Title: Efficacy of multivitamin/mineral supplementation to reduce chronic disease risk: a critical review of the evidence from observational studies and randomized controlled trials

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This manuscript has not been published elsewhere nor has it been submitted for publication elsewhere.

Disclosure Information:

Pfizer Consumer Healthcare has sponsored the writing of the manuscript and provided payment to a medical communications agency, Peloton Advantage, LLC, for editorial assistance. Reprints will not be available from the author. GA and VJD received an honorarium from Pfizer in connection with the development of this manuscript. BF is a consultant for Pfizer Inc.

Running Head

Multivitamin/minerals and chronic disease risk

Keywords

Multivitamin/minerals; chronic disease risk; randomized controlled trials; prospective cohort studies; micronutrient inadequacies

ABSTRACT

We reviewed recent scientific evidence regarding the effects of MVM supplements on risk of chronic diseases, including cancer, cardiovascular disease, and age-related eye diseases. Data from randomized controlled trials (RCTs) and observational, prospective cohort studies were examined. The majority of scientific studies investigating the use of MVM supplements in chronic disease risk reduction reported no significant effect. However, the largest and longest RCT of MVM supplements conducted to date, the Physicians' Health Study II (PHS II), found a modest and significant reduction in total and epithelial cancer incidence in male physicians, consistent with the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) trial. In addition, PHS II found a modest and significant reduction in the incidence of nuclear cataract, in agreement with several other RCTs and observational, prospective cohort studies. The effects of MVM use on other subtypes of cataract and age-related macular degeneration remain unclear. Neither RCTs nor prospective cohort studies are without their limitations. The placebo-controlled trial design of RCTs may be inadequate for nutrient interventions, and residual confounding, measurement error, and the possibility of reverse causality are inherent to any observational study. National surveys show that micronutrient inadequacies are widespread in the US and that dietary supplements, of which MVMs are the most common type, help fulfill micronutrient requirements in adults and children.

INTRODUCTION

In general, a multivitamin/mineral (MVM) supplement is a dietary supplement that contains about 100% of the recommended levels (Food and Drug Administration, 2013; National Academy of Sciences, Institute of Medicine et al., 2010; Pfizer Consumer Healthcare, 2013) of daily intake of most vitamins and essential minerals (**Table 1**). However, there are no standardized definitions for MVMs, and the composition of commercial MVM products varies widely, potentially including such non-nutrient ingredients as herbals, phytochemicals, or hormones. No MVM supplement contains the recommended levels of intake for calcium, magnesium, potassium, and phosphorus since the resulting pill would be too bulky.

Use of dietary supplements has become increasingly common among adults in the US (Bailey R. L., Gahche, J. J. et al., 2011; Briefel R. R., Johnson, C. L., 2004), with MVMs being the most popular type (Bailey R. L., Gahche, J. J. et al., 2013; Gahche J., Bailey, R. et al., 2011). According to the NHANES 2007–2010, approximately one-third of adults in the US ≥20 years of age take an MVM supplement, with the main motivation being "to improve overall health" (Bailey R. L., Gahche, J. J. et al., 2013). MVM use is more prevalent among women, older adults, non-Hispanic Whites, and those with higher education, as well as those who report participating in physical activity and those with a lower BMI (National Institutes of Health, 2006; Radimer K., Bindewald, B. et al., 2004). Overall, dietary supplement users are more likely to have healthier diets (Foote J. A., Murphy, S. P. et al., 2003; Li K., Kaaks, R. et al., 2010; Rock

C. L., 2007) or rate their health as excellent or very good (Bailey R. L., Gahche, J. J. et al., 2013; Radimer K., Bindewald, B. et al., 2004; Sullivan K. M., Ford, E. S. et al., 2009). On the other hand, individuals with chronic illness seeking to prevent recurrence are also frequent users of dietary supplements (Bender M. M., Levy, A. S. et al., 1992; National Institutes of Health, 2006; Patterson R. E., Neuhouser, M. L. et al., 2003).

Despite MVM use being so prevalent, US national surveys indicate that select micronutrient (vitamin and nutritionally essential minerals) inadequacies still exist. After calculating total usual nutrient intake from all food sources and supplements, a significant proportion of US adults ≥19 years of age still fall short of meeting the estimated average requirement (EAR) (**text box**) for certain micronutrients, namely vitamin D (68%), vitamin E (58%), vitamin A (37%), vitamin C (28%), calcium (36%), and magnesium (48%) (Fulgoni V. L., III, Keast, D. R. et al., 2011). The majority of US adults consume less than the Adequate Intake (AI) (**text box**) for potassium and vitamin K (Fulgoni V. L., III, Keast, D. R. et al., 2011). Additionally, many Americans consume foods with many calories and few nutrients. Data from NHANES (1988–1994) estimated that 27% of dietary calorie intake in the American diet is from energy-dense, nutrient-poor foods (Kant A. K., 2000). This survey also found that higher intakes of energy-dense, nutrient-poor foods were associated with lower serum concentrations of several micronutrients, including vitamin A, folate, vitamin B_{12}, vitamin C, and vitamin E (Kant A. K., 2000). According to the Dietary Guidelines for Americans (2010), Americans currently consume too much sodium and too many calories from solid fats, added sugars, and refined grains (US Department of Agriculture, 2010). This contributes to a situation where the over-consumption of high-calorie,

nutrient-poor foods meets or exceeds energy requirements but fails in the provision of essential vitamins and minerals.

Select micronutrient inadequacies are common in other industrialized nations (Elmadfa I., Freisling, H., 2009; Taylor J. P., Maclellan, D. L. et al., 2007; Whatham A., Bartlett, H. et al., 2008), and multiple micronutrient deficiencies, especially iron, vitamin A, zinc, and iodine, are prevalent in the developing world, affecting an estimated 2 billion people (Food and Agriculture Organization of the United Nations, 2004; Muller O., Krawinkel, M., 2005). In addition, vitamin D inadequacy may affect as many as 1 billion people (Holick M. F., 2007) and B-vitamin deficiencies are common in some populations (Ramakrishnan U., 2002). A situation of "hidden hunger" occurs when there is access to sufficient calories yet insufficient amounts of essential micronutrients (Burchi F., Fanzo, J. et al., 2011). Hidden hunger is common in developing and underdeveloped nations where there is a reliance on starchy food staples (Burchi F., Fanzo, J. et al., 2011) and is becoming more prevalent in developed nations where micronutrient inadequacies exist in spite of an abundance and diversity of food (Cole C. R., 2012). While effects of overt deficiencies are well documented, less is known regarding the health effects of marginal or subclinical micronutrient deficiencies, although some studies have reported links to general fatigue (Huskisson E., Maggini, S. et al., 2007), impaired immunity (Bhaskaram P., 2001; Ibs K.-H., Rink, L., 2004), and adverse effects on cognition (Kennedy D. O., Haskell, C. F., 2011). It has also been proposed that during chronic micronutrient inadequacies, short-term metabolic requirements take precedence over long-term needs (Ames B. N., 2006), thus

contributing to cumulative damage and dysfunction that increase one's risk of age-related chronic diseases (Ames B. N., 2006; Heaney R. P., 2008).

Correcting marginal inadequacies through daily MVM supplementation might reduce risk of chronic disease. However, epidemiological studies on the health effects of MVMs have reported conflicting results, and an NIH State-of-the-Science Panel concluded there was insufficient trial evidence to recommend either for or against the use of MVMs in chronic disease prevention as of 2006 (National Institutes of Health, 2006). A 2013 systematic review and meta-analysis from the US Preventive Task Force reported that there was limited evidence to support the use of vitamin and mineral supplements in the primary prevention of cancer and cardiovascular disease (CVD) (Fortmann S. P., Burda, B. U. et al., 2013). Notably, this analysis included only 4 RCTs and 1 cohort study that assessed MVM use; the remaining 23 studies reviewed only single or paired vitamin or mineral supplements, which are not considered MVMs by most standards. Here, we review scientific evidence regarding the effects of MVM supplements on risk of various chronic diseases, including cancer, CVD, and age-related eye diseases, and some basic biological functions. Data from both randomized controlled trials (RCTs) (Age-Related Eye Disease Study 2 Research Group, 2013; AREDS, 2001a; Avenell A., Campbell, M. K. et al., 2005; Bartlett H. E., Eperjesi, F., 2007; Blot W. J., Li, J. Y. et al., 1993; Bogden J. D., Bendich, A. et al., 1994; Gaziano J. M., Sesso, H. D. et al., 2012; Graat J. M., Schouten, E. G. et al., 2002; Hercberg S., Galan, P. et al., 2004; Leng G. C., Lee, A. J. et al., 1997; Li J. Y., Taylor, P. R. et al., 1993; Maraini G., Sperduto, R. D. et al., 2008; McNeill G., Avenell, A. et al., 2007; Richer S., 1996; Richer S., Stiles, W. et al., 2004; Sesso H. D., Christen, W. G. et al., 2012; Sperduto R.

D., Hu, T. S. et al., 1993; Wolters M., Hickstein, M. et al., 2005) and observational, prospective cohort studies (Christen W. G., Ajani, U. A. et al., 1999; Fuchs C. S., Willett, W. C. et al., 2002; Giovannucci E., Stampfer, M. J. et al., 1998; Hara A., Sasazuki, S. et al., 2011; Hotaling J. M., Wright, J. L. et al., 2011; Hunter D. J., Manson, J. E. et al., 1993; Iso H., Kubota, Y., 2007; Jacobs E. J., Connell, C. J. et al., 2002; Kim I., Williamson, D. F. et al., 1993; Larsson S. C., Akesson, A. et al., 2010; Lawson K. A., Wright, M. E. et al., 2007; Li K., Kaaks, R. et al., 2012; Losonczy K. G., Harris, T. B. et al., 1996; Mares-Perlman J. A., Lyle, B. J. et al., 2000; Messerer M., Hakansson, N. et al., 2008; Michaud D. S., Spiegelman, D. et al., 2000; Muntwyler J., Hennekens, C. H. et al., 2002; Mursu J., Robien, K. et al., 2011; Neuhouser M. L., Wassertheil-Smoller, S. et al., 2009; Park S. Y., Murphy, S. P. et al., 2011; Pocobelli G., Peters, U. et al., 2009; Rautiainen S., Akesson, A. et al., 2010; Rautiainen S., Lindblad, B. E. et al., 2010; Rimm E. B., Willett, W. C. et al., 1998; Stampfer M. J., Hennekens, C. H. et al., 1993; Stevens V. L., McCullough, M. L. et al., 2005; Watkins M. L., Erickson, J. D. et al., 2000; Wu K., Willett, W. C. et al., 2002; Zhang S., Hunter, D. J. et al., 1999; Zhang S. M., Giovannucci, E. L. et al., 2001; Zhang S. M., Moore, S. C. et al., 2006; Zhang W., Shu, X. O. et al., 2012) are examined, and the limitations of each study type are discussed.

REVIEW OF SCIENTIFIC EVIDENCE: CHRONIC DISEASE PREVENTION

Randomized controlled trials

RCTs are studies in which participants are allocated by chance alone to receive or not receive a clinical intervention (National Institutes of Health, 2006). There is much variation in the

composition of the MVM formulations used in supplementation trials; some trials use commercially available MVMs while others use specific multi-nutrient combinations that are considered functionally related. Existing reviews and meta-analyses have defined an MVM as a supplement that contains at least 3 vitamins and that may (Bailey R. L., Gahche, J. J. et al., 2011) or may not (Gahche J., Bailey, R. et al., 2011; Huang H. Y., Caballero, B. et al., 2007; Macpherson H., Pipingas, A. et al., 2013) include minerals. For the purpose of this review, we define an MVM as a supplement containing 3 or more vitamins and at least 1 mineral. We considered the same pool of trials from the recent systematic literature search and meta-analysis by Macpherson, et al. regarding the effect of MVM supplementation on mortality (Macpherson H., Pipingas, A. et al., 2013). Their search criteria included a definition of MVM more inclusive than our own, thus ensuring coverage of the pertinent literature (**Table 2**).

Cancer

The Physicians' Health Study II (PHS II) was a large-scale, randomized, double-blind, placebo-controlled trial that tested the long-term effects of a common MVM supplement (Centrum® Silver; Pfizer Consumer Healthcare, Madison, NJ) in the prevention of chronic disease in middle-aged and older male physicians (Christen W. G., Gaziano, J. M. et al., 2000). In the assessment of MVM supplementation in cancer prevention, men who received a daily MVM had a modest but statistically significant reduction in total cancer incidence after a mean of 11.2 years of treatment and follow-up compared to those taking placebo (Gaziano J. M., Sesso, H. D. et al., 2012). Baseline characteristics of the participants were evenly distributed between the MVM and placebo groups, thus minimizing residual confounding factors and strengthening the

assessment of MVM treatment effects. While total cancer (excluding non-melanoma skin cancer) was the primary cancer endpoint, secondary cancer endpoints included other site-specific cancers and cancer mortality. Men who received the MVM also had a reduction in epithelial cancer incidence, but no significant reductions in the incidence of individual site-specific cancers (prostate, lung, colorectal, bladder) or cancer mortality (Gaziano J. M., Sesso, H. D. et al., 2012). The male physician participants enrolled in PHS II differ from the general population in several important ways, namely that there were very few current smokers (4% in PHS II vs. 19% in the US (Schiller J. S., Lucas, J. W. et al., 2012) and 22% worldwide (Naurath N., Jones, J. M., 2007)), the subjects were well nourished, and a high fraction currently used aspirin (76%) (Gaziano J. M., Sesso, H. D. et al., 2012). This limits the relevance of the findings to the general population, younger men, women, and racial and ethnic groups not represented in PHS II.

Residents of Linxian County, China, display very high rates of esophageal/gastric cancers and exhibit subclinical deficiencies in several micronutrients (vitamin A, vitamin E, riboflavin, and vitamin C) (Li B., Taylor, P. R. et al., 1993). This region was therefore chosen for 2 randomized intervention trials testing the effect of micronutrient supplementation on rates of cancer incidence and mortality. In the first trial, 29,584 residents of the Linxian general population received 1 of 8 specific combinations of vitamins and minerals daily for 5.2 years (Blot W. J., Li, J. Y. et al., 1993). Only 1 multi-nutrient combination, vitamin E, beta-carotene, and selenium, significantly reduced the rates of cancer incidence and mortality in this high-risk population (Blot W. J., Li, J. Y. et al., 1993). In the second trial, 3,318 Linxian residents with cytological evidence of esophageal dysplasia received a commercial MVM supplement (Centrum®, 2 tablets

daily) and beta-carotene (Solatene®, Roche Laboratories, Nutley, NJ, 1 tablet daily) for 6 years (Li J. Y., Taylor, P. R. et al., 1993). MVM supplementation had no significant effect on the rates of cancer incidence or mortality in those with esophageal dysplasia (Li J. Y., Taylor, P. R. et al., 1993). As mentioned, the participants in the Linxian trials were at high risk for certain cancers and chronic deficiencies in several micronutrients, which limits the generalizability of the study results to the general population.

The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study was a randomized, placebo-controlled trial of the effects of a combination of antioxidant vitamins and minerals on the incidence of cancer and CVD in middle-aged French adults (Hercberg S., Galan, P. et al., 2004). After a mean of 7.5 years, daily supplementation with an antioxidant capsule significantly reduced total cancer incidence and all-cause mortality in men, but not in women (Hercberg S., Galan, P. et al., 2004). The authors noted that lower baseline beta-carotene status in the male participants of SU.VI.MAX might have contributed to the sex-specific efficacy.

Cardiovascular disease

PHS II also evaluated the effect of MVM supplementation on major cardiovascular events, with primary endpoints including nonfatal myocardial infarction (MI), nonfatal stroke, and CVD mortality (Sesso H. D., Christen, W. G. et al., 2012). Daily MVM supplementation for a mean of 11.2 years had no significant effect on major cardiovascular events in the male physician participants of PHS II (Sesso H. D., Christen, W. G. et al., 2012). Similarly, the SU.VI.MAX trial reported no effect of daily MVM supplementation for a mean of 7.5 years on ischemic CVD

incidence or all-cause mortality in either men or women (Hercberg S., Galan, P. et al., 2004). A small trial performed in patients with lower limb atherosclerosis also reported no significant effect of a combined antioxidant supplement on lower limb disease or the occurrence of cardiovascular events after 2 years of daily supplementation (Leng G. C., Lee, A. J. et al., 1997).

The consistent lack of effect of MVM supplementation on CVD risk may be related, in part, to the widespread use of aspirin, statins, and antihypertensive drugs for the primary and secondary prevention of CVD. For example, 77.4% of male physicians in PHS II used aspirin, and 42.0% and 35.4% had a medical history of hypertension or hypercholesterolemia, respectively (Sesso H. D., Christen, W. G. et al., 2012). Drug-nutrient interactions may be a confounding factor in RCTs but have been little studied thus far.

Age-related eye diseases

Here, age-related eye diseases include cataract and age-related macular degeneration (AMD). Two RCTs assessed the effect of MVM supplementation specifically on the development of age-related cataract, also referred to as lens opacities. The Italian-American Clinical Trial of Nutritional Supplements and Age-Related Cataract (CTNS) evaluated the effect of a commercial MVM supplement (Centrum®) on age-related lens opacities in 1,020 men and women (mean age 68±5 years) with early (N=710) or no (N=310) cataract (Maraini G., Sperduto, R. D. et al., 2008). After an average of 9 years of daily supplementation, “any” lens event (increased nuclear, cortical, or posterior subcapsular [PSC] cataract opacity grades) was significantly less common with MVM supplementation compared with placebo (Maraini G., Sperduto, R. D. et al., 2008).

However, closer examination of the specific types of lens events revealed a significant decrease in the progression or development of nuclear opacities and a significant increase in the development or progression of PSC cataract opacities in the supplement group (Maraini G., Sperduto, R. D. et al., 2008).

Upon completion of the Linxian cancer trials, an eye examination was included in order to assess if the 2 MVM interventions also affected the risk of developing age-related nuclear, cortical, and PSC cataracts (Sperduto R. D., Hu, T. S. et al., 1993). In 2,141 participants from the Linxian Dysplasia Trial, where subjects received 2 MVM (Centrum®) tablets plus beta-carotene daily for 6.0 years, there was a 36% reduction in the prevalence of nuclear cataract with MVM supplementation in those aged 65–74 years (Sperduto R. D., Hu, T. S. et al., 1993). In 3,249 individuals from the Linxian general population trial, a 44% reduction in the prevalence of nuclear cataract was observed only with niacin/riboflavin supplementation in those aged 65–74 years. Similar to the CTNS trial, however, niacin/riboflavin supplementation also had a negative effect on PSC cataracts (Sperduto R. D., Hu, T. S. et al., 1993).

The RCTs that have assessed the effects of MVM supplementation on AMD have each enrolled subjects with pre-existing eye diseases (Age-Related Eye Disease Study 2 Research Group, 2013; AREDS, 2001a; AREDS, 2001b; Bartlett H. E., Eperjesi, F., 2007; Richer S., 1996; Richer S., Stiles, W. et al., 2004). The initial Age-Related Eye Disease Study (AREDS) evaluated the effect of supplementation with high doses of zinc and select antioxidants (in various combinations) on the progression of AMD (AREDS, 2001b) and development of cataract

(AREDS, 2001a) in individuals with evidence of age-related eye disease in at least 1 eye. Treatment with zinc alone or in combination with antioxidants reduced the risk of progression to advanced AMD in high-risk category 3 and 4 participants only (AREDS, 2001b); notably, 80% of US adults over 70 years of age fall into low-risk categories 1 and 2 (Klein R., Klein, B. E. et al., 1992). The AREDS formulation had no effect on the development of cataract (AREDS, 2001a). In AREDS2, the supplement formulation was altered to reflect new information on the dose and types of nutrients most beneficial to eye health (Age-Related Eye Disease Study 2 Research Group, 2013). The addition of lutein and zeaxanthin, the only 2 antioxidants localized to the retina (Bone R. A., Landrum, J. T. et al., 1985), and omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid were administered in conjunction with the original AREDS supplement in a complex randomization scheme; for some participants, the AREDS supplement was altered such that beta-carotene was omitted and the dose of zinc lowered, given the potential adverse effects of these nutrients in certain individuals (Age-Related Eye Disease Study 2 Research Group, 2013). No significant reductions in the progression to advanced AMD occurred with any combination or formulation of the AREDS2 supplement (Age-Related Eye Disease Study 2 Research Group, 2013). Subgroup analysis revealed a beneficial effect of lutein and zeaxanthin supplementation only in those reporting low dietary intake of these carotenoids (Age-Related Eye Disease Study 2 Research Group, 2013).

Three other RCTs measured changes in visual function as their index of AMD progression. In the Lutein Antioxidant Supplementation Trial (LAST), men with atrophic AMD who received lutein alone or in combination with a “broad-spectrum” antioxidant supplement for 1 year

demonstrated improved visual function compared with those receiving placebo (Richer S., Stiles, W. et al., 2004). Patients with advanced, dry AMD who received a "broad-spectrum" MVM supplement for 1.5 years in the Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration (MONMD) study maintained visual acuity, but also experienced increased cortical opacification (Richer S., 1996). Finally, there was no significant effect of 9 months of MVM supplementation on contrast sensitivity score, a measure of visual function, in a small study of 25 subjects (mean age 69.2±7.8 years) with age-related maculopathy (Bartlett H. E., Eperjesi, F., 2007).

PHS II evaluated the effect of a daily MVM supplement (Centrum® Silver) on both cataract and AMD incidence in 14,641 healthy, middle-aged male physicians in the US (Christen W. G., Glynn, R. J. et al., 2014). After 11.2 years of follow-up, there was a significant 9% lower risk of total cataract and a 13% lower risk of "any" nuclear sclerosis (nuclear cataract) in the MVM compared to the placebo group. No significant effect of MVM supplementation was found on the incidence of cortical or PSC cataract. On the other hand, there was a significant 38% increased risk of total AMD in the oldest age group (≥70 years) of men randomized to MVM supplementation.

Limitations

While RCTs are considered the "gold standard" for determining the clinical efficacy of a given intervention, there are unique limitations inherent to nutrient supplementation trials. For one, there can never be a nutrient-free state in study volunteers, thus the "placebo" group in

micronutrient supplementation trials is not a true placebo or "non-exposed" group. Consequently, treatment exposure is blunted between the groups, potentially contributing to a null effect (Heaney R. P., 2008). Secondly, study participants may not represent the general population. For example, those who were willing and eligible to participate in the first Physicians' Health Study (PHS I) had healthier lifestyle traits, lesser history of disease, and lower relative risks of mortality compared with unwilling and ineligible participants (Sesso H. D., Gaziano, J. M. et al., 2002). Thirdly, the development and progression of chronic disease occur over decades, thus the timing and duration of the nutrient intervention with respect to chronic disease etiology are difficult to determine. And finally, there is much heterogeneity in trial designs, in which vastly different MVM formulations are administered and study participants with very different baseline characteristics are recruited; this adds to the challenge of comparing outcomes from the existing body of evidence.

Observational studies

An observational study is one in which no experimental intervention or treatment is applied, and participants are simply observed over time. Several large, long-term, observational, prospective cohort studies have been conducted that examined the association between MVM intake and the development of chronic disease. We considered prospective studies included in recent reviews of MVM use and the risk of cancer, CVD, and age-related eye diseases (Prentice R. L., 2007; Seddon J. M., 2007); more recent prospective cohort studies were obtained via a PubMed search (**Table 3**).

Cancer

The majority of prospective cohort studies demonstrated no association between MVM use and risk of cancer incidence or mortality (Hotaling J. M., Wright, J. L. et al., 2011; Hunter D. J., Manson, J. E. et al., 1993; Jacobs E. J., Connell, C. J. et al., 2002; Kim I., Williamson, D. F. et al., 1993; Li K., Kaaks, R. et al., 2012; Losonczy K. G., Harris, T. B. et al., 1996; Michaud D. S., Spiegelman, D. et al., 2000; Mursu J., Robien, K. et al., 2011; Neuhouser M. L., Wassertheil-Smoller, S. et al., 2009; Park S. Y., Murphy, S. P. et al., 2011; Pocobelli G., Peters, U. et al., 2009; Wu K., Willett, W. C. et al., 2002; Zhang S., Hunter, D. J. et al., 1999; Zhang S. M., Moore, S. C. et al., 2006). In some instances, a statistically significant association between MVM use and cancer risk in specific populations has been noted in both beneficial (Fuchs C. S., Willett, W. C. et al., 2002; Giovannucci E., Stampfer, M. J. et al., 1998) and harmful (Hara A., Sasazuki, S. et al., 2011; Larsson S. C., Akesson, A. et al., 2010; Messerer M., Hakansson, N. et al., 2008; Watkins M. L., Erickson, J. D. et al., 2000; Zhang S. M., Giovannucci, E. L. et al., 2001; Zhang W., Shu, X. O. et al., 2012) directions.

Among specific cancers studied, a negative effect of MVM use on prostate cancer has been demonstrated in several instances. In the NIH-American Association of Retired Persons Diet and Health Study, after a mean follow-up of 5 years, regular MVM use was not associated with prostate cancer risk, while excessive MVM use (greater than 7 times per week) was associated with an increased risk of aggressive and fatal prostate cancer compared to never users (Lawson K. A., Wright, M. E. et al., 2007). In an updated analysis of data from the Cancer Prevention Study II, regular use of MVMs (≥15 times/month) was associated with an increased risk of death from prostate cancer compared with non-users; this increased risk was confined to men who

regularly used MVMs alone (relative risk [RR]: 1.15; 95% confidence interval [CI]: 1.05–1.26) and limited to the early years of follow-up (RR: 1.41; 95% CI: 1.03–1.92) (Stevens V. L., McCullough, M. L. et al., 2005). The reasons behind the variable associations between MVM use and prostate cancer endpoints are unclear. It is cautioned that confounding by stage of disease might be present and that MVM use occurring before or after the establishment of prostate cancer might have differential effects on disease outcomes (Lawson K. A., Wright, M. E. et al., 2007; Stevens V. L., McCullough, M. L. et al., 2005; Watkins M. L., Erickson, J. D. et al., 2000). Notably, there was no effect of MVM supplementation on prostate cancer incidence in PHS II, where prostate cancer comprised more than half of all confirmed cancer cases (Gaziano J. M., Sesso, H. D. et al., 2012).

Because use of dietary supplements is an inconsistent behavior, some prospective cohort studies have collected supplement use data at several time points in order to glean more information about the associations between patterns of MVM use and disease risk. In the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heidelberg study, regular MVM use was not associated with mortality from any cause, but MVM use initiated during follow-up was associated with an increased risk of mortality from cancer and all causes (Li K., Kaaks, R. et al., 2012). After excluding cancer cases that occurred between baseline and the third follow-up, the negative association between MVM use and mortality became insignificant, suggesting a “sick user effect” or reverse causality, a phenomenon in which people tend to start taking MVMs after a diagnosis of disease has been made. In the Japan Public Health Center-based Prospective Study, only 4.1% of men and 5.8% of women continued to use vitamin supplements from the

first to the second surveys, a period spanning approximately 5 years (Hara A., Sasazuki, S. et al., 2011). At the end of the study, there was no association between any pattern of supplement use and risk of cancer or CVD in men. In women, however, past and recent supplement use was associated with a higher risk of cancer. These 2 patterns of use in women were also associated with higher BMI, greater likelihood of smoking, and higher use of certain medications, suggesting that the negative association may be partially explained by unhealthy characteristics that accompany the decision to use a dietary supplement (Hara A., Sasazuki, S. et al., 2011).

Cardiovascular disease

Most observational, prospective cohort studies assessing supplement use at multiple time points have found no association with CVD incidence or mortality. In particular, multivitamin or MVM use was not associated with MI (Neuhouser M. L., Wassertheil-Smoller, S. et al., 2009; Stampfer M. J., Hennekens, C. H. et al., 1993), stroke (Neuhouser M. L., Wassertheil-Smoller, S. et al., 2009), venous thromboembolism (Neuhouser M. L., Wassertheil-Smoller, S. et al., 2009), or mortality from coronary heart disease (CHD) (Losonczy K. G., Harris, T. B. et al., 1996; Stampfer M. J., Hennekens, C. H. et al., 1993) or CVD (Li K., Kaaks, R. et al., 2012; Park S. Y., Murphy, S. P. et al., 2011; Pocobelli G., Peters, U. et al., 2009). However, long-term follow-up in the Nurses' Health Study found women who took multiple vitamins had a 24% lower risk for CHD, defined by nonfatal MI or fatal CHD, and this inverse association was stronger in women taking at least 4 multivitamin supplements weekly for at least 5 years (Rimm E. B., Willett, W. C. et al., 1998).

Age-related eye diseases

A 2007 review summarized the results from both clinical trials and observational, prospective cohort studies that investigated the relationship between dietary supplements and age-related eye diseases, including cataract and AMD (Seddon J. M., 2007). With one exception (Mares-Perlman J. A., Lyle, B. J. et al., 2000), prospective cohort studies that specifically assessed multivitamins showed no association between multivitamin use and the risk of cataract or AMD. In the Beaver Dam Eye Study, only those who self-reported use of a multivitamin for more than 10 years had a decreased risk of nuclear and cortical cataracts, but not of PSC cataracts (Mares-Perlman J. A., Lyle, B. J. et al., 2000). A prospective cohort analysis from the AREDS study (Milton R. C., Sperduto, R. D. et al., 2006) showed that participants who elected to supplement with an MVM (Centrum®) throughout the trial had a lower risk of progression of "any" lens opacity and nuclear opacity; no association was found between elective MVM supplementation and cortical or PSC opacities. Since 2007, two population-based prospective cohort studies reported that MVM use was not associated with the risk of cataract in men (Zheng Selin J., Rautiainen, S. et al., 2013) or with cataract extraction in women (Rautiainen S., Lindblad, B. E. et al., 2010). Observational evidence indicates that other nutrients from foods, particularly lutein, zeaxanthin, and omega-3 fatty acids, may be most important for AMD (Seddon J. M., 2007).

Limitations

Observational, prospective cohort studies, which reveal associations between a given behavior and the subsequent development of disease, are subject to several important limitations that must be considered when interpreting results. First, accurately measuring MVM use and compliance over many years is difficult. There are wide variations in MVM supplement composition, dose,

and duration of use. Furthermore, MVM use is an inconsistent behavior, and it is likely that study participants alter their patterns of use over the long time period between study enrollment, when information on MVM use is collected, and the development of chronic disease many years later. Some investigators attempt to overcome this limitation by collecting MVM use data at additional time points during follow-up. Even with multiple data points, however, the assessment of MVM use comes from very general questions that rely on accurate recall by study participants. Secondly, MVM use is broadly associated with health-conscious behaviors as well as with poor health (Hara A., Sasazuki, S. et al., 2011; National Institutes of Health, 2006). Thus, MVM use (or lack thereof) may be associated with other unmeasured behaviors that contribute to the study outcome, an epidemiological phenomenon known as residual confounding. Finally, individuals may initiate MVM use when symptoms or diagnosis of chronic disease occurs (Bender M. M., Levy, A. S. et al., 1992; Kwan M. L., Greenlee, H. et al., 2011; Patterson R. E., Neuhouser, M. L. et al., 2003). In this case, the health status of the individual, rather than the MVM supplement by itself, influences the development of disease (i.e., reverse causality).

REVIEW OF SCIENTIFIC EVIDENCE: SUPPORTING NORMAL BIOLOGICAL FUNCTIONS

Immune function

Two RCTs reported that daily MVM supplementation for 1 year had no effect on the risk of infection in community-dwelling older adults (Avenell A., Campbell, M. K. et al., 2005; Graat J. M., Schouten, E. G. et al., 2002). In another trial, 1 year of daily supplementation with a

commercial MVM (Theragran M®, Bristol-Myers Squibb, New York, NY) increased serum and plasma concentrations of certain micronutrients (vitamin C, beta-carotene, folate, vitamin B_6, and alpha-tocopherol) and improved delayed-type hypersensitivity skin test (DHST) response compared with those taking placebo (Bogden J. D., Bendich, A. et al., 1994).

Cognitive function

The Mineral and Vitamin Intervention Study (MAVIS) tested possible effects of MVM supplementation on cognitive function in 910 older adults (median age 72 years) who received daily MVM tablet or placebo for 1 year (McNeill G., Avenell, A. et al., 2007). Supplementation had no overall effect on short-term memory (digit span forward test) or executive functioning (verbal fluency test) in the total sample of older adults. Subgroup analysis revealed a mild beneficial effect on verbal fluency scores in 2 subgroups: (1) those 75 years and older, and (2) those at increased risk for micronutrient deficiency as assessed by questionnaire (McNeill G., Avenell, A. et al., 2007). In another RCT, 220 healthy, older women (median age 63 years) received an MVM or placebo capsule daily for 6 months (Wolters M., Hickstein, M. et al., 2005). MVM supplementation resulted in higher serum concentrations of all vitamins, yet had no effect on cognitive performance compared with placebo (Wolters M., Hickstein, M. et al., 2005).

A substudy within PHS II evaluated the effect of long-term daily supplementation with a commercial MVM (Centrum® Silver) on cognitive function in older (≥65 years) male physicians(Grodstein F., O'Brien, J. et al., 2013). Up to 4 repeated cognitive assessments were completed by telephone interview in 5,947 participants over a mean of 8.5 years of follow-up.

No differences in mean cognitive change over time or mean level of cognition were observed between the MVM and placebo groups.

Meeting nutrient requirements

Recommended levels of nutrient intake are defined by using specific scientific criteria for nutrient adequacy (**text box**). While the specific criterion varies for each micronutrient, examples of adequate nutritional states include normal growth, maintenance of normal levels of nutrients in plasma, and other aspects of general health and well-being (Otten J. J., Hellwig, J. P. et al., 2006). National surveys indicate that a considerable percentage of US adults and children consume inadequate levels of vitamins and nutritionally essential minerals from food sources alone (Fulgoni V. L., III, Keast, D. R. et al., 2011). Use of dietary supplements, of which MVMs are the most common type, can make a significant contribution to daily micronutrient intakes, effectively reducing the prevalence of inadequate intakes in all vitamins and minerals examined in representative populations of adults, children, and seniors from the US and Canada (Bailey R. L., Fulgoni, V. L., III et al., 2012a; Bailey R. L., Fulgoni, V. L., III et al., 2012b; Bailey R. L., Gahche, J. J. et al., 2011; Fulgoni V. L., III, Keast, D. R. et al., 2011; Sebastian R. S., Cleveland, L. E. et al., 2007; Shakur Y. A., Tarasuk, V. et al., 2012). For example, according to the Dietary Guidelines for Americans (2010), vitamin D, calcium, and potassium are among several "nutrients of concern" within the US population (Otten J. J., Hellwig, J. P. et al., 2006; US Department of Agriculture, 2010). Use of dietary supplements further reduced the percentage of the total population with usual intakes below the EAR for vitamin D (93% to 70%), calcium

(49% to 38%), vitamin C (37% to 25%), vitamin E (91% to 60%), and magnesium (55% to 45%) (Fulgoni V. L., III, Keast, D. R. et al., 2011).

Safety

Notably, documented cases of nutrient toxicity are generally caused by supplementation, not by food (Hunt J. R., 1996). Thus, while dietary supplements reduce the percentage of the population consuming less than the EAR for all micronutrients, they also contribute to excess intake for some vitamins and minerals (Sebastian R. S., Cleveland, L. E. et al., 2007; Shakur Y. A., Tarasuk, V. et al., 2012). Given the high prevalence of MVM use in the US population, there is concern that individuals may exceed the Tolerable Upper Intake Level (UL) for certain micronutrients (**text box**) (Mulholland C. A., Benford, D. J., 2007; National Institutes of Health, 2006; Otten J. J., Hellwig, J. P. et al., 2006). A recent national survey tallying nutrient intake from all sources (natural, enriched or fortified, and supplements) indicated that the percentage of US adults ≥19 years of age at or exceeding the UL was low for most nutrients and was highest for niacin (8.5%), followed by zinc (3.3%), calcium (3.2%), and folate (2.6%) (Fulgoni V. L., III, Keast, D. R. et al., 2011). Similarly, in Europe, the risk of excessive intakes was low for the majority of nutrients, with possible exceptions being vitamin A, zinc, iodine, copper, and magnesium (Flynn A., Hirvonen, T. et al., 2009). However, dietary supplement use contributed to total micronutrient intakes above the UL for a sizeable proportion of US children and adolescents (2–18 years old) for zinc (24%), niacin (16%), vitamin A (15%), and folate (15%) (Fulgoni V. L., III, Keast, D. R. et al., 2011). Although dosages of micronutrients included in most commercial MVMs are close to 100% of the recommended dietary allowance (RDA),

dietary supplements contribute significantly to total nutrient intakes and one must pay attention to their contribution to total daily nutrient exposure.

CONCLUSIONS

The majority of scientific studies investigating the use of MVM supplements in the reduction of the risk of chronic disease report no significant effect (**Tables 2 and 3**). In select populations, both beneficial and adverse outcomes have been documented. Closer examination of study participant characteristics as well as constraints of the existing methodology offers explanations for these variable outcomes.

Much emphasis is placed on PHS II for its strong study design and data set, spanning over 10 years of controlled supplementation with a commercial MVM. There was a modest reduction in total and nuclear cataract, as well as total and epithelial cancer incidence observed in the male physician participants of PHS II, consistent with, e.g., the CTNS with respect to cataract and the SU.VI.MAX trial for total cancer incidence. While these results are meaningful, caution must be used when extrapolating the results from PHS II and other RCTs to the general population. Study participants often have unique characteristics that likely influence the effect of an MVM in the experimental population (e.g., gender, disease history or status, baseline nutritional status). In addition, the overall effect of MVM supplementation on age-related eye diseases remains unclear given the potentially opposing effects on nuclear and PSC cataract subtypes. With respect to AMD, PHS II found an increased risk of total AMD incidence in the oldest age group (≥70

years) with MVM supplementation; the effect of MVM supplementation on AMD progression is unclear based on currently available data. For trial data on cardiovascular diseases addressed in this review, there was a consistent lack of an effect of daily MVM supplementation, which could be due, in part, to the confounding effect of the polypharmacy often used in CVD prevention.

Overall, observational, prospective cohort studies demonstrate no association between MVM use and the risk of chronic disease. In fact, there are several instances where MVM use is associated with an increased risk of specific cancers and age-related eye diseases. The negative associations detected in observational study subanalyses may be due to inherent methodological limitations regarding patterns of MVM use and the inability to control for this variable with the existing methodology. Supplement use might accompany a healthy lifestyle or a newly diagnosed disease, both of which independently affect disease etiology yet cannot always be accounted for in the final analysis.

The development of chronic disease has been described as a long-latency deficiency disease (Heaney R. P., 2008) or the result of accumulated cellular damage due to chronic micronutrient insufficiency (Ames B. N., 2006). Consistent with these hypotheses, MVM supplementation appears to benefit individuals who are most at risk for nutritional deficiencies. In those studies where nutrient status was assessed, MVM supplementation helped maintain adequacy in older adults, offsetting some age-related declines in immune and cognitive function. Moreover, dietary supplements contributed significantly to daily micronutrient intakes, reducing the prevalence of

inadequacy for all vitamins and minerals examined in nationally representative populations in the US and Canada.

Recommendation

The current dietary pattern of Western populations is energy dense and nutrient poor, itself a risk factor for the development of chronic disease (Otten J. J., Hellwig, J. P. et al., 2006; US Department of Agriculture, 2010). Although it is possible to meet the RDA of all essential vitamins and minerals through diet alone by choosing nutrient-dense foods in the proper proportions (United States Department of Agriculture, 2013; US Department of Agriculture, 2010), national surveys reveal that certain micronutrients are consistently under-consumed in the typical Western diet (Bailey R. L., Fulgoni, V. L., III et al., 2012a; US Department of Agriculture, 2010) or are difficult to obtain from food sources alone (i.e., vitamin D).

The primary indication for an MVM is to supplement a diet lacking adequate amounts of certain micronutrients in order to maintain normal cell and tissue function, metabolism, growth, and development. Additionally, there is the potential to reduce risk of some chronic diseases with minimal risk of harm (Frei B., Ames, B. N. et al., 2014). For some people, an MVM thus represents an effective, safe, and affordable means of filling micronutrient gaps. That said, one first needs to know a gap exists. While national survey estimates are informative, dietary assessment is the only way to identify one's actual nutrient intake, revealing potential inadequacies or excesses. Should one decide to supplement with an MVM, it is also important to

consider other personal issues in the decision-making process, such as life stage, disease status, risk factors, and lifestyle.

Acknowledgments

GA, VJD, and BF designed the research for this review article, conducted the literature research, analyzed the data, and wrote the paper. GA had primary responsibility for final content. All authors read and approved the final manuscript. Editorial support was provided by Diane Sloan, PharmD, of Peloton Advantage, LLC, and was funded by Pfizer.

REFERENCES

Age-Related Eye Disease Study 2 Research Group. (2013). Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA.* **309** : 2005-2015.

Ames B. N. (2006). Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. *Proc Natl Acad Sci U S A.* **103** : 17589-17594.

AREDS. (2001a). A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. *Arch Ophthalmol.* **119** : 1439-1452.

AREDS. (2001b). A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol.* **119** : 1417-1436.

Avenell A., Campbell M.K., Cook J.A., et al. (2005). Effect of multivitamin and multimineral supplements on morbidity from infections in older people (MAVIS trial): pragmatic, randomised, double blind, placebo controlled trial. *BMJ.* **331** : 324-329.

Bailey R. L., Fulgoni V.L., III, Keast D.R., Dwyer J.T. (2012a). Examination of vitamin intakes among US adults by dietary supplement use. *J Acad Nutr Diet.* **112** : 657-663.

Bailey R. L., Fulgoni V.L., III, Keast D.R., Lentino C.V., Dwyer J.T. (2012b). Do dietary supplements improve micronutrient sufficiency in children and adolescents? *J Pediatr.* **161** : 837-842.

Bailey R. L., Gahche J.J., Lentino C.V., et al. (2011). Dietary supplement use in the United States, 2003-2006. *J Nutr.* **141** : 261-266.

Bailey R. L., Gahche J.J., Miller P.E., Thomas P.R., Dwyer J.T. (2013). Why US adults use dietary supplements. *JAMA Intern Med.* **173** : 355-361.

Bartlett H. E., Eperjesi F. (2007). Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial. *Eur J Clin Nutr.* **61** : 1121-1127.

Bender M. M., Levy A.S., Schucker R.E., Yetley E.A. (1992). Trends in prevalence and magnitude of vitamin and mineral supplement usage and correlation with health status. *J Am Diet Assoc.* **92** : 1096-1101.

Bhaskaram P. (2001). Immunobiology of mild micronutrient deficiencies. *Br J Nutr.* **85 Suppl 2** : S75-S80.

Blot W. J., Li J.Y., Taylor P.R., et al. (1993). Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst.* **85** : 1483-1492.

Bogden J. D., Bendich A., Kemp F.W., et al. (1994). Daily micronutrient supplements enhance delayed-hypersensitivity skin test responses in older people. *Am J Clin Nutr.* **60** : 437-447.

Bone R. A., Landrum J.T., Tarsis S.L. (1985). Preliminary identification of the human macular pigment. *Vision Res.* **25** : 1531-1535.

Briefel R. R., Johnson C.L. (2004). Secular trends in dietary intake in the United States. *Annu Rev Nutr.* **24** : 401-431.

Burchi F., Fanzo J., Frison E. (2011). The role of food and nutrition system approaches in tackling hidden hunger. *Int J Environ Res Public Health.* **8** : 358-373.

Christen W. G., Ajani U.A., Glynn R.J., et al. (1999). Prospective cohort study of antioxidant vitamin supplement use and the risk of age-related maculopathy. *Am J Epidemiol.* **149** : 476-484.

Christen W. G., Gaziano J.M., Hennekens C.H. (2000). Design of Physicians' Health Study II--a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Ann Epidemiol.* **10** : 125-134.

Christen W. G., Glynn R.J., Manson J.E., et al. (2014). Effects of multivitamin supplement on cataract and age-related macular degeneration in a randomized trial of male physicians. *Ophthalmology.* **121** : 525-534.

Cole C. R. (2012). Preventing hidden hunger in children using micronutrient supplementation. *J Pediatr.* **161** : 777-778.

Elmadfa I., Freisling H. (2009). Nutritional status in Europe: methods and results. *Nutr Rev.* **67 Suppl 1** : S130-S134.

Flynn A., Hirvonen T., Mensink G.B., et al. (2009). Intake of selected nutrients from foods, from fortification and from supplements in various European countries. *Food Nutr Res.* **53** .

Food and Agriculture Organization of the United Nations. *The State of Food Insecurity in the World 2004*. 6th ed. Rome, Italy: Food and Agriculture Organization of the United Nations; 2004.

Food and Drug Administration. Guidance for industry: a food labeling guide (14. appendix F: calculate the percent daily value for the appropriate nutrients). Food and Drug Administration. Available at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064928.htm. Accessed August 2, 2013

Foote J. A., Murphy S.P., Wilkens L.R., et al. (2003). Factors associated with dietary supplement use among healthy adults of five ethnicities: the Multiethnic Cohort Study. *Am J Epidemiol.* **157** : 888-897.

Fortmann S. P., Burda B.U., Senger C.A., Lin J.S., Whitlock E.P. (2013). 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.* **159** : 824-834.

Frei B., Ames B.N., Blumberg J.B., Willett W.C. (2014). Enough is enough: stop wasting money on vitamin and mineral supplements. *Ann Intern Med.*

Fuchs C. S., Willett W.C., Colditz G.A., et al. (2002). The influence of folate and multivitamin use on the familial risk of colon cancer in women. *Cancer Epidemiol Biomarkers Prev.* **11** : 227-234.

Fulgoni V. L., III, Keast D.R., Bailey R.L., Dwyer J. (2011). Foods, fortificants, and supplements: Where do Americans get their nutrients? *J Nutr.* **141** : 1847-1854.

Gahche J., Bailey R., Burt V., et al. (2011). Dietary supplement use among U.S. adults has increased since NHANES III (1988-1994). *NCHS Data Brief.* 1-8.

Gaziano J. M., Sesso H.D., Christen W.G., et al. (2012). Multivitamins in the prevention of cancer in men. The Physicians' Health Study II Randomized Controlled Trial. *JAMA.* **308** : 1871-1880.

Giovannucci E., Stampfer M.J., Colditz G.A., et al. (1998). Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. *Ann Intern Med.* **129** : 517-524.

Graat J. M., Schouten E.G., Kok F.J. (2002). Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA.* **288** : 715-721.

Grodstein F., O'Brien J., Kang J.H., et al. (2013). Long-term multivitamin supplementation and cognitive function in men: a randomized trial. *Ann Intern Med.* **159** : 806-814.

Hara A., Sasazuki S., Inoue M., et al. (2011). Use of vitamin supplements and risk of total cancer and cardiovascular disease among the Japanese general population: a population-based survey. *BMC Public Health.* **11** : 540.

Heaney R. P. (2008). Nutrients, endpoints, and the problem of proof. *J Nutr.* **138** : 1591-1595.

Hercberg S., Galan P., Preziosi P., et al. (2004). The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med.* **164** : 2335-2342.

Holick M. F. (2007). Vitamin D deficiency. *N Engl J Med.* **357** : 266-281.

Hotaling J. M., Wright J.L., Pocobelli G., et al. (2011). Long-term use of supplemental vitamins and minerals does not reduce the risk of urothelial cell carcinoma of the bladder in the VITamins And Lifestyle study. *J Urol.* **185** : 1210-1215.

Huang H. Y., Caballero B., Chang S., et al. (2007). Multivitamin/Mineral supplements and prevention of chronic disease: executive summary. *Am J Clin Nutr.* **85** : 265S-268S.

Hunt J. R. (1996). Position of the American Dietetic Association: vitamin and mineral supplementation. *J Am Diet Assoc.* **96** : 73-77.

Hunter D. J., Manson J.E., Colditz G.A., et al. (1993). A prospective study of the intake of vitamins C, E, and A and the risk of breast cancer. *N Engl J Med.* **329** : 234-240.

Huskisson E., Maggini S., Ruf M. (2007). The role of vitamins and minerals in energy metabolism and well-being. *J Int Med Res.* **35** : 277-289.

Ibs K-H, Rink L. Zinc. In: Hughes DA, Darlington LG, Bendich A, editors. *Diet and Human Immune Function*.Totowa, NJ: Humana Press Inc.; 2004. p. 241-59.

Iso H., Kubota Y. (2007). Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev.* **8 Suppl** : 35-80.

Jacobs E. J., Connell C.J., McCullough M.L., et al. (2002). Vitamin C, vitamin E, and multivitamin supplement use and stomach cancer mortality in the Cancer Prevention Study II cohort. *Cancer Epidemiol Biomarkers Prev.* **11** : 35-41.

Kant A. K. (2000). Consumption of energy-dense, nutrient-poor foods by adult Americans: nutritional and health implications. The third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr.* **72** : 929-936.

Kennedy D. O., Haskell C.F. (2011). Vitamins and cognition: what is the evidence? *Drugs.* **71** : 1957-1971.

Kim I., Williamson D.F., Byers T., Koplan J.P. (1993). Vitamin and mineral supplement use and mortality in a US cohort. *Am J Public Health.* **83** : 546-550.

Klein R., Klein B.E., Linton K.L. (1992). Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology.* **99** : 933-943.

Kwan M. L., Greenlee H., Lee V.S., et al. (2011). Multivitamin use and breast cancer outcomes in women with early-stage breast cancer: the Life After Cancer Epidemiology study. *Breast Cancer Res Treat.* **130** : 195-205.

Larsson S. C., Akesson A., Bergkvist L., Wolk A. (2010). Multivitamin use and breast cancer incidence in a prospective cohort of Swedish women. *Am J Clin Nutr.* **91** : 1268-1272.

Lawson K. A., Wright M.E., Subar A., et al. (2007). Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. *J Natl Cancer Inst.* **99** : 754-764.

Leng G. C., Lee A.J., Fowkes F.G., et al. (1997). Randomized controlled trial of antioxidants in intermittent claudication. *Vasc Med.* **2** : 279-285.

Li B., Taylor P.R., Li J.Y., et al. (1993). Linxian nutrition intervention trials. Design, methods, participant characteristics, and compliance. *Ann Epidemiol.* **3** : 577-585.

Li J. Y., Taylor P.R., Li B., et al. (1993). Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. *J Natl Cancer Inst.* **85** : 1492-1498.

Li K., Kaaks R., Linseisen J., Rohrmann S. (2010). Consistency of vitamin and/or mineral supplement use and demographic, lifestyle and health-status predictors: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heidelberg cohort. *Br J Nutr.* **104** : 1058-1064.

Li K., Kaaks R., Linseisen J., Rohrmann S. (2012). Vitamin/mineral supplementation and cancer, cardiovascular, and all-cause mortality in a German prospective cohort (EPIC-Heidelberg). *Eur J Nutr.* **51** : 407-413.

Losonczy K. G., Harris T.B., Havlik R.J. (1996). Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr.* **64** : 190-196.

Macpherson H., Pipingas A., Pase M.P. (2013). Multivitamin-multimineral supplementation and mortality: a meta-analysis of randomized controlled trials. *Am J Clin Nutr.* **97** : 437-444.

Maraini G., Sperduto R.D., Ferris F., et al. (2008). A randomized, double-masked, placebo-controlled clinical trial of multivitamin supplementation for age-related lens opacities. Clinical trial of nutritional supplements and age-related cataract report no. 3. *Ophthalmology.* **115** : 599-607.

Mares-Perlman J. A., Lyle B.J., Klein R., et al. (2000). Vitamin supplement use and incident cataracts in a population-based study. *Arch Ophthalmol.* **118** : 1556-1563.

McNeill G., Avenell A., Campbell M.K., et al. (2007). Effect of multivitamin and multimineral supplementation on cognitive function in men and women aged 65 years and over: a randomised controlled trial. *Nutr J.* **6** : 10.

Messerer M., Hakansson N., Wolk A., Akesson A. (2008). Dietary supplement use and mortality in a cohort of Swedish men. *Br J Nutr.* **99** : 626-631.

Michaud D. S., Spiegelman D., Clinton S.K., et al. (2000). Prospective study of dietary supplements, macronutrients, micronutrients, and risk of bladder cancer in US men. *Am J Epidemiol.* **152** : 1145-1153.

Milton R. C., Sperduto R.D., Clemons T.E., Ferris F.L., III. (2006). Centrum use and progression of age-related cataract in the Age-Related Eye Disease Study: a propensity score approach. AREDS report No. 21. *Ophthalmology.* **113** : 1264-1270.

Mulholland C. A., Benford D.J. (2007). What is known about the safety of multivitamin-multimineral supplements for the generally healthy population? Theoretical basis for harm. *Am J Clin Nutr.* **85** : 318S-322S.

Muller O., Krawinkel M. (2005). Malnutrition and health in developing countries. *CMAJ.* **173** : 279-286.

Muntwyler J., Hennekens C.H., Manson J.E., Buring J.E., Gaziano J.M. (2002). Vitamin supplement use in a low-risk population of US male physicians and subsequent cardiovascular mortality. *Arch Intern Med.* **162** : 1472-1476.

Mursu J., Robien K., Harnack L.J., Park K., Jacobs D.R., Jr. (2011). Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med.* **171** : 1625-1633.

National Academy of Sciences, Institute of Medicine, and Food and Nutrition Board. Dietary Reference Intakes: Recommended Dietary Allowances and Adequate Intakes for Vitamins and Elements. U.S. Department of Agriculture. Available at: http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables. Accessed August 2, 2013

National Institutes of Health. (2006). National Institutes of Health State-of-the-science conference statement: multivitamin/mineral supplements and chronic disease prevention. *Ann Intern Med.* **145** : 364-371.

Naurath, N. and Jones, J. M. Smoking rates around the world - how do Americans compare? Available at: www.gallup.com/poll/28432/smoking-rates-around-world-how-americans-compare.aspx.?version=print.

Neuhouser M. L., Wassertheil-Smoller S., Thomson C., et al. (2009). Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Arch Intern Med.* **169** : 294-304.

Otten JJ, Hellwig JP, Meyers LD. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: The National Academies Press; 2006.

Park S. Y., Murphy S.P., Wilkens L.R., Henderson B.E., Kolonel L.N. (2011). Multivitamin use and the risk of mortality and cancer incidence: the multiethnic cohort study. *Am J Epidemiol.* **173** : 906-914.

Patterson R. E., Neuhouser M.L., Hedderson M.M., et al. (2003). Changes in diet, physical activity, and supplement use among adults diagnosed with cancer. *J Am Diet Assoc.* **103** : 323-328.

Pfizer Consumer Healthcare. What's Inside Centrum? Pfizer Consumer Healthcare. Available at: http://www.centrum.com/whats-inside/products. Accessed August 2, 2013

Pocobelli G., Peters U., Kristal A.R., White E. (2009). Use of supplements of multivitamins, vitamin C, and vitamin E in relation to mortality. *Am J Epidemiol.* **170** : 472-483.

Prentice R. L. (2007). Clinical trials and observational studies to assess the chronic disease benefits and risks of multivitamin-multimineral supplements. *Am J Clin Nutr.* **85** : 308S-313S.

Radimer K., Bindewald B., Hughes J., et al. (2004). Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. *Am J Epidemiol.* **160** : 339-349.

Ramakrishnan U. (2002). Prevalence of micronutrient malnutrition worldwide. *Nutr Rev.* **60** : S46-S52.

Rautiainen S., Akesson A., Levitan E.B., et al. (2010). Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women. *Am J Clin Nutr.* **92** : 1251-1256.

Rautiainen S., Lindblad B.E., Morgenstern R., Wolk A. (2010). Vitamin C supplements and the risk of age-related cataract: a population-based prospective cohort study in women. *Am J Clin Nutr.* **91** : 487-493.

Richer S. (1996). Multicenter ophthalmic and nutritional age-related macular degeneration study--part 2: antioxidant intervention and conclusions. *J Am Optom Assoc.* **67** : 30-49.

Richer S., Stiles W., Statkute L., et al. (2004). Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry.* **75** : 216-230.

Rimm E. B., Willett W.C., Hu F.B., et al. (1998). Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA.* **279** : 359-364.

Rock C. L. (2007). Multivitamin-multimineral supplements: who uses them? *Am J Clin Nutr.* **85** : 277S-279S.

Schiller J. S., Lucas J.W., Ward B.W., Peregoy J.A. (2012). Summary health statistics for U.S. adults: National Health Interview Survey, 2010. *Vital Health Stat 10.* 1-207.

Sebastian R. S., Cleveland L.E., Goldman J.D., Moshfegh A.J. (2007). Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes. *J Am Diet Assoc.* **107** : 1322-1332.

Seddon J. M. (2007). Multivitamin-multimineral supplements and eye disease: age-related macular degeneration and cataract. *Am J Clin Nutr.* **85** : 304S-307S.

Sesso H. D., Christen W.G., Bubes V., et al. (2012). Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA.* **308** : 1751-1760.

Sesso H. D., Gaziano J.M., VanDenburgh M., et al. (2002). Comparison of baseline characteristics and mortality experience of participants and nonparticipants in a randomized clinical trial: the Physicians' Health Study. *Control Clin Trials.* **23** : 686-702.

Shakur Y. A., Tarasuk V., Corey P., O'Connor D.L. (2012). A comparison of micronutrient inadequacy and risk of high micronutrient intakes among vitamin and mineral supplement users and nonusers in Canada. *J Nutr.* **142** : 534-540.

Sperduto R. D., Hu T.S., Milton R.C., et al. (1993). The Linxian cataract studies. Two nutrition intervention trials. *Arch Ophthalmol.* **111** : 1246-1253.

Stampfer M. J., Hennekens C.H., Manson J.E., et al. (1993). Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med.* **328** : 1444-1449.

Stevens V. L., McCullough M.L., Diver W.R., et al. (2005). Use of multivitamins and prostate cancer mortality in a large cohort of US men. *Cancer Causes Control.* **16** : 643-650.

Sullivan K. M., Ford E.S., Azrak M.F., Mokdad A.H. (2009). Multivitamin use in pregnant and nonpregnant women: results from the Behavioral Risk Factor Surveillance System. *Public Health Rep.* **124** : 384-390.

Taylor J. P., Maclellan D.L., van T.L., Sweet L. (2007). Widespread micronutrient inadequacies among adults in prince edward island. *Can J Diet Pract Res.* **68** : 23-29.

United States Department of Agriculture. Choosemyplate.gov. United States Department of Agriculture. Available at: http://www.choosemyplate.gov/. Accessed June 13, 2013

US Department of Agriculture. Dietary guidelines for Americans, 2010. Available at: www.dietaryguidelines.gov. Accessed December 10, 2013

Watkins M. L., Erickson J.D., Thun M.J., Mulinare J., Heath C.W., Jr. (2000). Multivitamin use and mortality in a large prospective study. *Am J Epidemiol.* **152** : 149-162.

Whatham A., Bartlett H., Eperjesi F., et al. (2008). Vitamin and mineral deficiencies in the developed world and their effect on the eye and vision. *Ophthalmic Physiol Opt.* **28** : 1-12.

Wolters M., Hickstein M., Flintermann A., Tewes U., Hahn A. (2005). Cognitive performance in relation to vitamin status in healthy elderly German women-the effect of 6-month multivitamin supplementation. *Prev Med.* **41** : 253-259.

Wu K., Willett W.C., Chan J.M., et al. (2002). A prospective study on supplemental vitamin e intake and risk of colon cancer in women and men. *Cancer Epidemiol Biomarkers Prev.* **11** : 1298-1304.

Zhang S., Hunter D.J., Forman M.R., et al. (1999). Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. *J Natl Cancer Inst.* **91** : 547-556.

Zhang S. M., Giovannucci E.L., Hunter D.J., et al. (2001). Vitamin supplement use and the risk of non-Hodgkin's lymphoma among women and men. *Am J Epidemiol.* **153** : 1056-1063.

Zhang S. M., Moore S.C., Lin J., et al. (2006). Folate, vitamin B6, multivitamin supplements, and colorectal cancer risk in women. *Am J Epidemiol.* **163** : 108-115.

Zhang W., Shu X.O., Li H., et al. (2012). Vitamin intake and liver cancer risk: a report from two cohort studies in China. *J Natl Cancer Inst.* **104** : 1173-1181.

Zheng Selin J., Rautiainen S., Lindblad B.E., Morgenstern R., Wolk A. (2013). High-dose supplements of vitamins C and E, low-dose multivitamins, and the risk of age-related cataract: a population-based prospective cohort study of men. *Am J Epidemiol.* **177** : 548-555.

Text box

Governments of individual nations often set recommendations to assess adequacy of nutrient intake and for dietary planning. Jointly, the US and Canadian governments support the Dietary Reference Intakes (DRIs), which include micronutrient intake recommendations for healthy individuals when sufficient scientific evidence exists and are designed to prevent deficiency disease and reduce the risk of chronic disease. The DRIs are comprised of 4 reference values that can be used to assess the adequacy of diets in individuals and populations (Otten J. J., Hellwig, J. P. et al., 2006):

Estimated Average Requirement (EAR). The average daily nutrient intake level that is estimated to meet the requirements of half of the healthy individuals in a particular life stage and gender group. The EAR is defined by using specific scientific criteria for nutrient adequacy and serves as the primary reference point for assessing the adequacy of nutrient intakes of groups. It is not meant to be used as a goal for daily intake by individuals.

Recommended Dietary Allowance (RDA). The average daily dietary nutrient intake level that is sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals in a particular life stage and gender group. The RDA is mathematically derived from the EAR and is used to guide daily intake by individuals. Because the RDA exceeds the requirements of nearly all members of the group, intakes below the RDA cannot be assessed as being inadequate.

Adequate Intake (AI). The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people who are assumed to be maintaining an adequate nutritional state. The AI is used when an RDA cannot be determined, indicating that more research is needed to determine with some degree of certainty the requirements for a specific nutrient.

Tolerable Upper Intake Level (UL). The highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase.

Table 1. Comparison between the daily values,[1] dietary reference intakes for adults, and a representative commercially available MVM supplement

Micronutrient	**DV** (Food and Drug Administration, 2013)	**RDA or AI for adult males (amount/day)** (National Academy of Sciences, Institute of Medicine et al., 2010)	**RDA or AI for adult females (amount/day)** (National Academy of Sciences, Institute of Medicine et al., 2010)	**Centrum® Adults (under 50 years) (amount/serving)** (Pfizer Consumer Healthcare, 2013)	**Centrum® Adults (under 50 years) (% DV)** (Pfizer Consumer Healthcare, 2013)
Biotin	300 mcg	30 mcg	30 mcg	30 mcg	10
Folate	400 mcg	400 mcg[2]	400 mcg[2]	400 mcg (folic acid)	100
Niacin	20 mg	16 mg[3]	14 mg[3]	20 mg	100
Pantothenic acid	10 mg	5 mg	5 mg	10 mg	100
Riboflavin	1.7 mg	1.3 mg	1.1 mg	1.7 mg	100
Thiamin	1.5 mg	1.2 mg	1.1 mg	1.5 mg	100
Vitamin A	5,000 IU	3,000 IU[4]	2,333 IU[4]	3,500 IU (29% as beta-carotene)	70
Vitamin B_6	2 mg	1.3–1.7 mg	1.3–1.5 mg	2 mg	100

Vitamin B_{12}	6 mcg	2.4 mcg[5]	2.4 mcg[5]	6 mcg	100
Vitamin C	60 mg	90 mg	75 mg	60 mg	100
Vitamin D	400 IU	600–800 IU	600–800 IU	400 IU	100
Vitamin E	30 IU	22.5–33 IU[6]	22.5–33 IU[6]	30 IU	100
Vitamin K	80 mcg	120 mcg	90 mcg	25 mcg	31
Calcium	1,000 mg	1,000–1,200 mg	1,000–1,200 mg	200 mg	20
Chloride	3,400 mg	1,800–2.300 mg	1,800–2,300 mg	72 mg	2
Chromium	120 mcg	30–35 mcg	20–25 mcg	35 mcg	29
Copper	2 mg	900 mcg	900 mcg	0.5 mg	25
Iodine	150 mcg	150 mcg	150 mcg	150 mcg	100
Iron	18 mg	8 mg	8–18 mg	18 mg	100
Magnesium	400 mg	400–420 mg	310–320 mg	50 mg	13
Manganese	2 mg	2.3 mg	1.8 mg	2.3 mg	115
Molybdenum	75 mcg	45 mcg	45 mcg	45 mcg	60
Phosphorus	1,000 mg	700 mg	700 mg	20 mg	2
Potassium	3,500 mg	4,700 mg	4,700 mg	80 mg	2
Selenium	70 mcg	55 mcg	55 mcg	55 mcg	79
Zinc	15 mg	11 mg	8 mg	11 mg	73
Choline	Not established	550 mg	425 mg	—	—
Boron	Not established	—	—	75 mcg	Not established
Nickel	Not established	—	—	5 mcg	Not established
Silicon	Not established	—	—	2 mg	Not established

Tin	Not established	—	—	10 mcg	Not established
Vanadium	Not established	—	—	10 mcg	Not established

[1]Established by the United States Food and Drug Administration, the daily value (DV) is meant to inform consumers on the nutrient content of a food product. The DV itself is a nutrient reference value based on a caloric intake of 2,000 calories/day for adults and children 4 or more years of age. The %DV (the ratio between the amount of nutrient per serving of food and the DV for the given nutrient) reflects the nutrient content of the food product.

[2]Dietary folate equivalents.

[3]Niacin equivalent (NE): 1 mg NE=60 mg tryptophan=1 mg niacin.

[4]Retinol activity equivalents.

[5]Intake for adults >50 years of age should be from supplements or fortified foods due to the age-related increase in food-bound malabsorption.

[6]22.5 IU of natural-source of alpha tocopherol (d-alpha-tocopherol); 33 IU of synthetic alpha-tocopherol (dl-alpha-tocopherol).

AI, adequate intake; DV, daily value; IU, international units; MVM, multivitamin/mineral supplement; RDA, recommended dietary allowance.

Table 2. Randomized controlled trials

Cancer							
Reference	**Trial name**	**Participants**	**Treatment**	**Formulation[1]**	**Mean follow-up**	**Primary endpoint(s)**	**Key outcomes**
Gaziano, 2012 (Gaziano J. M., Sesso, H. D. et al., 2012)	PHS II	14,641 US male physicians, mean (SD) age 64.3 (9.2) y	Daily MVM (Centrum® Silver, Pfizer Consumer Healthcare, Madison, NJ) or placebo	Vitamin A 5,000 IU, vitamin C 60 mg, vitamin D 400 IU, vitamin E 45 IU, vitamin K 10 mcg, thiamin 1.5 mg, riboflavin 1.7 mg, niacin 20 mg, vitamin B_6 3 mg, folic acid 400 mcg, vitamin B_{12} 25 mcg, biotin 30	11.2 y	Total cancer (excluding non-melanoma skin cancer)	Daily MVM **reduced the risk** of total cancer by 8% (HR: 0.92; 95% CI: 0.86–0.998; *P*=0.04)

mcg, pantothenic acid 10 mg, calcium 200 mg, iron 4 mg, phosphorus 48 mg, iodine 150 mcg, magnesium 100 mg, zinc 15 mg, selenium 20 mcg, copper 2 mg, manganese 3.5 mg, chromium 130 mcg, molybdenum 160 mcg, chloride 72.6 mg, potassium 80 mg, boron 150 mcg,

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				nickel 5 mcg, vanadium 10 mcg, silicon 2 mg			
Blot, 1993 (Blot W. J., Li, J. Y. et al., 1993)	Linxian Cancer Prevention Trial	29,584 Chinese men & women, aged 40–69 y	1 of 8 nutrient combos: AB, AC, AD, BC, BD, CD, ABCD, or placebo	(A) retinol 5,000 IU and zinc 22.5 g; (B) riboflavin 3.2 g and niacin 40 mg; (C) ascorbic acid 120 mg and molybdenum 30 mcg; (D) beta-carotene 15 mg, selenium 50 mcg, and alpha-tocopherol 30 mg	5.25 y	Total mortality; cancer incidence and mortality	9% **reduction** in total mortality only with beta-carotene, selenium, and alpha-tocopherol supplementation (RR: 0.91; 95% CI: 0.84–0.99; *P*=0.03); 13% **reduction** in cancer mortality only with beta-carotene, selenium, and

							alpha-tocopherol supplementation (RR: 0.87; 95% CI: 0.75–1.00)
Li, 1993 (Li J. Y., Taylor, P. R. et al., 1993)	Linxian Dysplasia Study	3,318 Chinese adults, aged 40–69 y (median 54 y), with cytological evidence of esophageal dysplasia	Daily MVM (2 x Centrum® tablets and 1 x beta-carotene capsule) or placebo	Beta-carotene 15 mg, vitamin A 10,000 IU, vitamin E 60 IU, vitamin C 180 mg, folic acid 800 mcg, vitamin B_1 5 mg, vitamin B_2 5.2 mg, niacinamide 40 mg, vitamin B_6 6 mg, vitamin B_{12} 18 mcg, vitamin D 800 IU, biotin	6.0 y	Esophageal/gastric cardia cancer incidence and mortality	**No significant effect**

				90 mcg, pantothenic acid 20 mg, calcium 324 mg, phosphorus 250 mg, iodine 300 mcg, iron 54 mg, magnesium 200 mg, copper 6 mg, manganese 15 mg, potassium 15.4 mg, chloride 14 mg, chromium 30 mcg, molybdenum 30 mcg, selenium 50 mcg, zinc 45 mg			
Hercberg,	SU.VI.MAX	12,741 French	Daily	Ascorbic acid 120	7.5 y	Cancer incidence;	Antioxidant

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2004 (Hercberg S., Galan, P. et al., 2004)		adults, women aged 35–60 y and men aged 45–60 y: 7,713 women, mean (SD) age 46.6 (6.6) y; 5,028 men, mean (SD) age 51.3 (4.7) y	antioxidant capsule or placebo	mg, vitamin E 30 mg, beta-carotene 6 mg, selenium 100 mcg (selenium-enriched yeast), zinc gluconate 20 mg		ischemic CVD incidence; all-cause mortality (secondary)	supplementation **reduced** total cancer incidence (RR: 0.69; 95% CI: 0.53–0.91) and all-cause mortality (RR: 0.63; 95% CI: 0.42–0.93) in men but not in women
			CVD				
Sesso, 2012 (Sesso H. D., Christen, W. G. et al., 2012)	PHS II	14,641 US male physicians; mean (SD) age 64.3 (9.2) y	Daily MVM (Centrum® Silver) or placebo	Vitamin A 5,000 IU, vitamin C 60 mg, vitamin D 400 IU, vitamin E 45 IU, vitamin K 10 mcg, thiamin 1.5 mg, riboflavin	11.2 y	Composite endpoint of major CV events: nonfatal MI, nonfatal stroke, CVD mortality	**No significant effect** on any endpoint

1.7 mg, niacin 20 mg, vitamin B_6 3 mg, folic acid 400 mcg, vitamin B_{12} 25 mcg, biotin 30 mcg, pantothenic acid 10 mg, calcium 200 mg, iron 4 mg, phosphorus 48 mg, iodine 150 mcg, magnesium 100 mg, zinc 15 mg, selenium 20 mcg, copper 2 mg, manganese 3.5 mg, chromium 130 mcg,

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				molybdenum 160 mcg, chloride 72.6 mg, potassium 80 mg, boron 150 mcg, nickel 5 mcg, vanadium 10 mcg, silicon 2 mg			
Hercberg, 2004 (Hercberg S., Galan, P. et al., 2004)	SU.VI.MAX	12,741 French adults, women aged 35–60 y and men aged 45–60 y: 7,713 women, mean age (SD) 46.6 (6.6) y; 5,028 men, mean age (SD) 51.3 (4.7) y	Daily antioxidant capsule or placebo	Ascorbic acid 120 mg, vitamin E 30 mg, beta-carotene 6 mg, selenium 100 mcg (selenium-enriched yeast), zinc gluconate 20 mg	7.5 y	Cancer incidence; ischemic CVD incidence; all-cause mortality	**No significant effect** on CVD incidence

Leng, 1997 (Leng G. C., Lee, A. J. et al., 1997)		120 patients with lower limb atherosclerosis /intermittent claudication	Antioxidant supplement or placebo	Beta-carotene 3 mg, vitamin C 100 mg, pyridoxine hydrochloride 25 mg, zinc 100 mg, nicotinamide 10 mg, sodium selenite 1 mg	2 y	Cholesterol, lipoproteins, hemostatic, and rheological factors; ankle/brachial pressure index; lower limb function; incidence of CV events; CV mortality	**No significant effect** on any endpoint
Age-related eye diseases							
Christen, 2014 (Christen W. G., Glynn, R. J. et al., 2014)	PHS II	14,641 US male physicians, aged ≧50 years	Daily MVM (Centrum® Silver) or placebo	Vitamin A 5,000 IU, vitamin C 60 mg, vitamin D 400 IU, vitamin E 45 IU, vitamin K 10 mcg, thiamin 1.5 mg, riboflavin 1.7 mg, niacin 20	11.2 y	Incident cataract (total, cortical, PSC, and "any" nuclear sclerosis); visually significant AMD, total AMD, and advanced AMD	**Significant reduction** of total cataract incidence (HR: 0.91; 95% CI: 0.83–0.99); **Significant reduction** of "any" nuclear

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	mg, vitamin B_6 3 mg, folic acid 400 mcg, vitamin B_{12} 25 mcg, biotin 30 mcg, pantothenic acid 10 mg, calcium 200 mg, iron 4 mg, phosphorus 48 mg, iodine 150 mcg, magnesium 100 mg, zinc 15 mg, selenium 20 mcg, copper 2 mg, manganese 3.5 mg, chromium 130 mcg, molybdenum 160	sclerosis incidence (HR: 0.87; 95% CI: 0.79–0.96); **No significant effect** on cortical or PSC cataract incidence; **Significant increase** in total AMD (HR: 1.22; 95% CI: 1.03–1.44); **No significant effect** on visually significant or advanced AMD

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				mcg, chloride 72.6 mg, potassium 80 mg, boron 150 mcg, nickel 5 mcg, vanadium 10 mcg, silicon 2 mg			
Maraini, 2008 (Maraini G., Sperduto, R. D. et al., 2008)	CTNS	1,020 Italian adults, mean age (SD) 68 (5) y, with early (n=710) or no (n=310) cataract	Daily MVM (Centrum®) or placebo	Vitamin A 5,000 IU, vitamin E 30 IU, vitamin C 60 mg, folic acid 400 mcg, vitamin B_1 1.5 mg, vitamin B_2 1.7 mg, niacinamide 20 mg, vitamin B_6 2 mg, vitamin B_{12} 6 mcg, vitamin D	9 y	Nuclear, cortical, or PSC cataract opacity grades; cataract surgery	"Total lens events" were **less common** in participants who took the MVM formulation, but treatment had **opposite effects** on the development or progression of

	400 IU, biotin 30 mcg, pantothenic acid 10 mg, calcium 162 mg, phosphorus 125 mg, iodine 150 mcg, iron 18 mg, magnesium 100 mg, copper 2 mg, zinc 15 mg, manganese 2.5 mg, selenium 25 mcg, chromium 25 mcg, vitamin K 25 mcg, molybdenum 25 mcg, chloride 36.3 mg,	nuclear (decreased) and PSC cataract (increased) opacities

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				potassium 40 mg			
Sperduto, 1993 (Sperduto R. D., Hu, T. S. et al., 1993)	Linxian Eye Study	2,141 from the Linxian Dysplasia trial, mean age 59 y	Daily MVM (2 x Centrum® tablets and 1 x beta-carotene capsule) or placebo	Beta-carotene 15 mg, vitamin A 10,000 IU, vitamin E 60 IU, vitamin C 180 mg, folic acid 800 mcg, vitamin B_1 4.5 mg, vitamin B_2 5.2 mg, niacinamide 40 mg, vitamin B_6 6 mg, vitamin B_{12} 18 mcg, vitamin D 800 IU, biotin 90 mcg, pantothenic acid 20 mg, calcium	6.0 y	Prevalence of nuclear, cortical, and PSC cataract	MVM supplementation resulted in a 36% **reduction** in the prevalence of nuclear cataract in those aged 65–74 y

				324 mg, phosphorus 250 mg, iodine 300 mcg, iron 54 mg, magnesium 200 mg, copper 6 mg, manganese 15 mg, potassium 15 mg, chloride 14 mg, chromium 30 mcg, molybdenum 30 mcg, selenium 50 mcg, zinc 45 mg			
Sperduto, 1993 (Sperduto R. D., Hu,	Linxian Eye Study	3,249 from the Linxian general population trial, mean age 56–57	1 of 8 nutrient combos: AB, AC, AD, BC, BD, CD,	(A) retinol 5,000 IU and zinc 22 mg; (B) riboflavin 3 g and niacin 40	6.0 y	Prevalence of nuclear, cortical, and PSC cataract	A 44% **reduction** in prevalence of nuclear cataract in those aged 65–74

T. S. et al., 1993)		y	ABCD, or placebo	mg; (C) ascorbic acid 120 mg and molybdenum 30 mcg; (D) beta-carotene 15 mg, selenium 50 mcg, and alpha-tocopherol 30 mg			y with niacin/riboflavin supplementation only; a **deleterious effect** of niacin/riboflavin supplementation on PSC cataract in those aged 65–74 y
AREDS study group, 2013 (Age-Related Eye Disease Study 2	AREDS2	4,203 men & women, aged 50-85 y, at high-risk for progression to advanced AMD	1 of 4 AREDS1 formulations in conjunction with (1) lutein and zeaxanthin,	(1) “placebo” consisting of 1 of 4 possible AREDS1 formulations: 1. Original, 2. Without beta-	4.9 y	Progression to advanced AMD; visual acuity	**No significant effect** of any combination or formulation

Research Group, 2013)			(2) omega-3 fatty acids, or (3) lutein, zeaxanthin, and omega-3 fatty acids	carotene, 3. With less zinc (25 mg), 4. Without beta-carotene and with less zinc, (2) lutein (10 mg) and zeaxanthin (2 mg) plus AREDS placebo, (3) DHA (350 mg) and EPA (650 mg) plus AREDS placebo, and (4) lutein, zeaxanthin, DHA, and EPA plus AREDS placebo			
AREDS	AREDS1	4,629 men and	Daily tablet (3	(1) antioxidants:	6.3 y	Progression to	Zinc alone or in	

study group, 2001 (AREDS, 2001a)	Report No. 9	women, aged 55-80 y, with vision issues or AMD in at least 1 eye	possible treatments) or placebo; 66% of participants also elected to take a daily MVM (Centrum®)	vitamin C (500 mg), vitamin E (400 IU), and beta-carotene (15 mg), (2) minerals: zinc (80 mg) and copper (2 mg), or (3) antioxidants plus zinc		advanced AMD; visual acuity	combination with antioxidants **reduced** the progression to advanced AMD in high-risk participants only
Richer, 1996 (Richer S., 1996)	MONMD	71 patients with advanced, dry AMD	Twice daily "broad spectrum" antioxidant capsule (OcuGuard®; Twinlab, New York, NY) or placebo	Beta-carotene 20,000 IU, vitamin E 200 IU, vitamin C 750 mg, citrus bioflavonoid complex 125 mg, quercetin 50 mg, bilberry extract 5	1.5 y	Visual acuity, contrast sensitivity, and lens opacification	Supplement group **maintained** visual acuity but also had **increased** cortical opacification

				mg, rutin 50 mg, zinc picolinate 12.5 mg, selenium 50 mcg, taurine 100 mg, n-acetyl cysteine 100 mg, l-glutathione 5 mg, vitamin B_2 25 mg, chromium 100 mcg			
Richer, 2004 (Richer S., Stiles, W. et al., 2004)	LAST	90 male patients with AMD	(1) lutein alone, (2) lutein plus "broad-spectrum" supplement (OcuPower®, Vitacost,	Lutein 10 mg, vitamin A 2,500 IU, beta-carotene 15,000 IU, vitamin C 1,500 mg, vitamin D 400 IU, vitamin E 500 IU, vitamin	1 y	MPOD; measures of visual function (visual acuity, contrast sensitivity)	**Improved** visual function with lutein alone or lutein plus MVM compared with placebo

Lexington, NC), or (3) placebo	B_1 50 mg, vitamin B_2 10 mg, vitamin B_3 70 mg, vitamin B_5 50 mg, vitamin B_6 50 mg, vitamin B_{12} 500 mcg, folic acid 800 mcg, biotin 300 mcg, calcium 500 mg, magnesium 300 mg, iodine 75 mcg, zinc 25 mg, copper 1 mg, manganese 2 mg, selenium 200 mcg, chromium 200 mcg, molybdenum 75

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mcg, lycopene 600 mcg, bilberry extract 160 mg, alpha-lipoic acid 150 mg, N-acetyl cysteine 200 mg, quercetin 100 mg, rutin 100 mg, citrus bioflavonoids 250 mg, plant enzymes 50 mg, black pepper extract 5 mg, malic acid 325 mg, taurine 900 mg, L-glycine 100 mg, L-

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				glutathione 10 mg, boron 2 mg			
Bartlett, 2007 (Bartlett H. E., Eperjesi, F., 2007)		20 adults; mean (SD) age 69.2 (7.8) y with age-related maculopathy	Lutein combined with antioxidant vitamins and minerals or placebo	Lutein 6 mg, retinol 750 mcg, vitamin C 250 mg, vitamin E 34 mg, zinc 10 mg, copper 0.5 mg	9 mos	Contrast sensitivity score	**No significant effect**
Cognitive function							
McNeill, 2007 (McNeill G., Avenell, A. et al., 2007)	MAVIS	910 community-dwelling Scottish adults, aged ≥65 y; median age 72 y	Daily MVM tablet or placebo	Vitamin A 800 mcg, vitamin C 60 mg, vitamin D 5 mcg, vitamin E 10 mg, thiamin 1.4 mg, riboflavin 1.6 mg, niacin 18 mg, pantothenic	12 mos	Immediate memory (digit span forward test); executive functioning (verbal fluency test)	**No effect** on immediate memory; **beneficial effect** of supplementation on executive functioning in

			acid 6 mg, pyridoxine 2 mg, vitamin B_{12} 1 mcg, folic acid 200 mcg, iron 14 mg, iodine 150 mcg, copper 0.75 mg, zinc 15 mg, manganese 1 mg			subgroup analysis: (1) those ≥75 y; (2) those at increased risk for micronutrient deficiency
Wolters, 2005 (Wolters M., Hickstein, M. et al., 2005)	220 women, aged 60–91 y; median age 63 y	Daily MVM (Nobilin® Q10, Medicom Pharma GmbH, Baierbrunn, Germany) or placebo	Vitamin C 150 mg, magnesium 50 mg, vitamin E 36 mg, niacin 34 mg, pantothenic acid 16 mg, beta-carotene 9 mg, pyridoxine 3.4 mg, riboflavin 3.2	6 mos	Cognitive performance (Symbol Search subtest of the Wechsler Adult Intelligence Scale-Revised III, the Kurztest Allgemeine Intelligenz, and the	**No effect** on cognitive performance

			capsules	mg, thiamine 2.4 mg, folic acid 400 mcg, biotin 200 mcg, selenium 60 mcg, cobalamin 9 mcg		pattern-recognition subtest of the Berliner Amnesietest)	
Grodstein, 2013 (Grodstein F., O'Brien, J. et al., 2013)	PHS II	5,947 US male physicians, aged ≥65 y	Daily MVM (Centrum® Silver) or placebo	Vitamin A 5,000 IU, vitamin C 60 mg, vitamin D 400 IU, vitamin E 45 IU, vitamin K 10 mcg, thiamin 1.5 mg, riboflavin 1.7 mg, niacin 20 mg, vitamin B_6 3 mg, folic acid 400 mcg, vitamin B_{12} 25 mcg, biotin 30	8.5 y	Composite score average of 5 tests of global cognition, verbal memory, and category fluency; cognitive assessments by telephone interview	**No effect** on mean cognitive change over time or mean level of cognition

mcg, pantothenic acid 10 mg, calcium 200 mg, iron 4 mg, phosphorus 48 mg, iodine 150 mcg, magnesium 100 mg, zinc 15 mg, selenium 20 mcg, copper 2 mg, manganese 3.5 mg, chromium 130 mcg, molybdenum 160 mcg, chloride 72.6 mg, potassium 80 mg, boron 150 mcg,

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				nickel 5 mcg, vanadium 10 mcg, silicon 2 mg			
Immune function							
Avenell, 2005 (Avenell A., Campbell, M. K. et al., 2005)	MAVIS	910 community-dwelling Scottish adults, aged ≥65 y; median age 72 y	Daily MVM tablet or placebo	Vitamin A 800 mcg, vitamin C 60 mg, vitamin D 5 mcg, vitamin E 10 mg, thiamin 1.4 mg, riboflavin 1.6 mg, niacin 18 mg, pantothenic acid 6 mg, pyridoxine 2 mg, vitamin B_{12} 1 mcg, folic acid 200 mcg, iron 14 mg, iodine 150	1 y	Self-reported infection, quality of life, and primary care visits for infection	**No effect** on any outcomes measured

			mcg, copper 0.75 mg, zinc 15 mg, manganese 1 mg			
Graat, 2002 (Graat J. M., Schouten, E. G. et al., 2002)	652 community-dwelling adults aged ≥60 y	Daily MVM (2 capsules per day), vitamin E 200 mg, both, or placebo	Retinol 600 mcg, beta-carotene 1.2 mg, ascorbic acid 60 mg, vitamin E 10 mg, cholecalciferol 5 mcg, vitamin K 30 mcg, thiamin 1.4 mg, riboflavin 1.6 mg, niacin 18 mg, pantothenic acid 6 mg, pyridoxine 2.0 mg, biotin 150 mcg, folic acid	15 mos	Incidence and severity of acute respiratory tract infections	**No effect** on any outcomes measured

			200 mcg, cyanocobalamin 1 mcg, zinc 10 mg, selenium 25 mcg, iron 4.0 mg, magnesium 30 mg, copper 1.0 mg, iodine 100 mcg, calcium 74 mg, phosphorus 49 mg, manganese 1.0 mg, chromium 25 mcg, molybdenum 25 mcg, silicium 2 mcg			
Bogden,	56 healthy adults	Daily	Vitamin A 1000	1 y	Serum concentrations	**Improved** DHST

1994 (Bogden J. D., Bendich, A. et al., 1994)	aged 59–85 y	micronutrient supplement (Theragran M) or placebo	mcg, beta-carotene 0.75 mg, vitamin C 90 mg, vitamin E 20 mg, vitamin D 10 mcg, thiamine 3 mg, riboflavin 3.4 mg, niacin 30 mg, vitamin B_6 3 mg, vitamin B_{12} 9 mcg, folic acid 0.40 mg, pantothenic acid 10 mg, biotin 35 mcg, zinc 15 mg, iodine 150 mcg, iron 27 mg, copper 2 mg,	9 micronutrients; DHST response to 7 recall antigens	responses in supplement group

		selenium 10 mcg, manganese 5 mg, chromium 15 mcg, molybdenum 15 mcg, magnesium 100 mg, calcium 40 mg, phosphorus 31 mg

[1]Total daily amounts noted in parentheses, accounting for trials that administered more than 1 pill per day.

AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; CI, confidence interval; CTNS, Italian-American Clinical Trial of Nutritional Supplements and Age-Related Cataract; CVD, cardiovascular disease; DHST, delayed-type hypersensitivity skin test; HR, hazard ratio; IU, international units; LAST, Lutein Antioxidant Supplementation Trial; MAVIS, Mineral and Vitamin Intervention Study; MI, myocardial infarction; MONMD, Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration study; MPOD, macular pigment optical density; MVM, multivitamin/mineral supplement; PHS II, Physicians' Health Study II; PSC, posterior subcapsular; RE, retinol equivalents; RR, relative risk; SD, standard deviation; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants study; US, United States.

Table 3. Observational studies

Cancer						
Reference	**Study name**	**Participants (age at enrollment)**	**Assessment of MVM use**	**Mean follow-up**	**Primary endpoints**	**Key outcomes**
Li, 2012 (Li K., Kaaks, R. et al., 2012)	EPIC-Heidelberg	23,943 men and women aged 35–64 y	In-person interview at baseline: (1) Did you regularly take any medications or vitamin/mineral supplements in the last 4 weeks?" and (2) If yes, what was the brand name? Also, a self-administered FFQ at baseline, 2nd, and 3rd follow-up visits:	11 y	Mortality from all-causes, cancer, and CVD	**No association** between regular MVM use and any endpoint

			subject asked if he/she took any vitamin/mineral supplements ≥4 weeks in the last 12 months.			
Zhang, 2012 (Zhang W., Shu, X. O. et al., 2012)	Shanghai Women's Health Study; Shanghai Men's Health Study	72,486 women (aged 40–70 y) and 60,351 men (aged 40–74 y)	In-person interviews on dietary habits, including use of supplements (if subject used a multivitamin ≥3 times/week continuously for >2 months), at baseline and first follow-up (2–3 y post-baseline)	10.9 y (women); 5.5 y (men)	Incidence of liver cancer	**No association** between MVM use and liver cancer in women; **increased risk** of liver cancer in men with a history of disease
Hara, 2011	The Japan	62,629 men and	Self-reported use of	7-11 y	Risk of cancer and	**No association**

(Hara A., Sasazuki, S. et al., 2011)	Public Health Center–Based Prospective Study	women from the Japanese general population (aged 40–69 y)	vitamin supplements at 2 time points (never, past, recent, consistent); in survey I, asked the frequency and type; in survey II, brand names were requested		CVD	between any pattern of multivitamin supplement use and risk of cancer in men; **increased risk** of cancer with past (HR: 1.17; 95% CI: 1.02–1.33) and recent (HR: 1.24; 95% CI: 1.01–1.52) use of multivitamins in women
Park, 2011 (Park S. Y., Murphy, S. P.	Multiethnic Cohort Study	182,099 US adults from 5 ethnic groups (aged 45–	Self-administered questionnaire at baseline and 5-year	11 y	Mortality from all-causes, cancer, or CVD; incidence of	**No association** between supplement use

et al., 2011)		75 y)	follow-up; subject asked if he/she had used multivitamins (with/without minerals) and 7 single vitamin/mineral supplements at least weekly during the previous year; also asked about frequency and duration (at baseline only) for each supplement used		cancer, overall and at major sites	and any endpoint
Hotaling, 2011 (Hotaling J.	VITAL	77,050 US men and women (aged 50–76 y)	Self-administered questionnaire on supplement use,	6 y	Incidence of urothelial cancer	**No association** between multivitamin use

M., Wright, J. L. et al., 2011)			including questions on brand, duration, and frequency of multivitamin use			and urothelial cancer risk
Mursu, 2011 (Mursu J., Robien, K. et al., 2011)	Iowa Women's Health Study	38,772 US postmenopausal women (aged 55–69 y)	Self-administered questionnaire on multivitamin use at baseline and at 11- and 18-year follow-up	19 y	Total mortality, cancer mortality, CVD mortality	**No association** between multivitamin use and cancer mortality
Larsson, 2010 (Larsson S. C., Akesson, A. et al., 2010)	Swedish Mammography Cohort	35,329 women (aged 49–83 y)	Self-administered questionnaire at baseline	9.5 y	Incidence of breast cancer	Multivitamin use was associated with **increased risk** of breast cancer (HR: 1.19; 95% CI: 1.03–1.37)
Neuhouser,	Women's Health	161,808 US	In-person clinic	8 y	(1) Incidence of	**No association**

2009 (Neuhouser M. L., Wassertheil-Smoller, S. et al., 2009)	Initiative	postmenopausal women (aged 50–79 y)	visits to collect detailed information on multivitamin supplement use (designate multivitamin, MVM, or stress supplement); subjects brought supplement bottles to baseline and follow-up visits (annually or every 3 years); questioned on frequency (pills/week) and duration (months and years) of use	cancer (breast, colon/rectum, endometrium, kidney, bladder, stomach, ovary, lung), (2) incidence of CVD (MI, stroke, venous thromboembolism), and (3) total mortality	between MVM use and any endpoint

Pocobelli, 2009 (Pocobelli G., Peters, U. et al., 2009)	VITAL	77,673 US men and women (aged 50–76 y)	Self-administered questionnaire at baseline; ever use of supplements was defined as use of at least once/week for 1 year during the 10-year period before baseline; "multivitamin" defined as a supplement containing at least 10 vitamins and/or minerals	5 y	Total mortality, CVD mortality, and cancer mortality	**No association** between MVM use and cancer mortality
Messerer, 2008 (Messerer M.,	COSM	38,994 Swedish men (aged 45–79 y)	Self-administered questionnaire at baseline; asked	7.7 y for all-cause mortality;	Mortality from all-causes, cancer, and CVD	**No association** between MVM use and any

Hakansson, N. et al., 2008)			regarding regular, occasional, or no use of dietary supplements; further specified type used (multivitamin, vitamin C, vitamin E, and fish oil)	5.9 y for cancer and CVD mortality		endpoint; use of any supplement was associated with **increased risk** of cancer mortality in current smokers (HR: 1.46; 95% CI: 1.06–1.99)
Lawson, 2007 (Lawson K. A., Wright, M. E. et al., 2007)	NIH-AARP Diet and Health Study	295,344 US men (aged 50–71 y)	Self-administered questionnaire at baseline	5 y	Risk of prostate cancer	**No association** between regular MVM use and risk of prostate cancer; excessive MVM use (>7 times/week) associated with

						increased risk of advanced and fatal prostate cancer compared with never users
Stevens, 2005 (Stevens V. L., McCullough, M. L. et al., 2005)	CPS II	475,726 men (aged 47–70 y)	Self-administered questionnaire on supplement use at enrollment; (1) asked about duration and frequency of current use of 4 vitamin supplements (multivitamins, vitamins A, C, and E) and (2) asked about the number of times in last month	18 y	Risk of prostate cancer mortality	Regular use of MVMs alone (≥15 times/month) was associated with an **increased risk** of death from prostate cancer compared with non-users (RR: 1.15; 95% CI: 1.05–1.26)

			and the number of years each supplement was used			
Zhang, 2006 (Zhang S. M., Moore, S. C. et al., 2006)	Women's Health Study	37,916 female US health professionals (≥45 y)	Self-administered questionnaire at baseline, including questions on MVM supplement use	10.1 y	Risk of colorectal cancer	**No association** between MVM use and colorectal cancer risk
Fuchs, 2002 (Fuchs C. S., Willett, W. C. et al., 2002)	NHS	88,758 female US registered nurses (mean age 47 y)	Self-administered FFQ in 1980	16 y	Risk of colon cancer	**No association** between MVM use and risk of colon cancer in women without a familial history of disease; MVM use for >5 y was associated with a **decreased**

						risk of colon cancer in women with a family history of disease
Jacobs, 2002 (Jacobs E. J., Connell, C. J. et al., 2002)	CPS II	1,045,923 US adults	Self-administered questionnaire at baseline	16 y	Mortality from stomach cancer	**No association** between MVM use and stomach cancer mortality
Wu, 2002 (Wu K., Willett, W. C. et al., 2002)	NHS & HPFS	87,998 women from NHS and 47,344 men from HPFS	Mailed FFQ at baseline; follow-up questionnaires mailed every 2 years for NHS and every other year for HPFS; asked about current use and dosage of any supplement, and the brand and type of	Presented as total-person y for each level of vitamin E intake	Risk of colon cancer	**No association** between MVM use and risk of colon cancer

			MVM			
Zhang, 2001 (Zhang S. M., Giovannucci, E. L. et al., 2001)	NHS & HPFS	88,410 women (aged 30–55 y) & 47,336 men (aged 40–75 y)	Self-administered FFQ at baseline	16 y (women); 10 y (men)	Risk of non-Hodgkin's lymphoma	Regular use of MVM (>6/week for >10 y) was associated with an **increased risk** of non-Hodgkin's lymphoma in women but not in men
Watkins, 2000 (Watkins M. L., Erickson, J. D. et al., 2000)	CPS II	1,063,023 US adults (≥30 y)	Self-administered questionnaire on MVM use at baseline; separate questions on the use of MVMs, vitamins A, E, and C, and 11 other medications	7 y	Risk of mortality from cancer, CVD, and all-causes	MVM use was associated with **increased risk** of cancer mortality in male smokers (HR: 1.13; 95% CI: 1.05–1.23)

Michaud, 2000 (Michaud D. S., Spiegelman, D. et al., 2000)	HPFS	47,909 men (aged 40–75 y)	Self-administered FFQ at 2 time points	12 y	Risk of bladder cancer	**No association** between MVM use and risk of bladder cancer
Zhang, 1999 (Zhang S., Hunter, D. J. et al., 1999)	NHS	77,925 women (aged 33–60 y)	Self-administered FFQ in 1980	14 y	Risk of breast cancer	**No association** between MVM use and risk of breast cancer in either pre- or postmenopausal women
Giovannucci, 1998 (Giovannucci E., Stampfer,	NHS	88,756 women (aged 34–59 y in 1980)	Self-administered questionnaire at baseline (1980) and biennially (1980–	14 y	Risk of colon cancer	**Reduced risk** of colon cancer only after >15 y of multivitamin use

M. J. et al., 1998)			1992); asked about type, brand, and how many years of use			(RR: 0.25; 95% CI: 0.13–0.51)
Losonczy, 1996 (Losonczy K. G., Harris, T. B. et al., 1996)	Established Populations for Epidemiologic Studies of the Elderly	11,178 US elderly men and women (>65 y)	Use of MVM supplements obtained from in-person interviews at enrollment and every 3 years; first follow-up visit at year 3 was used as baseline; respondents were asked whether they had taken any medicines or drugs not prescribed by a doctor in the past 2 weeks; respondents	6 y	Risk of mortality from cancer, CHD, and all causes	**No association** between MVM use and mortality from any cause

			were told to include vitamins among these drugs at 2 of 4 study sites			
Hunter, 1993 (Hunter D. J., Manson, J. E. et al., 1993)	NHS	89,494 women (aged 34–59 y)	Self-administered FFQ in 1980	8 y	Risk of breast cancer	**No association** between MVM use and risk of breast cancer
Kim, 1993 (Kim I., Williamson, D. F. et al., 1993)	NHEFS	10,758 US adults (mean age 50.2 y)	Questionnaire at baseline: "Are you taking vitamins or minerals?" (regularly, irregularly, or none)	13 y	Risk of mortality from cancer and all causes	**No association** between MVM use and mortality from any cause
			CVD			
Stampfer, 1993 (Stampfer M.	NHS	87,245 US women (34–59 y)	Multivitamin use assessed at baseline and every 2 years	Up to 8 y	Nonfatal MI and fatal CHD presented together as major	**No association** with major CHD in the basic

J., Hennekens, C. H. et al., 1993)			thereafter: regular use of multivitamins and, if so, type and brand		CHD	multivariate model
Rimm, 1998 (Rimm E. B., Willett, W. C. et al., 1998)	NHS	80,082 US women (aged 30–55 y)	Questionnaire at baseline and every 2 years; use of multiple vitamin supplements, type and brand, usual number taken/week, and years of past use	14 y	Nonfatal MI and fatal CHD presented together as CHD risk	**Reduced risk** of CHD in women who reportedly took at least 4 multiple vitamin supplements weekly for at least 5 y (HR: 0.71; 95% CI: 0.56–0.90)
Rautiainen, 2010 (Rautiainen S., Akesson,	Swedish Mammography Cohort	33,932 Swedish women (48–83 y); 31,670 CVD-free and 2,262 with	Baseline questionnaire assessing MV use with or without	10.2 y	Incident MI	**Reduced risk** for women with no history of CVD vs. no supplement

A. et al., 2010)		history of CVD at baseline	minerals			use (HR: 0.73; 95% CI: 0.57–0.93) and the association was stronger in those using multivitamins for at least 5 y; **no association** in those with a history of CVD
Watkins, 2000 (Watkins M. L., Erickson, J. D. et al., 2000)	CPS II	1,063,023 US men and women (aged >30 y)	Self-administered questionnaire at baseline	7 y	Ischemic heart disease and stroke mortality, cancer mortality	**No association** with stroke mortality in men or women; **no association** with ischemic heart disease in

		men and women with no history at baseline, but a 7% and a 6% **lower risk** of ischemic heart disease found, respectively, for men and women with a history of the disease; **no associations** found when duration or frequency of multivitamin supplementation was examined

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Pocobelli, 2009 (Pocobelli G., Peters, U. et al., 2009)	VITAL	77,673 US men and women (aged 50–76 y)	Self-administered questionnaire at baseline; ever use of supplements defined as use at least once/week for 1 year during the 10-year period before baseline; "multivitamin" defined as a supplement containing at least 10 vitamins and/or minerals	5 y	Total mortality, CVD mortality, cancer mortality	Frequent multivitamin use (6–7 d/week over the 10- y period) was associated with a **lower risk** of CVD mortality (HR: 0.84; 95% CI: 0.70–0.99; *P*=0.019); stronger association in those with no history of CVD at baseline (HR: 0.78; 95% CI: 0.62–0.98; *P*=0.012); and not

						significant in those with a history of CVD at baseline
Iso, 2007 (Iso H., Kubota, Y., 2007)	Japan Collaborative Cohort Study for Evaluation of Cancer	Japanese adults aged 40–79 y who completed a self-administered questionnaire	Multivitamin use		All-cause mortality and disease-specific mortality, including ischemic heart disease and cerebrovascular disease	**Reduced risk** of mortality from cerebrovascular disease in women (HR: 0.77; 95% CI: 0.60–0.99)
Losonczy, 1996 (Losonczy K. G., Harris, T. B. et al., 1996)	Established Populations for Epidemiologic Studies of the Elderly	11,178 US elderly men and women (aged >65 y)	Use of MVM supplements obtained from in-person interviews at enrollment and every 3 years; first follow-up visit at year 3 was	6 y	All-cause mortality, CHD mortality, cancer mortality	**No association** with CHD mortality

			used as baseline; respondents were asked whether they had taken any medicines or drugs not prescribed by a doctor in the past 2 weeks; respondents were told to include vitamins among these drugs at 2 of 4 study sites			
Muntwyler, 2002 (Muntwyler J., Hennekens, C. H. et al., 2002)	PHS I	83,639 US male physicians (aged 40–84 y)	Questionnaire at baseline: current use of multivitamin supplements, number of years of vitamin supplementation,	5.5 y	CHD mortality and total CVD mortality	**No association** with any endpoint

			brand used, number of pills taken/week			
Li, 2012 (Li K., Kaaks, R. et al., 2012)	EPIC-Heidelberg	23,943 men (aged 40–64 y) and women (aged 35–64 y)	In-person interview ("Did you regularly take any medications or vitamin/mineral supplements in the last 4 weeks?") and self-administered FFQ (vitamin/mineral supplements ≥4 weeks in last 12 months?) at baseline; self-administered FFQs at 2nd and 3rd follow-up	11 y	Mortality from all-causes, cancer, and CVD	**No association** between regular MVM use at baseline and any endpoint; MVM use initiated during follow-up associated with **increased risk** of all-cause mortality (HR: 1.58; 95% CI: 1.17–2.14)
Mursu, 2011	Iowa Women's	38,772 US	Self-administered	19 y	Total mortality,	**No association**

(Mursu J., Robien, K. et al., 2011)	Health Study	postmenopausal women (aged 55–69 y)	questionnaire at baseline and at 2 points (year 11 and 18 of follow-up)		cancer mortality, CVD mortality	between multivitamin use and CVD mortality
Messerer, 2008 (Messerer M., Hakansson, N. et al., 2008)	COSM	38,994 Swedish men (aged 45–79 y)	Self-administered questionnaire at baseline; for supplements, subjects asked about regular, occasional, or no use; study provided mean content of a multivitamin, containing 7 vitamins; no mention of minerals	7.7 y	Mortality from all causes, cancer mortality, and CVD mortality	**No association** between multivitamin use and CVD mortality; sub-analysis revealed a **reduced risk** of use of any supplement and CVD mortality in men reporting inadequate diets (assessed by Recommended

						Food Score; HR: 0.72; 95% CI: 0.57–0.91)
			Age-related eye diseases			
Rautiainen, 2010 (Rautiainen S., Lindblad, B. E. et al., 2010)	Swedish Mammography Cohort	24,593 women (aged 49–83 y)	Self-administered questionnaire at baseline: (1) asked about regular, occasional, or non-use of dietary supplements; (2) if yes, asked about duration of use	8.2 y	Cases of cataract extraction surgery	**No association** between MVM use and cataract extraction
Milton, 2006 (Milton R. C., Sperduto, R. D. et al., 2006)	AREDS cohort	4,590 men and women with complete covariate data, aged 55–80 y,	66% (3,037) of participants elected to take a daily MVM (Centrum®)	6.3 y	Progression of "any" lens opacity or type-specific (nuclear, cortical, or PSC) opacity	Centrum® use was associated with a **reduction** in the progression of "any" lens opacity

		with vision issues or AMD in at least 1 eye				(OR: 0.84; 95% CI: 0.72–0.98) and nuclear opacity (OR: 0.75; 95% CI: 0.61–0.91)
Mares-Perlman, 2000 (Mares-Perlman J. A., Lyle, B. J. et al., 2000)	Beaver Dam Eye Study	3,089 subjects (aged 43–86 y)	In-person interviews at final follow-up visit	5 y	Incidence of nuclear, cortical, and PSC cataract	Reported use of multivitamin supplements for >10 y associated with a **reduced risk** of nuclear (OR: 0.6; 95% CI: 0.4–0.9) and cortical (OR: 0.4; 95% CI: 0.2–0.8) but not PSC (OR: 0.9; 95% CI: 0.5–

						1.9) cataracts
Christen, 1999 (Christen W. G., Ajani, U. A. et al., 1999)	PHS I	21,120 male US physicians (aged 40–84 y)	Questionnaire at baseline: (1) asked about supplement use (never, past only, or current); (2) asked number of y taken (if current)	12.5 person-y	Risk of AMD	**No association** between MVM use and AMD

AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; CHD, coronary heart disease; CI, confidence interval; COSM, Cohort of Swedish Men; CPS, Cancer Prevention Study; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HPFS, Health Professionals' Follow-up Study; HR, hazard ratio; MI, myocardial infarction; MVM, multivitamin/mineral supplement; NHEFS, National Health and Nutrition Examination Survey I Epidemiological Follow-up Study; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health-American Association of Retired Persons; OR, odds ratio; PHS I, Physicians' Health Study I; PSC, posterior subcapsular; RR, relative risk; US, United States; VITAL, Vitamins and Lifestyle study.