

More Nonsense in Vitamin Research

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A report in *Archives of Internal Medicine*, an AMA journal, tells us that “the Women’s Health Initiative study provided convincing evidence that multivitamin use has little or no influence on the risk of common cancers, CVD, or total mortality in postmenopausal women.” A closer look at that report reveals serious shortcomings in its references and logic, leading to questions about its validity. In spite of these defects, this report got extensive press coverage (“Study Says Multivitamins Not Effective”) to promote the view that multivitamins are worthless. Having read the report and reviewed its references, I have serious questions about its importance, which I can back up by reviewing some of its own references.

First of all, on what basis do the authors base their assertion that this report was needed? Actually, on pretty flimsy grounds. They list two references to justify the belief that there is a common “belief that these preparations will prevent chronic diseases, such as cancer and cardiovascular disease (CVD)”, which this report claims to disprove. Their first reference (by the lead author of the current report) actually states that multivitamin nutrients have been effective and accepted in medical practice for the prevention of other conditions: “First, research findings published throughout the past 10–20 years have established that some supplements are very effective for disease prevention and their use has become a part of routine clinical practice [e.g., folic acid during the periconceptual period to reduce the risk of neural tube defects and iron to prevent or treat anemia during pregnancy].” This statement indirectly undermines the underlying argument in the current report that vitamins are worthless against chronic disease.

This same reference directly undermines the current report by asserting that most people use multivitamins for general health, not for prevention of serious diseases as is claimed in the current report: “Multivitamins (with or without minerals), the supplements most commonly used by American women, are most likely to be used to maintain general good health.” While this reference mentions that most American women with cancer do take vitamins, it does not pretend to know why they do so. In fact, there is no assertion that people claim to take vitamins to prevent cancer and CVD, and this reference actually gives alternative reasons for that use by patients with those conditions. This reference, like the current study by the same lead author, is dismissive of a law (DSHEA) regulating dietary supplements; and while it decries this law as reducing regulation in some areas, it ignores significant increases in scrutiny that the same law establishes, which I will explore in a subsequent section. To me, for the lead author to twice publish reports focusing on perceived negatives in the law while ignoring its clear positives and other applicable laws that increase federal regulation - implies an agenda that goes beyond scientific inquiry. 1

The second reference listed for justifying the report also does not provide the supposed justification. On the contrary, it states, “Generally, participants took multivitamins to feel better... Nearly half of participants reported that they take

multivitamins because it is hard to eat a balanced diet.” An objective observer reading these two references finds that they do not provide the promised justification for testing their own assertion that people take multivitamins to prevent cancer and CVD. Obviously, the current authors have not provided adequate references to support their claimed hypothesis; their own references betray them.

Next, the authors claim that dietary supplements are “an industry that is largely unregulated owing to the 1994 Dietary Supplement and Health Education Act [sic].” Two references are listed to defend this assertion. The first is the law itself, which actually creates clear new authority for federal regulation of supplement manufacturing, federal regulation of labels and health claims, federal regulation of new ingredients, making illegal any mislabeled or adulterated products, etc. A fair reading of this law, and of the subsequent regulations that have been written to enforce it, including the mandatory Good Manufacturing Practices currently being implemented, do not support the authors’ claim.

The second reference given also fails to support its use as a justification for the belief that supplements are largely unregulated: “DS are regulated under food law, but with certain provisions that apply only to DS...Health claims have already been authorized for folic acid and calcium, but not for several others. In 1994, when the Dietary Supplement Health and Education Act (DSHEA) was passed, it expanded and clarified the definition of DS, specified additional requirements for safety and provided for four types of claims of nutritional support...Although S/F [affecting the structure and functions of the body] effects result from both foods and drugs, representation that a product will treat, cure, mitigate or diagnose a disease is reserved for drugs.”

The current report also fails to note industry-supported legislation that now requires serious adverse events to be reported to the FDA’s MedWatch system, which serves as an early warning system for safety problems.

We have seen that the first two claims in the current report, namely that people take multivitamins to prevent certain chronic major diseases and that dietary supplements are largely unregulated, are not supported by the report’s own selected references. In other words, there is not any real justification provided to support the need for this particular report. How could the authors cite references that don’t really support their claims? How does this undermine their reasons for doing this study?

Another problem is that the current authors rather arbitrarily ignore numerous FDA-approved health claims for dietary supplements in their argument against the use of multivitamins to prevent chronic diseases, including the benefits of calcium for osteoporosis, fiber to prevent coronary heart disease, soy protein to prevent coronary heart disease, plant sterol/stanol esters and risk of coronary heart disease, potassium and the risk of high blood pressure and stroke; claims that already have met the agency’s Significant Scientific Agreement (SSA) standard. Even more bizarrely, they ignore substantial scientific agreements that were

mentioned in the lead author's own previous publication (which is referenced by the current report) which identified an accepted use of "iron to prevent or treat anemia during pregnancy" and reported "at least 35 randomized-controlled trials have shown that supplemental calcium or calcium–vitamin D combinations increase bone mass and decrease fracture risk in adult females." 6

Yet the current authors claim: "Despite the widespread use of supplements and the strong consumer beliefs about benefits, convincing scientific data to support efficacy are lacking. With the exception of recommending a folic acid–containing supplement to women of childbearing potential and advising avoidance the use of high-dose beta carotenesupplements by smokers, current data are insufficient to formulate public health recommendations for dietary supplement use for otherwise healthy persons."

Also, the FDA has also approved a number of less definitive Qualified Health Claims (QHCs) including calcium and colon/rectal cancer & calcium and recurrent colon/rectal polyps, green tea and cancer, selenium and cancer, antioxidant vitamins & cancer, omega-3 fatty acids & coronary heart disease, B vitamins & vascular disease, phosphatidylserine & cognitive dysfunction and dementia, chromium picolinate & diabetes, calcium & hypertension, pregnancy-induced hypertension and preeclampsia. The FDA-Approved Health Claims and QHCs are the only disease claims authorized for dietary supplements in the United States, with all others prohibited under the supposedly deregulating DSHEA law. 7

Another reference mischaracterization is the authors' statement that "One study of more than 1 million Americans reported no association of multivitamin use with total mortality, coronary heart disease mortality, or cancer mortality." If, in fact, one were to read the reference carefully, one might find a more contradictory and less definitive tone: "Because CPS-II collected information on vitamin supplement use only once, in 1982, our measurement of duration of use is imprecise, and we potentially misclassify people who changed their use of multivitamin during the 7-year follow-up. This is an important limitation and may explain why we did not find a reduced risk of colon cancer among women with long duration of multivitamin use, as was found in the Nurses' Health Study, which had repeat assessments of multivitamin use." The imprecise nature of this reference must be emphasized. The Cancer Prevention Study II (CPS-II), which relied on a single survey of multivitamin use to classify as users those who claimed to have taken a multivitamin of any strength at least once during the month preceding the survey, was likely to be more and more inaccurate over time, and wherein only about half of the people surveyed claimed to have taken their multivitamin supplement daily during the previous month, is not a strong reference because its weak design does not establish any definitive effects clearly attributed to multivitamins. 13

Contrast this with the admittedly more rigorous Nurses' Health Study, showing benefits in those taking supplements that were validated by repeatedly assessing whether or not the subjects kept taking their vitamins. While the current report has an 8-year follow up period, the Nurses' Health Study reported significant benefits only after 15 years of multivitamin use, concluding that such "Long-term use of

multivitamins may substantially reduce risk for colon cancer.” This is another indication that the current report’s authors have failed to design their study in such a way as to follow previous successes and avoid known shortcomings of previously published studies; surprisingly, not even the ones that they themselves have referenced or written. By looking at only half as much time as was previously shown to be effective, they have produced a far less rigorous and less convincing report. The incubation period of cancers and heart disease is often estimated to be many years. As the National Cancer Institute reports, “Prostate cancer often does not cause symptoms for many years.” Other sources confirm the lengthy breeding time of cancers. Mouth cancer has a ten-year incubation period. Because “the “incubation period between HPV infection and development of invasive cervical cancer is long, prevention of cancer by a vaccination programme will not be obvious for 10 to 20 years.” Asbestos dust can cause lung cancer some 10 to 30 years after exposure. Cervical cancer “has a long incubation period, between three to 17 years.” Likewise, “the ‘incubation period’ between exposure to major coronary risk factors and the maximum effects on mortality may be 10 years or more.”

In the current report, “stress multivitamins” [sic] consisting of B-Complex vitamins along with additional factors such as vitamin C or single minerals were classified as multivitamins, though they could lack essential vitamins A, D, and E, as well as most or all of the essential minerals. This is not a normal definition of a multivitamin formula. Stress formulas are normally considered B-Complex supplements that are fortified with one or more additional nutrients to help the body deal with stress, but not as a general all-in-one daily nutritional supplement. People tend to take stress supplements because they feel under stress, not as a general insurance against incomplete diets as multivitamins are taken. 3,6 While the percentage of subjects in this category is small, I question why they would be included as multivitamin users in the current report at all. Perhaps this design flaw betrays a lack of understanding of the topic being investigated, with a strangely unscientific willingness to throw too many doses and formulas in the supposedly controlled mix of variables.

In the case of multivitamins, most studies have shown overwhelmingly positive effects; such as one report evidencing reduced infections in nursing homes with vitamins over placebo (73% vs. 43%). Intervention was with a multivitamin containing beta-carotene. Infection-related absenteeism was higher in the placebo group than in the treatment group (57% vs. 21%). Perhaps most importantly, 93% of participants with diabetes mellitus reported an infection versus only 17% of those receiving supplements.

Interesting, the current report being reviewed also indicates that nonusers had a higher rate of diabetes treatment than multivitamin users; nonusers were treated at a rate of 5.2% while users ranged only from 2.7 to 3.5%. Nonusers also had slightly lower rates (81.4%) of mammograms compared with users (85.7 to 87.2%), which could imply greater rates of undetected breast cancer that may confound comparisons. 1

Another study reported in the Journal of the National Cancer Institute looked at death rates in a population given multivitamins or other nutrients. After supplements were given for 5.25 years in the general population trial of 30,000 people, significant reductions in total [relative risk (RR) = 0.91] and cancer (RR = 0.87) mortality were observed in subjects receiving beta-carotene, alpha-tocopherol, and selenium combined. These nutrients are common in multivitamin formulas. The same researchers reported on a subgroup of 3,318 persons with esophageal Dysplasia (a precursor to esophageal cancer) that was given either a multiple vitamin-and-mineral supplement or a placebo for 6 years. In this portion of the trial, a trend towards small reductions in total (RR 0.93) and cancer (RR =0.96) mortality were observed that did not reach statistical significance. In any case, no increase in cancer rates was noted in the group taking multivitamins; there was actually a possible small benefit in terms of reducing this risk. The participants getting the multivitamin took a daily beta-carotene capsule along with two multivitamin tablets. This was a group of subjects at high risk of getting throat cancer.

Another problem with the current study is that these are nutrients and there are several important yet uncontrolled variables preventing meaningful conclusions:

- The same nutrients are found in people's diet, confounding researchers more used to novel drug studies who may be unfamiliar with the need to control additional variables in nutrient study design
- The variety of formulations and nutrients included prevent a meaningful comparison by individual or groups of vitamins or minerals, present or absent
- The potency of various nutrients taken could vary from absent to very high; there is no dose-dependent data possible in this particular study design that lumped together a wide range of non-homogenous dietary supplements

In conclusion, there are many basic omissions and errors in this report's rationale and design that should have dramatically reduced its importance and avoided a media frenzy over its flimsy conclusions. Unfortunately, nutrient studies often lack adequate critical review and the researchers tend to jump to unsupported conclusions by ignoring important variables. In this case, one problem was the design of a study that was simply too short to show any benefits. Another is the absolute lack of control over potencies and nutrient content. Rather than blaming the vitamins, it was probably pre-existing conditions and supplemental intervention was too little, too late. This report's authors seem to lack objectivity by referring to an industry that has had numerous new regulatory controls imposed as "unregulated". They have also chosen to ignore numerous approved health claims for vitamins, as well as evidence of benefits for those suffering from diseases other than cancer and cardiovascular disease. Additionally, they have described unsubstantiated motives for why people take vitamins, designing a study that was too short and included too many uncontrolled variables to be definitive, thus undermining their entire project's basis and conclusions. Nutrient studies are simply more complex than drug studies and require a much higher level of careful planning

to ensure meaningful results and eliminate as many variables as possible. In this case, I fear that the current report failed to do this, in the process generating much heat but little light on the topic.

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