Circulation: Cardiovascular Quality and Outcomes

EDITORIAL

Multivitamins Do Not Reduce Cardiovascular Disease and Mortality and Should Not Be Taken for This Purpose

How Do We Know That?

See Article by Kim et al

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Many US adults take dietary supplements, with up to 70% of older adults (>64 years of age) consuming at least one.[1] Together, they account for sizable expenditure on vitamins and herbal supplements ($21 billion in 2015),[2] all in hopes of preventing disease and improving health. Data from the National Health and Nutrition Examination Survey estimate that the percentage of US adults who consume a multivitamin increased from 30% to almost 40% between 1988 to 1994 and 2003 to 2006, with a modest a decline in recent years.[1] Multivitamins are often recommended by well-intentioned physicians.[3] Unfortunately, the results from a variety of previous studies do not support the practice of multivitamin supplementation for cardiovascular disease and mortality.[4,5]

In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Kim et al[6] present results from their meta-analysis. Kim et al[6] defined multivitamins as dietary supplements comprising >3 vitamin and mineral ingredients. They found that, in 18 reviewed articles, multivitamin supplementation was not associated with the risk of cardiovascular disease mortality (relative risk (RR), 1.00; 95% confidence interval [CI], 0.97–1.04), coronary heart disease (CHD) mortality (RR, 1.02; 95% CI, 0.92–1.13), stroke mortality (RR, 0.95; 95% CI, 0.82–1.09), or stroke incidence (RR, 0.98; 95% CI, 0.91–1.05). However, multivitamin use was associated with a lower risk of CHD incidence (RR, 0.88; 95% CI, 0.79–0.97), but this result was primarily driven by observational studies.

There are 2 important concepts worth considering when assessing these largely null findings. (1) Often, there is confounding when examining the effects of diet or supplements on health outcomes in observational data. (2) The choice of adjusting for some, but not other variables, can allow researchers to search a range of potential models, choosing which one they want to report, a phenomenon called vibration of effects. These are related concepts, in that, depending on which variables are included and which assumptions are being made in the analysis, different measures of effect and different conclusions may follow.

Confounding means that some variable, which was either unmeasured or unadjusted for, affects the observed association. Confounding is a common limitation in studies that evaluate dietary exposures, in part because dietary or supplement use is tied to broader patterns of socioeconomics and lifestyle. In this meta-analysis, we see a suggestion of confounding in the data for at least some studies, showing that CHD incidence and CHD mortality are different for studies that adjusted for fruit and vegetable intake versus those that do not adjust for this. The risk of CHD mortality among people taking multivitamins was higher in studies that did not adjust for fruit and vegetable intake than in studies that did adjust for fruit and vegetable consumption (RR, 1.14; 95% CI, 0.99–1.32 versus RR, 0.95; 95%

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CI, 0.88–1.02; *P*=0.02 for interaction). Alternatively, the risk of CHD incidence among people taking multivitamins was lower in studies that did not adjusted for fruits and vegetables than studies that did adjust for fruits and vegetables (RR, 0.74; 95% CI, 0.62–0.89 versus RR, 0.91; 95% CI, 0.83–1.00; *P*=0.01 for interaction). Fruit and vegetable intake may represent far more than dietary intake. Fruits and vegetables can be more expensive than other foods when considering the cost per calorie,[7] so people who consume more fruits and vegetables may be more likely have different overall diet habits, different access to health care, and different engagement in other salutatory health behaviors.[3] Statistical adjustment can help to minimize confounding, but it often cannot fully adjust for all confounding. In support of this concept, the authors of this meta-analysis report risk differences for CHD between studies done in the United States and those done outside of the United States. Diet and lifestyle are obvious reasons for this difference between countries, but there may also be other explanatory factors that are unmeasurable.

The one hopeful finding from Kim et al[6]—multivitamin supplementation being protective of CHD incidence—was of limited value because this finding was only significant in observational studies (RR, 0.90; 95% CI, 0.85–0.96), whereas the risk from the 2 randomized trials was null (RR, 0.97; 95% CI, 0.80–1.19). This pattern of significant findings in observational studies only to be followed by null findings in randomized controlled trials (RCTs) has been repeated many times in nutritional epidemiology (β-carotene or folic acid for cancer prevention, antioxidants for the prevention of cardiovascular disease, and even vitamin C for the common cold). Bias in observational studies is common but is minimized in well-conducted RCTs. Moreover, there is an additional concern. In observational data sets, there are often many possible variables that researchers may choose to adjust for, potentially creating a situation where multiple hypotheses are tested but only some presented.

The effect of variable selection or picking what variables you adjust for was examined in a recent study using National Health and Nutrition Examination Survey data.[8] The authors modeled the outcome of mortality across all possible scenarios. For 417 exposures, they sought to produce estimates of the effect on all-cause mortality, using 15 commonly used covariates in observational studies, including age, sex, and smoking. Then, they ran models with all 15 covariates and every possible combination of the 15 covariates. The end result was over 8000 potential models of association for each exposure and outcome. Each model could have been its own observational study, and, in effect, the researchers modeled a large segment of the biomedical arena in a single publication. They found that simply picking and choosing what variables to adjust for results in a vibration of effect for the association between any exposure and mortality. With 31% of the exposures, they got positive and negative associations, meaning that the results can appear to be protective or risky, depending on what variables or combinations of them are included in the statistical model. Thus, observational data may not only be limited by confounding but also by multiple hypothesis testing. This further underscores the need for performing well-done randomized control trials to corroborate results from observational studies.

Often in biomedicine, practices are adopted because they appeal to our hopes and there is biological plausibility. In the case of multivitamins, it is logical that some vitamins may reduce cardiovascular events because they are anti-inflammatory or more broadly improve health and well-being. Yet, in this case, it appears they do not, and as such, multivitamins for cardiovascular disease joins the list of plausible but failed practices in cardiology.

The findings by Kim et al[6] may not ultimately be surprising in 2018. Preventing or treating disease with vitamin supplements was relatively simple when foods were limited, frank vitamin deficiency was possible, and common diseases had a clear cause, such as vitamin C deficiency for scurvy or thiamine deficiency for beriberi. Now that diets are more varied, supplemented, and fortified, diseases of frank vitamin deficiency are rare, and the most commonly occurring diseases have a multifactorial cause. It may be unlikely for a supplement ingested once a day to confer a health benefit, and the study by Kim et al[6] provides no reason to take one.

ARTICLE INFORMATION

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REFERENCES

1. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999–2012. *JAMA*. 2016;316:1464–1474. doi: 10.1001/jama.2016.14403.
2. Scott C. Americans are wasting billions of dollars every year on health supplements that don't even work. *Business Insider*. 2015. http://www.businessinsider.com/money-wasted-on-health-supplements-2015-3.
3. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. *JAMA Intern Med*. 2013;173:355–361. doi: 10.1001/jamainternmed.2013.2299.

4. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013;159:824–834. doi: 10.7326/0003-4819-159-12-201312170-00729.
5. Lamas GA, Boineau R, Goertz C, Mark DB, Rosenberg Y, Stylianou M, Rozema T, Nahin RL, Lindblad L, Lewis EF, Drisko J, Lee KL; TACT (Trial to Assess Chelation Therapy) Investigators. Oral high-dose multivitamins and minerals after myocardial infarction: a randomized trial. *Ann Intern Med*. 2013;159:797–805. doi: 10.7326/0003-4819-159-12-201312170-00004.
6. Kim J, Choi J, Kwon SY, McEvoy JW, Blaha MJ, Blumenthal RS, Guallar E, Zhao D, Michos ED. Association of multivitamin and mineral supplementation and risk of cardiovascular disease: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004224. doi: 10.1161/CIRCOUTCOMES.117.004224.
7. Drewnowski A, Specter SE. Poverty and obesity: the role of energy density and energy costs. *Am J Clin Nutr*. 2004;79:6–16. doi: 10.1093/ajcn/79.1.6.
8. Patel CJ, Burford B, Ioannidis JP. Assessment of vibration of effects due to model specification can demonstrate the instability of observational associations. *J Clin Epidemiol*. 2015;68:1046–1058. doi: 10.1016/j.jclinepi.2015.05.029.

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