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叶酸联合维生素B补充剂与老年心血管疾病患者预后及全因死亡率相关性META分析

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摘　要

背景：在观察性研究中，同型半胱氨酸水平降低，冠心病和中风发病率也相应降低。叶酸、维生素B6和B12可使同型半胱氨酸水平降低。本文目的旨在研究补充剂能否降低心血管疾病患者发生死亡事件的风险及改善预后。方法：我们对前瞻性研究进行了系统回顾和荟萃分析，以阐明叶酸、维生素B补充与老年心血管疾病患者预后及死亡率之间的关系。本文将“室性心律失常”“心室颤动”“心源性猝死”等作为检索词，通过Pubmed、Cochrane library、Embase、CNKI、万方数据库进行检索，对所有检索到的随机对照试验进行质量评估，Meta分析通过ReviewManger5.3统计软件进行。结果：共纳入8项符合入选标准的随机对照试验(RCT)，试验组(服用叶酸及维生素B)患者共计11840例，对照组(服用安慰剂)患者共计15913例，将心源性猝死及其他原因致死的发生率作为观察的重点事件。Meta分析结果显示，服用叶酸及维生素B的试验组与对照组比较在预防心源性猝死方面无显著性差异(OR = 1.04, 95% CI 0.94~1.16, P = 0.46)；服用叶酸及维生素B的试验组在与对照组的全因死亡率无显著性差异(OR = 1.04, 95% CI 0.95~1.15, P = 0.38)。结论：虽然叶酸和维生素B6摄入与冠心病风险呈线性负相关，但在老年人群中，叶酸和维生素B的补偿并不能减少心源性猝死及其他原因致死的发生。分析结果不支持使用维生素B作为冠心病患者预防心源性猝死及其他原因致死的有效措施。

关键词

心脏性猝死(SCD)，心血管疾病，叶酸，维生素B6，Meta分析

Folic Acid plus B Vitamin Supplementation on Prognosis and All-Cause Mortality in Older Patients with Cardiovascular Disease: A Meta Analysis

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Abstract

Background: In observational studies, the lower the level of homocysteine, the lower the incidence of coronary heart disease and stroke. Folate, vitamin B6 and B12 can reduce the level of homocysteine. The purpose of this paper is to investigate whether supplements can reduce the risk of mortality events and improve outcomes in patients with cardiovascular diseases. Methods: A systematic review and meta-analysis of prospective studies were conducted to clarify the relationship between folic acid and vitamin B supplements and the prognosis and mortality of elderly patients with cardiovascular disease. "Ventricular arrhythmia", "ventricular fibrillation", "sudden cardiac death", were used as search terms and searched through Pubmed, Cochrane library, Embase, CNKI, Wanfang database. After the quality of the retrieved RCTs was evaluated, Meta-analysis was conducted using ReviewManger5.3 statistical software. Results: A total of 8 randomized controlled trials (RCT) meeting the inclusion criteria, 11840 patients in test group (taking folic acid and vitamin B) and 15913 patients in control group (taking placebo) were included. The end event was the incidence of sudden cardiac death and other causes. Meta analysis showed that there was no significant difference between the test group and the control group in sudden cardiac death (OR = 1.04, 95% CI 0.94~1.16, P = 0.46) and all-cause mortality (OR = 1.04, 95% CI 0.95~1.15, P = 0.38). Conclusion: Although folate and vitamin B6 intake are linearly inverse associated with coronary heart disease risk, compensation of folate and vitamin B does not reduce the occurrence of sudden cardiac death and other causes in the elderly population. The results of the analysis do not support the use of vitamin B as an effective measure to prevent sudden cardiac death and other causes in patients with coronary heart disease.

Keywords

Sudden Cardiac Death (SCD), Cardiovascular Disease, Folic Acid, Vitamin B6, Meta Analysis

1. 引言

心源性猝死(SCD)可能在症状发作后瞬间发生，没有典型的警告信号，因此留给任何类型的医疗干预的时间都非常有限[1]。由于广泛的公共健康影响，预防仍然是降低一般人群中 SCD 风险的最可行的方法[2]。

同型半胱氨酸(Homocysteine Hcy)是甲硫氨酸－半胱氨酸途径的代谢中间产物，是一种含硫的兴奋性氨基酸。在病理条件下，如营养(B 族维生素/叶酸)缺乏、高膳食蛋氨酸、参与 Hcy 代谢的酶的遗传多态性或肾脏疾病，Hcy 在循环中积累，产生高同型半胱氨酸血症(Hyperhomocysteinemia HHcy)，这是一种与心律失常和心脏性猝死(SCD)相关的疾病[3]。最近一项动物研究揭示了血浆 Hcy 升高的小鼠的异常传导。观察到接近 500 lsec 的长时间心搏停止、P 波下降、QTc 间期延长以及其他心电图异常[4]。证据[5] [6]

[7] [8]表明，循环中兴奋性氨基酸的病理性增加，可能增加心脏特殊传导系统中的钙渗透性离子通道的活性，特别是在窦房结和房室结中，缩短传导时间，并潜在地为室上性和室性快速性心律失常的发生创造底物。

很多研究表明，对于心血管疾病来说，同型半胱氨酸可能是一个可以改变的危险因素。实验研究证实同型半胱氨酸会引起氧化应激，损伤内皮细胞，从而促使血栓形成[9]。流行病学研究表明，同型半胱氨酸水平与心血管风险之间存在着独立的分级关联[10] [11] [12]。观察数据表明，即使轻度到中度的同型半胱氨酸升高，也会增加心血管疾病罹患风险；这一观察[11]结果很重要，因为这种增加很常见，并且可以通过安全且廉价的治疗轻松纠正。同型半胱氨酸中最重要的饮食决定因素是叶酸；每日补充 0.5~5.0 毫克叶酸，通常可使血浆同型半胱氨酸水平降低 25%左右[13]。每天补充至少 0.4 毫克的维生素 B12 可进一步降低约 7%的水平，补充维生素 B6 在蛋氨酸负荷后降低同型半胱氨酸方面可能特别重要。

病例对照研究和前瞻性研究[14] [15]表明，血浆总同型半胱氨酸水平是冠心病(CHD)和脑卒中强有力的、分级且独立的危险因子。来自所谓孟德尔随机化研究的证据，证明 CHD 与 677C→T 亚甲基四氢叶酸还原酶多态性之间存在关联，为同型半胱氨酸与冠心病之间的因果关系提供了证据支持[16] [17]。通过补充 B 族维生素叶酸和维生素 B12，可降低血浆总同型半胱氨酸水平[12]，血浆水平高或膳食摄入叶酸和维生素 B6 的人患冠心病的风险降低[18] [19] [20]。在美国，通过用叶酸强化食物来降低总同型半胱氨酸的人口平均水平[21]据估计每年可防止 17000 人死于冠状动脉疾病[22]，并且有人建议将叶酸加入复方药丸中，作为预防心血管疾病的一种手段[23]。与基于流行病学证据的预期相反，一项大型随机试验[24]发现，使用 B 族维生素降低总同型半胱氨酸水平无法预防近期中风患者的复发性中风、心肌梗死或死亡。然而，事后疗效分析表明，试验中的一大群参与者可能受益于 B 族维生素治疗。因此本文旨在研究补充剂能否降低心血管疾病患者发生死亡事件的风险及改善预后。

2. 材料与方法

2.1. 文献检索

通过计算机检索 Pubmed、Embase、Cochrane library、CNKI、万方数据库，检索时间范围均从建库至 2022 年 3 月份。检索有关叶酸联合维生素 B 补充预防或干预心源性猝死的随机对照试验(RCT)。英文检索词为“Ventricular tachycardia”“ventricular fibrillation”“folic acid ”“vitamin B6”“vitamin B12”“Sudden cardiac death”，中文检索词为“心源性猝死”“叶酸”“维生素 B6”“维生素 B12”。

2.2. 文献纳入和排除标准

纳入标准：1) 比较服用叶酸、维生素 B6 和维生素 B12 的试验组与安慰剂的结果；2) 随机双盲设计；3) 存在对照组(安慰剂对照组或活性对照组)；4) 主要终点为心脏性猝死或其他原因死亡者；5) 至少随访 24 个周。排除标准：1) 心血管疾病诊断不明确、无法或不愿遵守研究治疗；2) 具有重复数据的研究；3) 研究数据不完整；4) 确定为同一作者或同一机构在重叠时期发表的研究。在重复数据的情况下，只选择包含相关变量的患者人数较多的研究。

2.3. 文献质量评价

所有纳入的文献均按照改良的 Jadad 评分量表标准进行方法学质量评价[25]，该量表以内部效度为中心。Jadad 评分项目包括四部分：随机化、盲法、分配隐藏以及退出或失访。其中评分标准认定：高质量文献 4~7 分，低质量文献 1~3 分。由两名独立评审员进行了评估，并咨询第三名研究人员以解决可能存在的分歧。

2.4. 数据提取

筛选符合条件的研究进行全面审查。如果研究中未报告相关变量结果(心律失常终点)，我们在ClinicalTrials.gov 上搜索补充材料和相关研究的结果(不良事件)部分。由两名研究人员独立进行数据搜索和研究。对于文章存在的分歧，经与作者沟通并达成一致后得以解决。

2.5. 统计学方法

用 ReviewManger5.4.1 统计软件进行数据分析。用固定效应模型预测所测结果的低异质性，当发现显著异质性时，使用随机效应模型。优势比(OR)和 95%置信区间(CI)作为效应大小的度量。如果 $P < 0.05$ 认为差异有统计学意义。

3. 结果

3.1. 文献的检索和筛选

在计算机人工搜索中共选出 1350 项研究。其中有 56 篇因重复而被删除。在审阅了标题和摘要之后，1016 项研究被排除在外，对剩余的 278 项研究进行全文分析。其中 52 项研究不包含结局指标，218 篇文章诊断标准不一致，最终纳入符合入选标准的 RCT 共 8 篇。

3.2. 纳入文献的基本特征

研究人群的平均年龄在 59.8 至 68.9 岁之间；女性的比例从 17%到 100%。心肌梗死的发病率在 4 个试验[24] [26] [27] [28] (7, 8, 14, 15)中<40%，在 3 个试验[29] [30] [31] (9, 11~13)中>40%。中位随访时间为 52.2 个月(范围：18~87.6 个月)。该随机对照试验中，共有 6 项[24] [26] [27] [29] [30] [31]均报告 SCD 和心脏死亡，有 8 项[24] [26]-[32]报告全因死亡。纳入文献的基本特征见表 1。

Table 1. The basic characteristics of the included literature
表 1. 纳入文献基本特征

纳入研究	干预措施(T 组/C 组) (mg/d)	样本量(T 组/C 组，例)	平均年龄 (T 组/C 组，岁)		研究类型	随访时间(月)	结局指标
Armitage, 2010	叶酸 2，维生素 B12 1，Qd/安慰剂	6033/6031	59.8	59.8	RCT	72	①②
Albert, 2008	叶酸 2.5，维生素 B6 50，维生素 B12 1，Qd/安慰剂	2721/2721	62.8 ± 8.8	62.8 ± 8.8	RCT	87.6	①②
Bønaa, 2006	叶酸 0.8，维生素 B6 40，维生素 B12 0.4，Qd/安慰剂	937/943	63.6 ± 11.9	62.6 ± 11.4	RCT	36	①
Toole, 2004	叶酸 2.5，维生素 B6 25，维生素 B12 0.4，Qd/安慰剂	1827/1853	66.2 ± 10.8	66.4 ± 10.8	RCT	24	①
Lonn, 2006	叶酸 2.5，维生素 B6 50，维生素 B12 1，Qd/安慰剂	2758/2764	68.8 ± 7.1	68.9 ± 6.8	RCT	60	①
Wang, 2014	叶酸 0.4，维生素 B6 2，维生素 B12 0.01，Qd/安慰剂	195/195	66.7 ± 4.5	66.8 ± 4.2	RCT	18	②
Ebbing, 2008	叶酸 0.8，维生素 B6 40，维生素 B12 0.4，Qd/安慰剂	772/780	61.7 ± 10.3	62.0 ± 9.9	RCT	48	②
Galan P, 2010	叶酸 0.56，维生素 B6 3，维生素 B12 0.02，Qd/安慰剂	620/626	60.7 ± 8.0	60.9 ± 7.2	RCT	56.4	①②

注：T 组为试验组，C 组为对照组；RCT：随机对照试验；PCS：前瞻性队列研究：① 心源性猝死率，② 全因死亡率。

3.3. 纳入文献的质量评估

依据 Jadad 评分标准，各纳入文献的质量评分结果见表 2。

Table 2. The quality assessment results of included RCTs
表 2. 纳入 RCT 的质量评估结果

作者	发表时间/年	随机化	盲法	分配隐藏	失访	Jadad 评分/分
Albert CM	**2008**	1	2	1	1	5
Bønaa KH	**2006**	2	2	2	1	7
Ebbing M	**2008**	1	2	1	1	5
Galan P	**2010**	2	2	2	1	7
Lonn E	**2006**	2	2	2	1	7
Stott DJ	**2005**	2	2	2	1	7
Toole JF	**2004**	1	1	1	1	4
Wang L	**2015**	2	2	2	1	7

3.4. Meta 分析结果

对六项试验的荟萃分析结果显示，口服补充叶酸、维生素 B6 和维生素 B16 在预防心源性猝死方面的试验结果之间没有显著差异，(OR = 1.04, 95% CI 0.94~1.16, P = 0.46)。异质性检验 I_2 = 22%，P = 0.27，因此，采用随机效应模型对各项指标进行合并分析。结果如图 1 所示。

对八项试验进行荟萃分析结果显示，口服补充叶酸、维生素 B6 和维生素 B12 的补偿的试验组与对照组在全因死亡方面试验结果之间没有显著差异，(OR = 1.04, 95% CI 0.95~1.15, P = 0.38)。异质性检验 I_2 = 35%，P = 0.15，因此，采用随机效应模型对各项指标进行合并分析。结果如图 2 所示。

对二项试验进行荟萃分析结果显示，口服补充叶酸和维生素 B12 的补偿的试验组与对照组在全因死亡方面试验结果之间没有显著差异，(OR = 1.02, 95% CI 0.74~1.41, P = 0.89)。异质性检验 I_2 = 34%，P = 0.22，因此，采用随机效应模型对各项指标进行合并分析。结果如图 3 所示。

对二项试验进行荟萃分析结果显示，单独口服补充维生素 B6 补偿的试验组与对照组在全因死亡方面试验结果之间没有显著差异，(OR = 1.02, 95% CI 0.80~1.30, P = 0.88)。异质性检验 I_2 = 0%，P = 0.73，因此，采用随机效应模型对各项指标进行合并分析。结果如图 4 所示。

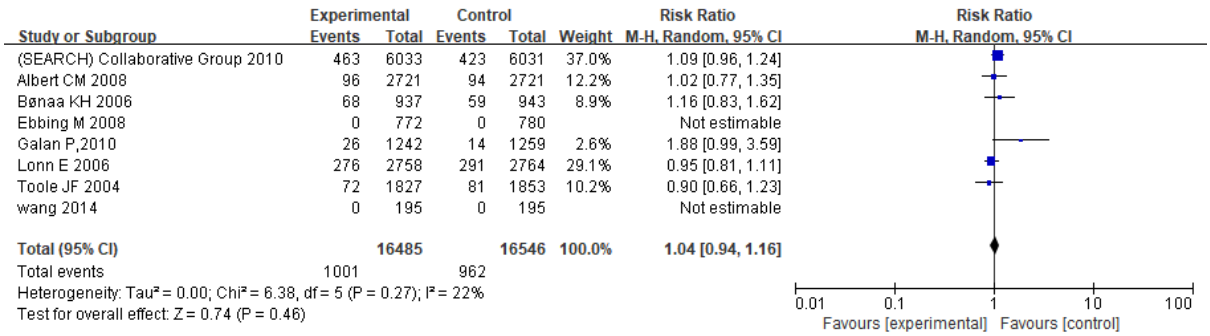

Figure 1. Meta-analysis of the incidence of sudden cardiac death in the trial group compared to the control group
图 1. 试验组与对照组心源性猝死的发生率比较的 Meta 分析

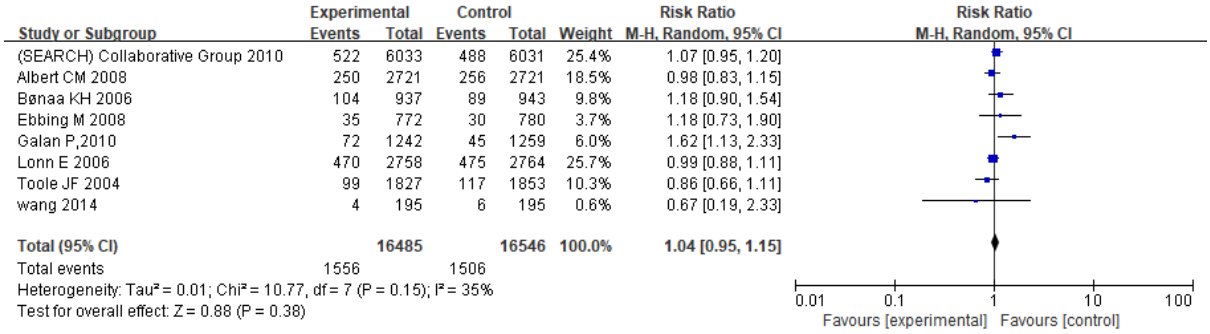

Figure 2. Meta-analysis of all-cause mortality outcomes in the experimental group (folic acid plus vitamin B6, vitamin B12) and the control group
图 2. 试验组(叶酸联合维生素 B6、维生素 B12)与对照组全因死亡率结果的荟萃分析

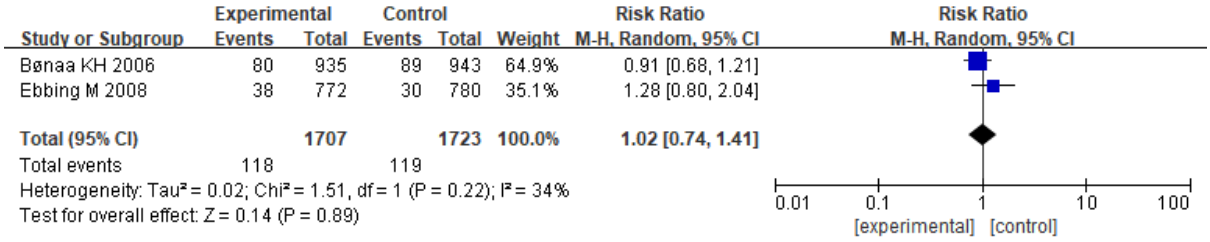

Figure 3. Meta-analysis of all-cause mortality outcomes in the experimental group (folic acid plus vitamin B12) and the control group
图 3. 试验组(叶酸联合维生素 B12)与对照组全因死亡率结果的荟萃分析

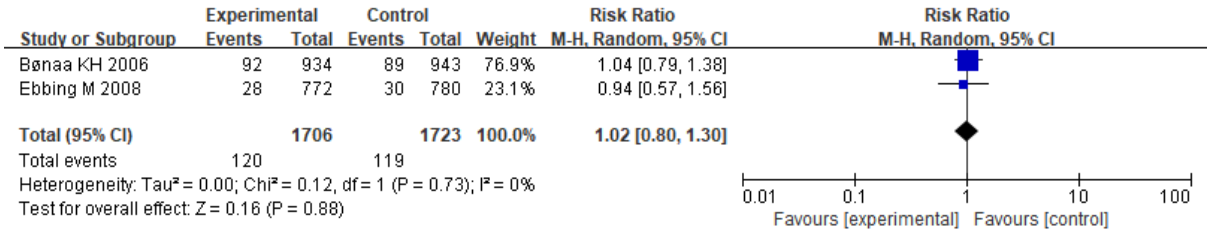

Figure 4. Meta-analysis of all-cause mortality outcomes in the experimental group (vitamin B6) versus the control group
图 4. 试验组(维生素 B6)与对照组全因死亡率结果的荟萃分析

4. 讨论

通过对所收录的 8 项临床试验进行荟萃分析，结果表明服用叶酸、维生素 B6 和维生素 B12 并没有降低患者罹患室性心律失常和发生心源性猝死的风险。纳入的临床研究大多在早期，但随着当代他汀类药物、抗血小板、心力衰竭、心律失常药物以及血管再通和射频消融治疗的逐步发展，使得单纯服用叶酸、维生素 B6 和维生素 B12 预防心源性猝死及其他死亡事件发生概率降低。

相关研究发现，虽然经过叶酸治疗的病人血浆总同型半胱氨酸水平明显降低，但没有发现单独或联合使用叶酸(加上维生素 B12)和维生素 B6 的二次干预可降低近期心肌梗死患者因心血管疾病引起的并发症和死亡风险。与预期相反，出现了一种服用 B 族维生素，尤其是叶酸、维生素 B6 和维生素 B12 的患者的事件发生率增加的趋势。然而不依从性并不是这些负面结果的可能解释，因为高依从率虽然可能被过度报道，但可以通过维生素状态的生化评估得以体现。多项观察性研究结果显示[33]，血浆总同型半胱氨酸水平是预测心血管事件发生的关键因素。但在一般人群[14]以及诊断为心血管疾病的患者[15]中，涉

及降低同型半胱氨酸治疗的干预试验结果并未证实同型半胱氨酸的致病作用。一项大型二级干预试验[24]和三项较小的研究[34] [35]的结果表明，维生素 B 治疗对中风复发或心血管原因引起的并发症和死亡没有影响。在报道的 B 族维生素治疗高危患者的心脏结局预防评估(HOPE) 2 试验中也发现了类似的结果[36]。叶酸联合维生素 B6 可降低接受冠状动脉球囊成形术的患者的再狭窄率[37]，但可增加冠状动脉支架置入术后的再狭窄率。一项研究[38]结果显示接受叶酸加高剂量维生素 B6 治疗的患者事件发生率增加。因此，在心血管疾病患者中使用高剂量 B 族维生素进行的二次干预试验基本上没有显示出效果，这与使用高剂量单一营养素(如维生素 E、C 和 A)预防心脏病的失败效果相似。一些[39] [40] [41] [42]研究证明了功能的改善，但并非所有研究[43] [44] [45] [46] [47]都证明了这一点。

降低同型半胱氨酸治疗在临床上缺乏益处，这表明这种治疗可能具有促进动脉粥样硬化血栓形成的作用。叶酸可能通过独立于同型半胱氨酸的机制影响内皮功能[39]并支持细胞生长[48]。血管平滑肌细胞增殖和基质形成的增加被认为是服用叶酸和维生素 B6 的患者支架内再狭窄风险增加的可能机制[38]。此外，维生素 B6 高水平可能会抑制血管生成[49]。所以高剂量的维生素 B6 对血管重塑、心肌修复都可能带来不良影响，导致心血管疾病患者出现更多并发症，并导致死亡率上升。总之试验证明，叶酸干预以及是否给予大剂量维生素 B6 及维生素 B12，并不能降低急性心肌梗死后心血管疾病复发或死亡的风险。在急性心肌梗死或冠状动脉支架植入术后，这种治疗甚至可能有害，因此不应予以推荐。

另外本研究存在一定局限性，首先，纳入研究的人群在基线特征和共病患病率方面存在异质性。异质性的另一个来源是由于纳入的研究规模不同，从几百到几万个样本不等。因此，在固定效应模型中运行死亡率和住院分析更为现实。其次，一些已完成的研究没有提供足够的数据来分析基线特征和其他终点，包括心血管/非心血管死亡率、心肌梗死住院以及全因死亡率和心肌梗死住院的组合，导致缺乏统计能力。本文仅考虑了可用的关键基线特征，分析中不包括体重指数、慢性肾脏病、慢性阻塞性肺病、贫血等因素。因此，与随机对照试验中治疗良好的人群相比，全因死亡率估计可能更高，并且可能存在时间效应。

综上所述，通过荟萃分析结果显示，叶酸、维生素 B6 和维生素 B12 可能仅对患有高半胱氨酸血症的心肌梗死患者有一定作用，并没有减少心源性猝死等死亡事件的发生。

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