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Review Article

The association between B vitamins supplementation and adverse cardiovascular events: a meta-analysis

Wen-Feng Li[1*], Dan-Dan Zhang[2*], Ji-Tian Xia[1], Shan-Fan Wen[3], Jun Guo[1], Zi-Cheng Li[1]

[1]Department of Cardiovascular Medicine, The First Affiliated Hospital of Jinan University, Guangzhou 510630, China; [2]Department of Anatomy, Medical College of Jinan University, Guangzhou 510630, China; [3]Department of Clinical Laboratory, Medical College of Foshan, Guangdong Province, China. [*]Equal contributors.

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Abstract: This study is to explore the association of adverse cardiovascular events with B vitamins supplementation. Rev.Man 5.1 and Stata 11.0 software were applied for the meta-analysis. The number of cardiovascular events was collected and calculated using indicates of odds ratio and 95% confidence intervals in a fixed-effects or a random-effects model when appropriate. The study includes 15 studies which consists of 37,358 study objects (experimental group: 19,601; control group: 17,757). This study showed that the pooled ORs was 1.01 (95% CI = 0.96~1.06, P > 0.05) for objects with Experimental group (B vitamins supplementation) vs. Control group (placebo or regular treatment), which suggests no significant differences were found in the overall effect of the number of cardiovascular events between the two groups. Further stratification of subgroup analysis indicates no significant differences were found between the two groups as well. There were also no publication bias existing by the Egger's linear regression test (P > 0.05). Our result indicates that the number of cardiovascular events in experimental group using B vitamins supplementation during the treatment is equal to placebo or regular treatment group thus further studies is necessary.

Keywords: B vitamins supplementation, folic acid, cardiovascular events, meta-analysis

Introduction

Cardiovascular disease is one of the main risks of death around the world [1, 2], the annual mortality is higher than any other diseases. It has been shown to increase with symptomatic disease locations as well [3]. Cardiovascular disease recurrences after acute coronary syndrome remain high [4], patients with cardiovascular disease risk is difficult to distinguished [5]. Study showed that high plasma homocysteine level is a risk factor which influences mortality [6] and cardiovascular disease [7]. Study also suggested folic acid, vitamins B6 and vitamins B12 may lower homocysteine level after intake from diet [8]. B vitamins supplementation can lower plasma total homocysteine level [9]. Cardiovascular diseases rates would be higher with elevated plasma homocysteine levels [10], but whether elevated plasma homocysteine levels were associated with cardiovascular disease is uncertain, and it was indicated that the association between them was causal [11]. Current studies showed that the supplementation of vitamin B reduces the risk of hyperhomocysteinemia, but it is uncertain if vitamin B supplementation reduces the rate of cardiovascular diseases [12]. Furthermore, recent studies with vascular diseases failed to prove the association between B-vitamin supplementation and cardiovascular diseases [13].

The association between B vitamins supplementation and adverse cardiovascular events for objects in the studies is controversial [8, 10, 11, 13-17]. In order to achieve a comprehensive understanding regarding the effect of the difference between B vitamins supplementation and placebo of the objects in the study, we consider to perform a meta-analysis of the published studies.

Materials and methods

Source of material

We retrieved the relevant trials up to September 2013 from several public databases, including

PubMed, Medline, Springer, Elsevier Science Direct, Cochrane Library and Google scholar. The key words "B vitamins supplementation", "cardiovascular events", "folic acid", "complication", "stroke", "coronary heart disease", "study" and "trial" were used for to retrieve data. At the same time, references from searched studies were verified for additional reports. We collected information from all full-published English papers. Meeting or conference abstract papers are excluded.

In the assumption of differences may occur (such as the included literature was not consistent with another investigator), a third investigator (C) will make additional assessment. If the third investigator' assessment is consistent with one of them, then the discussion should be made for the final decision of the included literatures.

Inclusion and exclusion standards of studies

The comparison between experimental group (B vitamins supplementation) and control group (placebo or regular treatment) were provided in the papers, the study design was randomized controlled trial (RCT), the effect size of the number of cardiovascular events was odds ratio (*OR*), and sample size or range of age were not limited. Studies which not described cardiovascular events data in the review or report, reduplicated studies or records, and not comparing experimental group vs control group were excluded.

Evaluation of quality and extraction of data

We evaluated the quality of the study using JADAD score. We developed and extracted the data after all investigators received prior training. Data items including study details (e.g., the first author's name, research year of the study, year publication, location of participants, design of studies.), and participants characteristics (e.g., age, gender and sample size). Two investigators (A and D) extracted the data independently using the standard protocol, and the third investigator (E) reviewed their results of studies. Discrepancies were resolved by discussing within our research team or contacting the original investigators via e-mail. We recorded the first author's name, year of publication, sample size, country, mean duration of follow up, and folic acid food reinforcement in experimental group vs. control group.

Meta-analysis methods

The meta-analysis combined the *OR* of adverse cardiovascular events in the objects of study between experimental group and control group, and then studies were stratified by sample size, mean duration of follow-up and folic acid food reinforcement, using subgroup analysis.

The overall or pooled estimation of the Odds ratio (*OR*) was obtained using Mantel-Haenszel method in the fixed effect model [18] or using DerSimonian and Laid method in the random effect model [19]. We assessed the within- and between-study variation or heterogeneity by testing Cochran's Q-statistic [20]. We also quantified the effect of heterogeneity using $I^2 = 100\% \times (Q\text{-df})/Q$ [21]. A significant *Q*-statistic ($P < 0.10$) or I^2-statistic ($I^2 > 50\%$) indicates heterogeneity across the studies, and then the random effects model was used for meta-analysis. The fixed effects model was used as alternative.

Evaluation of publication bias

We evaluated the publication bias using Egger's linear regression test [22], which measures funnel plot asymmetry by the natural logarithm scale of the effect size.

Statistical analysis

The meta-analysis was performed using the Review Manager 5.1 software (Cochrane Collaboration, http://ims.cochrane.org/revman), and the publication bias of the included studies were calculated using the STATA package v.11.0 (Stata Corporation, College Station, TX, USA). All the *P*-values were two-sided. *P* value less than 0.05 considered statistically significant, while *P* value less than 0.1 considered statistically significant in heterogeneity analysis.

Results

Characteristics of eligible studies

Overall, 1,062 papers potentially relevant to the search terms (PubMed: 352; Medline: 108; Springer: 153; Elsevier Science Direct: 99; Cochrane Library: 31; Google Scholar: 319). **Figure 1** illustrates the study selection process. After removing duplicates or irrelevant studies, 96 studies were potentially relevant. During abstracts screening, 49 articles were excluded

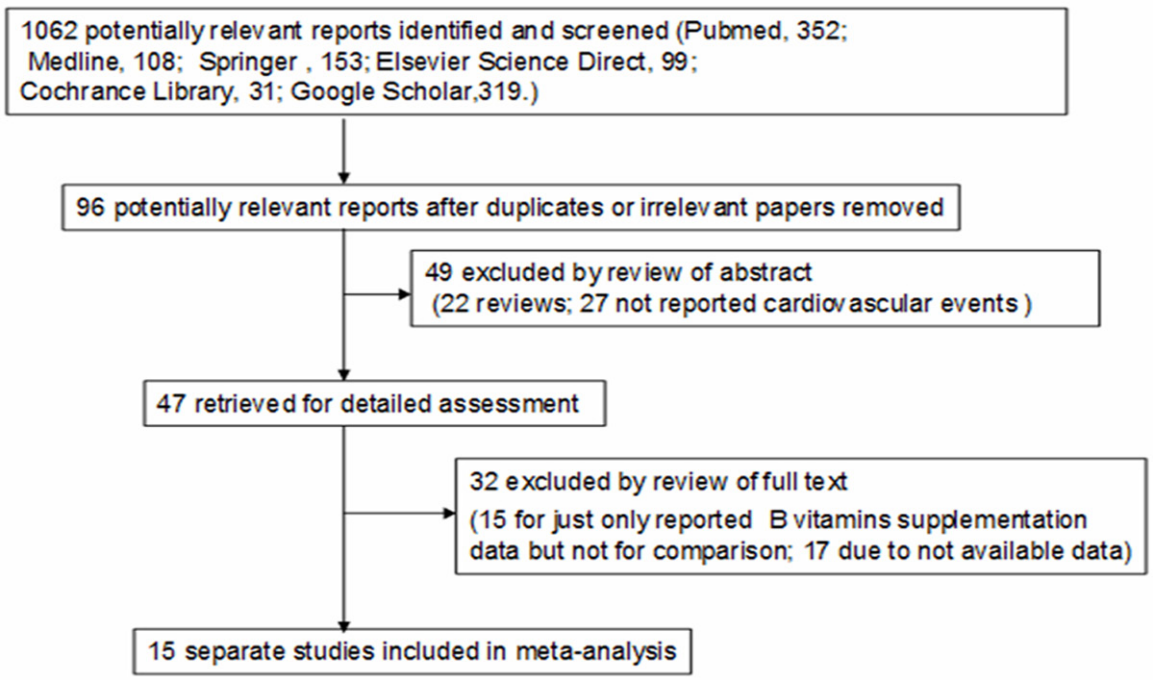

Figure 1. Flow diagram for the selection of studies.

(22 were review articles; 37 not report the cardiovascular events). Forty seven studies remained for full publication review, 32 of which were excluded (15 only reports B vitamin supplementation data but no comparison; 17 provides no available data).

Table 1 showed 15 studies [6-17, 23-25] in the meta-analysis, and the characteristics of included studies were presented. The included studies were published between 2002 and 2010. A total of 37,358 objects of study (experimental group: 19,601; control group: 17,757) were considered in the meta-analysis. The studies' sample size was between 81 and 12,064, and the average age was between 56.0 and 72.2 years old. Six studies reached 5 in Jadad score, six studies reached 4, and the rest of three studies were 3 (**Table 2**).

Overall effects of the number of cardiovascular events

The summary of the meta-analysis for the number of cardiovascular events between experimental group and control group is shown in **Table 3** and **Figure 2**. There were 15 separate studies consisting of 37358 objects of study (experimental group: 19601; control group: 17757) been analyzed in the meta-analysis. No heterogeneities were found between studies (Q^2 = 16.71, I^2 = 16.4%, P > 0.1) were found, so we used the fixed effects model to compare the number of cardiovascular events between this two groups. The overall meta-analysis showed that there were significant differences (*OR* = 1.01, 95% *CI* = 0.96 to 1.06, P > 0.05) between the two groups, suggesting that the number of cardiovascular events of study objects in experimental group may be higher than control group.

Subgroup analyses of the number of cardiovascular events

We performed subgroup analyses stratified by sample size, mean duration of follow-up and folic acid food reinforcement. As shown in **Table 3**, the further stratification of subgroup analysis indicates that for patients with experimental group *vs.* control group the pooled *OR* was 1.02 (95% *CI* = 0.97~1.08, P > 0.05) in studies with sample size more than 1,000; 0.87 (95% *CI* = 0.73~1.03, P > 0.05) in studies with sample size less than or equal to 1000; 1.02 (95% *CI* = 0.96~1.08, P > 0.05) in studies with mean duration of follow-up more than 36 months; 0.97 (95% *CI* = 0.86~1.09, P > 0.05) in studies with mean duration of follow-up less than or equal to 36 months; 0.99 (95% *CI* = 0.92~1.07,

Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Sample size	Mean duration of follow-up, months	Folic acid food reinforcement	Experimental group (B vitamins supplementation)				Control group			
					Sample size	Age, years (mean)	Therapeutic schedule	Male (%)	Sample size	Age, years (mean)	Therapeutic schedule	Male (%)
Schnyder, 2002. [23]	Switzerland	553	6	No	272	63.4±10.6	Folic acid (1 mg/d), vitamin B12 (cyanocobalamin, 0.4 mg/d), and vitamin B6 (pyridoxine hydrochloride, 10 mg/d)	79	281	61.8±11.0	Placebo	82
Righetti, 2003. [14]	Italy	81	12	No	51	64±2	Folic acid (5 or 15 mg/d)	45	30	64±3	Regular treatment	43
Toole, 2004. [24]	USA	3680	24	Yes	1827	66.4±10.8	Folic acid (2.5 mg/d), vitamin B12 (0.4 mg/d), and vitamin B6 (25 mg/d)	62	1853	66.2±10.8	Folic acid (0.02 mg/d), vitamin B12 (6 micro g/d), and vitamin B6 (0.2 mg/d)	62
Wrone, 2004. [25]	USA	510	24	Yes	342	59.5±15.4	Folic acid (5 or 15 mg/d)	50	168	61.3±14.6	Folic acid (1mg/d),	50
Liem, 2005. [15]	The Netherlands	593	42	No	300	NA	Folic acid (0.5 mg/d)	NA	293	NA	Regular treatment	NA
Zoungas, 2006. [16]	Australia	315	43	Yes	156	56±13	Folic acid (15 mg/d)	73	159	56±14	Placebo	63
Bonaa, 2006. [7]	Norway	2815	36	No	1872	63.2±11.7	Folic acid (0.8 mg/d), vitamin B12 (0.4 mg/d), and vitamin B6 (40 mg/d)	73	943	62.6±11.4	Placebo	75
Lonn, 2006. [8]	Canada	5522	60	Yes	2758	68.8±7.1	Folic acid (2.5 mg/d), vitamin B12 (1 mg/d), and vitamin B6 (50 mg/d)	71	2764	68.9±6.8	Placebo	71
Righetti, 2006. [12]	Italy	88	29	No	37	63.9±1.6	Folic acid (5 mg/d)	65	51	65.1±1.9	Regular treatment	49
Jamison, 2007. [6]	USA	2056	38	Yes	1032	65.4±12.0	Folic acid (40 mg/d), vitamin B12 (2 mg/d), and vitamin B6 (100 mg/d)	98	1024	66.2±11.5	Placebo	98
Heijer, 2007. [17]	The Netherlands	701	36	No	353	NA	Folic acid (5 mg/d), vitamin B12 (0.4 mg/d), and vitamin B6 (50 mg/d)	52	348	NA	Placebo	51
Albert, 2008. [13]	USA	5442	87	Yes	2721	62.8±8.8	Folic acid (2.5 mg/d), vitamin B12 (1 mg/d), and vitamin B6 (50 mg/d)	NA	2721	62.8±8.8	Placebo	NA
Mann, 2008. [10]	Canada	619	60	Yes	307	72.2±6.6	Folic acid (2.5 mg/d), vitamin B12 (1 mg/d), and vitamin B6 (50 mg/d)	67	312	72.2±6.5	Placebo	66
Ebbing, 2008. [9]	Norway	2319	38	No	1540	61.4±10.1	Folic acid (0.8 mg/d), vitamin B12 (0.4 mg/d), and vitamin B6 (40 mg/d)	80	779	62.0±9.9	Placebo	77
Armitage, 2010. [11]	The United Kingdom	12064	80	No	6033	NA	Folic acid (2 mg/d), vitamin B12 (1 mg/d)	83	6031	NA	Placebo	83

Table 2. Jadad scoring items of each eligible study for meta-analysis

Study	Was the study randomized?	Was the randomization method described and appropriate?	Was the study described as double-blind?	Was the method of blinding described and appropriate?	Was there a description of withdrawals and dropouts?	Jadad scores
Schnyder, 2002.	Yes	NA	Yes	Yes	Yes	4
Righetti, 2003.	Yes	Yes	No	No	Yes	3
Toole, 2004.	Yes	Yes	Yes	Yes	Yes	5
Wrone, 2004.	Yes	Yes	Yes	Yes	Yes	5
Liem, 2005.	Yes	Yes	No	No	Yes	3
Zoungas, 2006.	Yes	NA	Yes	Yes	Yes	4
Bonaa, 2006.	Yes	Yes	Yes	Yes	Yes	5
Lonn, 2006.	Yes	Yes	Yes	Yes	Yes	5
Righetti, 2006.	Yes	Yes	No	No	Yes	3
Jamison, 2007.	Yes	NA	Yes	Yes	Yes	4
Heijer, 2007	Yes	Yes	Yes	NA	Yes	4
Albert, 2008.	Yes	Yes	Yes	Yes	Yes	5
Mann, 2008.	Yes	Yes	Yes	NA	Yes	4
Ebbing, 2008.	Yes	Yes	Yes	NA	Yes	4
Armitage, 2010.	Yes	Yes	Yes	Yes	Yes	5

Table 3. Pooled odds ratios for experimental group versus control group in meta-analyses

Subgroups	No. of studies	Random model			Test of heterogeneity			Egger's test for publication bias	
		OR (95% CI)	*Z*	*P* value	Q	*P* value	I^2 (%)	*t*	*P* value
Overall effects	15	1.01 (0.96, 1.06)	0.28	0.78	16.74	0.27	16.4	-1.80	0.09
Sample size									
More than 1000	7	1.02 (0.97, 1.08)	0.80	0.42	3.78	0.71	0.0	0.33	0.75
Less than or equal to 1000	8	0.87 (0.73, 1.03)	1.62	0.11	9.79	0.20	28.5	-1.11	0.31
Mean duration of follow-up									
More than 36 months	8	1.02 (0.96, 1.08)	0.58	0.56	5.7	0.58	0.0	-0.44	0.68
Less than or equal to 36 months	7	0.97 (0.86, 1.09)	0.58	0.56	10.45	0.11	42.6	-1.69	0.15
Folic acid food reinforcement									
Yes	7	0.99 (0.92, 1.07)	0.21	0.83	3.88	0.69	0.0	0.93	0.39
No	8	1.02 (0.95, 1.09)	0.58	0.56	12.55	0.08	44.2	-2.44	0.05

$P > 0.05$) in studies with folic acid food reinforcement; and 1.02 (95% *CI* = 0.95~1.09, $P > 0.05$) in studies without folic acid food reinforcement, respectively.

Evaluation of publication bias analysis

The Egger's linear regression test (**Table 3**) showed no publication bias existing in our study ($P > 0.05$).

Discussion

Many studies [8, 10-12, 16, 17] reported the comparison of effect between B vitamins supplementation and adverse cardiovascular events. Nevertheless, the studies indicate different consequences due to low statistical power or small sample size. To explore and signify the association, we performed a meta-analysis of 15 studies which includes 37,358 objects of study (experimental group: 19601; control group: 17757). The meta-analysis showed the pooled *OR* was 1.01 (95% *CI* = 0.96~1.06, P > 0.05) for objects with B vitamins supplementation vs. Placebo, which suggested no significant differences were found in the overall effect of the number of cardiovascular events between the two groups. Further stratification of subgroup analysis indicates no significant differences between the two groups as well.

Observational studies have demonstrated that the concentration of total homocysteine in blood is associated with risk of coronary artery disease (CAD) and stroke [26]. Clinicians and trialists have difficulty with identifying which

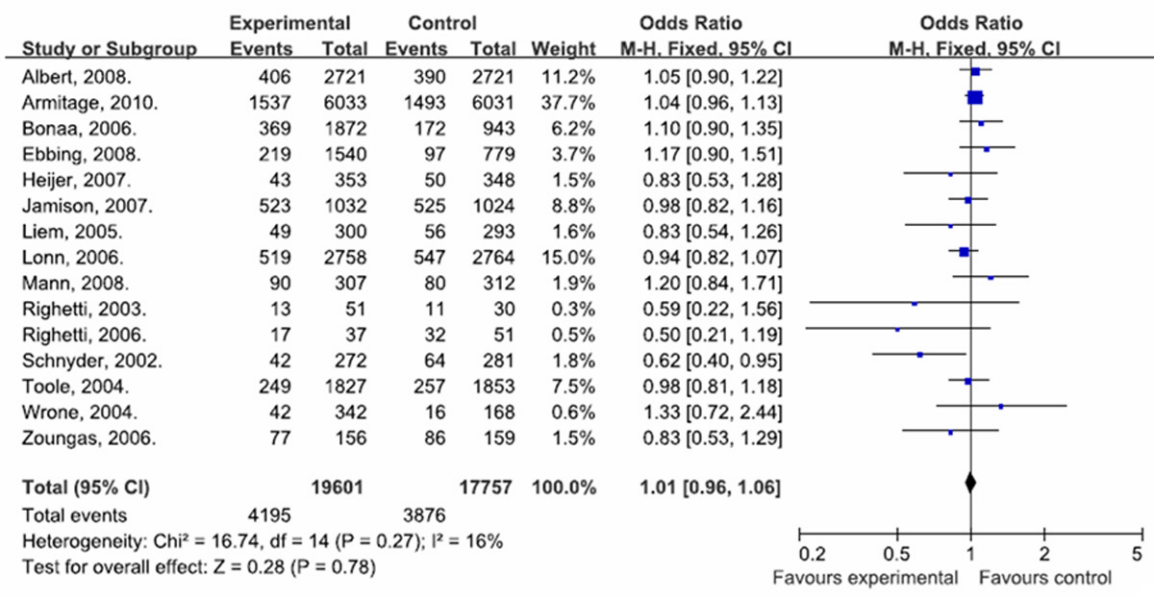

Figure 2. Forest plot of cardiovascular events with experimental group vs. control group.

patients is highest risk for cardiovascular events [5]. Study suggested that serum homocysteine level would be associated with cardiovascular events, which predicts that patients would happen adverse cardiac events with the serum homocysteine level [23], thus high serum total homocysteine in the body should be considered as a risk factor for cardiovascular events in human [25]. Because plasma total homocysteine levels can be easily lowered by oral administration of folic acid, trials to investigate whether cardiovascular disease could be prevented by such homocysteine-lowering therapy were called for [26].

Several limitations of this study should be discussed. Firstly, the sample size of some recruited studies were small [15], more high-quality studies is needed to test and verify the association of adverse cardiovascular events with B vitamins supplementation. Therefore, we performed earnest study for all-published reports and used explicit means for research selection, data extraction and analysis.

Conclusions

Our study indicates that the number of cardiovascular events in experimental group with B vitamins supplementation during the treatment is equal to placebo or regular treatment group. Thus, further studies are necessary.

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Disclosure of conflict of interest

The authors have declared that no competing interests exist.

Address correspondence to: Zi-Cheng Li, Department of Cardiovascular Medicine, The First Affiliated Hospital of Jinan University, Guangzhou 510630, China. Tel: +086-020-38688967; E-mail: 1099293158@qq.com

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