Vitamin Supplementation in Cardiovascular Disease Prevention: A Systematic Review

Naina Bhoyar [1*], Aayush Vaishnaw [1]

Abstract

Background: Cardiovascular diseases (CVD) remain the leading cause of mortality worldwide, contributing to a significant public health burden. While pharmaceutical interventions like statins are effective, the increasing interest in non-pharmaceutical approaches has sparked debates on the role of vitamin supplementation in CVD prevention. Despite some studies suggesting benefits from vitamins with antioxidant properties, evidence remains inconclusive. This review aimed to evaluate the efficacy of various vitamins in reducing CVD risk using a network meta-analysis. Methods: A systematic review and network meta-analysis were conducted on clinical trials investigating vitamin supplementation for CVD prevention. Data were sourced from MEDLINE, Embase, Cochrane, and other databases. Studies were selected based on specific criteria, including randomized controlled trials with at least six months of follow-up and reported CVD outcomes. The primary outcomes included CVD mortality and risk of heart disease, while secondary outcomes focused on stroke and myocardial infarction. A random-effects model was employed to calculate risk ratios (RR), and meta-regression analyses explored the relationship between vitamin use and lipid levels.

Discussion: The analysis revealed that vitamins B, D, and E were particularly effective in reducing CVD risk. However, there was no significant added benefit from combining multiple vitamins over using individual vitamins. While niacin showed potential benefits in reducing stroke and coronary artery disease in statin-intolerant populations, its overall impact on CVD mortality was not significant. Conclusion: This review provides valuable insights into the role of vitamins in CVD prevention, demonstrating that individual vitamins like B, D, and E are effective in reducing risk, while multivitamin combinations offer no additional advantage. The lack of correlation between HDL-C changes and CVD outcomes suggests that future research should focus on other mechanisms beyond lipid management.

Keywords: Cardiovascular disease (CVD), Vitamin supplementation, Antioxidants, Niacin, Meta-analysis

Significance | This review determines the impact of vitamins in CVD prevention, revealing B, D, and E's efficacy while questioning multivitamin use.

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Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality and morbidity worldwide. In the past decade, global mortality due to CVD has risen by 12.5%, making CVD a significant public health concern (Chieng & Kistler, 2022). CVD is associated with high medical costs as patients often require multiple medications for symptom management. While traditional pharmaceutical treatments are effective, the cost burden associated with them has prompted interest in alternative preventive measures, such as the use of vitamin supplements (Ingles, Cruz Rodriguez, & Garcia, 2020).

Vitamin supplements are widely promoted as over-the-counter

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products aimed at preventing or managing various health conditions, including CVD. Epidemiological studies have produced mixed results on the efficacy of vitamin supplementation in reducing the risk of CVD. Some studies suggest that certain vitamins, particularly those with antioxidant properties, help modulate enzymes and reduce Low-Density Lipoprotein Cholesterol (LDL-C), potentially lowering the risk of CVD (Zhang et al., 2021). However, other research findings indicate that excessive vitamin consumption provides no significant protective effect against CVD, leading to unnecessary healthcare expenditures (Camgözlü & Kutlu, 2023). This discrepancy in findings has fueled ongoing debate about the efficacy of specific vitamins in preventing CVD.

Various vitamins have been examined for their potential role in CVD prevention, including vitamins A, B, C, D, and E, as well as folic acid and beta-carotene (Ingles et al., 2020). These vitamins are believed to exert positive effects on cardiovascular health through mechanisms such as antioxidant activity and cholesterol modulation. However, while some research supports the use of these vitamins in reducing CVD risk, other studies have found no conclusive benefit. The controversy extends to whether a multivitamin approach is more effective than using individual vitamin supplements (Loftfield et al., 2024).

One tool that can help resolve these inconsistencies is network meta-analysis. Unlike traditional head-to-head meta-analysis, network meta-analysis allows researchers to compare multiple treatments simultaneously, providing a comprehensive ranking of all available therapies (Jairath et al., 2021). By integrating data from various studies, network meta-analysis offers a more robust evaluation of vitamin treatments for CVD prevention.

This review aimed to perform a network meta-analysis to systematically assess the effectiveness of different vitamin supplements in reducing the risk of CVD. The primary outcomes assessed were the prevalence of CVD and mortality rates, while secondary outcomes included the incidence of stroke and myocardial infarction. By comparing various vitamin treatments, this review sought to provide a clearer understanding of their potential role in CVD prevention.

Despite the widespread use of vitamin supplements, evidence regarding their efficacy in CVD prevention remains inconclusive. While some vitamins may offer protective benefits, excessive or inappropriate use may not yield the desired results and could contribute to unnecessary healthcare costs. This review will explore the available evidence to determine which, if any, vitamins provide significant protective effects against CVD, with the goal of informing future clinical recommendations.

2. Methodology

The data collection for this review occurred from October 2023 to March 2024. The research aimed to identify clinical studies examining the impact of niacin treatment on cardiovascular disease (CVD) risk, selecting trials suitable for meta-analysis of the effects of niacin on CVD health and meta-regression studies analyzing the relationship between changes in high-density lipoprotein cholesterol (HDL-C) levels and CVD morbidity and mortality (Surendar et al., 2024). Due to the absence of initial data collection, the procedure was exempt from institutional review board approval, and informed consent was unnecessary. Data analysis was conducted in March 2024, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for reporting (O'Dea et al., 2021).

2.1 Systematic Review

A comprehensive search of databases, including MEDLINE, Embase, Cochrane Controlled Trials Register, ClinicalTrials.gov, and TrialResults-center, was performed to identify clinical trials investigating niacin as a treatment for CVD up until October 2023. The search used terms such as niacin, nicotinic acids, Niaspan, coronary heart diseases, and lipid disorders (Lavanya et al., 2024). Publications in English, Italian, and Spanish were included based on the language proficiency of the researchers involved in this review study. Duplicate entries were independently removed by three reviewers who screened titles and abstracts to identify relevant studies (Begum, 2022). Any discrepancies were resolved through discussion or, if needed, by the entire author team. Data on authors, publication year, drug exposure duration, sample size, and outcomes were collected, classifying studies into those assessing surrogate markers and those reporting clinical CVD outcomes.

2.2 Meta-Analysis

To conduct the meta-analysis, studies were selected based on randomized allocation, control groups with niacin treatment, follow-up periods of at least six months, and reported outcomes related to CVD death or other events, such as revascularization and cerebrovascular incidents (Xue et al., 2021). Data included trial characteristics such as blinding, treatment dosages, and participant demographics (Satish & Herald, 2024). A random-effects model was used to calculate the Risk Ratio (RR), and sensitivity analyses examined the impact of bias risk by removing trials with high or unclear bias (Andrade, 2023). Heterogeneity was assessed using a leave-one-out method, and trials with no events in both arms were excluded from the analysis.

2.3 Meta-Regression Analysis

Studies that did not provide HDL-C values were excluded from the meta-regression analysis. A weighted random-effects meta-regression was conducted to evaluate the relationship between changes in HDL-C levels and the logarithmic RR of CVD events (Andrade, 2023). The analysis considered various covariates, including changes in LDL-C concentrations and participant

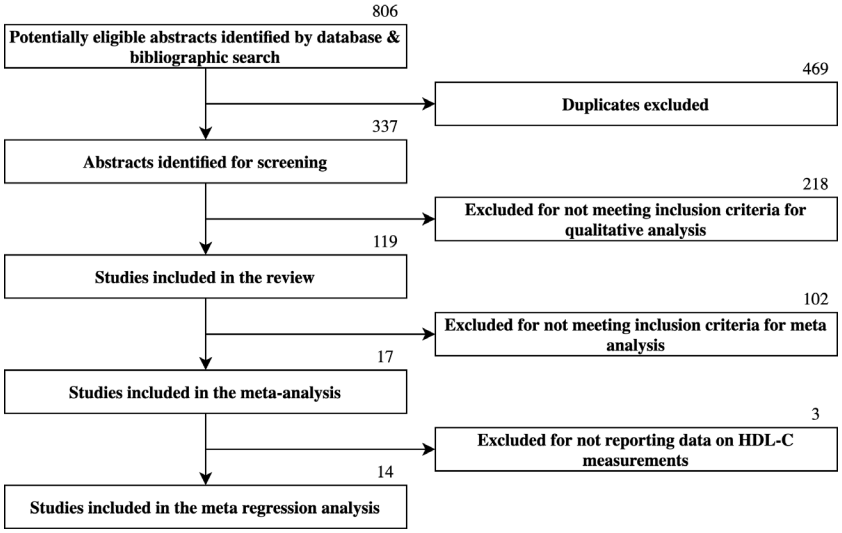

Figure 1. This systematic process of selecting and analyzing 119 clinical trials for evaluating niacin's effects on cardiovascular disease (CVD) outcomes. Seventeen trials specifically investigated the impact of niacin on CVD, while the remaining 102 studies utilized surrogate markers, such as changes in HDL-C, LDL-C, or triglycerides. Among the 17 CVD-focused studies, six considered CVD events as primary endpoints, and 87 trials focused on dyslipidemia. Additionally, 26 studies examined coronary artery disease (CAD) and atherosclerosis, and six addressed hybrid populations with additional conditions. This workflow highlights the selection and categorization of studies in the meta-analysis.

subgroups, comparing the percentage change in HDL-C levels with the overall effect of niacin treatment on CVD outcomes.

2.4 Data Selection

A comprehensive search of PubMed, MEDLINE, Embase, and the Cochrane databases was conducted to identify relevant Randomized Controlled Trials (RCTs) from the inception of these databases (Eichler et al. 2021). The goal was to assess the effectiveness of vitamin supplements in preventing cardiovascular diseases (CVD). The search strategy focused on studies evaluating the impact of various vitamins, including A, B, C, D, E, folic acid, beta-carotene, and lycopene, on CVD outcomes such as heart disease, angina, myocardial infarction, and stroke. Cross-referencing with existing meta-analyses and reviews was employed to ensure no studies were overlooked.

2.5 Inclusion Criteria

Inclusion criteria were as follows: RCTs that reported on the effectiveness of vitamin supplements in preventing CVD. The interventions involved oral vitamin supplementation, with varying doses and durations. All studies included recorded total CVD incidence. No restrictions were applied regarding language or publication date.

2.6 Data Extraction and Quality Assessment

Two independent reviewers screened the studies by title and abstract, with full-text evaluations conducted when necessary. Discrepancies were resolved through discussion. The quality of the trials was assessed using the Cochrane Risk of Bias tool, classifying each study as 'low risk,' 'unclear risk,' or 'high risk' in key domains.

2. Discussion

The findings from this meta-analysis provide important insights into the effects of niacin on cardiovascular disease (CVD) outcomes, particularly when compared to other lipid-lowering therapies such as statins. Despite the inclusion of 119 clinical trials, only 17 focused specifically on CVD outcomes, while the majority relied on surrogate measures like changes in HDL-C or LDL-C levels (Figure 1). These results emphasize the complex relationship between niacin therapy and cardiovascular health, raising questions about its clinical utility, particularly in patients who are not receiving statins.

In terms of overall CVD outcomes, the meta-analysis did not show a significant association between niacin and reduced risk of mortality from CVD or coronary artery disease (CAD), nor did it demonstrate a reduction in the incidence of acute coronary events, strokes, or major adverse cardiovascular events. This finding is consistent with previous studies that have questioned the efficacy of niacin as a primary therapy for preventing cardiovascular events, particularly when added to standard care, including statin therapy (Cosentino et al., 2021). It suggests that niacin alone may not be sufficient to reduce the burden of cardiovascular diseases, particularly in populations with established risk factors like atherosclerosis and dyslipidemia.

However, in the subset of patients who were not receiving statins, niacin showed more promising results, particularly in reducing the risk of CAD and stroke. The 27.2% reduction in CAD and 25.2% reduction in stroke risk among these patients highlight a potential role for niacin in statin-intolerant populations or in settings where statin therapy is not indicated (Ingles, Cruz Rodriguez, & Garcia, 2020). This finding supports the notion that while niacin may not provide significant additional benefits when combined with statins, it could serve as an alternative lipid-lowering agent in certain subgroups. It also raises the possibility of niacin's benefit in improving lipid profiles, specifically in patients who cannot tolerate statins due to side effects such as myalgia (Lavanya et al., 2024).

The metaregression analysis added another layer of complexity to the interpretation of niacin's effects by examining the relationship between changes in HDL-C levels and cardiovascular outcomes. Contrary to earlier assumptions that raising HDL-C levels would necessarily translate into improved cardiovascular outcomes, this analysis found no significant correlation between the increase in HDL-C levels and the reduction in cardiovascular events (Zhang et al., 2021). This reinforces growing evidence that simply raising HDL-C may not be enough to reduce cardiovascular risk, and that HDL-C functionality may be more important than its absolute levels (Chieng & Kistler, 2022).

One limitation of this review was the heterogeneity of the included trials, particularly in terms of patient populations, niacin dosages, and review designs. The trials also varied significantly in terms of bias risk, with several showing attrition bias due to missing data. While the meta-analysis attempted to account for these differences using sensitivity analyses and random-effects models, the potential for bias in some studies limits the generalizability of the findings (Jairath et al., 2021). The exclusion of studies focusing on patients with comorbid conditions such as diabetes and chronic kidney disease further limits the applicability of the results to broader populations, as these comorbidities are common among patients with CVD (Loftfield et al., 2024).

As the quality of life improves globally, more patients are opting for non-pharmaceutical treatments, such as exercise, vitamins, and dietary supplements, to maintain health and prevent diseases. Many individuals are increasingly turning to diet and music therapy as complementary approaches for both preventing and recovering from illness. In the context of cardiovascular disease (CVD), numerous clinical trials have investigated the effectiveness of vitamins in reducing CVD risk, though no definitive consensus has been reached regarding their preventive efficacy.

This review focused on two primary aspects of CVD: mortality and heart disease risk. It systematically compared various types of vitamins to assess their overall impact on CVD risk and their

potential role in preventing diseases associated with CVD. The aim was to develop a novel framework for evaluating the need for vitamin supplementation and provide a ranked analysis of different vitamins to help prevent CVD.

One key challenge in assessing vitamin supplementation is the variability in dosage and frequency across studies. Many vitamins are difficult to categorize and evaluate uniformly due to inconsistent administration protocols in the literature. To address this, the review categorized vitamins into ten distinct classes, enabling more accurate comparisons. By explicitly categorizing vitamins, the review mitigated the bias that often arises from the diverse methodologies found in different research studies.

Despite efforts to standardize these comparisons, variations in approach and dosage between studies are inevitable and must be considered. Nonetheless, the network meta-analysis revealed that vitamins B, D, and E were particularly effective in reducing the risk of CVD. However, the analysis also found that combining multiple vitamins did not provide any additional benefit over the use of a single vitamin in preventing CVD.

3. Conclusion

In conclusion, the meta-analysis explored the role of various vitamin supplements in reducing cardiovascular disease (CVD) risk, with a focus on mortality, heart disease, stroke, and myocardial infarction. Findings revealed mixed results regarding the efficacy of vitamins such as A, B, C, D, E, folic acid, and beta-carotene. While some studies indicated benefits, particularly with vitamins B, D, and E, the overall evidence remained inconclusive.

Network meta-analysis ranked vitamin supplements based on their effectiveness, highlighting vitamins B, D, and E as the most promising for CVD prevention. However, combining multiple vitamins did not provide additional benefits over single supplements. Variability in dosage and study methodologies complicated a definitive conclusion. Further research is required to clarify the potential of individual vitamins and provide solid recommendations for CVD prevention.

While it suggests that niacin does not provide additional benefits when added to statin therapy, it highlights a potential role for niacin in statin-intolerant populations. The lack of correlation between HDL-C changes and cardiovascular outcomes also suggests that focusing solely on HDL-C levels may be insufficient, and that future research should explore other lipid-related mechanisms and outcomes. Ultimately, the findings underscore the need for more targeted therapies that can address the complexities of lipid metabolism and cardiovascular disease risk. Vitamin supplementation should be approached cautiously, with attention to dosage and specific health conditions.

Author contributions

NB and AV contributed to conceptualization, fieldwork, data analysis, drafting the original manuscript, editing, funding acquisition, and manuscript review. Both NB and AV were involved in research design, methodology validation, data analysis, visualization, and manuscript review and editing. Additionally, NB took the lead in methodology validation, investigation, funding acquisition, supervision, and final revisions. All authors have reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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