

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Self-reported health without clinically measurable benefits among adult users of multivitamin and multimineral supplements: a cross-sectional study
<b>AUTHORS</b>	Paranjpe, Manish; Chin, Alfred; Paranjpe, Ishan; Reid, Nicholas J; Duy, Phan Q; Wang, Jason K; O'Hagan, Ross; Arzani, Artine; Haghdel, Arsalan; Lim, Clarence C; Orhurhu, Vwaire; Urits, Ivan; Ngo, Anh L; Glicksberg, Benjamin S; Hall, Kathryn T; Mehta, Darshan; Cooper, Richard S; Nadkarni, GN

### VERSION 1 – REVIEW

<b>REVIEWER</b>	H Cena University of Pavia, Italy
<b>REVIEW RETURNED</b>	23-Jun-2020

<b>GENERAL COMMENTS</b>	<p>1. Authors use MV and MVM indistinctively, make it consistent through out the text (ex.: lines 19-33) to my knowledge Physicians' Health Study II was a randomized, double-blind, placebo-controlled study designed to test four supplements among which Centrum Silver, a vitamin/mineral combination so MVM.</p> <p>2. Most people should get all the nutrients they need by having a varied and balanced diet, although some few people may need to take extra supplements. This is not addressed (Blumberg JB, Cena H, Barr SI, et al. The Use of Multivitamin/Multimineral Supplements: A Modified Delphi Consensus Panel Report. Clin Ther. 2018;40(4):640-657. doi:10.1016/j.clinthera.2018.02.014) Besides authors do not consider inadequate/adequate dietary intake and the consequent useful/useless need to take vitamins or minerals to prevent or make up for a micronutrient inadequacy/deficiency (Blumberg JB, Frei BB, Fulgoni VL, Weaver CM, Zeisel SH. Impact of Frequency of Multi-Vitamin/Multi-Mineral Supplement Intake on Nutritional Adequacy and Nutrient Deficiencies in U.S. Adults. Nutrients. 2017;9(8):849. Published 2017 Aug 9. doi:10.3390/nu9080849) This should be acknowledged as a limit of the study and addressed in the discussion.</p> <p>"U-shaped association", with elevated disease risks at both high and low vitamins and mineral levels is well known for most of the micronutrients</p> <p><a href="http://www.fao.org/3/a-y2809e.pdf">http://www.fao.org/3/a-y2809e.pdf</a>  <a href="https://apps.who.int/iris/bitstream/handle/10665/42716/9241546123.pdf;jsessionid=05F37E2D5624456F7E1D4D638922EFA7?sequence=1">https://apps.who.int/iris/bitstream/handle/10665/42716/9241546123.pdf;jsessionid=05F37E2D5624456F7E1D4D638922EFA7?sequence=1</a></p>
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<b>REVIEWER</b>	Sakari Suominen University of Turku, Finland University of Skövde, Sweden
<b>REVIEW RETURNED</b>	01-Jul-2020

	<p>Thank you for giving me the opportunity to review this paper. The study is of mediocre public health interest as it deals with the association between self-reported health and reported use of multivitamin and multi-mineral (MVM) supplements in a sample representative of the population of the U.S. in 2012. The topic deserves scientific attention and generally the manuscript is well written and easy to follow.</p> <p>However, I have several concerns that should according to my evaluation be addressed by the co-authors before the study could be published. The greatest problem, naturally is the cross-sectional design which does not in practice allow any kind of firm conclusions of direction of influence between the variables studied. Hence, as a minor detail I would recommend that all the wordings of 'effects' studied should be replaced with the more neutral expression of 'association between the variables or phenomena in question'. The cross-sectional design, however, is mentioned among the limitations.</p> <p>The Introduction is not focusing solely on the topic of the study as it mostly deals with previous studies on the predominantly not shown real health effects of MVM use. These studies are of course of relevance but I miss potential studies on perceived benefits of the use of MVM supplements since I believe that these expectations among the population are far more important in guiding people to start using MVM:s in comparison with the objectively shown effects that are not yet very much acknowledged by laymen, otherwise the use of the MVM:s would decrease.</p> <p>The use of MVM:s is based on one question and this is dealt with in the limitations of the study but it is not mentioned that the question does not allow any kind of dose-response evaluation. Moreover, both multi-vitamin and mineral substitutes are included in the same item and these two aspects are not mentioned in the limitations. The determinants of use of the two types of substitutes might differ among the population. Additionally, do we know that the general population can make a proper difference between multi-vitamin and mineral preparations?</p> <p>The data is derived from the 2012 The National Health Interview Survey (NHIS) with very good response rate close to 80 percent. I find this hard to achieve in the present Western world and would call for more information regarding the original sample and potential bias related to the final respondents and discussion of these, if necessary.</p> <p>Generally, I can agree with the Conclusions but I find the principal finding of better self-reported health among MVM users not very surprising and find the results from the stratified analyses as the most interesting. I do not agree with the co-authors' claim that particularly greater cohorts could yield more reliable results, I think that especially follow up studies could add to existing knowledge.</p>
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<b>REVIEWER</b>	Gabriele Berg-Beckhoff University of Southern Denmark
<b>REVIEW RETURNED</b>	07-Jul-2020

<b>GENERAL COMMENTS</b>	<p>The article provides important results with regard to the use of multi-vitamin and multi-mineral supplementation in a general adult population. The article is nicely written, introduction is nicely deduced, results are carefully presented. Therefore, the article is worthwhile to be published.</p> <p>Abstract: contains all necessary information</p> <p>Introduction: Important literature is cited. However, I do not get why the authors mention that results as inconclusive (see p 4 line45ff; ... “also inconclusive”). Please introduce the literature as it is. All your cited literature showed that multivitamin supplementation does not have an effect of cardiovascular health outcome. Which is of course not inconclusive. Your opinion can be mentioned in the discussion. Furthermore, the authors shall explain more about the quality and content of multivitamin supplements. How much of the content of these multi-vitamin and multi-mineral supplements is adsorbed and accessible to the individual that is taking the supplements. It would also be worthwhile to differentiate the unspecific multi-vitamin and multi-mineral supplementation in the general population from specific vitamin supplements that is recommended in specific deficiency situation.</p> <p>Methods and results: Congratulation. Good job, Methods and results are nicely explained.</p> <p>Discussion: The discussion is limited by the in-depth description of multivitamin and multi-mineral (MVM) supplementation. Which vitamins and minerals are added? Do they interact with each other? Are they adsorbed? Once again, specific medication to treat vitamin or mineral deficiency shall not be mixed up with these not clinical used multi vitamin and multi mineral supplements in a general population. It needs be discussed, how much of the vitamin and or mineral contents reach the individual organism. How good the vitamins and minerals are adsorbed and can be used from the individual? If you do not have in depth information about the metabolism, further recommendation for the use of these supplements does not make sense. If you do not find published information on resorption and metabolism these synthetic MVM products, please mention what is still missing before suggesting effective MVM use practices.</p> <p>Conclusion is unclear: What is meant with the suggestion to educate the general public about effective MVM use practices. No effective practice of MVM use is introduced, explained, analyzed, and discussed. Please conclude based on your presented results.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

We thank the reviewer for their helpful comments. We have addressed the reviewer’s concerns and believe the manuscript is improved as result. Please see below for point-to-point responses.

Authors use MV and MVM indistinctively, make it consistent through out the text (ex:: lines 19-33) to my knowledge Physicians' Health Study II was a randomized, double-blind, placebo-controlled study designed to test four supplements among which Centrum Silver, a vitamin/mineral combination so MVM.

Response: Thank you for this important point. We have replaced all mention of MV to MVM in the revised manuscript.

Most people should get all the nutrients they need by having a varied and balanced diet, although some few people may need to take extra supplements. This is not addressed (Blumberg JB, Cena H, Barr SI, et al. The Use of Multivitamin/Multimineral Supplements: A Modified Delphi Consensus Panel Report. *Clin Ther.* 2018;40(4):640-657. doi:10.1016/j.clinthera.2018.02.014). Besides authors do not consider inadequate/adequate dietary intake and the consequent useful/useless need to take vitamins or minerals to prevent or make up for a micronutrient inadequacy/deficiency (Blumberg JB, Frei BB, Fulgoni VL, Weaver CM, Zeisel SH. Impact of Frequency of Multi-Vitamin/Multi-Mineral Supplement Intake on Nutritional Adequacy and Nutrient Deficiencies in U.S. Adults. *Nutrients.* 2017;9(8):849. Published 2017 Aug 9. doi:10.3390/nu9080849). This should be acknowledged as a limit of the study and addressed in the discussion. "U-shaped association", with elevated disease risks at both high and low vitamins and mineral levels is well known for most of the micronutrients

Response: Thank you for raising these important concerns. We have cited the references mentioned by the Reviewer in the revised manuscript. We also have greatly expanded the Discussion section to include discussion on potential indication bias from including individuals prescribed MVMs by their physician for micronutrient deficiencies and other conditions. Specifically, we have added the following to the Discussion section to discuss indication bias:

"A portion of our cohort may have been prescribed MVMs, specific vitamins or specific minerals for indications including micronutrient deficiency, pregnancy, iron deficiency anemia, osteoporosis, Crohn's disease and others, thereby contributing to indication bias<sup>1-6</sup>. Previous estimates have suggested approximately 1% of physician office visits in the United States include a prescription or recommendation for MVMs<sup>7</sup>. One can imagine a scenario in which MVM users and non-users are imbalanced in the proportion of medical cases that require MVM supplementation (ie. micronutrient deficiency or pregnancy). In such a scenario, it may falsely appear that MVM use is not associated with clinical benefits. In the present study, owing to a lack of information regarding the reason for taking MVMs, we were unable to fully account for indication bias present in our cohort."

We added the following to the Discussion section to discuss dose-dependent effects and known U-shaped effects of MVMs:

"In addition to reporting bias and residual confounding, a self-reported binary response to the question of whether one has taken MVMs in the past 12 months precludes any analysis of dose-dependent effects of MVMs in our cohort. This is especially important considering some vitamins and minerals have known U-shaped associations with disease in which disease risk is elevated at both high and low vitamin and mineral levels<sup>8-11</sup>."

Reviewer: 2

We thank the Reviewer for their helpful comments. Please see below for point-to-point responses.

I have several concerns that should according to my evaluation be addressed by the co-authors before the study could be published. The greatest problem, naturally is the cross-sectional design which does not in practice allow any kind of firm conclusions of direction of influence between the variables studied. Hence, as a minor detail I would recommend that all the wordings of 'effects'

studied should be replaced with the more neutral expression of 'association between the variables or phenomena in question'. The cross-sectional design, however, is mentioned among the limitations.

Response: This is an important point. We have replaced any mention of "effects" to "association" in the revised manuscript. As an example, in the revised manuscript the Results subheading now reads:

Stratified Analyses: Association between MVM Usage and Self-Reported Overall Health in Sociodemographic Subgroups

The Introduction is not focusing solely on the topic of the study as it mostly deals with previous studies on the predominantly not shown real health effects of MVM use. These studies are of course of relevance but I miss potential studies on perceived benefits of the use of MVM supplements since I believe that these expectations among the population are far more important in guiding people to start using MVM:s in comparison with the objectively shown effects that are not yet very much acknowledged by laymen, otherwise the use of the MVM:s would decrease.

Response: We appreciate the Reviewer's concern. However, the overwhelming majority of randomized clinical trials and observational studies on MVM use and disease risk have shown no added benefit of MVMs. It is unlikely that consumer proclivity towards MVMs are driven by the small minority of studies that demonstrate a positive health benefit of MVMs. We have added the following to the Introduction to discuss possible reasons underlying consumers' positive expectation regarding MVM use and health:

"While numerous reports on MVM consumption establish the lack of broad-spectrum, clinically measurable health benefits, the determinants of widespread MVM use by the general population are not well understood. That the majority (52%) of MVM users report using MVMs in an effort to prevent disease is even more puzzling in light of the paucity of randomized and observation data showing a positive health benefit of MVMs<sup>12</sup>."

The use of MVMs is based on one question and this is dealt with in the limitations of the study but it is not mentioned that the question does not allow any kind of dose-response evaluation. Moreover, both multi-vitamin and mineral substitutes are included in the same item and these two aspects are not mentioned in the limitations. The determinants of use of the two types of substitutes might differ among the population. Additionally, do we know that the general population can make a proper difference between multi-vitamin and mineral preparations?

Response: Thank you for raising this important concern. In the revised manuscript, we added the following to the Limitations section to address this point:

"In addition to reporting bias and residual confounding, a self-reported binary response to the question of whether one has taken MVMs in the past 12 months precludes any analysis of dose-dependent effects of MVMs in our cohort. Further, use of both multivitamins and multimineral were asked as part of the same question in the NHIS questionnaire. This prevented us from analyzing multivitamin and multimineral effects in isolation. As different MVM preparations can differ in their nutritional composition, it was also not possible for us to identify differences in nutritional composition that may be driving the results in this study."

The data is derived from the 2012 The National Health Interview Survey (NHIS) with very good response rate close to 80 percent. I find this hard to achieve in the present Western world and would call for more information regarding the original sample and potential bias related to the final respondents and discussion of these, if necessary.

Response: Thank you for this important point. We have amended the Discussion to include a detailed discussion on non-response bias present within NHIS. Specifically, we added the following to the Discussion section:

In addition to indication bias, the NHIS, like other surveys, is known to suffer from nonresponse bias<sup>13</sup>. For example, a previous study found that the 1990-2009 NHIS population had an approximately 14% lower mortality than the general population<sup>13</sup>. Post-hoc methods to address nonresponse bias include creating sample weights based on demographic variables and selection probabilities, as was used in the present study. However, survey weighting, while a standard practice, may not fully account for nonresponse bias, especially if the survey weights do not take into account common differences between survey responders and non-responders such as smoking and alcohol use<sup>14</sup>. As a result, non-response bias may limit the generalizability of our results to the broader population

Generally, I can agree with the Conclusions but I find the principal finding of better self-reported health among MVM users not very surprising and find the results from the stratified analyses as the most interesting. I do not agree with the co-authors' claim that particularly greater cohorts could yield more reliable results, I think that especially follow up studies could add to existing knowledge.

Response: Our intention was to admit that some of the stratified analyses, particularly a lack of association between MVM usage and self-reported health in individuals with family income greater than 300% FPL, may be related to sample size and that a larger cohort could be used to validate these findings. In the revised manuscript, we have replaced "larger cohort" with "follow-up study" as follows in the Discussion section:

"The lack of association between MVM usage and self-reported health in individuals with family income greater than 300% FPL may be related to sample size and should be replicated in a follow up study."

Reviewer: 3

We thank the reviewer for their helpful comments. We have addressed the reviewer's concerns and believe the manuscript is improved as result. Please see below for point-to-point responses.

The article provides important results with regard to the use of multi-vitamin and multi-mineral supplementation in a general adult population. The article is nicely written, introduction is nicely deduced, results are carefully presented. Therefore, the article is worthwhile to be published.

Response: Thank you for your kind words and support.

Furthermore, the authors shall explain more about the quality and content of multivitamin supplements. How much of the content of these multi-vitamin and multi-mineral supplements is adsorbed and accessible to the individual that is taking the supplements. It would also be worthwhile to differentiate the unspecific multi-vitamin and multi-mineral supplementation in the general population from specific vitamin supplements that is recommended in specific deficiency situation.

Response: We have expanded the Discussion section to address these concerns. We have discussed indication bias from individuals needing prescription MVMs for specific deficiencies in our response to the Reviewer's point 3. We have added the following to the Discussion to address the composition of MVMs, evaluation of multivitamin and multimineral effects isolation and bioavailability:

"Further, use of both multivitamins and multimineral were asked together as part of the same question in the NHIS questionnaire. This prevented us from analyzing multivitamin and multimineral effects in isolation. Moreover, different MVM preparations can differ in their nutritional composition, quality, and bioavailability. Some individuals may take multiple MVMs whose constituents could interact with each other. Because the brand of multivitamin an individual reported taking is not

available within NHIS, we could not identify differences in nutritional composition, quality, bioavailability, and chemical interaction that may be driving the results in this study.”

The discussion is limited by the in-depth description of multivitamin and multi-mineral (MVM) supplementation. Which vitamins and minerals are added? Do they interact with each other? Are they adsorbed? Once again, specific medication to treat vitamin or mineral deficiency shall not be mixed up with these not clinical used multi vitamin and multi mineral supplements in a general population.

Response: This is an important point that we need to address as a limitation. Because the brand of multivitamin being taken was not asked of MVM users in NHIS, we could identify differences in nutritional composition, bioavailability, and chemical interaction that may be driving the results in this study. The goal of this study was to study MVM use in general rather than the effect of specific MVM characteristics on health. Further, it is also possible that a proportion of our study cohort were prescribed MVMs for specific indications. However, owing to a lack of information regarding the reason for taking MVMs, we were unable to fully account for indication bias present in this study. We have expanded the Discussion to discuss these limitations as follows:

“In addition to reporting bias and residual confounding, a self-reported binary response to the question of whether one has taken MVMs in the past 12 months precludes any analysis of dose-dependent effects of MVMs in our cohort. Further, use of both multivitamins and multimineral were asked together as part of the same question in the NHIS questionnaire. This prevented us from analyzing multivitamin and multimineral effects in isolation. Moreover, different MVM preparations can differ in their nutritional composition and bioavailability. Some individuals may take multiple MVMs whose constituents could interact with each other. Because the brand of multivitamin being taken was not asked of MVM users in NHIS, we could identify differences in nutritional composition, bioavailability, and chemical interaction that may be driving the results in this study.

A portion of our cohort may have been prescribed MVMs, specific vitamins or specific minerals for indications including pregnancy, iron deficiency anemia, osteoporosis, Crohn’s disease and others, thereby contributing to indication bias<sup>1-4</sup>. Previous estimates have suggested approximately 1% of physician office visits in the United States include a prescription or recommendation for MVMs<sup>7</sup> One can imagine a scenario in which MVM users and non-users are imbalanced in the proportion of medical cases that require MVM supplementation (ie. fat malabsorption). In such a scenario, it may falsely appear that MVM use is not associated with clinical benefits. In the present study, owing to a lack of information regarding the reason for taking MVMs, we were unable to fully account for indication bias present in our cohort.”

It needs be discussed, how much of the vitamin and or mineral contents reach the individual organism. How good the vitamins and minerals are adsorbed and can be used from the individual? If you do not have in depth information about the metabolism, further recommendation for the use of these supplements does not make sense. If you do not find published information on resorption and metabolism these synthetic MVM products, please mention what is still missing before suggesting effective MVM use practices.

Response: The bioavailability of MVMs will differ based on the brand and formulation of the MVM. Because the brand of multivitamin an individual reported taking is not available within NHIS, we could identify differences in nutritional composition, quality, bioavailability, and chemical interaction that may be driving the results in this study. We have added a section in the Discussion to address this specific concern. Please see our response the Reviewer’s point 3 in which we explain our response to concerns of bioavailability differences between MVMs.

Conclusion: What is meant with the suggestion to educate the general public about effective MVM use practices. No effective practice of MVM use is introduced, explained, analyzed, and discussed. Please conclude based on your presented results.

Response: Thank you for this important point. In the revised manuscript, we have changed the last author of the Conclusion to follow our results more closely as follows:

“Our findings suggest that widespread use multivitamins in adults may be a result of individuals’ positive expectation that multivitamin use leads to better health outcomes or a self-selection bias in which MVM users intrinsically harbor more positive views regarding their health.”

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Sakari Suominen University of Turku, Department of Public Health, Finland University of Skövde, School of Health Sciences, Sweden
<b>REVIEW RETURNED</b>	16-Jul-2020

<b>GENERAL COMMENTS</b>	<p>The authors have addressed my comments adequately. However, I would still like to pay attention to a couple of minor details. Although I am not a native English speaker and knowing that the authors are I still wonder about the expressions ‘increased perceived health’ in the Introduction and ‘greater self-reported health’ in the Discussion. Would it not be more accurate to say ‘improved’ and/or just ‘better’? I wanted to point this out already during review round one but then I forgot.</p> <p>In the Conclusions there is something wrong with the sentence ‘The multibillion-dollar nature of the nutritional supplement industry makes understanding the determinants of widespread MVM have significant medical and financial consequences.’ Finally, although well known I would prefer to explain the abbreviation FDR.</p>
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<b>REVIEWER</b>	Gabriele Berg-Beckhoff University of Southern Denmark
<b>REVIEW RETURNED</b>	10-Aug-2020

<b>GENERAL COMMENTS</b>	The authors answered carefully to the reviewers comments I do not have any further comment, congratulation
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### VERSION 2 – AUTHOR RESPONSE

#### Reviewer: 2

We thank the reviewer for their helpful comments. We have addressed the reviewer’s concerns and believe the manuscript is improved as result. Please see below for point-to-point responses.

1. **The authors have addressed my comments adequately. However, I would still like to pay attention to a couple of minor details. Although I am not a native English speaker and knowing that the authors are I still wonder about the expressions `increased perceived health` in the Introduction and `greater self-reported health` in the Discussion. Would it not be more accurate to say `improved` and/or just `better`? I wanted to point this out already during review round one but then I forgot.**

Response: Thank you for this important point. We have replaced all mention of “increased perceived health” and “greater self-reported health” to “better perceived health” and “better self-reported health” in the revised manuscript.

2. **In the Conclusions there is something wrong with the sentence `The multibillion-dollar nature of the nutritional supplement industry makes understanding the determinants of widespread MVM have significant medical and financial consequences.`**

Response: Thank you for pointing this out. We have changed the sentence as follows:

The multibillion-dollar nature of the nutritional supplement industry makes understanding the determinants of widespread MVM use have significant medical and financial consequences.

3. **Finally, although well known I would prefer to explain the abbreviation FDR.**

Response: Thank you for pointing this out. We have included the long form of FDR with the first mention of FDR in the Methods section:

“P values were adjusted for multiple comparisons using a Benjamini-Hochberg procedure with False Discovery Rate (FDR) <0.01 deemed significant.”