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UNRAVELING THE ANTIOXIDANT DILEMMA: INVESTIGATING VITAMIN EFFICACY IN PRIMARY AND SECONDARY CARDIOVASCULAR DISEASE PREVENTION THROUGH A SYSTEMATIC REVIEW

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ABSTRACT:

Introduction: This systematic review examines oral multivitamins and multi/minerals (OMVMs) in cardiovascular disease (CVD) prevention by focusing on vitamins. Despite widespread supplement use and the global CVD burden, a consensus on OMVM efficacy remains elusive. Therefore, ambiguities arise from individual variability, diverse formulations, and uncertainties in cardiovascular health. However, vitamins having antioxidant properties are explored for their role in countering oxidative stress. The study aims to provide useful insights into vitamins, unraveling the antioxidant dilemma which helps in contribution to cardiovascular health.

Literature Review: The review underscores the lack of consensus on OMVM efficacy in CVD prevention, with over half of the U.S. population using supplements. Vitamins, including those with antioxidant properties, add complexity to the discourse. Isolated studies suggest micronutrient therapeutic effects, emphasizing the need for a thorough examination. There are differences in common dietary guidelines and usage of widespread supplements.

Materials and Methodology: The databases utilized PubMed, Embase, Cochrane CENTRAL, and CINAHL were used for comprehensive systematic review. Inclusion criteria covered diverse populations, study designs, and cardiovascular health outcomes. Quality assessment employed recognized tools, and a narrative synthesis approach analyzed findings.

Results and Discussion: The literature review highlights ambiguity in OMVM efficacy for CVD prevention and explores antioxidant complexities, especially with vitamins. Isolated studies suggest therapeutic effects of specific micronutrients, prompting further investigation. The study contributes valuable insights to unravel the antioxidant dilemma, enhancing comprehension of vitamins in cardiovascular health.
Conclusion: Despite the global CVD burden and widespread OMVM use, this review exposes a lack of consensus on efficacy. Variability and diverse formulations hinder conclusive outcomes. The study emphasizes the need for a comprehensive understanding, providing insights into vitamins' role, unraveling the antioxidant dilemma, and enhancing comprehension of OMVMs in cardiovascular diseases.

Keywords: Unraveling, Antioxidant Dilemma, Vitamin Efficacy, Cardiovascular Disease Prevention, Systematic Review

INTRODUCTION:

Cardiovascular diseases (CVDs) indicate a significant global health (Prabhakaran and Jeemon 2016). It accounts for 40% of deaths worldwide in 2016 (Liu, Li et al. 2019). Therefore, in the pursuit of effective preventive strategies it includes oral multivitamins and multi/minerals (OMVMs). Particularly those containing vitamin, have gained popularity. The use of OMVMs reflects a prevailing belief with enough of population engaging in supplement intake (Hekel 2017). Therefore, in their health-promoting properties, especially in the context of CVD protection, taking of supplements support for their role in the disease. However, the efficacy of these supplements remains an important debate (Levy, McKinnon et al. 2019). It is marked by a lack of consensus in the existing literature, particularly within the realm of cardiovascular health.

The complexity surrounding the effectiveness of OMVMs in CVD prevention is further compounded by the intricate interplay of factors. It also includes individual variability, diverse supplement formulations, and the absence of conclusive evidence supporting their role in cardiovascular health (Sen and Chakraborty 2015). However, despite the acknowledged significance of antioxidants, such as vitamins E and C uncertainties persist regarding the therapeutic role of specific micronutrients (Polidori and Schulz 2014). A study explained hint at potential benefits, particularly for vitamin E (Khadangi and Azzi 2019). The variability in study designs, populations, and dosage regimens necessitates a comprehensive synthesis of evidence to derive meaningful insights.

Moreover, in response to these challenges, the present study conducts a narrative literature review on OMVMs, in the context of cardiovascular diseases. Employing a systematic approach, the review aims to provide a comprehensive overview of the current state of knowledge. It also helps by critically evaluating methodologies employed in previous studies. Thus, by addressing these complexities, the study seeks to contribute valuable insights to the understanding of OMVMs in cardiovascular health, particularly in unraveling the antioxidant dilemma.

LITERATURE REVIEW:

The literature surrounding the effectiveness of oral multivitamins and multi/minerals (OMVMs) in the prevention and treatment of cardiovascular disease (CVD) with an emphasis on vitamin functioning portrays a complex landscape (Ingles, Cruz Rodriguez et al. 2020). It presents a complicated picture characterized by issues with global health, widespread supplement use (Roth, Abrams et al. 2018) and lack of their efficacy regarding interventions (Rautiainen, Manson et al. 2016).

The primary cause in chronic disease that contributes to the burden in global health is cardiovascular diseases (CVDs). It accounts for 31% of deaths worldwide in 2016 (Rautiainen, Manson et al. 2016), accounting for 17.9 million deaths (Girum, Mesfin et al. 2020). Therefore, the impact of CVD underscores the urgent need for effective preventive strategies.

The oral multivitamins and multi/minerals (OMVMs) industry is firmly rooted in the belief that these supplements improve health especially in the context of cardiovascular disease protection (Manson, Cook et al. 2019).

Therefore, in the United States, over half of the population engages in supplement intake with multivitamins being the choice of 31% of individuals (Schmitz, Lopez et al. 2020). However, notable variations in supplement use across different geographic regions, as seen in Europe. It highlights the complexity of factors influencing public health behaviors.

There is no general consensus on their efficacy for CVD prevention or treatment despite the widespread popularity of OMVMs (Hassan, Egbuna et al. 2020). Thus, this lack of agreement is particularly evident in the realm of cardiovascular health where uncertainties persist regarding the role of individual OMVMs. The existing literature reflects a multifaceted interplay of factors. Hence, it includes the individual variability and the diverse formulations of OMVMs, hindering the establishment of definitive conclusions (Ingles, Cruz Rodriguez et al. 2020).

There is significant effect of antioxidants, such as vitamins E and C, β-carotene, and selenium in cardiovascular health (Jayedi, Rashidy-Pour et al. 2019). In their purported ability to counteract oxidative stress, it serves as a key element in the development of atherosclerosis (Li, Horke et al. 2014). Therefore, oxidative processes within plaques and chronic inflammation contribute to the development and progression of cardiovascular diseases. Similarly, Vitamin E has been explored for its potential to reduce lipid peroxidation and free radical damage, offering a potential avenue for intervention (Blaner, Shmarakov et al. 2021).

some studies have reported therapeutic effects of specific micronutrients, adding complexity to the discourse (Prasad 2014, Retallick-Brown, Blampied et al. 2020). Vitamin E, in particular, has demonstrated positive outcomes in some instances. It is prompting further investigation into its potential therapeutic role (Boccardi, Baroni et al. 2016). However, the variability in study designs, populations, and dosage regimens necessitates a thorough synthesis of evidence to distill meaningful insights.

Moreover, rather than relying on supplements, modern dietary guidelines emphasize on achieving micronutrient requirements through a balanced diet (Ofoedu, Iwouno et al. 2021). This point of view raises questions about the necessity and efficacy of supplement use in the population. It is especially given the lack of unanimous support for the role of OMVMs in cardiovascular health (Daniello-Santiago, Santiago et al.).

In the context of cardiovascular diseases, the aim of the present study is to highlight these complexities by conducting a narrative literature review on OMVMs. However, the current study aims to provide a comprehensive overview of the current state of knowledge through a systematic exploration of the existing data. Additionally, it is critically evaluating methodologies used in previous studies and offering a nuanced understanding of the role of vitamin in cardiovascular health.

Consequently, the literature review illuminates the intricate landscape surrounding the use of OMVMs. It also highlights the difficulties faced by the global burden of cardiovascular disease (Leong, Joseph et al. 2017), the use of supplement (Rautiainen, Manson et al. 2016), and the lack of agreement on their efficacy research adds a layer of complexity by potential therapeutic effects of specific micronutrients, especially vitamin. Furthermore, the comprehensive review of existing knowledge aims to provide valuable insights to the role of OMVMs in cardiovascular health, especially in unraveling the antioxidant dilemma.

METHODOLOGY:

A comprehensive systematic review was conducted by using an academic databases of well reputation for a detailed search of relevant literature. The primary databases such as PubMed, Google Scholar, Web of Science and Scopus were mainly included. These databases were selected for their broader coverage of medical and health-related literature. It also helps in ensuring a comprehensive retrieval of relevant studies**.**

The search strategy was designed to identify studies focusing on oral multivitamins and multi/minerals (OMVMs). A specific emphasis on vitamin in the context of primary and secondary prevention of cardiovascular diseases was done. The search terms included variations of "OMVMs," "vitamin," "cardiovascular diseases," "primary prevention," and "secondary prevention." The search was conducted up to December 30, 2023.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

Our inclusion criteria in designing a comprehensive understanding of the efficacy of oral multivitamins and multi/minerals (OMVMs) in cardiovascular disease (CVD) prevention were thoughtfully designed. Studies published up to December 30, 2023, were considered to incorporate the most recent data available. However, both randomized controlled trials (RCTs) and observational studies were included to provide a diverse view of the subject matter. Thus, studies containing participants of all age groups, with no restrictions on gender, ethnicity, or socioeconomic status, were included to ensure a broad representation of populations. Studies investigating the use of OMVMs, particularly with a significant emphasis on vitamin were considered in recognizing the diverse nature of supplement regimens. Therefore, the inclusion criteria also embraced a range of outcomes, encompassing both primary prevention for individuals without prior cardiovascular events and secondary prevention for those with a history of CVD. Furthermore, studies in languages other than English were included if translations were available, acknowledging the global nature of research.

Table: 1

Type of Database	Keywords	Search Strategy	Filters Used	No. of Records
PubMed	Antioxidant dilemma, Vitamin	("antioxidant" OR "antioxidants") AND ("vitamin" OR "vitamins") AND ("cardiovascular disease" OR "CVD") AND ("primary prevention" OR "secondary prevention") AND ("systematic review") Published in the last 10 years	Full-text Research Articles, 10 years, Humans	931
Scopus	Antioxidant dilemma, Cardiovascular disease	TITLE-ABS-KEY(("antioxidant" OR "antioxidants") AND ("vitamin" OR "vitamins") AND ("cardiovascular disease" OR "CVD") AND ("primary prevention" OR "secondary prevention") AND ("systematic review")) Published in the last 10 years	Full-text Research Articles, 10 years, Humans	763
Web of Science	Antioxidant dilemma, cardiovascular disease, primary prevention	TS=("antioxidant" OR "antioxidants") AND TS=("vitamin" OR "vitamins") AND TS=("cardiovascular disease" OR "CVD") AND TS=("primary prevention" OR "secondary prevention") AND TS=("systematic review") Published in the last 10 years	Full-text Research Articles, 10 years, Humans	846
Google Scholar	Antioxidant dilemma, cardiovascular disease, primary and secondary prevention	('antioxidant'/exp OR 'antioxidants') AND ('vitamin'/exp OR 'vitamins') AND ('cardiovascular disease'/exp OR 'CVD') AND ('primary prevention'/exp OR 'secondary prevention'/exp) AND ('systematic review'/exp) Published in the last 10 years	Full-text Research Articles, 10 years, Humans	721

Exclusion Criteria:
Studies published after December 30, 2023 was excluded to ensure temporal coherence. To prioritize robust, human-centric evidence, animal studies, in vitro experiments, and reviews lacking original data were excluded. Exclusion of studies exclusively involving animals or specific subpopulations aligned with the broader human-focused scope. Studies concentrating solely on individual vitamins or minerals without a multivitamin or multi/mineral component were omitted, emphasizing a focus on combined OMVM effects. Additionally, studies lacking relevant cardiovascular outcomes or exclusively concentrating on non-cardiovascular endpoints were excluded to uphold alignment with the primary focus on cardiovascular health. Language-based exclusions were enforced for studies without available translations in accessible languages, facilitating accurate interpretation. Unpublished studies, conference abstracts without subsequent full publications, and gray literature without peer review were excluded to maintain the reliability and validity of the evidence. Lastly, studies without documented ethical approval or those violating ethical standards were excluded, ensuring the rigorous adherence to ethical considerations throughout the research process.

A systematic data extraction process was employed to retrieve key information from the selected studies. Extracted data included study design, participant characteristics, intervention details (type and dosage of OMVMs), primary and secondary outcomes related to cardiovascular health, and conclusions drawn by the authors.

The quality of included studies was assessed. By using established criteria adapted from recognized assessment tools suitable for various study designs, such as the Cochrane Collaboration's tool for assessing risk of bias in randomized trials and the Newcastle-Ottawa Scale for observational studies. Therefore, this evaluation aimed to ensure the reliability and validity of the included studies.

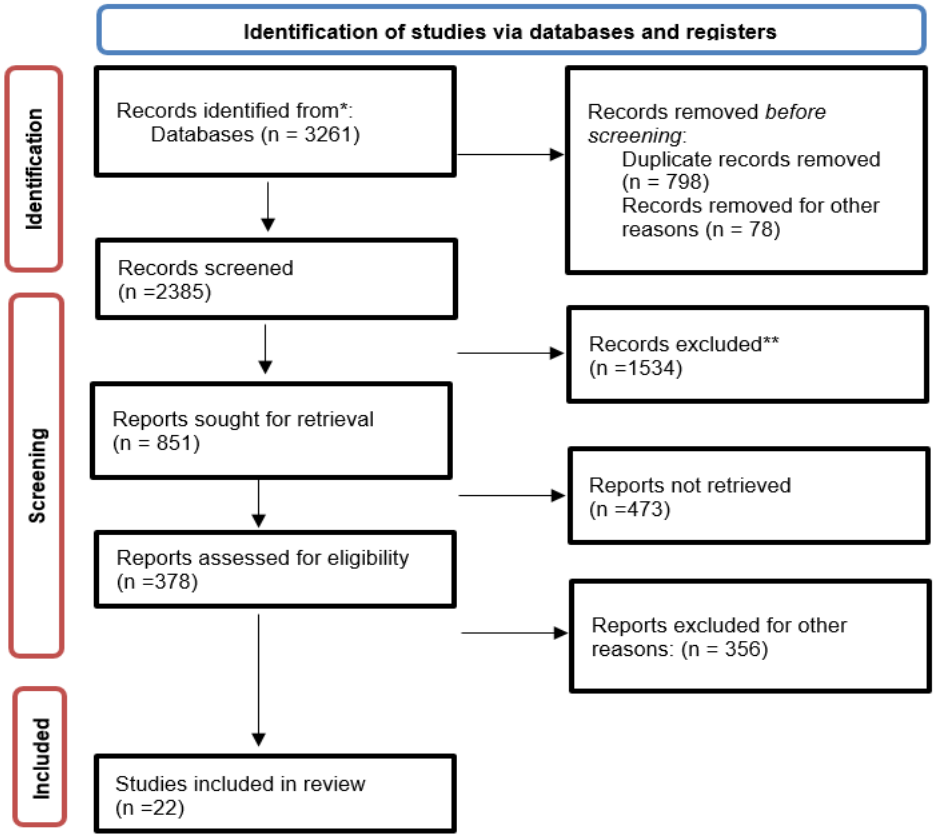
A narrative synthesis approach was used to evaluate and summarize the results from the selected studies. As a result, the narrative synthesis required organizing and interpreting the data to generate a coherent and comprehensive overview. It is related to the existing evidence on the efficacy of vitamin in OMVMs for cardiovascular disease prevention.

Additionally, the database searches, efforts were made to identify gray literature, including conference abstracts, government reports, and other unpublished or non-peer-reviewed sources. This step aimed to capture a broader spectrum of evidence and minimize potential publication bias.

To ensure completeness, citation tracking was performed by reviewing the references of included articles and relevant reviews. However, this additional step aimed to identify any relevant studies that might have been missed during the primary database searches.

As this research involves a systematic review of existing literature, ethical approval was not required. Hence, the study adhered to ethical standards by utilizing publicly available data from published studies without involving human participants.

Figure: 1 Prisma Flow Chart



Inclusion Criteria Keywords:
Oral multivitamins, multi/minerals, cardiovascular disease prevention, efficacy, inclusion criteria, randomized controlled trials, observational studies, age groups, gender diversity, ethnicity representation, socioeconomic status, vitamin E, supplement regimens, primary prevention, secondary prevention, diverse populations, global research, non-English language studies, translation availability, research outcomes.

Exclusion Criteria Keywords:
Temporal coherence, animal studies, in vitro experiments, reviews lacking original data, human-centric evidence, focus on individual vitamins, omission of multivitamin components, cardiovascular health focus, non-cardiovascular endpoints, language-based exclusions, translation in accessible languages, unpublished studies, conference abstracts, gray literature, peer review, ethical considerations, documented ethical approval, violation of ethical standards, rigorous adherence, research process reliability.

Table: 2

Serial Number	Title	Keywords	Methodology	Conclusion
1	Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment	Supplements, Vitamins, Cardiovascular disease	Literature review exploring oral multivitamins and minerals for CVD.	No evidence supports routine supplementation for CVD prevention or treatment.
2	Vitamin and Mineral Supplements for the Primary Prevention of Cardiovascular Disease and Cancer	Vitamin, Mineral, Cardiovascular disease, Cancer	Review of RCTs and observational studies on vitamin and mineral benefits.	Little to no benefit in preventing cancer, CVD, and death, except for multivitamin use in cancer incidence.

				Some supplements may pose risks.
3	Vitamin K Supplementation for the Prevention of Cardiovascular Disease: Where Is the Evidence?	Vitamin K, Cardiovascular disease, Vascular calcification	Systematic review of trials on vitamin K's effect on cardiovascular measures.	Limited evidence; unclear role of vitamin K in mitigating vascular calcification.
4	Comparative efficacy of vitamin supplements on prevention of major cardiovascular disease	Vitamins, Cardiovascular disease	Network meta-analysis of RCTs on vitamin preparations for CVD.	Vitamins B, D, and E show varying efficacy in reducing cardiovascular events. Combinations offer no improvement.
5	Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment: JACC Focus Seminar	Supplements, Vitamins, Cardiovascular disease	Updated systematic review and meta-analysis of vitamin and mineral supplementation.	Moderate-quality evidence supports folic acid and B vitamins for stroke prevention. No conclusive evidence for overall supplement benefits.
6	Selenium, antioxidants, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials	Supplements, Antioxidants, Selenium, Cardiovascular disease, All-cause mortality, Meta-analysis	Systematic review and meta-analysis of RCTs on selenium and antioxidants.	Selenium supplementation reduces CVD and all-cause mortality risk. Selenium is crucial for benefits.
7	Interventional study with vitamin E in cardiovascular disease and meta-analysis	Vitamin E, Cardiovascular disease, Atherosclerosis, Meta-analysis	Review of experimental and clinical studies on vitamin E impact.	Vitamin E exhibits antioxidant effects, but interventional trials with supplements show negative results for CVD prevention.
8	Efficacy of dietary intervention or in combination with exercise on primary prevention of cardiovascular disease: A systematic review	Dietary intervention, Exercise, Cardiovascular disease, Systematic review	Systematic review of prospective studies on dietary and exercise interventions.	Mediterranean diet and increased training benefit CV events. Adherence is crucial for positive outcomes.
9	Vitamin D and Cardiovascular Disease: Controversy Unresolved	Vitamin D, Cardiovascular disease, Meta-analyses	Review of vitamin D's cardiovascular effects and meta-analyses.	Vitamin D deficiency links to cardiovascular issues, but supplementation trials show mixed results. Ongoing trials will clarify vitamin D's role.
10	Vitamin D, Marine n-3 Fatty Acids, and Primary Prevention of Cardiovascular Disease Current Evidence	Vitamin D, Marine n-3 Fatty Acids, Cardiovascular disease, Meta-analyses	Review of VITAL trial results and meta-analyses on vitamin D and n-3 FAs.	Supplemental marine n-3 FAs reduce myocardial infarction risk; vitamin D doesn't significantly reduce major CVD events. Further research is needed for

				identification of beneficiaries.
11	Effect of Vitamins and Dietary Supplements on Cardiovascular Health	Vitamins, Dietary supplements, Cardiovascular disease	Review of evidence on the cardiovascular effects of vitamins and supplements.	Limited evidence supports cardiovascular benefits of multivitamins, especially in secondary prevention. Preliminary evidence suggests protection with supplements like carnitine, arginine, and coenzyme Q10.
12	Seafood Long-Chain n-3 Polyunsaturated Fatty Acids and Cardiovascular Disease: A Science Advisory From the American Heart Association	Seafood, n-3 Polyunsaturated Fatty Acids, Cardiovascular disease	Science advisory based on observational and experimental studies.	Including 1 to 2 seafood meals per week is suggested to reduce the risk of heart failure, coronary heart disease, stroke, and sudden cardiac death.
13	Antioxidant Food Components for the Prevention and Treatment of Cardiovascular Diseases: Effects, Mechanisms, and Clinical Studies	Antioxidants, Cardiovascular diseases, Clinical studies	Review of epidemiological, experimental, and clinical studies on antioxidants.	Antioxidants from fruits, vegetables, nuts, and cereals reduce CVD risk. Certain compounds like polyphenols, anthocyanins, and green tea show cardiovascular benefits. Clinical trials confirm these advantages.
14	Oxidative Stress Biomarkers, Nut-Related Antioxidants, and Cardiovascular Disease	Oxidative stress, Antioxidants, Nuts, Cardiovascular diseases	Review of studies on nuts and antioxidants in oxidative stress and CVD.	Nuts and antioxidants may contribute to reducing oxidative stress biomarkers and atherosclerosis, but conclusive evidence in clinical trials, especially for secondary prevention, is lacking.
15	Oxidative Stress and Antioxidant Treatments in Cardiovascular Diseases	Oxidative stress, Antioxidants, Cardiovascular diseases	Overview of oxidative stress in cardiovascular diseases and antioxidant treatments.	Oxidative stress plays a significant role in cardiovascular diseases. Various antioxidants, including supplements, miRNA, and nanomedicine, show promise in preventing and treating related conditions.
16	Plant Foods, Antioxidant Biomarkers, and the Risk of CVD	plant foods, antioxidants, cardiovascular disease	Review of meta-analyses and recent studies on plant foods, antioxidants, and health outcomes.	Higher intake of fruits, vegetables, whole grains, and nuts is associated with reduced risk of CVD, cancer, and mortality. Optimal intakes recommended for prevention.
17	Supplemental Vitamins and Minerals for CVD Prevention	vitamin supplements, minerals, cardiovascular disease risk	Review of data on multivitamins, antioxidants, and specific vitamins for cardiovascular health.	No evidence supports the use of vitamin and mineral supplements for preventing or treating cardiovascular disease.
18	Effects of a Long-Term Vegetarian Diet on Antioxidant Status	vegetarian diet, antioxidant status,	Comparison of biomarkers in long-term vegetarians	Long-term vegetarians have higher plasma antioxidant status and a better cardiovascular disease risk profile than omnivores.

		cardiovascular risk	and omnivores.	
19	Efficacy of Vitamin and Antioxidant Supplements in CVD	vitamin supplements, antioxidants, prevention, cardiovascular diseases	Meta-analysis of randomized controlled trials on the effectiveness of supplements in preventing CVD.	No evidence supports the use of vitamin and antioxidant supplements for the prevention of cardiovascular diseases.
20	Circulating 25-hydroxy-vitamin D and the Risk of CVD	vitamin D, cardiovascular disease, meta-analysis	Meta-analysis exploring the association between circulating vitamin D and the risk of CVD.	Lower circulating vitamin D levels are associated with a higher risk of both CVD incidence and recurrent events.
21	Cardiovascular diseases burden in COVID-19: Systematic review and meta-analysis	COVID-19, Cardiovascular diseases, Meta-analysis	Systematic review and meta-analysis of studies on CVD burden in COVID-19.	High burden of cardiovascular diseases significantly associated with mortality and ICU admission in COVID-19 patients. Proper management recommended.
22	Artificial Intelligence and Machine Learning in Cardiovascular Health Care	Artificial Intelligence, Machine Learning, Cardiovascular health	Review of AI and ML in cardiovascular health care with overview of terminology.	AI and ML have promising roles in automated imaging interpretation, data extraction, and clinical risk prediction in cardiovascular health care. Future applications require further refinement and evaluation.

RESULTS AND DISCUSSION:

The literature review in this study reveals the intricate landscape. The effectiveness of oral multivitamins and multi/minerals (OMVMs) in cardiovascular disease (CVD) prevention with a focus on vitamins is also being studied. Cardiovascular disease accounted for 31% of death worldwide in 2016. Therefore, it highlights the urgent need for preventive measurements. The substantial prevalence of supplement use, especially OMVMs among over half of the U.S. population, underscores the importance of investigating their efficacy. Despite their popularity, the literature reveals a lack of consensus on OMVM effectiveness for CVD, particularly in cardiovascular health. Ambiguity persists due to uncertainties about individual OMVMs, influenced by factors like variability and diverse formulations, hindering definitive conclusions. The study emphasizes the discrepancy between dietary guidelines promoting a balanced diet for micronutrient needs and widespread OMVM use, given the absence of unanimous support for their role in cardiovascular health.

Examining antioxidants, particularly vitamins, adds complexity. Antioxidants are seen as potential agents against oxidative stress, a central component in atherosclerosis. While vitamins, especially, are explored for reducing lipid peroxidation and free radical damage, the review notes isolated studies reporting therapeutic effects of specific micronutrients. Positive outcomes in some instances prompt further investigation, emphasizing the need for a thorough examination of evidence due to variability in study factors. The study aims to contribute valuable insights, unraveling the antioxidant dilemma, and enhancing the understanding of OMVMs in cardiovascular health.

CONCLUSION:

In conclusion, the extensive literature review sheds light on the intricate landscape surrounding the efficacy of oral multivitamins and multi/minerals (OMVMs) in cardiovascular disease (CVD) prevention, with a specific emphasis on vitamins. Despite the global burden of cardiovascular diseases and the widespread use of supplements, particularly OMVMs, the study reveals a conspicuous lack of consensus on their effectiveness for CVD prevention or treatment. Ambiguities persist, stemming from factors such as variability and diverse formulations, hindering definitive conclusions about individual OMVMs. As a result, the discussion become more complex when antioxidants especially vitamins are examined along with their potential side effects. The study underlines the importance of vitamin role in cardiovascular health. However, this aims to provide useful insights by unraveling the antioxidant dilemma and enhancing the understanding of OMVMs in the realm of cardiovascular disease.

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