HHS Public Access

Author manuscript

Ann Intern Med. Author manuscript; available in PMC 2021 March 12.

Published in final edited form as:

Ann Intern Med. 2019 August 06; 171(3): 216–217. doi:10.7326/M19-1498.

Dispense With Supplements for Improving Heart Outcomes

Amitabh C. Pandey, MD, **Eric J. Topol, MD**

Scripps Research Translational Institute, Scripps Research, and Scripps Clinic, La Jolla, California

Diets and supplements are 2 of the most intense areas of public interest but are among the most lacking in adequate data. The use of supplements continues to increase in the United States and worldwide, largely without evidence for their efficacy or safety. Nearly 3 in 4 persons in the United States use some form of supplements, so it is no wonder that the supplement market is estimated to reach nearly $300 billion in the next 5 years (1). In addition to the unbridled uptake, the U.S. Food and Drug Administration lacks regulatory authority over supplements. Yet, the safety of supplements remains unclear, with several studies showing potential harm due to dosing or impurities (2). Similarly, there are limited data to support or refute the health claims of various diets (3). With this murky landscape, a study that might illuminate the field would be especially welcome.

In their article, Khan and colleagues report an ambitious meta-analysis of recent randomized controlled trials and systematic reviews with the intent of identifying whether supplements and dietary interventions are associated with an improvement in cardiovascular outcomes (4). On the basis of their analysis encompassing 277 trials in nearly 1 million people, the authors concluded that only a few of the 16 supplements assessed and only 1 of the 8 dietary modifications evaluated had a proven effect on cardiovascular outcomes. The primary conclusions were that a low-salt diet may reduce the risk for all-cause mortality in persons without high blood pressure and that, with low certainty, omega-3 fatty acid and folate supplementation have a salutary effect on heart attack and stroke, respectively. These findings are nonetheless contrary to many previous reports that have found no significant benefit to the same diet modification or supplements (1, 3, 5).

A study of 2 019 862 patients found no significant improvements in cardiovascular outcomes with supplement use in the general population (1). In addition, Chen and colleagues evaluated supplementation and its source-exogenous supplementation compared with increased intake from natural foods-and found a similar lack of tangible benefits (5); the only source associated with any benefit was nutrient intake from foods. Many supplements may cause harm, and Khan and colleagues also reported a possible relationship

Corresponding Author: Eric J. Topol, MD, Scripps Research Translational Institute, Scripps Research, 3344 North Torrey Pines Court, Suite 300, La Jolla, CA 92037; etopol@scripps.edu.
Current author addresses are available atAnnals.org.
Current Author Addresses: Dr. Topol: Scripps Research Translational Institute, Scripps Research, 3344 North Torrey Pines Court, Suite 300, La Jolla, CA 92037.
Dr. Pandey: Scripps Clinic, 9898 Genesee Avenue, AMP400, La Jolla, CA 92037.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed atwww.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-1498.

between calcium plus vitamin D supplementation and increased risk for stroke (4, 5). It remains uncertain whether this can be attributed to oversupplementation in a Western diet that already has significant dietary fortification with calcium plus vitamin D.

Fish oils are the most widely used supplements, and recent randomized trials add to the contradictory findings. Although the analysis by Khan and colleagues found low-certainty evidence for omega-3 long-chain polyunsaturated fatty acid, recent randomized trials in the general population and in patients with diabetes have failed to confirm any benefit in cardiovascular outcomes (6, 7). The results of these trials would tend to downgrade the low-certainty rating of omega-3 fatty acid supplements to uncertain at best.

A peculiar and controversial finding on the benefit of a low-salt diet deserves highlighting. Khan and colleagues suggest that low-salt diets can improve cardiovascular outcomes, but effects differed between normotensive and hypertensive patients (4). It seems odd that a low-salt diet would decrease the risk for all-cause mortality in normotensive patients but not in hypertensive patients, for whom there was evidence of reduced cardiovascular mortality. Recent reports suggest that low-salt diets result in no significant increase in urinary sodium excretion, countering the current perspective in medicine of restricted sodium intake (8). A longitudinal study of nearly 95 000 people from 18 countries lasting more than 8 years showed an inverse correlation between sodium intake and cardiovascular outcomes (8). Accordingly, the 2019 National Academies Consensus Study Report states that “there remains insufficient evidence to establish Estimated Average Requirements (EARs) or Recommended Dietary Allowances (RDAs) for sodium” (9).

Geographic considerations among the studies included in Khan and colleagues' analysis are also notable. For example, the reported benefit of folate seems to be largely driven by the inclusion of 1 study from China, where a folate-rich diet is not routine. With regard to salt intake, Messerli and colleagues have noted that “with an average lifespan of 87.3 years, women in Hong Kong top life expectancy worldwide despite consuming an average of 8–9 g of salt per day.” (10). This exemplifies the problem of amalgamating data from people and cultures with markedly different diet and supplement baselines.

In addition, differences in geography, dose, and preparation–most studies rely on food diaries, which are based on a person's memory of what they consumed–raise questions about the veracity of the data (3). Perhaps, however, the biggest difference that needs to be considered in the future is the individual. Only recently with machine learning of large data sets, which include multimodal data on physical activity, sleep, medications, demographic characteristics, intake and timing of all foods and beverages, and gut microbiome constituents, have we begun to learn that the use of any specific diet or supplement is likely to have markedly heterogeneous effects. Testing any diet or supplement in a broad population without acknowledging interindividual variability seems like a recipe for failure, especially because most trials are not randomized, are not of sufficient duration, or do not have enough hard outcome events.

Unfortunately, the current study leaves us with the same foggy conditions that we started with. Until these conditions clear, it would be reasonable to hold off on any supplement or diet modification in all guidelines and recommendations.

References

1. Kim J, Choi J, Kwon SY, et al. 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 [PubMed: 29991644]
2. Heid M The problem with supplements. Accessed at https://elemental.medium.com/the-problem-with-supplements-e0f5f2fb1d74 on 8 5 2019.
3. loannidis JPA. The challenge of reforming nutritional epidemiologic research. JAMA. 2018;320:969–70. doi:10.1001/jama.2018.11025 [PubMed: 30422271]
4. Khan SU, Khan MU, Riaz H, et al. Effects of nutritional supplements and dietary interventions on cardiovascular outcomes. An umbrella review and evidence map. Ann Intern Med. 2019;171:190–8. doi:10.7326/M19-0341 [PubMed: 31284304]
5. Chen F, Du M, Blumberg JB, et al. Association among dietary supplement use, nutrient intake, and mortality among U.S. adults: a cohort study. Ann Intern Med. 2019;170:604–13. doi:10.7326/M18-2478 [PubMed: 30959527]
6. Bowman L, Mafham M, Wallendszus K, et al.; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med. 2018;379:1540–50. doi:10.1056/NEJMoa1804989 [PubMed: 30146932]
7. Manson JE, Cook NR, Lee IM, et al.; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med. 2019;380:33–44. doi:10.1056/NEJMoa1809944 [PubMed: 30415629]
8. Mente A, O'Donnell M, Rangarajan S, et al. Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. Lancet. 2018;392:496–506. doi:10.1016/S0140-6736(18)31376-X [PubMed: 30129465]
9. National Academies of Sciences, Engineering, and Medicine. Dietary Reference Intakes for Sodium and Potassium. Washington, DC: National Academies Pr; 2019.
10. Messerli FH, Hofstetter L, Bangalore S. Salt and heart disease: a second round of “bad science”? Lancet. 2018;392:456–8. doi:10.1016/S0140-6736(18)31724-0 [PubMed: 30129446]