GlobalResearch
Center for Research on Globalization

Flawed Research Used to Attack Multivitamin Supplements

By Global Research News
Global Research, January 16, 2014
lef.org

Theme: Science and Medicine

By Blake Gossard, Kira Schmid, ND, Luke Huber, ND, MBA, Steven V. Joyal, MD

Two flawed studies, a rehashed review, and an editorial published in the December 17th issue of the *Annals of Internal Medicine* have attempted to discredit the value of multivitaminsupplements.[1-3]

Both of the studies were plagued by grievous methodological flaws.

In one of the studies, subjects were given low-quality, low-potency multivitamin supplements. Treatment adherence rates and drop-out rates were *horrendous* in the studies. Nevertheless, mainstream sources are using these reprehensible studies to undermine dietary supplements.

The first study examined the cognitive effects of low-potency multivitamin supplementation in aging male participants. [2] Not surprisingly, the conclusions in the present analysis question the value of multivitamin benefits for cognition.

In the other study, subjects with a history of heart attack were given a multivitamin supplement or placebo and monitored for about 4.5 years for cardiovascular events.[1]

Despite succumbing to heinous *design flaws*, this study actually revealed evidence that multivitamins reduced cardiovascular risk. However, the investigators constructed the study so as to ignore anything short of miraculous cardiovascular risk reduction, so the conclusion drawn questions multivitamin benefits.

These major gaffes in study design and methodology are not being discussed by conventional sources or the media. Instead, these untoward studies are fueling the mainstream effort to undermine high-quality dietary supplements.

Concerns with the Cognitive Function Study

Poor Adherence Criteria

Subjects in the first study were considered to have adhered to their multivitamin regimen appropriately if they took it just two-thirds of the time. In other words, even subjects who skipped their multivitamin **4 months** out of the year were deemed “adherent” to the intervention.

Weak Questionnaire Data that Relies on Recollection

In addition, the method by which adherence was assessed in this study is inherently weak. Study subjects were simply asked to report how adherent they were to their assigned intervention once a year. This approach is based on recollection and is particularly prone to bias.[4] More rigorous studies properly measure compliance by asking participants to return unused study product so adherence can by directly quantified.

Low-Potency Multivitamin

The multivitamin utilized in this study contained woefully inadequate nutrient concentrations. For example, the formula contained only 60 mg of vitamin C, 25 mcg of vitamin B12, and 20 mcg of selenium.

Health-conscious people know that these abysmally small nutrient doses are very unlikely to deliver any considerable health benefits. Even the researchers state a limitation of their study is "[the] doses of vitamins may be too low…"

Some Cognitive Benefits Despite Low Dose

Despite the low potency vitamins used in this trial, benefits were seen in the multivitamin group. For example, after 2.5 years of treatment with the low potency multivitamin, there was an improvement seen in cognitive function compared to controls, although this did not reach statistical significance.

Other Evidence Shows Nutrient Supplementation Supports Cognitive Function

Multivitamins contain several nutrients shown to affect cognitive decline.

Vitamins B6, B12, and folic acid are important for methylation reactions that are crucial to the health of brain tissue. Deficiency of these nutrients is associated with severe impairment of brain function.[5] One placebo-controlled trial revealed that men and women with mild cognitive impairment who were supplemented with vitamins B6, B12, and folic acid for 24 months experienced 29% less brain atrophy and higher cognitive test scores compared to those who received placebo.[6]

Numerous studies have implicated oxidative stress in the pathology of mild cognitive impairment and Alzheimer's disease.[7-9] Antioxidant vitamins C, E, and beta carotene protect the brain from oxidative damage.[10]

Evidence strongly suggests that vitamin A exerts actions on brain physiology and behavior in adult life. For example, an active metabolite of vitamin A, retinoic acid, is a potent signaling molecule in the brain and helps regulate nerve cell growth, nerve survival, and synaptic plasticity.[11]

In a double-blind, placebo-controlled clinical trial involving over 200 healthy middle-aged individuals, subjects were given either a multivitamin or placebo for more than two months, and both groups were then assessed for cognitive function. It was shown that those taking the multivitamin displayed less fatigue during extended cognitive challenges and were more accurate. Also, those taking multivitamins were able to more quickly complete mathematical

processing tests than subjects receiving placebo.[12]

An 8-week, double-blind, placebo-controlled trial of multivitamins in men aged 50 – 74 was published in 2012 by Australian researchers. They found that multivitamin supplementation significantly improved some aspects of memory and concluded that "… *relatively short-term supplementation with a multivitamin can benefit […] risk factors for cognitive decline*."[13]

Concerns with the Cardiovascular Event Study

Poor Adherence Standards

In the cardiovascular event study, a staggering **46%** of subjects discontinued the multivitamin regimen during the study.

It is incomprehensible that the investigators felt it was acceptable to generate an analysis of efficacy when nearly half of the active-treatment group failed to adhere to the treatment. In addition, it is reprehensible that the editors at the *Annals of Internal Medicine* allowed this methodologically flawed research to be published in their journal.

Life Extension® members are well aware that optimal health benefits cannot be achieved by haphazardly or intermittently eating a healthy diet or taking nutritional supplements. Attaining ideal health is a lifelong endeavor that requires regular use of high-quality and comprehensive nutritional supplements.

Study Downplays Reduced Cardiovascular Risk from Multivitamins

Two figures included in the report demonstrated reduced cardiovascular event rates for the multivitamin group, although these did not reach statistical significance. This benefit generally increased over the duration of the 4.5 year follow-up period.

For example, despite concluding that multivitamins don't protect against cardiovascular risk, the investigators did find an **11% *reduction*** in their primary endpoint (composite of time to death from any cause, heart attack, stroke, coronary revascularization or hospitalization for angina) among those taking multivitamins.

Also, there was an **18% *reduction*** in the secondary endpoint (composite time to cardiovascular death, heart attack or stroke).

Absurd Efficacy Assumptions

A major part of study design involves defining effect thresholds that can be statistically elucidated based upon the number of subjects and trial duration. In this study, the authors designed the trial to detect a **25%** reduction in cardiovascular risk. In other words, for this trial to conclude that multivitamins provide cardiovascular benefit, the intervention would have had to eliminate 1 in 4 cardiovascular event outcomes.

By setting the bar for efficacy so high, this study was set up to conclude that multivitamins would provide no benefit from the outset.

More Diabetes Patients Selected For Group Receiving Multivitamins

Diabetes is one of the strongest known risk factors for cardiovascular disease. Therefore, it

is critically important that any study examining cardiovascular outcomes make sure that all groups of participants have similar baseline rates of diabetes. If not, the group with greater diabetes frequency will almost certainly have disproportionately higher cardiovascular risk.

In this flawed *Annals of Internal Medicine* study, subjects in the multivitamin group had a **higher** rate of diabetes at baseline than those who received the placebo. This difference in diabetes rate may have biased the results.

Low Dose Vitamin D and Vitamin B12

Although the researchers who conducted this study referred to the multivitamin preparation as "high-potency," one of the most critically important components for cardiovascular health was virtually absent from the formula.[14]

The multivitamin utilized in this study contained a mere **100 IU** of ***vitamin D***.

Life Extension advocates having at least 2,000 IU of vitamin D in a multivitamin with increasing levels to maintain 25-hydroxy vitamin D levels of 50 – 80 ng/mL.

Another critical heart-health nutrient is **vitamin B12**. It lowers levels of the blood-vessel-damaging amino acid ***homocysteine***, which is associated with cardiovascular risk.[15]

The multinutrient formula used in this flawed study contained **100 mcg** of vitamin B12. Life Extension advocates for having 300 – 600 mcg of vitamin B12 in multivitamin formulas with increasing doses as needed to maintain optimal homocysteine levels of <8 µmol/L.[16]

Critical Importance of Gamma Tocopherol Overlooked

While the alpha tocopherol form of vitamin E was included in the multivitamin, the gamma tocopherol form was not. This is important because evidence shows that in the absence of gamma tocopherol, alpha tocopherol alone may not provide meaningful cardiovascular protection. Moreover, evidence suggests that supplementation with only alpha tocopherol might actually reduce levels of cardioprotective gamma tocopherol.

The alpha form of vitamin E decreases oxidative damage to the arterial lining, reduces dangerous aggregation and clumping of blood cells, and delays clot formation.[17] It also inhibits smooth muscle proliferation (involved in the plaque-forming process),[18] improves stability of fatty plaques, enhances function of cells lining the arteries, regulates vascular tone, and fights inflammation.[19] Despite these impressive findings, however, clinical trials of alpha tocopherol alone have yielded mixed results concerning its cardioprotective effects.

This may be due to the role of gamma tocopherol on cardiovascular health. Since high-dose alpha tocopherol supplementation dramatically reduces gamma tocopherol levels, alpha tocopherol's benefits may be overshadowed by the adverse effects of diminished gamma tocopherol levels.[20]

Gamma tocopherol is important in defending against cardiovascular disease. Several investigations confirm that higher tissue concentrations of gamma tocopherol are associated with lower rates of illness and death due to cardiovascular events.[21]

In fact, several studies show that patients with advanced cardiovascular disease exhibit normal plasma levels of alpha tocopherol but have substantially lower levels of gamma tocopherol.[22-24] In a seven-year follow-up study of more than 334,000 postmenopausal women with no previous heart disease, greater intake of dietary vitamin E — consisting predominantly of gamma tocopherol — was strongly associated with a lower risk of death from cardiovascular disease. The data did not appear to demonstrate a similarly protective role for supplemental alpha tocopherol.[25]

The Editorial Downplays the Researched Benefits of Vitamins and Minerals

Despite the opinions shared by the authors of the editorial, other research has shown multivitamins protect against cancer and cardiovascular disease. [26,27]

For example, the Physician's Health Study II (PHS-II) found that multivitamin supplementation was associated with an **8% reduction in overall cancer incidence** and a **12% reduction in cancer death** after 11.2 years of follow up.[26]

In addition, the Supplementation in Vitamins and Mineral Antioxidants Study (SU.VI.MAX) found a **31% reduction in total cancer incidence in men** that supplemented with a multivitamin.[27]

When SU.VI.MAX's results in men were combined with the PHS-II results, the risk for all cancer incidence was reduced over 10 years of follow-up. [28]

The PHS-II study also found a **39% reduction in fatal heart attack risk** in those taking a multivitamin.[32]

In addition, several trials have shown considerable benefits associated with supplementation. A small sample of the vast number of robust studies that support vitamin and mineral supplementation is provided below.

A 2013 study that enrolled 88,045 postmenopausal women reported that vitamin B6 and riboflavin intake from diet and supplements reduces the risk of colorectal cancer in postmenopausal women,[10] and a 2007 study that enrolled 81,184 subjects found that low vitamin B6 intake is associated with an increased risk of colorectal cancer.[29]

Another 2013 study that examined 77,446 men and women aged 50 – 76 found an inverse relationship between dietary selenium and the risk of pancreatic cancer.[30]

In 2012, European researchers published results of a large study on 23,943 subjects who took antioxidant vitamin supplements over an average of 11 years. Individuals who used antioxidant multivitamins were 48% less likely to die from cancer and 42% less likely to die due to any cause compared to antioxidant vitamin nonusers.[31]

Conclusion

Based upon an analysis of these studies and the existing research, Life Extension continues to recommend members supplement with a high quality multivitamin containing physiologic

doses of a broad array of vitamins and minerals, along with high-dose omega-3s, vitamin D, curcumin, coenzyme Q10, PQQ, carnosine, lipoic acid, other nutrients and hormones that play crucial roles in maintaining optimal health.

References

1. Lamas GA, Boineau R, Goertz C, et al. Oral High-Dose Multivitamins and Minerals After Myocardial Infarction. *Annals of Internal Medicine.* 2013;159(12).
2. Grodstein F, O'Brien J, Kang JH, et al. Long-Term Multivitamin Supplementation and Cognitive Function in Men: The Physicians' Health Study II. *Annals of Internal Medicine.* 2013;159(12).
3. Guallar E, Stranges S, Mulrow C, Appel LJ. Enough Is Enough: Stop Wasting Money on Vitamin and Mineral Supplements. *Annals of Internal Medicine.* 2013;159(12):850-852.
4. Bowling A. Mode of questionnaire administration can have serious effects on data quality. *Journal of Public Health (Oxford, England).* Sep 2005;27(3):281-291.
5. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. *The American Journal of Clinical Nutrition.* Feb 2000;71(2):614s-620s.
6. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PloS One.* 2010;5(9):e12244.
7. Lovell MA, Markesbery WR. Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. *Nucleic Acids Research.* 2007;35(22):7497-7504.
8. Butterfield DA, Sultana R. Redox proteomics identification of oxidatively modified brain proteins in Alzheimer's disease and mild cognitive impairment: insights into the progression of this dementing disorder. *Journal of Alzheimer's Disease : JAD.* Aug 2007;12(1):61-72.
9. Mecocci P, MacGarvey U, Beal MF. Oxidative damage to mitochondrial DNA is increased in Alzheimer's disease. *Annals of Neurology.* Nov 1994;36(5):747-751.
10. Sardesai VM. Role of antioxidants in health maintenance. *Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition.* Feb 1995;10(1):19-25.
11. Olson CR, Mello CV. Significance of vitamin A to brain function, behavior and learning. *Molecular Nutrition & Food Research.* Apr 2010;54(4):489-495.
12. Haskell CF, Robertson B, Jones E, et al. Effects of a multi-vitamin/mineral supplement on cognitive function and fatigue during extended multi-tasking. *Human Psychopharmacology.* Aug 2010;25(6):448-461.
13. Harris E, Macpherson H, Vitetta L, Kirk J, Sali A, Pipingas A. Effects of a multivitamin, mineral and herbal supplement on cognition and blood biomarkers in older men: a randomised, placebo-controlled trial. *Human Psychopharmacology.* Jul 2012;27(4):370-377.
14. Li YC. Vitamin D: roles in renal and cardiovascular protection. *Current opinion in nephrology and hypertension.* Jan 2012;21(1):72-79.
15. Casas JP, Bautista LE, Smeeth L, Sharma P, Hingorani AD. Homocysteine and stroke: evidence on a causal link from mendelian randomisation. *Lancet.* Jan 15-21 2005;365(9455):224-232.
16. Yajnik CS, Lubree HG, Thuse NV, et al. Oral vitamin B12 supplementation reduces plasma total homocysteine concentration in women in India. *Asia Pacific Journal of Clinical Nutrition.* 2007;16(1):103-109.
17. Saldeen T, Li D, Mehta JL. Differential effects of alpha- and gamma-tocopherol on low-density lipoprotein oxidation, superoxide activity, platelet aggregation and arterial

thrombogenesis. *Journal of the American College of Cardiology.* Oct 1999;34(4):1208-1215.
18. Keaney JF, Jr., Simon DI, Freedman JE. Vitamin E and vascular homeostasis: implications for atherosclerosis. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology.* Jun 1999;13(9):965-975.
19. Kaul N, Devaraj S, Jialal I. Alpha-tocopherol and atherosclerosis. *Experimental Biology and Medicine (Maywood, N.J.).* Jan 2001;226(1):5-12.
20. Huang HY, Appel LJ. Supplementation of diets with alpha-tocopherol reduces serum concentrations of gamma- and delta-tocopherol in humans. *The Journal of Nutrition.* Oct 2003;133(10):3137-3140.
21. Jiang Q, Christen S, Shigenaga MK, Ames BN. gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention. *The American Journal of Clinical Nutrition.* Dec 2001;74(6):714-722.
22. Ohrvall M, Sundlof G, Vessby B. Gamma, but not alpha, tocopherol levels in serum are reduced in coronary heart disease patients. *J Intern Med.* Feb 1996;239(2):111-117.
23. Kontush A, Spranger T, Reich A, Baum K, Beisiegel U. Lipophilic antioxidants in blood plasma as markers of atherosclerosis: the role of alpha-carotene and gamma-tocopherol. *Atherosclerosis.* May 1999;144(1):117-122.
24. Ohrvall M, Tengblad S, Vessby B. Tocopherol concentrations in adipose tissue. Relationships of tocopherol concentrations and fatty acid composition in serum in a reference population of Swedish men and women. *European Journal of Clinical Nutrition.* Mar 1994;48(3):212-218.
25. Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *The New England Journal of Medicine.* May 2 1996;334(18):1156-1162.
26. Gaziano JM, Sesso HD, Christen WG, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA : the Journal of the American Medical Association.* Nov 14 2012;308(18):1871-1880.
27. Hercberg S, Galan P, Preziosi P, et al. Background and rationale behind the SU.VI.MAX Study, a prevention trial using nutritional doses of a combination of antioxidant vitamins and minerals to reduce cardiovascular diseases and cancers. SUpplementation en VItamines et Mineraux AntioXydants Study. *International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition.* 1998;68(1):3-20.
28. 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.* Nov 12 2013.
29. Ishihara J, Otani T, Inoue M, Iwasaki M, Sasazuki S, Tsugane S. Low intake of vitamin B-6 is associated with increased risk of colorectal cancer in Japanese men. *The Journal of Nutrition.* Jul 2007;137(7):1808-1814.
30. Han X, Li J, Brasky TM, et al. Antioxidant intake and pancreatic cancer risk: the Vitamins and Lifestyle (VITAL) Study. *Cancer.* Apr 1 2013;119(7):1314-1320.
31. Li K, Kaaks R, Linseisen J, Rohrmann S. Vitamin/mineral supplementation and cancer, cardiovascular, and all-cause mortality in a German prospective cohort (EPIC-Heidelberg). *European Journal of Nutrition.* Jun 2012;51(4):407-413.
32. Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, . . . Gaziano JM. Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA : the journal of the American Medical Association. Nov 7 2012;308(17):1751-1760.
