What is the Effect of Vitamin Supplements in Healthy Adults Beyond Placebo Effect? A Systematic Review of Randomized Trials.

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This protocol will be registered at the PROSPERO site and is not an update or amendment of a previous systematic review

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MZ and AMH developed the topic for the systematic review protocol.
MZ and AMH formed the search strategy with support from the McMaster University Health Sciences Library.
MZ drafted the protocol under the guidance and editing of AMH.
MZ and AMH developed and pilot tested the screening, data extraction and the coding libraries.
AK will perform statistical analyses post data-screening.
MZ, ML, AM, CM, AV, MS, and AS will perform screening, data extraction, and risk of bias analyses.

Support
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Introduction

Rationale

Over the past decade there has been an accelerated increase in vitamin supplement consumption separate from the typical diet, by healthy adults[1]. Global revenue generated from sales of vitamin and mineral supplements has increased from C$25.00bn in 2016 to C$38.38bn in 2023, and is predicted to rise at a compound annual growth rate of 6.2% from 2016 to 2028, potentially reaching C$49.77bn in 2028[2]. Following these trends, market insights by Statista evaluated the Vitamin and Mineral supplement market in Canada at C$1.58bn in 2024, and analyses expect the market to continue to grow by 5.27% annually[2].

There is not currently a scientific consensus on how much of the effects of such supplements are the result of placebo or nocebo effect, versus the supplement itself, in healthy individuals. What is documented is a large body of work evaluating associations of clinical and functional outcomes with vitamin A[3], vitamin B-12[4], vitamin C[5-7], vitamin D[8-11], vitamin E[7,12], and vitamin K[13] supplements. Reviews of vitamin supplements found different conclusions in regard to the efficacy of supplements to affect clinical outcomes, which may be attributed to the specific vitamin and outcome investigated, or limitations in research quality[3-13]. The United States Preventive Services Task Force (USPSTF) found insufficient evidence to assess an association between vitamin A, B3, B6, C, E, or multivitamins and the prevention of cardiovascular disease or cancer; in the case of beta carotene it was found, with moderate or high certainty, that supplementation is ineffective at preventing cardiovascular disease or cancer, and may have an association with an increased risk of lung cancer in heavy smokers[14]. Observational studies reviewed and conducted by the USPSTF also could not find sufficient evidence to assess benefits and harms of vitamin D for the primary prevention of fractures in men and premenopausal women[15], and suggest with moderate to high certainty that supplementation has no net benefits, or that benefits are outweighed by harms, in preventing falls in community-dwelling adults 65+ years of age[16].

Though the USPSTF found insufficient evidence to assess the effects of vitamins A, B3, B6, C, and E on all-cause mortality, cardiovascular mortality, or cancer outcomes, their review may have been limited by the specificity of the evaluated outcomes and age of review [14]. This comprehensive systematic review will provide a holistic review of all vitamins over an expanded range of clinical and functional outcomes, which is currently missing from the specific reviews focused on individual vitamins and outcomes. A broader perspective that examines validated functional outcomes in addition to clinical outcomes will prioritize clinical relevance associations may provide valuable insights for clinical decision-making. This approach provides valuable insights into the impact of vitamins on individuals' daily functioning and quality of life, which may support clinical decision-making. A comprehensive review will also identify areas in which further research is needed by highlighting current limitations.

The definition of vitamin supplement utilized for this review is adapted from that of the FDA's Dietary Supplement Health and Education Act of 1994[17]. For the purposes of this study, vitamin supplements are defined as a product supplementing the diet containing a vitamin as the sole

dietary ingredient; is consumed systemically as one of: gelcaps, powders, capsules, or softgels and is not used as a sole food item or component of a conventional meal.

The placebo effect is defined as “any improvement of symptoms or signs following a physically inert intervention”, most commonly in the relief of subjective symptoms such as depression, pain, anxiety, or fatigue[18]. The nocebo effect is defined as “the induction or the worsening of symptoms induced by sham or active therapies”, and both effects rely on psychological and/or neurobiological underlying mechanisms[19,20].

Objective

Our objective is to systematically review the literature for randomized placebo-controlled trials involving healthy adults and studying the effect of vitamin supplements as defined above on important health outcomes.

Research Question

For community-dwelling healthy adults, what is the effect of consumption of vitamin supplements beyond that of placebo on important clinical outcomes in randomized trials of at least 4 weeks follow-up?

Methods

The protocol has been written according to PRISMA-P recommendations [21]. The PRISMA-P checklist is shown in Appendix A.

Eligibility Criteria

Study Design: Parallel, Crossover, Cluster, or Factorial Randomized Control Trials

Setting: Community (ie, not hospitalized or institutionalized individuals)

Participants: Healthy Adults 18 years or older

Interventions: Vitamins supplements as defined by the Oxford Concise Medical Dictionary[22].

Vitamin Supplement Definition

"any of a group of substances that are required, in very small amounts, for healthy growth anddevelopment: they cannot be synthesized by the body and are therefore essential constituents of the diet. Vitamins are divided into two groups, according to whether they are soluble in water or fat. The water-soluble group includes the vitamin B complex and vitamin C; the fat-soluble vitamins are vitamins A, D, E, and K. Lack of sufficient quantities of any of the vitamins in the diet results in specific vitamin deficiency diseases."[22,23]

Comparator: At least one arm of the trial must be a Placebo control.

Outcomes: Primary outcomes are validated patient-important clinical outcomes including death, and adverse clinical events such as cardiovascular events, incidence of serious disease, hospitalization, emergency department visits, and quality of life. Secondary outcomes include objectively measured and validated functional outcomes including the 6 Minute Walk Test[24], Clinical Frailty Scale[25], The Five Cognitive Tests[26], Berg Balance Scale[24], Functional Gait Assessment[24], etc. An extended sample list of acceptable functional outcomes is available in APPENDIX B.

Time Frame: 4 weeks minimum intervention duration

Other Study Characteristics: Only studies published from 1996 to 2023 will be considered for inclusion.

Inclusion:
Studies must be randomized trials.
One intervention arm must include a systemically delivered vitamin supplement structured in such a way that the effect of the vitamin alone can be determined.
Participants and populations eligible for inclusion are community dwelling healthy adults, of any socioeconomic group from any country.
Parallel, crossover, cluster and factorial randomized control trials will be considered.

Exclusion:
RCTs investigating adults with known vitamin deficiencies will be excluded. RCTs investigating patients using vitamin supplements for treatment of disease, hospitalized adults, or institutionalized adults will be excluded.
RCTs involving only active control groups or 'no treatment' controls will be excluded.
Studies involving only surrogate or biomarker outcomes will be excluded.

Information Sources

Relevant articles will be sought from the following databases; Medline, Embase, CINAHL, and Allied and Complementary Medicine Database (AMED). Planned dates of coverage are January 1996 – December 2023.

Search Strategy

The search strategy below was implemented on Medline with similar searches implemented on Embase, CINAHL, and AMED.

https://libaccess.mcmaster.ca/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=4tUza9Vc2xGrbMgROaREhcXw9ei73BGyHCXRCtgszjGGmb0RlbanUaFEb41pkrwMc

1. vitamin*.mp.
2. exp Vitamins/
3. 1 or 2

4. placebo.mp.
5. exp Placebo Effect/
6. nocebo.mp.
7. exp Nocebo Effect/
8. 4 or 5 or 6 or 7
9. healthy.mp.
10. exp Volunteer/
11. 9 or 10
12. 3 and 8 and 11
13. limit 12 to (humans and yr="1996 -Current" and "all adult (19 plus years)" and randomized controlled trial)

Study Records

Articles identified by our searches will first be uploaded to our reference management software – Endnote (https://endnote.com/?language=en) then duplicates removed. Two independent reviewers blinded to the other's rating will perform title and abstract screening to decide inclusion versus exclusion using Covidence (https://app.covidence.org/). Included articles will then undergo full text screening by two independent blinded reviewers using Covidence. A third senior independent reviewer will resolve any conflicts in inclusion/exclusion at every stage of screening. Articles that do not meet inclusion criteria will be excluded from the review.

Two reviewers will use pilot-tested data extraction forms to independently extract relevant data from the included full text articles.

Data Items

Data collected will include study details (countries represented, sample size, unit of randomization, follow-up, degree of blinding), patient demographics (age, sex), study comparisons (specific vitamin supplement administered, dosage, frequency, controls), outcomes studied, and study results including adverse events or discontinuations for any reasons. Disagreements will be resolved by a third senior reviewer.

Outcomes and Prioritization

Primary Outcome: Patient-important validated clinical outcomes including death, adverse clinical events such as cardiovascular events, hospitalization, emergency department visits, or quality of life.

Secondary Outcomes: Objectively measured, validated functional outcomes such as changes in strength, the 6 Minute Walk Test[24], Clinical Frailty Scale[25], The Five Cognitive Tests[26], Berg Balance Scale[24], Functional Gait Assessment[25], etc. An extended sample list of acceptable functional outcomes is available in APPENDIX B.

Prioritization of primary over secondary outcomes is based on level of directness and importance to health and health systems. Secondary outcomes add a more specific but important and evidence-based perspective.

Risk of Bias in Individual Studies

The quality of included studies will be assessed by two independent reviewers using a Risk of Bias Guide adapted from the Cochrane Risk of Bias version 2.0[27], and will be visualized using the Robvis visualization tool which illustrates domain-level risk of bias judgements in a green, yellow, and red traffic light plot for each individual study[28]. Cluster randomized trials will be assessed by two independent reviewers using the Cochrane Risk of Bias tool for cluster randomized trials[29], a supplement to the main Cochrane Risk of Bias version 2.0 tool[28]. Disagreements will be resolved by an independent third senior reviewer.

Data Synthesis

Data will be summarized and reported in adherence to the PRISMA systematic review reporting guidelines[21]. Extracted data will be analysed and visually represented in the R statistical software (https://www.r-project.org/) with an explanatory table to show detailed study characteristics, patient demographics, interventions, outcomes). We will use forest plots to show the effect size estimate of extracted results with P-values to show statistical significance and compile the results of individual studies to show overall effects, as well as pre- and post-specified subgroups. Due to the diversity of evaluated outcomes in this systematic review, the possibility persists that extracted data will not be suited for a quantitative analysis. If this scenario should arise, extracted data will be synthesized thematically, grouping outcome data into descriptive themes in order to capture the commonalities and patterns across included RCTs.

I^2 will be used to determine the degree of heterogeneity and whether the use of a fixed effects model or random effects model is warranted for subgroup and meta analyses. Subgroup analyses are planned based on I^2 statistics and will be conducted based on patient demographics and study intervention. Substantial heterogeneity will be noted if I^2 is greater than 50%.

Specific subgroups of interest include:

a) Specific vitamin administered. Differing vitamins may be absorbed along varying biological processes and are uniquely purposed within the body, thus the administration of different vitamin supplements may result in differing outcomes.
b) Sex (male or female or other). Men and women have different nutritional requirements and may have different responses to identical doses of supplements[29].
c) Age (subgroups 19-30y, 31-50y, 51-70y, 71+). Different age groups have different nutritional requirements and may have different responses to identical doses of supplements. Age subgroups reflect age groups set for differing nutritional requirements by Health Canada and the National Academy of Medicine[29].

A sensitivity analysis will be used to assess the robustness of our review results by repeating the analyses excluding high risk of bias studies, and the use of a continuity correction for studies of 0 events.

Meta-Bias

Publication bias will be assessed using Egger's Test. We will formulate funnel plots of the trials' effect estimates against sample size and apply linear regression to measure funnel plot asymmetry on the natural logarithm scale of the odds ratio[30].

Confidence in Cumulative Evidence

The reliability of review outcomes will be assessed by two independent reviewers using the GRADE approach with the GRADEpro tool. Any disagreements will be resolved by a senior third independent reviewer.

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APPENDIX A. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No.	Checklist item	Information Reported		Page Number
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title:					
Identification	1a	Identify the report as a protocol of a systematic review	☐	☐	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	☐	☐	
Authors:					
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐	☐	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐	☐	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	
Support:					
Sources	5a	Indicate sources of financial or other support for the review	☐	☐	
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐	☐	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐	☐	
METHODS					
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	☐	☐	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	☐	☐	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐	☐	
Study records:					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐	☐	

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	☐	☐
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐	☐
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	☐	☐
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐	☐
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐	☐
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	☐	☐
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	☐	☐
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	☐	☐
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	☐	☐
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	☐	☐

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647

APPENDIX B. Examples of Validated Functional Outcomes

1. 6 Minute Walk Test [1]
   The 6 Minute Walk Test is designed to measure the distance an individual can walk in six minutes, providing an assessment of aerobic capacity and endurance across different populations.
2. Berg Balance Scale [1]
   The Berg Balance Scale evaluates an individual's balance and risk of falling by assessing their performance in various functional tasks. It is commonly used in rehabilitation settings for older adults and those with neurological disorders.
3. Functional Gait Assessment[1]
   This assessment focuses on different components of gait, examining stability during various walking tasks to identify gait abnormalities and assess fall risk in individuals with balance impairments.
4. Clinical Frailty Scale [2]
   The Clinical Frailty Scale gauges the degree of frailty in older adults, providing insights into overall health and functional status. It is used to guide clinical decision-making, especially in geriatric care.
5. The Five Cognitive Tests [3]
   This term encompasses various cognitive assessments targeting different cognitive domains (such as memory, attention, and executive function) and is employed to screen for cognitive impairment or dementia.
6. Katz Index [4]
   The Katz Index assesses an individual's capability to perform basic activities of daily living. It serves as a means to evaluate functional independence and inform care planning in healthcare settings.
7. Timed Up and Go (TUG) Test [5]
   The TUG Test measures the time an individual takes to rise from a chair, walk a short distance, turn around, and return to a seated position. It serves as an assessment of mobility and fall risk, particularly in older adults.
8. Lawton Instrumental Activities of Daily Living (IADL) Scale [6]
   The Lawton IADL Scale evaluates an individual's ability to perform instrumental activities of daily living, such as managing finances and using transportation. It provides insight into higher-level functional skills beyond basic ADLs.
9. Barthel Index [7]
   The Barthel Index measures an individual's ability to independently perform basic self-care activities. It is commonly used in healthcare and rehabilitation to assess functional status and guide treatment planning.
10. Montreal Cognitive Assessment (MoCA) [8]
    The MoCA serves as a cognitive screening tool, detecting mild cognitive impairment and assessing various cognitive domains. It is commonly used to identify early signs of cognitive decline.
11. Mini-Mental State Examination (MMSE) [9]

The MMSE is a widely used cognitive screening tool that assesses orientation, memory, and other cognitive functions. It plays a crucial role in evaluating cognitive status in clinical and research settings.

12. Short Physical Performance Battery (SPPB) [10]
    The SPPB assesses lower extremity function, including balance, gait speed, and chair stands. It is commonly used in older adults to predict disability, mortality, and overall physical function.
13. Dynamic Gait Index (DGI) [11]
    The Dynamic Gait Index assesses an individual's ability to modify their gait in response to various tasks, providing insights into dynamic balance and gait performance.
14. 30-Second Chair Stand Test [12]
    The 30-Second Chair Stand Test evaluates lower extremity strength and endurance by measuring how many times an individual can stand up from a chair in 30 seconds.
15. Shuttle Walk Test (SWT) [13]
    The Shuttle Walk Test measures aerobic capacity and endurance by having individuals walk back and forth between two markers, providing information on cardiovascular fitness and functional capacity.
16. Diamond Steps Test (DST) [14]
    The Diamond Steps Test assesses agility and dynamic balance by having individuals step over and around markers arranged in a diamond shape, evaluating mobility and coordination.
17. Triple Hop Distance (THD) [15]
    The Triple Hop Distance assesses lower extremity strength and power by measuring the distance an individual can hop forward three times on one leg, providing information on lower limb function.
18. Y Balance Test [16]
    The Y Balance Test is designed to assess an individual's dynamic balance, functional stability, and reach distance, the individual stands on one leg at the center of a Y-shaped mat. They use the opposite foot to reach as far as possible along three different directions.
19. Hand Grip Strength Test [17]
    The Hand Grip Strength Test is designed to measure the maximum force a person can generate when squeezing a dynamometer or handgrip dynamometer.
20. Stair Ascend/Descend Test [18]
    Assessing an individual's ability to ascend and descend stairs is relevant for sports performance and daily living. It is used in rehabilitation to evaluate lower limb strength and mobility.
21. Functional Reach Test [19]
    This test assesses an individual's maximal forward reach without losing balance. It's used in both sports and rehabilitation settings to evaluate and improve dynamic stability.

References for Validated Functional Outcomes

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