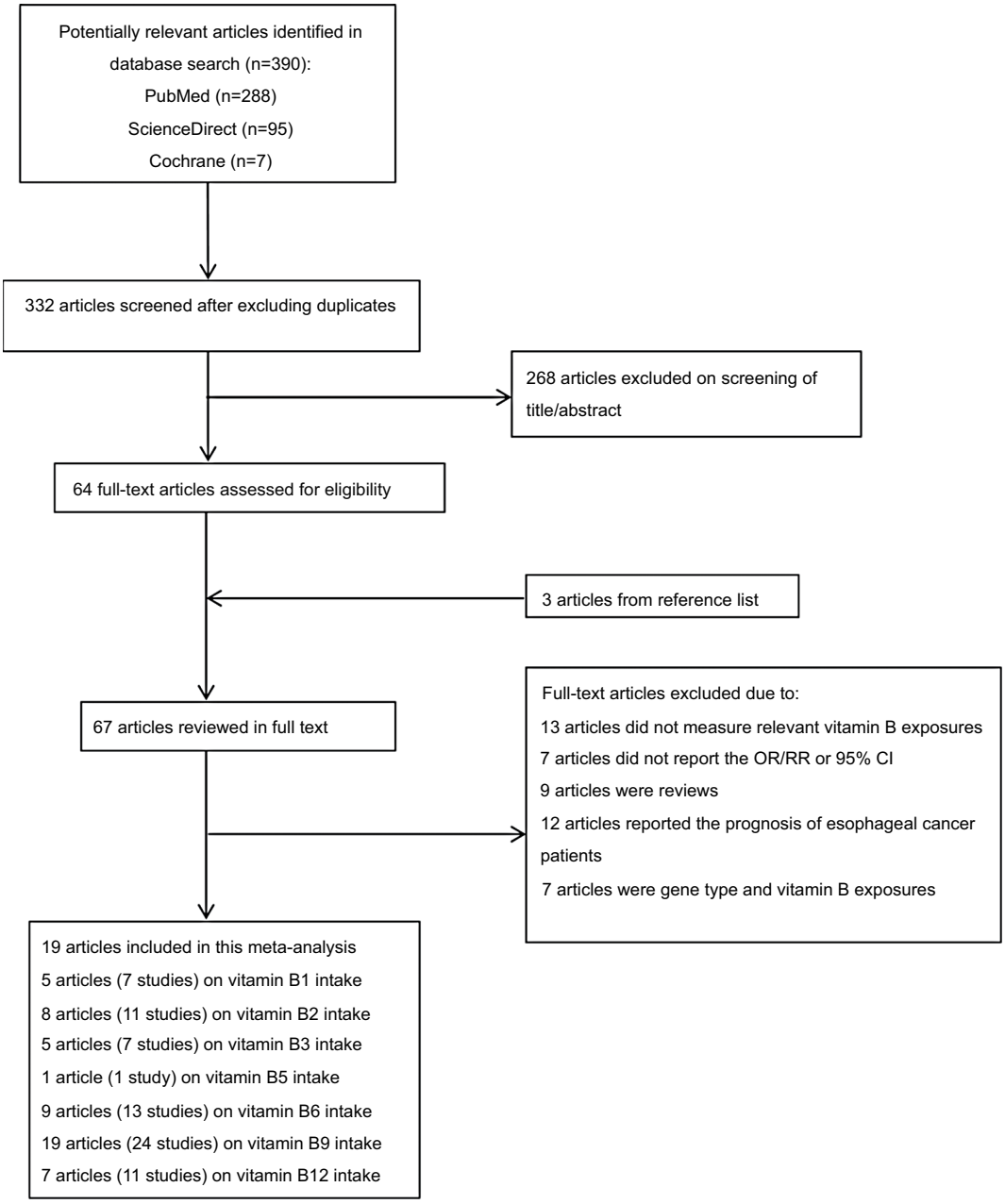

Figure 1 The flow diagram of screened, excluded, and analyzed publications.

reviews, 12 articles reported the prognosis of EC patients, five articles focused on gene type and vitamin B exposures, and two articles focused on blood vitamin B9, B12. As a result, 19 articles were finally selected for the meta-analysis.[8,9,26–42]

Characteristics and quality of included studies

We identified 19 articles in our study. Tables 1 and 2 show the main characteristics extracted from included studies. All the studies were conducted in Asia, Europe, America, and Australia and were published from 1988 to 2017. Among all the studies, one study was a cohort study[42] and 18 studies were case–control studies.[8,9,26–41]

The quality of all studies was assessed by using the NOS scale. The overall methodological quality of articles is presented in Table 1. Overall, eleven studies had a score of 8,[26,27,30,32,33,35–40] four had a score of 7,[8,9,34,42] and the remaining studies had a score of 6.[28,29,36,37,39,41]

Table 1 Characteristics of studies on B vitamin intake and esophageal cancer risk

Author	Year	Source of control	Study of design	Country	Cancer type	Vitamin B	Exposure ascertainment	OR (95% CI) for highest vs lowest category
Jessri et al	2011	HB	Case–control	Iran	ESCC	VB1	FFQ	0.34 (0.06–2.85)
Ibiebele et al	2011	PB	Case–control	Australian	EAC	VB1	FFQ	0.78 (0.57–1.07)
					ESCC	VB1	FFQ	0.41 (0.25–0.67)
Mayne et al	2001	PB	Case–control	US	EAC	VB1	FFQ	0.73 (0.50–1.07)
					ESCC	VB1	FFQ	0.78 (0.46–1.30)
Zhang et al	1997	HB	Case–control	US	EAC	VB1	FFQ	0.80 (0.30–2.10)
Brown et al	1988	HB	Case–control	US	EC	VB1	FFQ	0.60 (0.30–1.10)
Sharp et al	2013	PB	Case–control	Ireland	EAC	VB2	FFQ	1.07 (0.63–1.82)
Jessri et al	2011	HB	Case–control	Iran	ESCC	VB2	FFQ	0.22 (0.07–0.86)
Ibiebele et al	2011	PB	Case–control	Australian	EAC	VB2	FFQ	1.32 (0.98–1.80)
					ESCC	VB2	FFQ	0.78 (0.50–1.21)
Mayne et al	2001	PB	Case–control	US	EAC	VB2	FFQ	1.11 (0.82–1.52)
					ESCC	VB2	FFQ	1.26 (0.84–1.89)
Bao et al	2013	PB	Case–control	China	ESCC	VB2	Serum	0.46 (0.32–0.67)
Fanidi et al	2014	PB	Nested case–control	European	ESCC	VB2	Serum	1.21 (0.54–2.72)
					EAC	VB2	Serum	1.95 (0.84–4.52)
Zhang et al	1997	HB	Case–control	US	EAC	VB2	Food records	0.40 (0.20–1.10)
Chen et al	2009	PB	Case–control	US	EAC	VB2	Validated HHHQ	0.50 (0.20–1.00)
Jessri et al	2011	HB	Case–control	Iran	ESCC	VB3	FFQ	0.38 (0.15–1.82)
Ibiebele et al	2011	PB	Case–control	Australian	EAC	VB3	FFQ	0.71 (0.52–0.96)
					ESCC	VB3	FFQ	0.69 (0.43–1.12)
Mayne et al	2001	PB	Case–control	US	EAC	VB3	FFQ	1.07 (0.77–1.48)
					ESCC	VB3	FFQ	0.74 (0.48–1.16)
Zhang et al	1997	HB	Case–control	US	EAC	VB3	FFQ	0.20 (0.10–0.70)
Chen et al	2009	PB	Case–control	US	EAC	VB3	Validated HHHQ	0.80 (0.40–1.50)
Jessri et al	2011	HB	Case–control	Iran	ESCC	VB5	FFQ	0.49 (0.35–2.08)
Sharp et al	2013	PB	Case–control	Ireland	EAC	VB6	FFQ	0.37 (0.22–0.63)
Jessri et al	2011	HB	Case–control	Iran	ESCC	VB6	FFQ	0.17 (0.05–0.91)
Ibiebele et al	2011	PB	Case–control	Australian	EAC	VB6	FFQ	0.53 (0.39–0.74)
					ESCC	VB6	FFQ	0.66 (0.42–1.05)
Xiao et al	2014	PB	cohort	US	ESCC	VB6	FFQ	0.86 (0.51–1.45)
					EAC	VB6	FFQ	1.00 (0.76–1.32)
Mayne et al	2001	PB	Case–control	US	EAC	VB6	FFQ	0.53 (0.38–0.73)
					ESCC	VB6	FFQ	0.45 (0.30–0.69)
Fanidi et al	2014	PB	Nested Case–control	European	ESCC	VB6	Serum	2.26 (1.06–4.84)
					EAC	VB6	Serum	0.63 (0.30–1.33)
Galeone et al	2006	HB	Case–control	Italy and Swiss	ESCC	VB6	FFQ	0.99 (0.60–1.31)
Zhang et al	1997	HB	Case–control	US	EAC	VB6	FFQ	0.20 (0.10–0.70)
Chen et al	2009	PB	Case–control	US	EAC	VB6	Validated HHHQ	0.7 (0.30–1.30)
Ling	2013	PB	Case–control	China	ESCC	VB9	Serum	0.11 (0.04–0.33)
Sharp et al	2013	PB	Case–control	Ireland	EAC	VB9	FFQ	0.52 (0.30–0.89)
Zhao et al	2011	HB	Case–control	China	ESCC	VB9	FFQ	0.61 (0.36–1.07)

Participants (cases)	Adjust variables	New Castle–Ottawa scale
144 (48)	Age, gender, energy intake, BMI, smoking status, physical activity, education level, gastroesophageal reflux disease symptoms	8
519 (147)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
429 (57)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
969 (282)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
893 (206)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
48 (18)	NR	6
629 (207)	Smoking status, alcohol intake	6
129 (64)	Age, gender, total energy intake	9
144 (48)	Age, gender, energy intake, BMI, smoking status, physical activity, education level, gastroesophageal reflux disease symptoms	8
518 (146)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
422 (50)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
969 (282)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
893 (206)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
212 (106)	Age, gender, site	7
252 (123)	Age, gender, country, educational attainment, smoking status, alcohol intake	8
268 (26)	Age, gender, country, educational attainment, smoking status, alcohol intake	8
44 (13)	NR	6
573 (124)	Age, gender, respondent type, BMI, alcohol intake, tobacco use, education level, family history, vitamin supplement use	8
144 (48)	Age, gender, energy intake, BMI, smoking status, physical activity, education level, gastroesophageal reflux disease symptoms	8
515 (143)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
421 (49)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
969 (282)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
893 (206)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
44 (13)	NR	6
573 (124)	Age, gender, respondent type, BMI, alcohol intake, tobacco use, education level, family history, vitamin supplement use	8
144 (48)	Age, gender, energy intake, BMI, smoking status, physical activity, education level, gastroesophageal reflux disease symptoms	8
142 (46)	Age, gender, total energy intake	9
145 (49)	Age, gender, energy intake, BMI, smoking status, physical activity, education level, gastroesophageal reflux disease symptoms	8
517 (146)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
423 (52)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
4,471,303 (25)	Age, gender, race, education, marital status, health status, BMI, smoking status, alcohol, vigorous physical activity, multivitamin use, family history of cancer, energy intake	7
4,471,303 (98)	Age, gender, race, education, marital status, health status, BMI, smoking status, alcohol, vigorous physical activity, multivitamin use, family history of cancer, energy intake	7
969 (282)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
893 (206)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
257 (128)	Age, gender, country, educational attainment, smoking status, alcohol intake	8
270 (16)	Age, gender, country, educational attainment, smoking status, alcohol intake	8
405 (108)	Age, center, education, BMI, smoking, alcohol drinking	7
44 (13)	NR	6
573 (124)	Age, gender, respondent type, BMI, alcohol intake, tobacco use, education level, family history, vitamin supplement use	8
48 (6)	Age, gender, smoking habit, drinking	8
136 (55)	Age, gender, total energy intake	8
174 (52)	Age, gender	6

(*Continued*)

Table 1 (*Continued*)

Author	Year	Source of control	Study of design	Country	Cancer type	Vitamin B	Exposure ascertainment	OR (95% CI) for highest vs lowest category
Jessri et al	2011	HB	Case–control	Iran	ESCC	VB9	FFQ	0.08 (0.02–0.90)
Chang et al	2015	PB	Case–control	China	EC	VB9	Plasma	1.58 (0.95–2.64)
Ibiebele et al	2011	PB	Case–control	Australian	EAC	VB9	FFQ	0.72 (0.53–0.98)
					ESCC	VB9	FFQ	0.78 (0.51–1.19)
Aune et al	2011	HB	Case–control	Uruguay	EC	VB9	FFQ	0.29 (0.14–0.60)
Xiao et al	2014	PB	cohort	US	ESCC	VB9	FFQ	1.07 (0.59–1.94)
					EAC	VB9	FFQ	1.00 (0.76–1.31)
Mayne et al	2001	PB	Case–control	US	EAC	VB9	FFQ	0.48 (0.36–0.66)
					ESCC	VB9	FFQ	0.58 (0.39–0.86)
Bao et al	2013	PB	Case–control	China	ESCC	VB9	Serum	0.43 (0.29–0.62)
Fanidi et al	2014	PB	Nested case–control	European	ESCC	VB9	Serum	1.03 (0.47–2.24)
					EAC	VB9	Serum	1.68 (0.79–3.56)
Galeone et al	2006	HB	Case–control	Italy and Swiss	ESCC	VB9	FFQ	0.68 (0.46–1.00)
Tavani et al	2012	HB	Case–control	Italy	EC	VB9	FFQ	0.26 (0.14–0.48)
Bollschweil et al	2002	PB	Case–control	Germany	EAC	VB9	FFQ	5.00 (2.10–13.60)
					ESCC	VB9	FFQ	3.20 (1.30–9.10)
Zhang et al	1997	HB	Case–control	US	EAC	VB9	FFQ	0.70 (0.30–1.70)
Qin et al	2008	HB and PB	Case–control	China	EC	VB9	FFQ	0.52 (0.33–0.82)
Brown et al	1988	HB	Case–control	US	EC	VB9	FFQ	0.70 (0.40–1.30)
Chen et al	2009	PB	Case–control	US	EAC	VB9	HHHQ	0.50 (0.30–1.00)
Yang et al	2005	HB	Case–control	Japan	EC	VB9	SQFFQ	0.77 (0.45–1.31)
Sharp et al	2013	PB	Case–control	Ireland	EAC	VB12	FFQ	3.87 (2.22–6.73)
Jessri et al	2011	HB	Case–control	Iran	ESCC	VB12	FFQ	1.33 (0.60–3.03)
Chang et al	2015	PB	Case–control	China	EC	VB12	Plasma	3.07 (1.73–5.45)
Ibiebele et al	2011	PB	Case–control	Australian	EAC	VB12	FFQ	0.96 (0.71–1.30)
					ESCC	VB12	FFQ	0.89 (0.58–1.32)
Xiao et al	2014	PB	cohort	US	ESCC	VB12	FFQ	0.85 (0.52–1.41)
					EAC	VB12	FFQ	1.04 (0.80–1.34)
Mayne et al	2001	PB	Case–control	US	EAC	VB12	FFQ	1.39 (1.10–1.76)
					ESCC	VB12	FFQ	1.51 (1.15–2.00)
Fanidi et al	2014	PB	Nested case–control	European	ESCC	VB12	Serum	1.07 (0.51–2.23)
					EAC	VB12	Serum	1.17 (0.56–2.44)

Abbreviations: BMI, body mass index; EAC, esophageal adenocarcinoma; EC, esophageal carcinoma; ESCC, esophageal squamous cell carcinoma; HB, hospital-based; N/A, not available; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PB, population-based; VB, vitamin B; FFQ, food frequency questionnaires; HHQ, health habits and history questionnaires.

Multivitamin B intake

Our results showed a statistically significant inverse association between use of multivitamin B supplements and EC (OR=0.70; 95% CI: 0.59–0.83). There was statistically significant heterogeneity among all the studies (I^2=77.9%; P=0.00).

Subgroup analysis of the source of the control group

Subgroup analysis of the source of the control group showed that dietary vitamin B was a protective factor for EC in both subgroups (hospital-based: OR=0.575, 95% CI: 0.492–0.672; population-based: OR=0.868, 95% CI: 0.820–0.919).

Participants (cases)	Adjust	New Castle–Ottawa scale
144 (48)	Age, gender, energy intake, BMI, smoking status, physical activity, education level, gastroesophageal reflux disease symptoms	8
178 (75)	Age, gender, BMI, education, smoking status, alcohol drinking frequency	8
491 (117)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
430 (56)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
2,102 (70)	Age, gender, residence, education, income, interviewer, smoking status, alcohol, dietary fiber, iron, BMI, energy intake	7
4471303 (21)	Age, gender, race, education, marital status, health status, BMI, smoking status, alcohol, vigorous physical activity, multivitamin use, family history of cancer, energy intake	7
4471303 (98)	Age, gender, race, education, marital status, health status, BMI, smoking status, alcohol, vigorous physical activity, multivitamin use, family history of cancer, energy intake	7
969 (282)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
893 (206)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
212 (106)	Age, gender, site	7
255 (126)	Age, gender, country, educational attainment, smoking status, alcohol intake	8
274 (26)	Age, gender, country, educational attainment, smoking status, alcohol intake	8
404 (90)	Age, center, education, BMI, smoking, alcohol drinking	7
443 (128)	Age, gender, study center, year of interview, education, alcohol drinking, tobacco smoking, BMI, energy intake, physical activity	6
38 (25)	NR	6
29 (16)	NR	6
49 (18)	NR	6
360 (120)	NR	5
629 (207)	Smoking status, alcohol intake	6
573 (124)	Age, gender, respondent type, BMI, alcohol intake, tobacco use, education level, family history, vitamin supplement use	8
270 (62)	Smoking status, alcohol intake, total energy intake	6
124 (81)	Age, gender, total energy	8
143 (47)	Age, gender, energy intake, BMI, smoking status, physical activity, education level, gastroesophageal reflux disease symptoms	8
195 (93)	Age, gender, BMI, education, smoking status, alcohol drinking frequency	8
528 (155)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
438 (65)	Age, gender, education, BMI, alcohol intake, smoking status, energy intake, NSAID use	8
4471303 (28)	Age, gender, race, education, marital status, health status, BMI, smoking status, alcohol, vigorous physical activity, multivitamin use, family history of cancer, energy intake	7
4471303 (123)	Age, gender, race, education, marital status, health status, BMI, smoking status, alcohol, vigorous physical activity, multivitamin use, family history of cancer, energy intake	7
969 (282)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
893 (206)	Age, gender, site, race, proxy status, income, education, BMI, smoking status, alcohol, energy intake	8
274 (145)	Age, gender, country, educational attainment, smoking status, alcohol intake	8
298 (18)	Age, gender, country, educational attainment, smoking status, alcohol intake	8

Subgroup analysis of EC pathological types

Subgroup analysis based on EC pathological types showed that dietary vitamin B was protective against esophageal squamous cell carcinoma (OR=0.762, 95% CI: 0.697–0.833) and esophageal adenocarcinoma (OR=0.870, 95% CI: 0.811–0.933).

Vitamin B1 intake

The association between vitamin B1 intake and EC risk was examined in seven case–control studies. The multivariable adjusted ORs for each study and combination of all studies for the highest vs lowest level of dietary vitamin B1 intake are shown in Figure 2. The pooled OR of EC for the highest

Table 2 Characteristics of studies on B vitamin intake

Author	Year	Vitamin B	Exposure ascertainment	Highest vs lowest category
Jessri et al	2011	VB1	FFQ	–
Ibiebele et al	2011	VB1	FFQ	0.4–1.5 vs 2.1–5.8 (mg/d)
		VB1	FFQ	0.4–1.5 vs 2.1–5.8 (mg/d)
Mayne et al	2001	VB1	FFQ	–
		VB1	FFQ	–
Zhang et al	1997	VB1	FFQ	–
Brown et al	1988	VB1	FFQ	–
Sharp et al	2013	VB2	FFQ	≤1.8 vs ≥2.8 mg (mg/d)
Jessri et al	2011	VB2	FFQ	–
Ibiebele et al	2011	VB2	FFQ	0.5–1.8 vs 2.7–7.1 (mg/d)
		VB2	FFQ	0.5–1.8 vs 2.7–7.1 (mg/d)
Mayne et al	2001	VB2	FFQ	–
		VB2	FFQ	–
Bao et al	2013	VB2	Serum	<2,401.86 vs >2845.42 (μg/L)
Fanidi et al	2014	VB2	Serum	2.5–9.4 vs 21.4–199 (nmol/L)
		VB2	Serum	2.5–9.4 vs 21.4–199 (nmol/L)
Zhang et al	1997	VB2	Food records	–
Chen et al	2009	VB2	Validated HHHQ	–
Jessri et al	2011	VB3	FFQ	–
Ibiebele et al	2011	VB3	FFQ	28–50 mg
		VB3	FFQ	28–50 mg
Mayne et al	2001	VB3	FFQ	–
		VB3	FFQ	–
Zhang et al	1997	VB3	FFQ	–
Chen et al	2009	VB3	Validated HHHQ	–
Jessri et al	2011	VB5	FFQ	–
Sharp et al	2013	VB6	FFQ	≤2.3 vs ≥3.2 (mg/d)
Jessri et al	2011	VB6	FFQ	–
Ibiebele et al	2011	VB6	FFQ	0.3–1.1 vs 1.5–3.0 (mg/d)
		VB6	FFQ	0.3–1.1 vs 1.5–3.0 (mg/d)
Xiao et al	2014	VB6	FFQ	–
		VB6	FFQ	–
Mayne et al	2001	VB6	FFQ	–
		VB6	FFQ	–
Fanidi et al	2014	VB6	Serum	7.2–25.6 vs 47.7–272 (nmol/L)
		VB6	Serum	7.2–25.6 vs 47.7–272 (nmol/L)
Galeone et al	2006	VB6	FFQ	–
Zhang et al	1997	VB6	FFQ	–
Chen et al	2009	VB6	Validated HHHQ	–
Ling	2013	VB9	Serum	<17.04 vs >34.19 (μg/L)
Sharp et al	2013	VB9	FFQ	≤318 vs ≥421 (μg/d)
Zhao et al	2011	VB9	FFQ	<230 vs >300 (μg/d)
Jessri et al	2011	VB9	FFQ	–
Chang et al	2015	VB9	Plasma	≤8.90 vs >17.66 (nmol/L)
Ibiebele et al	2011	VB9	FFQ	42–230 vs 336–673 (μg/d)
		VB9	FFQ	42–230 vs 336–673 (μg/d)
Aune et al	2011	VB9	FFQ	–
Xiao et al	2014	VB9	FFQ	–
		VB9	FFQ	–
Mayne et al	2001	VB9	FFQ	–
		VB9	FFQ	–
Bao et al	2013	VB9	Serum	<28.27 vs >35.06 (μg/L)
Fanidi et al	2014	VB9	Serum	0.3–9.1 to -18.2–109 (nmol/L)
		VB9	Serum	0.3–9.1 to -18.2–109 (nmol/L)
Galeone et al	2006	VB9	FFQ	–
Tavani et al	2012	VB9	FFQ	<208.77 vs >312.47 (μg/d)

(*Continued*)

Table 2 (*Continued*)

Author	Year	Vitamin B	Exposure ascertainment	Highest vs lowest category
Bollschweiler et al	2002	VB9	FFQ	0–164 (μg/d)
		VB9	FFQ	0–164 (μg/d)
Zhang et al	1997	VB9	FFQ	–
Qin et al	2008	VB9	FFQ	–
Brown et al	1988	VB9	FFQ	–
Chen et al	2009	VB9	HHHQ	–
Yang et al	2005	VB9	SQFFQ	<300 vs >400 (μg/d)
Sharp et al	2013	VB12	FFQ	≤6.4 vs ≥9.7 (μg/d)
Jessri et al	2011	VB12	FFQ	–
Chang et al	2015	VB12	Plasma	≤154.23 vs >324.06 (pmol/L)
Ibiebele et al	2011	VB12	FFQ	0–1.1 vs 2.1–7.8 (μg/d)
		VB12	FFQ	0–1.1 vs 2.1–7.8 (μg/d)
Xiao et al	2014	VB12	FFQ	–
		VB12	FFQ	–
Mayne et al	2001	VB12	FFQ	–
		VB12	FFQ	–
Fanidi et al	2014	VB12	Serum	75.1–265 vs 392–2,737 (pmol/L)
		VB12	Serum	75.1–265 vs 392–2,737 (pmol/L)

Abbreviations: VB, vitamin B; FFQ, food frequency questionnaires; HHHQ, health habits and history questionnaires; SQFFQ, semi-quantitative food frequency questionnaires.

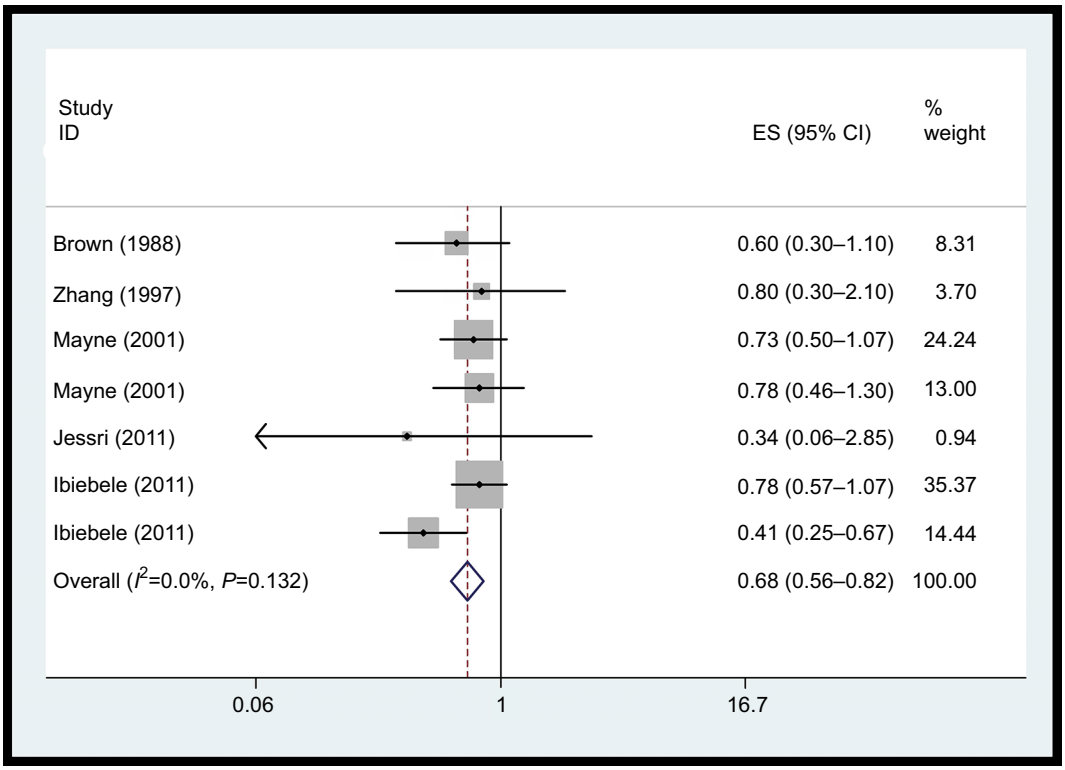

Figure 2 Forest plot between highest vs lowest categories of vitamin B1 intake and EC risk.
Abbreviation: EC, esophageal cancer.

vs lowest level of vitamin B1 intake was 0.68 (95% CI: 0.56–0.82). No heterogeneity was detected (I^2=0.0%, P=0.432). It was not possible to perform dose–response meta-analyses due to limited data.

Vitamin B2 intake

We did not observe a statistically significant association for vitamin B2 supplements and EC risk (Figure 3, OR=0.86; 95% CI: 0.64–1.16) based on eleven studies. There was

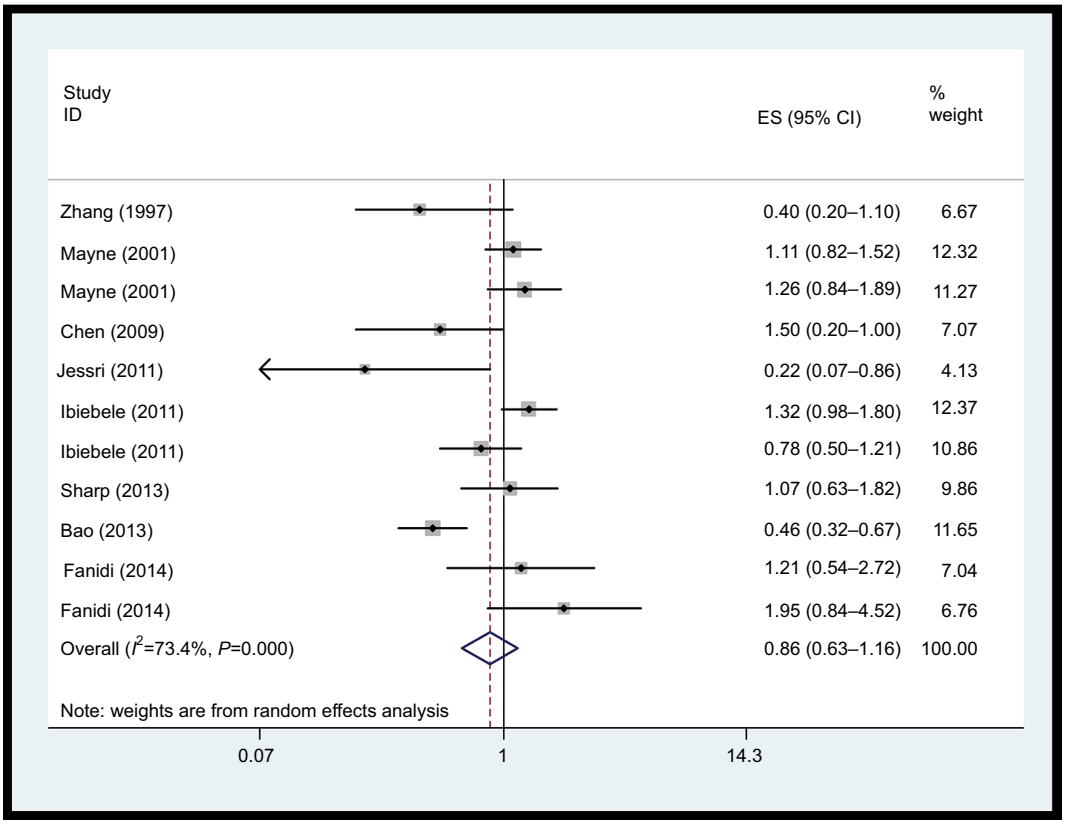

Figure 3 Forest plot between highest vs lowest categories of vitamin B2 intake and esophageal cancer risk.
Abbreviation: ES, esophageal squamous carcinoma.

statistically significant heterogeneity among the studies on dietary vitamin B2 intake (I^2=70.2%; P<0.001).

Vitamin B3 intake

As shown in Figure 4, seven studies examined the association between vitamin B3 intake and EC risk. The pooled OR for the highest vs lowest vitamin B3 intake was 0.70 (95% CI: 0.53–0.94, I^2=53.9%, P=0.043). Dose–response meta-analyses were not done due to data limitations.

Vitamin B5 intake

There was only one study which showed the association between vitamin B5 intake and EC risk (OR=0.49, 95% CI:0.20–1.20), suggesting that vitamin B5 intake was not significantly associated with the risk of EC.

Vitamin B6 intake

A total of 13 studies assessed the association between dietary vitamin B6 intake and EC risk. Figure 5 shows that the pooled OR of EC risk for the highest vs the lowest categories of vitamin B6 intake was 0.64 (95% CI: 0.49–0.83, I^2=73.0%, P=0.00), indicating that vitamin B6 intake had a protective effect against EC risk. For an increase of 100 μg/day of dietary vitamin B6 intake, a statistically significant, inverse association with EC risk (OR=0.98, 95% CI: 0.98–0.99) was detected.

Vitamin B9 intake

The association between dietary folate intake and EC risk was examined in 15 studies. The multivariable adjusted ORs for each study and combination of all studies for the highest vs lowest level of dietary folate intake are shown in Figure 6. The pooled OR of EC for the highest vs lowest level of dietary folate intake was 0.63 (95% CI: 0.56–0.71). There was statistically significant heterogeneity among the studies on dietary folate intake (I^2=70.2%; P=0.00). Dose–response meta-analysis was based on seven studies. A statistically significant, inverse association was observed for an increase of 100 μg/day in supplemental vitamin B9 and EC risk (OR=0.89; 95% CI: 0.86–0.94).

Vitamin B12 intake

Inconsistent associations were observed for use of vitamin B12 supplements and EC risk in our study (OR=1.34, 95%

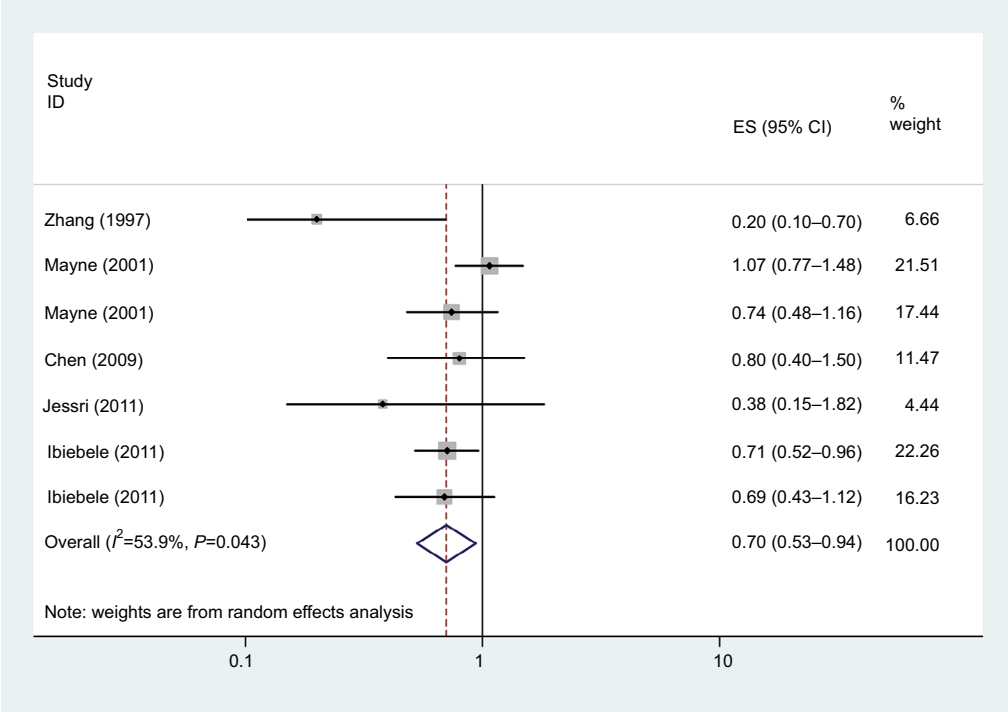

Figure 4 Forest plot between highest vs lowest categories of vitamin B3 intake and esophageal cancer risk.
Abbreviation: ES, .

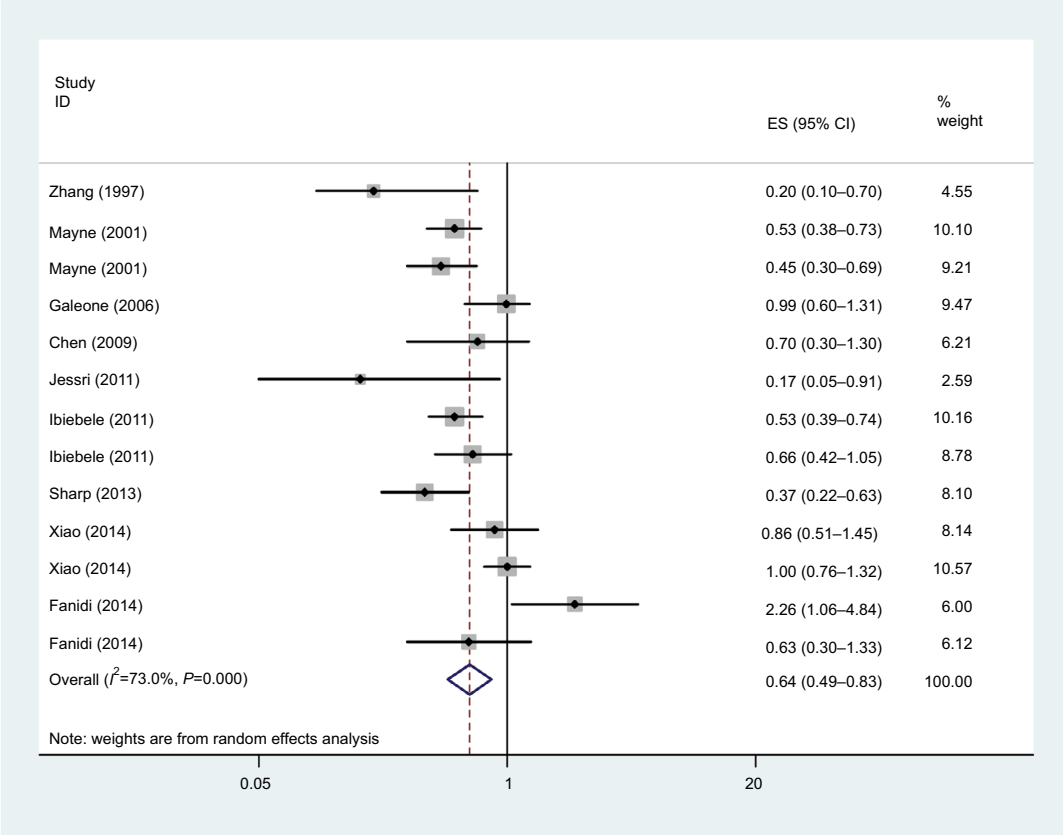

Figure 5 Forest plot between highest vs lowest categories of vitamin B6 intake and esophageal cancer risk.
Abbreviation: ES, .

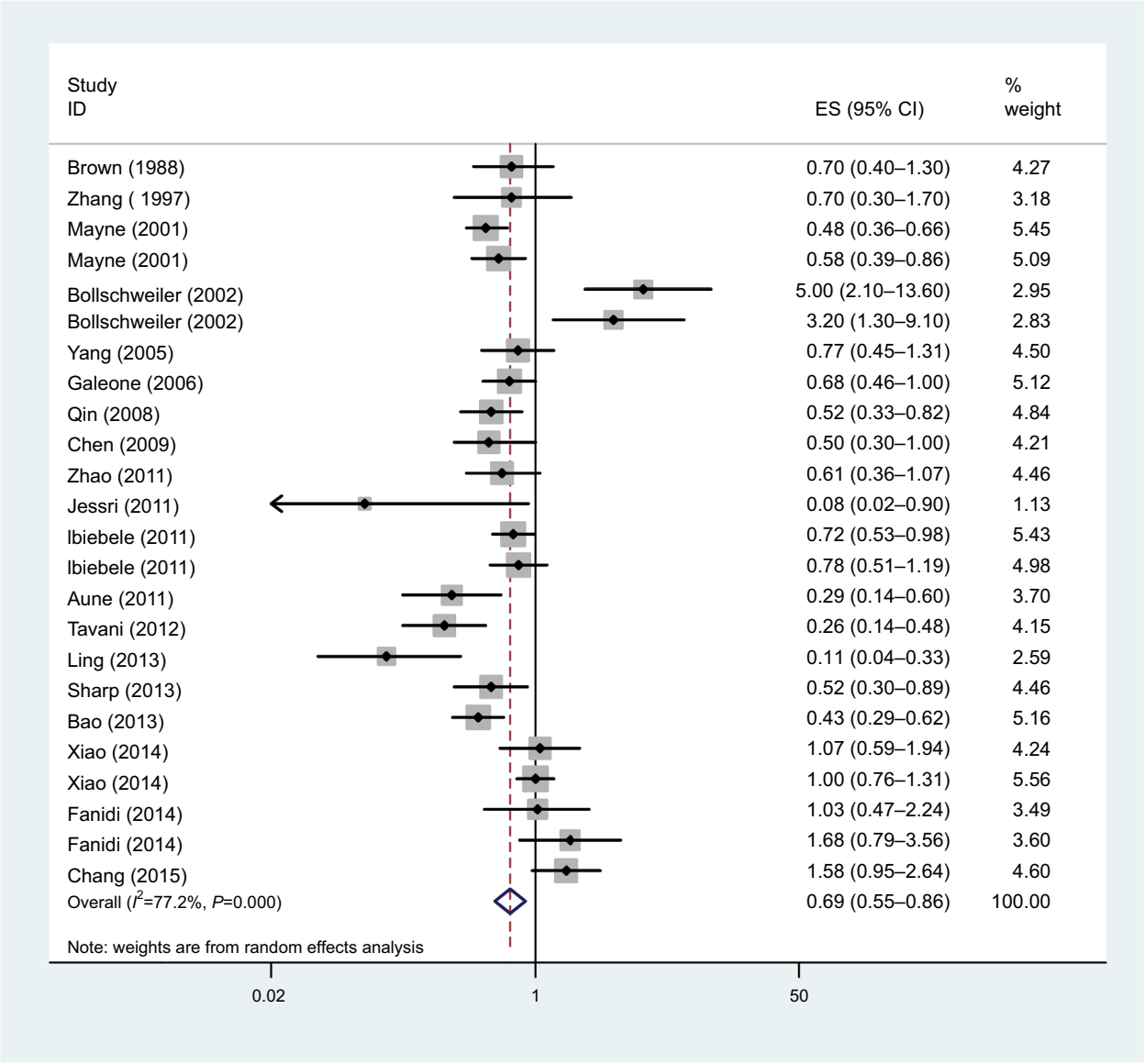

Figure 6 Forest plot between highest vs lowest categories of vitamin B9 intake and esophageal cancer risk.
Abbreviation: ES, .

CI: 1.05–1.70). Heterogeneity was high (I^2=73.6%, P=0.00), as shown in Figure 7. Using restricted cubic spline function, we found a potential non-linear dose–response association between dietary vitamin B12 intake and EC risk ($P_{non\text{-}linearity}$= 0.0001) (Figure 8). The non-linear curve showed that there was a dose–response association between vitamin B12 dose and decreased risk of EC approximately below 5.5 μg/day, whereas the EC risk did not decrease further above 5.5 μg/day.

Publication bias

Publication bias was evaluated by Egger's[24] and Begg's tests.[25] The results disclosed no evidence of publication bias for EC (Egger: t=0.38, P=0.575; Begg: z=1.34 P=0.179).

Sensitivity analysis

As a result, a sensitivity analysis of multivitamin B intake was conducted, and after each study was sequentially excluded from the pooled analysis, the conclusion was not affected by exclusion of any specific study.

Discussion

Epidemiological investigations have suggested that there are significant relationships between diet-associated factors and EC. B vitamins may be one factor. Because some B vitamins cannot be synthesized in the human body, they can only be obtained through dietary. Fruit and vegetables are important dietary sources of some B vitamins. The reason why vitamin

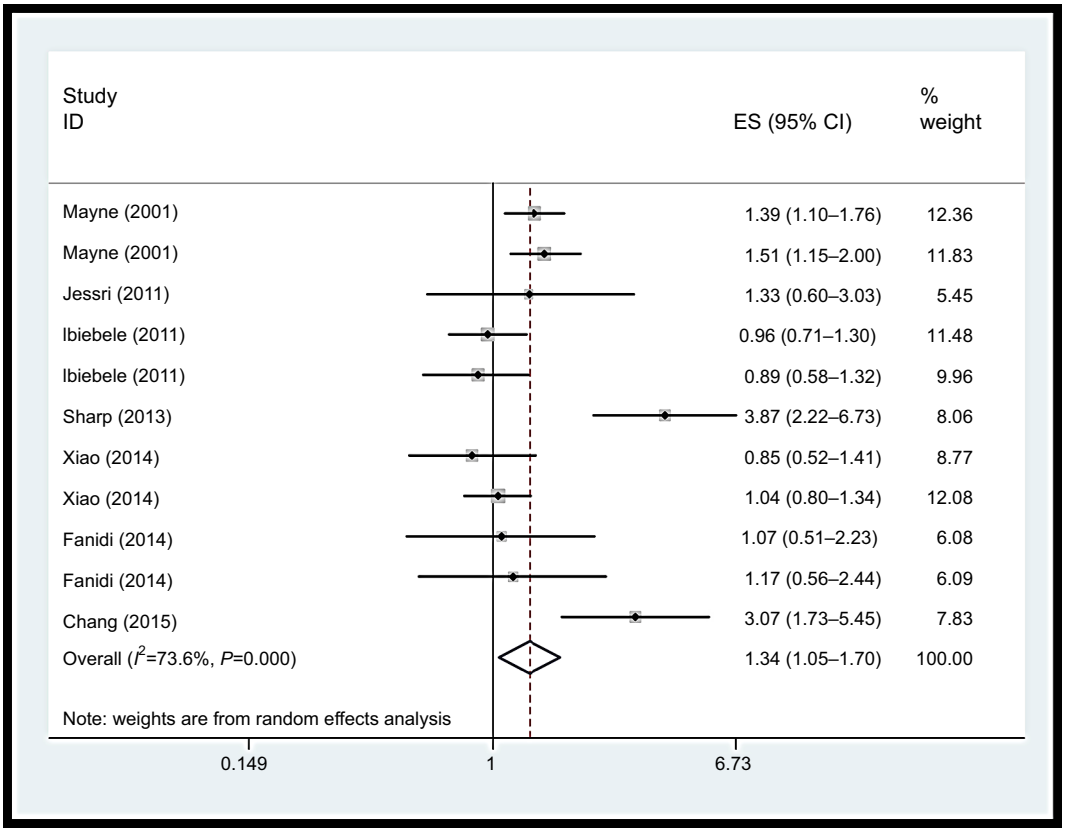

Figure 7 Forest plot between highest vs lowest categories of vitamin B12 intake and esophageal cancer risk.
Abbreviation: ES, .

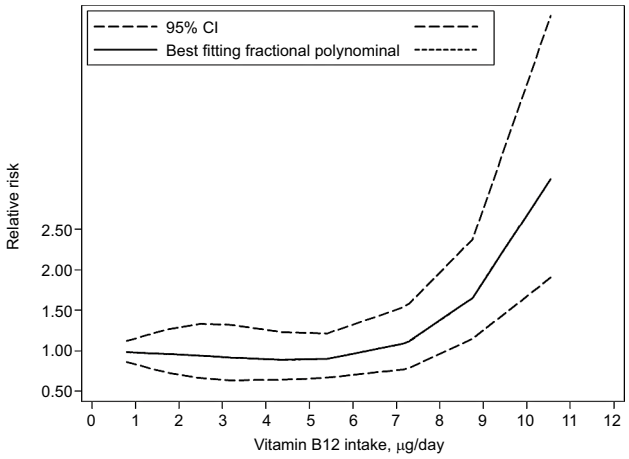

Figure 8 Non-linear dose–response analysis on vitamin B12 intake and esophageal cancer risk.

B affects the risk of cancer may be because it is essential for the biosynthesis of nucleotides, replication of DNA, supply of methyl groups, and the growth and repair of cells.[43–46]

In the present review, there was no epidemiologic research that assessed the association between total B vitamin consumption and EC risk among people. There were only studies which evaluated the relationship between several subclasses of B vitamins and EC risk. Thus, this study is the most comprehensive meta-analysis providing evidence to indicate these results. We found that total vitamin B intake was significantly associated with reduced EC risk. In addition, we evaluated the potential association of vitamin B subclasses and EC risk, respectively. In the subgroup analysis, we found that vitamin B1, B3, B6, and B9 may be protective factors, but vitamin B12, in contrast, was positively associated with risk of EC.

Previous studies have shown that consuming large quantities of vegetables, fruit, vitamins, and antioxidants can reduce the risk of EC.[47–49] One potential reason for vitamin B12 being different from other B vitamins may be because it is derived exclusively from foods of animal origin, and it is simply a marker for consumption of animal protein. In previous studies, the risk of adenocarcinomas of the esophagus was linked to high-fat diets[50,51] because esophageal adenocarcinoma generally arises from Barrett's epithelium.[52] Additionally, research has shown that diets low in animal protein and rich in fruit, vegetables, and fiber can reduce the risk of malignant transformation.[33,47]

B-group vitamin supplementation may have antioxidant and anti-inflammatory effects.[53,54] The biological mechanisms responsible for the protective effect of high-dosage vitamin B are unclear. One possible explanation is that B vitamins and additional nutrients sourced from fruit and vegetables are involved in the one-carbon metabolism.[55–57] The metabolic pathway of one-carbon metabolism has been frequently implicated in carcinogenesis, because of its involvement in maintaining nucleotide biosynthesis and methylation reactions. Imbalances and deficiencies among crucial one-carbon metabolism nutrients may interfere with DNA replication, DNA repair, and regulation of gene expression, any of which could promote carcinogenesis.[58,59] Like the vitamin B3, vitamin B6 and vitamin B9, they are indispensable in the biosynthesis of four bases of DNA (thymidine, guanine, adenine, and cytosine). Deficiency of one or more of the three vitamins required for DNA maintenance is known to cause abnormal pairing of the four bases, which can then result in mutations and the development of cancer.[60] Intake of vitamin B6 was reported to increase immunoglobulin G and T4(helper) lymphocytes in humans.[61] Folate deficiency was suggested to be related to increased carcinogenesis, an effect that may be mediated through participation in methyl metabolism.[62]

Limitations

There were some limitations in our study that should be addressed. First, most studies included in our analysis were case–control studies, which may have caused recall bias, and could have caused potential heterogeneity, although the methodological quality of these observational studies was medium to high. More prospective cohort studies are needed to test this association. Second, it was a challenge to evaluate the quantity of vitamin B intake accurately because vitamin B can be sourced from various food types, and may be influenced by the type of cultivation, crop variety and location, as well as the specific morphological part of the plant eaten.

In conclusion, results from the present meta-analysis indicate that vitamin B intake is inversely associated with EC risk.

Conclusion

Our findings support that vitamin B may have an influence on carcinogenesis of the esophagus. Vitamin B1, B3, B6, and B9 showed a decreased risk of EC, vitamin B12 showed an increased risk of EC. (It is clear that scientists must apply the very best science in characterizing the safety of vitamin supplements.)

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Disclosure

The authors report no conflicts of interest in this work.

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