REVIEW

Recent Developments in Multivitamin/Mineral Research[1,2]

Kevin B. Comerford*

University of California at Davis Medical Center, Department of Internal Medicine, Division of Endocrinology, Diabetes and Metabolism, Sacramento, CA

ABSTRACT

The 2010 Dietary Guidelines Advisory Committee was charged with the task of investigating the effects of multivitamin/mineral supplements on healthy populations and also on those with chronic disease. The evidence from which the committee prepared its conclusions was graded on 5 fundamental criteria: quality, consistency, quantity, clinical impact, and generalizability. The committee concluded that for the general healthy population, evidence was insufficient to make a multivitamin/mineral recommendation. On the other hand, the committee noted the value of some supplemental nutrients for at-risk populations such as iron, folic acid, and vitamin B-12. However, most of the studies referenced for the research used the conventional, all-encompassing, and oversimplified definition of a multivitamin/mineral as being a supplement containing 3 or more vitamins with or without minerals. In the few years since the committee released its 2010 report, several randomized clinical trials showing the benefits of daily multivitamin/mineral supplementation have been completed using supplements containing at least 10 or more vitamins and/or minerals, but there also continues to be some reports that do not find benefit from such supplements. Furthermore, several steps have been taken to advance the science behind these supplements so that consumers, physicians, and government agencies can all have more confidence in understanding the role of supplemental nutrition in the American diet. This review provides new evidence from 2010 onward addressing the committee's primary concerns about multivitamin/mineral research in regard to improving public health. It also includes several recent studies that may be of interest to future committees indicating the potential benefits of these supplements on improving the cognitive performance and mental well-being of healthy populations. *Adv. Nutr. 4: 644–656, 2013.*

Introduction

The use of dietary supplements has been gradually increasing since the introduction of the first multivitamin/mineral (MVM)[3] formulas in the 1930s (1). This increase has ramped up considerably in the past 30 y as MVMs have become the most commonly used dietary supplements in the United States, with more than one-third of the population reporting use (2,3). United States MVM use varies considerably by demographic with, ~20% of adolescents and 50% of individuals 50 y or older reporting use. Females are also more likely than males to use MVMs as are individuals with healthier lifestyle habits, more education, higher socioeconomic status, and lower BMIs as well as those living in the western United States (4). The primary reasons reported for MVM use are to both improve health and prevent chronic disease by increasing nutrient intakes (4).

In 2010, the Dietary Guidelines for Americans (5) contained specific language pertaining to MVM use and human health, acknowledging that "supplements containing combinations of certain nutrients may be beneficial in reducing the risks of some chronic diseases when used by special populations." However, the guidelines also noted that a need existed for more scientific evidence on MVMs and that further investigation was necessary since certain supplements have the potential to be harmful if not manufactured or used correctly. This prompted the Dietary Guidelines Advisory Committee (DGAC) to call for future research on MVMs with a specific focus on the areas of increasing accuracy of self-reports, improving composition and bioavailability data, and conducting randomized controlled trials rigorously testing health outcomes (6).

Although the DGAC's directives on future research seem relatively straightforward, a major roadblock to progress has been simple semantics. For starters, no standardized

[1] Supported by the Council for Responsible Nutrition.

[2] Author disclosures: K. B. Comerford received consulting fees from the Council for Responsible Nutrition. All conclusions are the work of the author. There are no other potential conflicts of interest to be reported.

[3] Abbreviations used: CVD, cardiovascular disease; DGAC, Dietary Guidelines Advisory Committee; DSID, Dietary Supplement Ingredient Database; DSOL, Dietary Supplements On-Line Database; MVM, multivitamin/mineral; Office of Dietary Supplements (ODS), RCT, randomized controlled trial.

* To whom correspondence should be addressed: E-mail: kbcomerford@ucdavis.edu.

or regulatory definition of an MVM currently exists, and various organizations, experts, and authorities have used many different definitions over the years for these popular supplements. Thirteen vitamins and 15 minerals have been credited as essential for the maintenance of human health; however, past and present definitions of MVMs have been minimalistic, inconsistent, and inadequate. For example, the USDA has at times loosely defined an MVM "as containing more than two vitamins" (7). The most common definition in the body of research produced by experts and agencies alike has generally defined an MVM "as containing 3 or more vitamins with or without minerals" (4). A major problem with these popularized or marketing definitions is that they allow for the inclusion of products that are in direct contradiction to their key designation as containing "multiple" vitamins and minerals because both of these definitions require zero minerals to be present and allow for products containing simply a few B-vitamins or just the fat-soluble vitamins to be considered an MVM.

Other MVM definitions used in the last decade also vary between and within major governmental research organizations. A recent definition used by the NIH refers to an MVM as "any supplement containing three or more vitamins and minerals but no herbs, hormones, or drugs" (1), whereas the CDC's NHANES contradicts that definition, classifying an MVM "as a product containing three or more vitamins and one or more mineral" while also allowing for the addition of certain amounts of botanicals and amino acids (2). Granted, many supplements containing 3 or 4 vitamins and minerals have shown benefit for particular health issues, but it is arguable whether they should be classified in the same context as a supplement containing the majority of the nearly 30 essential micronutrients.

MVM Nomenclature

In addition to determining a solid definition for MVMs, the classifications of the different types of MVMs have been a continuing conundrum for researchers. The sheer number of different products available for various lifestyles and life stages is still growing as new products are introduced onto the market on a continual basis as evidenced by a recent sales growth of 4.4% (7). The NIH Office of Dietary Supplements (ODS) simply breaks down MVMs into different categories such as "once-daily" or "specialized" depending on their recommended frequency of intake or nutrient doses in relation to daily values, RDAs, or adequate intakes (4). Not only do MVMs fall into several different categories, but they also are marketed by several different names such as "multivitamins, multiminerals, multis, multiples and vitamins," further complicating the cataloguing process and database-building efforts (4). Formulators and manufacturers may also add nonvitamin and nonmineral ingredients such as herbs, botanicals, amino acids, fatty acids, and constituents from food (e.g., omega-3 fatty acids or lutein) to their products. Additionally, they may also promote them for an array of health issues such as eye health, energy production, and healthy immune function (6). Because of the lack of a standardized MVM definition, a product could be considered a MVM even if it includes a vast majority of nonvitamin or nonmineral ingredients as long as it contains a few vitamins and minerals.

As part of the 2006 reauthorization of the Older Americans Act, Congress provided the definition of a daily MVM as "a dietary supplement that is in compliance with all applicable United States government quality standards and provides at least 2/3 of the essential vitamins and minerals at 100% of the daily value amounts as determined by the Commissioner of Food and Drugs" (8). Although this definition is still not as popular as the all-encompassing "3 vitamins or more" definition still commonly used in research settings, it is a definition that is much more scientifically useful and informative for the purpose of addressing the 2010 DGAC's concerns for future MVM research.

Current Status of Knowledge

Many of the concerns from the 2007 NIH State-of-the-Science Conference Statement about MVM supplements and chronic disease are very similar to the concerns of the 2010 DGAC regarding future MVM research (1,6). In 2007, the NIH advisory committee performed a comprehensive review of the available MVM research and cited 7 areas where there were gaps in knowledge, shortcomings in data quality, and improvements needed in methodology and technology. Echoing 3 of these areas, the DGAC in its "Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010" (6)" explicitly expressed the need for future research on MVMs with the following aims: *1*) conduct studies on the precision of self-reported intakes of MVM supplements; *2*) develop accurate composition and bioavailability data across the multitude of vitamin, mineral, and nutrient supplements, and evaluate outcomes based on nutrient composition and bioavailability within the MVM matrix; and *3*) conduct randomized controlled trials (RCTs) that rigorously test health outcomes, including safety and risk assessment of nutrient supplements in a diverse range of healthy population groups.

Aim 1: Conduct Studies on the Precision of Self-Reported Intakes of MVM Supplements

In addition to the discrepancies in defining an MVM, many challenges and methodological issues impede the accuracy of self-reported MVM use (9–11). These barriers include factors such as communication and language issues between researchers and participants, outdated survey methodology, MVM labeling inconsistencies, and supplement database incompleteness. The 2010 DGAC report shared the same sentiment as the 2007 NIH State-of-the-Science Conference Statement on MVMs, which suggested that to produce more accurate MVM self-reports, future research opportunities should "capitalize on new electronic technologies, design and employ improved questionnaires, and develop new dietary and MVM recall methods, all to enhance accuracy and specificity of reported MVM intake" (1).

Language and communication improvements

One of the primary issues with self-reporting accuracy is miscommunication between the examiner and examinee. There is potential bias on both sides of the communication process, with examiner bias potentially influencing results (12,13) and with the examinee either not understanding the question or not wanting to be fully honest with his or her answers (12,14). The specific language on small-scale questionnaires and large national surveys has also played a large role in the communication (or miscommunication) process involved in the accuracy of self-reporting. For example, individuals may be supplementing with what has been considered by many to be an MVM, (i.e., a supplement with 3 or more vitamins and/or minerals, but both examiner and examinee might not know that the product is technically considered an MVM because the supplement was marketed and labeled for some other purpose such as promoting cardiovascular health, memory, energy production, or immune health (12,14). Another potential problem with survey language regarding supplements is that individuals may not know what certain ingredients are in their MVM if those ingredients have been labeled by their scientific names and not their common or usual vitamin names (i.e., pantothenic acid, thiamin, or riboflavin instead of their B-vitamin designations).

In recent years NHANES researchers have thoughtfully addressed a multitude of potential self-reporting pitfalls and have greatly improved their overall methodology. One of the fundamental changes to address these concerns has been undertaken by the 2007–2012 NHANES (15), in which for the first time participants were eligible for a second 24-h dietary recall interview 3–10 d after their first interview (8). This second recall was designed to correct for accounting errors and discrepancies in the initial interview and also give the researchers the ability to analyze the data using weighted averages to further ensure the accuracy of the data collected. The second recall also allowed for extended contact and improved rapport between examiners and examinees that could likely aid in better communication and trust building between the parties so that typical consumers could be more comfortable giving honest answers.

The NHANES group took further steps to ensure self-report accuracy by upgrading its 2007–2012 Dietary Screener Questionnaire in the household interview through incorporating additional information on supplement use. Information on amount and use of supplements was collected to coincide with the same 24-h time frame as food and beverage intake, thus allowing researchers to more accurately estimate total nutrient intake in that time period (8). Additionally, researchers began to attempt to physically identify and record the specific dietary supplements reported by participants. NHANES interviewers reported that they were able to see the particular dietary supplement bottles and labels in question to verify the accuracy of self-reports with an 85% success rate (2).

Database improvements

Dietary supplement ingredient database 1. The 2007 NIH State-of-the-Science Conference Statement on MVMs suggested that new databases be built and continuously updated for use by the research community to address data quality issues (1). This suggestion directly addressed the same concerns as the 2010 DGAC regarding more accurate self-reporting. During the research and creation process of the 2010 dietary guidelines, the Dietary Supplement Ingredient Database (DSID)-1 was just coming online (April 2009). This new database was a collaboration of several federal agencies, including the NIH ODS, USDA Agricultural Research Service, CDC, and FDA. The database originally contained the estimated amounts of 18 vitamin and mineral ingredients derived from analytical data for 115 unspecified adult MVMs. Its purpose was to provide a publicly available dietary supplement database that could provide reliable estimates of the ingredients in a host of dietary supplement products; analyze and compare amounts of ingredients to values stated on supplement labels; and support improved dietary intake assessments in research (16). MVMs were the top priority type of supplements to be included in this database because many national surveys, including the NHANES 2003–2006, revealed that MVMs were consumed by nearly 40% of those surveyed (17).

Before the release of the DSID-1, government-sponsored supplement information was limited or undependable and therefore not useful for individuals or health care providers. The DSID-1 directly addressed 1 of the primary concerns of the 2010 DGAC by making available more precise data for both the general public and scientific researchers on MVMs. Therefore, the database allowed for better precision of self-reported intakes by both consumers and individuals estimating nutrient intakes for MVM research surveys.

DSID-2. A major update to DSID-1, DSID-2, was released in March 2012. DSID-2 included additional information and corrected information on adult MVMs and also introduced estimates for the ingredients in many popular children's MVMs (16). However, DSID-2 is not the only supplement database available and has limitations. It is far from a comprehensive database, and many technical and standardization issues exist in how it defines MVMs. The definition, "dietary supplements containing 3 or more vitamins," is basic and broad (18). Although this definition allows for the inclusion of more products in the database, it also may include many products that are not marketed or intended for use as an MVM. For example, certain products labeled as MVMs in the database may contain no minerals at all, much less "multi" minerals. The "3 or more vitamins" definition is also a far cry from the congressional stance on MVMs stating that they "provide at least 2/3 of the essential vitamins and minerals" (5). Furthermore, data were not made available for prenatal vitamins or for important nutrients such as vitamin A, vitamin D, and chromium in the database, although new studies have been designed and implemented to address these issues (18).

Moreover, the DSID-2 MVM ingredient predictions are formulated from the labeled amounts and their analytical laboratory measurements but are not specific to any individual supplement product or brand. Accordingly, the DSID-2 is ideal for population-based studies but not useful for mining information on the specific products used in those studies (18). However, another new database known as the Dietary Supplements On-Line Database (DSOL) is also in use to address this issue.

DSOL. The DSOL is a sister database to the DSID-2 and covers many of the areas that the DSID-2 was not designed for. The DSOL was started in 2005 with funding from the CDC's National Center for Environmental Health and is now part of the National Library of Medicine's database system (19). The DSOL contains label ingredient information on thousands of specific national brands and was designed to educate supplement consumers and researchers and assist them with their queries. The particular supplement brands in the database were driven by the latest NHANES data and include products from retail stores, online sellers, and practitioner-supplied products. The DSOL was developed to be one of the largest centralized label databases of its kind. It is also electronically linked to other important health and safety Web sites and databases such as PubMed and MedlinePlus so that consumers can be more properly informed of their supplement usage (19). The DSOL does not actually test any supplements, but it does provide a clear and easy-to-use resource for checking the labeling of supplement ingredients to ensure self-reporting accuracy on both the consumer and researcher sides of the survey.

Although the DSID-2 and DSOL are stand-alone entities that are housed by different groups and used to index different types of information, their overall usefulness has been somewhat limited by their lack of integration with each other. In 2012, scientists from the ODS, USDA, CDC, FDA, and NIH released a paper on the need for a uniform database system for classifying dietary supplements and indexing their ingredients (20). These experts from several different government agencies borrowed from an existing food-based indexing framework called LanguaL and proposed modifications to create an interface tool called the LanguaL Dietary Supplement Structured Vocabulary. This interface allows for the collection, classification, and sharing of supplement information from various databases according to a dozen key "facets" such as product type, ingredients, dietary uses, label claim, and geographical region. Whereas the DSID-2 is a quantitative database used for estimating nutrient intakes, the LanguaL Dietary Supplement Structured Vocabulary allows for deep classification of MVMs based on their primary ingredients, number of ingredients, source of ingredients, and many other important descriptors that could be utilized for research purposes. Although the creation and upkeep of this tool call for a substantial time and resource investment and likely will only include the most applicable data or facets necessary for each supplement, it will greatly improve the accuracy of nutrient intake estimates from surveys and self-reports.

The effort to improve accurate self-reporting is far from complete, but the science has come a long way since the 2010 DGAC called for improvements. From upgraded survey design and better communication techniques to improved databases and database interfaces, the self-reporting data are becoming easier to decipher and incorporate into understanding how MVMs affect the health and diet of different populations, particularly those populations at risk of deficiencies in nutrients of concern as noted by the 2010 DGAC.

Aim 2: Develop Accurate Composition and Bioavailability Data Across the Multitude of Vitamin, Mineral, and Nutrient Supplements, and Evaluate Outcomes Based on Nutrient Composition and Bioavailability Within the MVM Matrix

Accurate composition of MVMs. A second major concern of the 2010 DGAC was to address the lack of data on the accurate composition and nutrient bioavailability of MVMs. Although this task is of utmost importance for understanding the benefits of supplemental nutrition, it is exceedingly more difficult than it may seem. To get accurate bioavailability information from commercially available MVMs, researchers must first depend on the label claims of those products. However, the actual nutrient amounts in a product can vary and differ from the values stated on the label (10). USDA measurements on numerous MVMs have revealed that certain vitamins such as folic acid and riboflavin average >13% from their stated label claims, whereas minerals such as iodine and selenium demonstrate greater variance, at a >25% difference from their stated labels (15). Independent researchers have also found variation within batches and between batches of the same products (1), but this issue may be somewhat dependent on when the product was tested in relation to when it was manufactured and may also be affected by environmental exposure through the supply chain.

Although the variability of vitamins and minerals in MVMs can often exceed 10–20% for each particular nutrient (5), these numbers are to be expected because certain nutrients may degrade over time. To address the issue of degradation, manufacturers often add a buffer amount of nutrients, called overage, so that the dietary supplement will provide adequate amounts to consumers throughout the duration of an extended shelf life, which is required by regulation. Regarding this matter, the FDA mandates that "Class I nutrients," or those nutrients added in fortified or fabricated foods, inclusive of vitamins, minerals, protein, dietary fiber, or potassium, must be present at 100% or more of the value declared on the label during the entire shelf life of the product (21). However, this practice can lead to potential inaccuracies in labeling, which sets the stage for inaccuracies in the science based on those labeled values if researchers do not apply the predicted difference provided by the DSID-2 to make adjustments to the stated label claim. For example, inaccurate label data that have not been

adjusted using the DSID-2–predicted differences affect the accuracy of bioavailability data and self-reporting. Furthermore, the effectiveness of supplement label databases (e.g., DSOL) (1) is limited if not used in conjunction with the DSID-2.

Bioavailability of MVMs. At the time of the DGAC's recommendations for further investigation into bioavailability research, no standardized definition for "bioavailability" regarding supplements existed (12). The makeup and metabolism of supplements vary considerably from those of foods and drugs, so the standard definitions of "bioavailability" used in those fields could not be successfully borrowed and applied to supplements. For example, supplements such as MVMs differ from natural foods, pharmaceuticals, and even other MVMs in their matrices, nutrient combinations, and nutrient compositions (5), all of which can affect bioavailability. Many bioavailability studies exist for foods and single-nutrient supplements; however, very few exist specific to the MVM matrix.

One of the particular reasons that a definition of "bioavailability" has been so elusive is that the nutrients in supplements are absorbed and utilized differently from whole foods, which contain a "food matrix" that needs to be broken down to release the nutrients from their macronutrient ensemble. However, this process does not necessarily occur for the nutrients added to fortified and processed foods, which may or may not share similar bioavailability characteristics to MVM supplements (22,23). The bioavailability of supplements also differs from that of pharmaceuticals because a major focus of drug bioavailability is not only a drug's absorption but also its utilization. However, Heaney et al. (16) pointed out that nutrients differ from drugs in that "for many nutrients, utilization is a function of the nutritional status and physiological state of the subject. The same nutrient will be utilized in some individuals and not in others." This same theory also applies to the bioavailability of nutrients in food, which also differs from the bioavailability of pharmaceuticals in many respects. So although it may be ideal to define the bioavailability of MVM similarly to that of a food or drug, the existing definitions need to be modified to ensure the accuracy of the science regarding supplements (12).

Additional factors hindering bioavailability research are that some vitamins can be made synthetically (i.e., natural source vitamin E as RRR-α-tocopherol vs. synthetic all-racemic-α-tocopherol), potentially altering their absorption. Furthermore, many vitamins and minerals come in several different forms or compounds (e.g., vitamin C as ascorbic acid, Ester-C, sodium ascorbate, ascorbyl palmitate) with varying degrees of bioavailability. With all of these variables taken into account, it cannot be assumed that the same amount of vitamin or mineral in an MVM will be absorbed to the same degree as another. There is also a potential for variations in the bioavailability of supplements if they use different forms (i.e., liquid, powder, tablet, capsule, softgel) or competing or synergistic combinations of nutrients and non-nutrients (e.g., vitamin D, calcium, vitamin C, iron, zinc, copper, and fiber are all known to encourage or inhibit the bioavailability of other nutrients).

The FDA has been using the term "bioequivalence" for decades to roughly compare the similarities in bioavailabilities and pharmokinetics between 2 proprietary preparations, but this term generally is not used in the supplement industry because it necessitates human clinical trials and is also not very applicable when dealing with multiple vitamins and minerals found in an MVM. However, the premise of measuring bioequivalence is ideal to supplement researchers because it takes into account the intersubject variation in the absorption of different vitamins and minerals. An appropriate modification to this methodology was investigated in 2009 through an NIH-sponsored workshop with the goal of creating a standardized set of data that would aid consumers and health care practitioners in becoming more informed about supplement bioavailability. The selected group of experts suggested a way of dealing with bioavailability data from clinical studies that rests largely on interpreting AUC measurements that include inherent intersubject variation and may give misleading results. The expert panel suggested incorporating specific terminology regarding the ability of a nutrient to be absorbed based on its available reported means and SDs. Based on this meeting, Kagan et al. (24) authored an article suggesting the use of the term "reliable" bioavailability to represent those supplements that are reliably absorbed in 84% of the study population, whereas "universal" bioavailability would represent those supplements that were well absorbed by 98% of the population. These claims would be dependent on an "inclusion" value that would be determined as the lowest absorbance value that still includes 84% (all values above the low SD) or 98% (all values above 2 SDs below the mean) of the results from all patients. Although the FDA system of bioequivalence and the newly proposed reliable/universal system both take into account intersubject variation, the statistics behind the reliable/universal system is more informative because it is focused on how supplements are biologically different, not just on how the FDA determines that they are biologically equivalent.

In addition to updating the definition of "bioavailability" to be more applicable to supplements, the analytical techniques allowing for collection and interpretation of the bioavailability data on MVMs need further attention from researchers (25). Before the 2010 DGAC's decision to focus on attaining more research on MVMs, the bioavailability data on different MVM formulations for use in humans were relatively scarce (26). However, it is becoming clearer that MVM supplements can improve the micronutrient status of at least some of the ingested vitamins and minerals in certain at-risk populations as evidenced by the current research (27–30). Recent findings on individual nutrient supplements such as folic acid and zinc have also shown their efficacy for improving micronutrient status in humans (26,31).

In 2007, Dwyer et al. (25) expressed concerns that researchers lacked appropriate and cost-effective analytical

techniques for determining the status of vitamin D, vitamin B-12, and folate in humans. These same concerns were still resonating years later and were also addressed by the 2010 DGAC report (6). Vitamin D, vitamin B-12, and folate, which are often present in MVMs, pose numerous problems for scientists using in vivo analytical assessments in human participants. In support of these findings, NHANES researchers have continued to make specific strides toward addressing and improving methodology issues regarding the bioavailability of these micronutrients. In July 2010, around the same time that the 2010 DGAC report was released, a roundtable discussion consisting of nearly 3 dozen experts and scientists was held to determine the proper actions to take regarding vitamin B-12 and folate-related biomarkers for future NHANES research. One of the main drivers of this meeting was the issue that from 2006 to 2010, NHANES researchers had stopped measuring vitamin B-12 status and its related biomarkers because of methodology concerns (32).

To address previous problems with the sensitivity and specificity of assays used for determining vitamin B-12 status, the panel decided to recommend a dual approach to measure for at least 1 biomarker of circulating vitamin B-12 and also 1 functional biomarker (32). The group also compared different folate bioassays from previous NHANES years and suggested data modifications based on their differences and also recommended improvements to the current procedure for determining folate status, to be further discussed and developed (33). These newly reinstated measures along with suggestions for improved methodology will allow for better tracking and understanding and interpretation of the bioavailability data on MVMs containing vitamin B-12 and folic acid. Other bioavailability improvements have also been made to the adult MVM data in the DSID-2 regarding the analytics of its vitamin data. In light of new bioavailability evidence regarding vitamin form (hydrochloride vs. free form), statistical adjustments were released in 2012 for both thiamin and vitamin B-6. These calculation adjustments were necessary to optimize the data based on improved final regression estimates (18). The newly updated information allows for a more accurate assessment of specific ingredient intakes from MVMs and further improves the state-of-the-science regarding these vitamins for use in informing public health policy.

Additional research by Maki et al. (26) on the bioavailability of a 1000-μg acute dose of folic acid tested folate absorption between different oral forms (softgel vs. tablet) and vitamin and mineral combinations (folic acid vs. MVM with 11 other micronutrients). In this randomized crossover trial, absorption between the different supplements appeared comparable because total mean serum folate concentrations were similar. The only major difference between the supplements was a slight time delay for the MVM softgel to reach its peak, suggesting that supplement form may not always be a major determinant of supplement function. Another RCT involving folate indicated that daily MVM supplementation leads to substantially increased blood concentrations of folate and vitamin B-12 after 8 wk in older men. In this study there was also a subsequent reduction in homocysteine concentrations, further demonstrating the ability of these MVM nutrients to be functionally utilized for addressing specific health needs (27).

To better understand and account for external factors that influence the bioavailability of supplements, NHANES has taken the approach of recording data on antacid use coinciding with their food and supplement data. This approach may be in light of recent evidence that antacid use potentially alters the bioavailability of many drugs and nutrients (34,35). Collecting supplement, antacid, and food data for the same 24-h period may also allow researchers to take into account information on bioavailability and absorption on foods containing certain antinutritive properties such as phytates (36) and oxalates (37) as well as certain fibers (38) that can interfere with nutrient absorption. On the other hand, in addition to the scientific information that was already available on specific foods that may help increase the absorption of certain nutrients such as the ability of citric acid and ascorbic acid in orange juice to facilitate absorption of iron from various inorganic salts (e.g., Fe sulfate, Fe gluconate, Fe phosphate, Fe lactate, Fe fumarate) (39), new dietary research is constantly becoming available showing that combining certain foods such as garlic and onions with grains may actually be beneficial for the absorption of certain nutrients such as iron and zinc in these foods (40).

Although the bioavailability information on single doses of individual vitamins and minerals is fairly well established, the bioavailability of MVMs is slightly more complex because of various nutrient-nutrient interactions. The standardization of testing for MVM bioavailability may prove difficult indeed, because each micronutrient is unique in its bioavailability characteristics. However, the bioavailability research has made impressive strides since 2010 (18,24,26,28,29,41). Although more research of this nature is necessary to better understand the differences in absorption kinetics of MVM ingredients and their various formulations and encapsulation techniques, the recent research has added key information to the understanding of the general science underlying MVM bioavailability.

Aim 3: Conduct RCTs That Rigorously Test Health Outcomes, Including Safety and Risk Assessment, of Nutrient Supplements in a Diverse Range of Healthy Population Groups

Before the 2010 DGAC report, the 2007 NIH State-of-the-Science Conference Statement on MVMs specifically mentioned the lack of well-designed RCTs on chronic diseases and MVM use and regarded it as a knowledge gap (1). Although there has been a long history of safe use and several large, well-designed epidemiological studies on MVMs and disease, relatively limited information is available on their safety and efficacy, especially in healthy populations. During their investigations into MVMs in 2007, NIH-sponsored researchers found only 5 RCTs on MVMs and chronic disease

that met their specific criteria to include in their report (42–46). RCTs are considered the gold standard for forming public policy about the absorption and functional benefit of food and nutrient supplementation. These types of studies often require more invasive actions and resources than other types of valuable research, but they also tend to yield direct and evidence-based information on cause-and-effect relations between nutrient supplementation and specific outcomes. However, many of the previously accepted diagnostic biomarkers are no longer considered valid, and many of the contemporary biomarkers have not been accepted or recognized by the medical communities or regulatory authorities. Thus, nutrition policy based on single biomarkers or datasets flush with biomarker inconsistencies can be challenging. Although RCTs are only 1 type of study that adds to the body of knowledge about health and disease, the 2010 DGAC made a specific point to address the need for more RCTs above any other type of research to help scientists better understand the cause-and-effect relations between consuming MVMs and health promotion and disease prevention.

In 2007, a majority of the RCTs available on MVMs focused on unhealthy or diseased populations, and most were performed on non-United States populations. Almost all of the available studies used different MVMs, controls, and inclusion criteria such as age range, BMI, and dietary habits. A major scientific limitation to extracting meaningful conclusions from these data is that there is no way to combine the data to get a better understanding of the overall efficacy of MVMs, which leaves substantial gaps in the understanding of how MVMs affect health and disease in different populations. Three years later, after the 2007 NIH consensus conference, the 2010 DGAC report also mentioned many of these same issues regarding the lack of completed RCTs necessary to help inform public policy decisions. Therefore, the committee specified that future RCTs should also focus on a diverse range of healthy populations (6).

In the years since the 2010 DGAC made its recommendations on RCTs, several new studies were completed and published that investigated MVM use in both healthy and unhealthy populations (**Table 1**). These studies were found in PubMed, Embase, ClinicalTrials.gov, Cochrane's Registry of Clinical Trials, and Cochrane's Registry of Systematic Reviews by using combinations of the search terms "randomized," "multivitamin," "multimineral," and "multiple micronutrient" and dates between March 2010 and May 2013. The search focused on original research, systematic reviews, and meta-analyses of RCTS. RCTs were included only if they used an MVM supplement that provided at least two-thirds of the essential vitamins and minerals at 100% of their daily value amounts. Systematic reviews and meta-analyses were included if they contained an RCT that followed this definition; however, many of the observational studies in these reviews did not necessarily adhere to this definition but still provide valuable information on a range of MVM research.

Using the much more specific and descriptive MVM definition put out by the 109th Congress in 2006 (8), several studies have been completed and published since the DGAC prepared its 2010 statement on future MVM research. The RCTs currently available range from those studying several dozen to several thousand participants and have investigated a host of different supplements, populations, measurements, and biomarkers. The current studies on both healthy and unhealthy populations have helped researchers better understand the implications and limitations of MVMs on the brain and body. Although more work is needed in this area before definitive dietary guidelines are produced on the relation of MVMs to general health in already healthy populations, research suggests that taking MVMs poses no harm to health and may help fill nutrient gaps for several shortfall nutrients.

The recent research on healthy populations has been focused largely on studies involving brain health concerns such as cognitive function, memory, and stress. Although the MVMs in RCTs vary (Table 1), they were selected to include 10 or more vitamins and/or 10 or more minerals, allowing for a better understanding of how a full-spectrum MVM supplement intended for daily use and not marketed for any one particular condition can affect mental health and functioning. In addition, selected systematic reviews and meta-analysis papers offer for a fuller picture of the state of the science, even though many of these publications did not specifically mention what type of MVM supplement was used (Table 1).

Mental health RCTs. Multiple Australian researchers have answered the DGAC calls for more RCTs on MVMs in healthy populations by producing impressive amounts of data spanning several studies in this area. Three different researchers showed some conformity by using the same MVM line (Swisse Ultivite) to conduct separate RCTs on mental health in relatively healthy and diverse populations. Sarris et al. (47) investigated the effects of 16 wk of daily MVM supplementation on a healthy, young (20–50 y), mixed-gender population in Australia and saw improvements in mood ($P = 0.027$) and increased energy concentrations ($P = 0.022$) in both males and females. Experimenting with the same brand of MVM supplements, Harris et al. (48) discovered that daily MVM supplementation in older men (50–69 y) was associated with substantially decreased ($P = 0.033$) depression, anxiety, and stress scale scores along with improvements in alertness and "general well-being" after 8 wk. Using a similar study design, the same group also found substantially improved measures in the specific area of contextual recognition memory ($P < 0.05$), but not in other measures of memory performance (27). However, further research from the Macpherson group also used the Swisse Ultivite brand and provided evidence that 16 wk of daily consumption of an MVM in elderly women with memory complaints could improve spatial working memory ($P < 0.05$) and increase measures of neural efficiency ($P = 0.007$) (49,50). Homocysteine concentrations were also reduced ($P < 0.05$) in

TABLE 1 Clinical effects of MVMs on health and disease: evidence from randomized controlled trials and meta-analyses[1]

Health or disease outcome (Reference)	Study design	Supplement (micronutrients)	Study location	Results compared with placebo
Academic performance (53)	RCT: 16 wk, 684 children aged 8–12 y attending schools in New Jersey	Tishcon Corp. children's chewable MVM (provided 100% of the RDI for ages 4–12 of most vitamins and minerals)	United States	Academic performance: no significant difference
Cognitive function (51)	RCT: 9 wk, 216 females aged 25–50 y	Supradyn Multivitamin (13 vitamins, 12 minerals)	United Kingdom	Multitasking accuracy: increased ($P < 0.05$) Mathematical processing: increased ($P < 0.05$) Performance speed: increased ($P < 0.05$)
Mood and stress (48)	RCT: 8 wk, 50 men aged 50–69 y	Swisse Men's Ultivite (10 vitamins; 10 minerals; and amino acids, plant extracts, and nutraceuticals)	Australia	Depression, anxiety, and stress scale score: decreased ($P = 0.03$) Alertness: increased ($P = 0.03$) Profile of mood states: no significant difference
Subjective well-being (47)	RCT: 16 wk, 114 healthy males and females aged 20–50 y	Swisse Ultivite (10 or more vitamins; 10 or more minerals; and amino acids, plant extracts, and nutraceuticals)	Australia	Mood enhancement: increased ($P < 0.05$) Energy levels: increased ($P < 0.05$)
Cognition and memory (27)	RCT: 8 wk, 51 men aged 50–74 y	Swisse Men's Ultivite (10 vitamins; 10 minerals; and amino acids, plant extracts, and nutraceuticals)	Australia	Contextual recognition memory performance: increased ($P < 0.05$) Working memory: no significant difference Spatial working memory: no significant difference
Neurocognition and brain activity (50)	RCT: 16 wk, 41 elderly women aged 64–79 y with subjective memory complaints	Swisse Women's Ultivite (13 vitamins; 11 minerals; and amino acids, plant extracts, and nutraceuticals)	Australia	Neural efficiency: increased ($P = 0.007$) Behavioral performance: no significant difference
Memory (49)	RCT: 16 wk, 56 community-dwelling elderly women with subjective complaints of memory loss	Swisse Women's Ultivite (13 vitamins; 11 minerals; and amino acids, plant extracts, and nutraceuticals)	Australia	Spatial working memory performance: increased ($P < 0.05$) Homocysteine: decreased ($P < 0.05$)
Aggression, impulsivity, and stress (52)	RCT: 12 wk, 42 men, mean age of 21 y	Centrum Advance 50+ (~100–150% RDI: 12 vitamins, 13 minerals)	United Kingdom	Perceived stress: decreased ($P < 0.07$) Aggression and impulsivity: no significant difference
Cognitive performance (54)	Meta-analysis of 10 RCTs: 3200 men and women volunteers	Variable (no data given on supplement ingredients). Inclusion criteria based on frequency of oral MVM intake (≥1 mo)	International	Immediate free recall memory: increased ($P < 0.01$) Delayed free recall memory: no significant difference Verbal fluency: no significant difference)
Stress and mood (55)	Meta-analysis of 8 RCTs: 1292 healthy adults aged 18–69 y	Variable (no data given on supplement ingredients). Inclusion criteria based on frequency of oral MVM intake (≥28 d)	International	Mild psychiatric symptoms: decreased ($P = 0.001$) Perceived stress and anxiety: decreased ($P = 0.001$) Depression: no significant difference
Adiposity, lipid profile, and energy expenditure (62)	RCT: 26 wk, 96 obese Chinese women aged 18–55 y with mean BMI of 28	Centrum (13 vitamins, 16 minerals)	China	Body weight, fat mass, TC, SBP, DBP, LDL-C: decreased ($P < 0.05$) REE, HDL-C: increased ($P < 0.05$) TG, glucose, insulin, FFM: no significant difference

(Continued)

TABLE 1 (*Continued*)

Health or disease outcome (Reference)	Study design	Supplement (micronutrients)	Study location	Results compared with placebo
Cardiovascular disease (59)	RCT: 14 y, 14,641 male United States physicians with mean age of 64 y, including 1732 with a history of CVD	Centrum Silver (13 vitamins, 16 minerals, and lutein and lycopene)	United States	Major CVD events: no significant difference Myocardial Infarction: no significant difference CVD mortality: no significant difference
Cancer (60)	RCT: 14 y, 14,641 male United States physicians with mean age of 64 y, including 1312 with a history of cancer	Centrum Silver (13 vitamins, 16 minerals, and lutein and lycopene)	United States	Total cancer incidence: decreased ($P = 0.04$) Prostate, colorectal cancer: no significant difference Cancer mortality: no significant difference
Breast cancer (64)	Meta-analysis of 2 RCTs and 3 cohort and 3 case-control studies: 355,034 women aged 20–83 y	Variable (no data given on supplement ingredients). Inclusion criteria based on frequency of MVM intake ≥7/wk)	International	Breast cancer risk: no significant difference
Prostate cancer (65)	Meta-analysis of 4 RCTs and 8 cohort and 2 case-control studies: >1 million adults	Variable (supplement criteria not clear)	International	Occurrence and severity of cancer: no significant difference
Mortality (66)	Meta-analysis of 21 RCTs: 91,074 adults with mean age of 62 y	Variable (no data given on supplement ingredients). Inclusion criteria based on frequency of oral MVM intake (≥1 y)	International	All-cause mortality: no significant difference Mortality from vascular causes, cancer: no significant difference

[1] CVD, cardiovascular disease; DBP, diastolic blood pressure; FFM, fat-free mass; MVM, multivitamin/multimineral; RCT, randomized controlled trial; RDI, recommended daily intake; REE, resting energy expenditure; SBP, systolic blood pressure; TC, total cholesterol.

1 of the studies (49), suggesting that there may be multiple and seemingly unrelated benefits to consuming a daily MVM for an elderly population with self-proclaimed memory issues.

MVM research from the United Kingdom on healthy patients has also included studies on mental health. Haskell et al. (51) used a Supradyn MVM to test the cognitive function and fatigue of 25- to 50-y-old females during an extended multitasking exercise. The participants displayed improvements ($P < 0.05$) in mathematical processing, multitasking accuracy, and performance speed after 9 wk of supplementation compared with a placebo. More recent research from the United Kingdom has focused on the mental health issues of aggression, impulsivity, and stress (52). Young adult men with a mean age of 21 y were given daily Centrum Advance 50+ for 12 wk and then asked to perform a battery of tests to gauge their responses to frustrating tasks, aggression, and stress scales and impulsivity paradigms. Results showed that taking a daily MVM indicated a trend in the ability to reduce perceived stress in these patients ($P < 0.07$) but had no effect on their aggression or impulsivity behaviors. An RCT by Perlman et al. (53) examined the academic performance of 684 healthy, American, school-aged children who were taking a children's chewable MVM. The researchers found no substantial differences between the MVM and placebo group in any measure of academic performance, including standard achievement tests, grade point averages, and school absences.

In 2012, Grima et al. (54) performed a systematic review and meta-analysis of 10 RCTs, pooling the data from >3000 participants to investigate the influence of MVMs on mental functioning and cognitive performance. The researchers found that only certain aspects of mental performance such as immediate free recall memory were improved ($P < 0.01$), but other aspects were either not affected or understudied. Long et al. (55) produced a similar meta-analysis in 2013, focusing on the mental health areas of mood and stress. This analysis included 8 RCTs and reported that MVM supplementation substantially reduced anxiety ($P < 0.001$), perceived stress ($P = 0.001$), and even some mild psychiatric symptoms ($P = 0.001$) but did not produce a noticeable effect on depression.

Chronic disease RCTs. Many observational studies on MVMs have provided evidence for their associations with reduced chronic disease risk, whereas other studies have shown no effect or even slightly elevated risk of certain ailments in at-risk populations (56–58). However, because of the lengthy time component and multiplicity of variables involved in chronic disease development, very few RCTs have investigated these relations in healthy populations. An additional obstacle for RCTs on MVMs and chronic diseases in healthy populations is that healthy people usually eat healthier and also have healthier lifestyles than unhealthy or sick populations,

resulting in skewed results and conclusions that are not always directly applicable to the people who need it the most.

Although the 2010 DGAC specifically called for new RCT research on healthy populations, there has also been a call for research on populations with chronic diseases and other health issues (1). One of the most prominent post-2010 RCTs on MVMs is the Physician's Health Study II, which investigated the effects of daily MVM use (Centrum Silver) on cardiovascular disease (CVD) (59) and cancer (60), the 2 leading causes of death in the United States. This particular trial was impressive because it tracked >14,500 middle-aged male patients for more than a decade and also specifically analyzed their data by special population subsets with a history of CVD and cancer. The results of the CVD research indicated that daily MVM had no substantial effect on heart attacks, strokes, or mortality rates in middle-aged male physicians both with and without a history of CVD. However, the authors acknowledged that CVD studies in this particular population may be misleading because the individuals tested had much more knowledge about the importance of protecting their hearts than the average American. The majority of the participants in the study was also on daily aspirin regimens and had unique access to premiere cardiovascular medications.

Another recent RCT also investigated a Centrum MVM on CVD markers. However, this research was conducted on 128 obese, 18- to 55-y-old Chinese woman with increased risk of CVD. The results from this trial were published in 2 different articles. One study was published in 2009 and was available for review by the DGAC before submitting its findings in 2010. It showed that the MVM group had substantially lower blood pressure and C-reactive protein concentrations compared with the placebo group after 26 wk ($P < 0.05$) (61). The other study was published in March 2010 just after the DGAC submitted its findings and demonstrated that MVM supplementation was associated with substantial reductions in body weight; body fat; total and LDL cholesterol, with concomitant increases in HDL cholesterol; and resting energy expenditure ($P < 0.05$) (62). Although the number of participants and trial length varied enormously between the Physicians Health Study II and the Chinese study, the immense difference in outcomes between the 2 studies shows just how different results can be when testing extremely different populations. Further evaluation of the baseline health characteristics of study participants in large RCTs and their division into subpopulations based on disease status would be beneficial to understanding the discrepancies in the outcomes between these types of studies.

The cancer-related results from Physician's Health Study II were important because MVMs led to substantial reductions in total cancer incidences in men without a history of cancer ($P = 0.04$) and in men with a history of cancer ($P = 0.02$), but not in cancer mortality. These results suggest that MVMs could help some people reduce the risk of developing cancer but not necessarily help them survive once the disease was diagnosed (60). The results also showed no substantial reductions in 2 of the most common male cancers: prostate and colorectal cancer. However, it is important to note that prostate cancer testing improved tremendously during the time period of this study as the more sensitive diagnostic method known as prostate-specific antigen screening began to be highly promoted by the medical community. The new method resulted in >1 million additional cases of prostate cancer in that timespan in the United States that should have been echoed in the study population (63). However, the prostate cancer rates in the Physician's Health Study II population did not have a similar or noticeable increase, suggesting the potential for a protective effect on prostate cancer from the MVMs the participants were taking.

In contrast, a 2011 meta-analysis by Chan et al. (64) evaluated 8 breast cancer studies, including 3 RCTs and concluded that MVMs did not appear to have an effect on breast cancer risk. Even though this analysis included >350,000 women, the researchers determined that more RCTs were necessary in this area. A similar gender-specific meta-analysis was conducted by Stratton et al. (65) in 2011. The researchers evaluated the results of 14 clinical studies, including 4 RCTs involving prostate cancer and also found no connection between cancer occurrence or severity and MVM use. However, the researchers noted that certain unidentified population subsets may be more affected than the general populations they studied.

Another major study of the effects or lack of effects of MVMs on human health was revealed by a systematic review and meta-analysis of 21 RCTs authored by Macpherson and colleagues (66) in 2013. This analysis concluded that MVM supplementation did not have any substantial effects on the all-cause mortality of 91,074 elderly adults, nor on their mortality rates from vascular or cancer-related causes. However, this analysis spanned decades, countries, ages, and health conditions as well as MVM consumption habits. It also did not specify exactly which MVMs were being consumed, when they were consumed, or whether they were consumed on a daily basis, so it cannot be accurately determined whether these results would hold up if all of these variables had been controlled for.

Several other recent MVM RCTs have also been completed that fall outside of the DGAC's inclusion criteria but show the value of taking an MVM nonetheless. They researched pregnant women regarding both maternal and neonate health (28,67) as well as HIV-infected children in Uganda (29,68,69). These studies used MVM supplements with 10 or more vitamins and/or minerals but investigated very specific indicators of health and disease such as diarrheal morbidity, $CD4^+$ immune cell counts, and nutrient concentrations in follicular fluid. These studies produced mixed results, but all individuals appeared to tolerate the MVMs and showed no consistent negative effects from supplementation. Many more recent RCTs have been conducted that fit the 2010 DGACs call for new MVM research, but their MVM definitions did not fit the criteria established for this review (70–77).

In summary, though there is not uniform agreement about the benefit of MVMs, recent RCTs have provided evidence that MVMs containing 10 or more vitamins and/or minerals may improve a vast array of health factors and reduce several disease risks with very little safety concerns. In addition to potentially reducing some risks associated with the onset of some chronic noncommunicable diseases, vitamins and minerals are able to fill nutrient gaps and therefore can reduce states of nutrient insufficiency or deficiency in ways that many pharmaceuticals and poor dietary patterns cannot. Yet, currently, there is no effective means for reconciling the variable differences among studies in MVM ingredient combinations, quantities, qualities, and bioavailabilities. These issues have stymied the science behind the policy-making decisions on the safety and efficacy of many potentially beneficial recommendations for both special populations and the general public. It is apparent that a better standardized set of definitions and methodologies is needed for MVM research so that different products and different study results can be properly compared, combined, and cross-referenced with an appropriate underlying or unifying theme. Future dietary supplement research should continue to investigate the effects of MVMs on diverse populations. Research efforts should include some uniformity in study design to produce results that can be utilized for improved and effective policy decisions.

Although many past large-scale observational studies have shown only mixed effects of MVM supplementation, there have likely been too many confounding variables such as variations in populations, dose, frequency, and number of included nutrients to accurately assess their effects. The lack of insightful observational and clinical data led the 2010 DGAC to declare the information on MVMs as limited. However, the DGAC's call for more clinical research to help it prepare statements for the 2015 guidelines has been admirably answered by several researchers hailing from a wide range of research areas. In light of all the recent RCTs on MVM use in healthy and chronically diseased populations, it appears that stronger and more consistent evidence is needed to readdress the previous DGAC stance on MVMs.

Whereas the 2010 DGAC claimed at the time that studies found limited evidence to suggest daily MVM use as beneficial for the prevention of chronic diseases, those studies often used MVMs containing only 3 or more vitamins or minerals. However, many recent studies using 10 or more vitamins and/or minerals have characteristically shown a mild to moderate beneficial effect on the reduced risk of developing chronic ailments ranging from cognitive impairments to the most deadly chronic conditions of cancer and CVD. In addition, a recent large-scale RCT, the Physician's Health Study II, showed modest and null effects of MVMs on cancer and CVD, respectively. Interestingly, this large RCT consisted of individuals who were highly educated, affluent, and health conscious, so the "modest" effects seen in this "abnormally healthy" population could potentially translate to substantial public health benefits for the general "less healthy population.

All the MVM RCTs conducted on healthy individuals in the past few years focusing on adult mental health, memory, and cognition had numerous positive results and potential benefits for both healthy and slightly memory impaired populations. According to these studies, "moderate" to "strong" evidence is emerging that MVMs should be considered as part of the first line of defense in these populations against the recently recognized wave of mental health issues such as anxiety, stress, depression, and cognitive or memory complaints (27,47–52). Medical professionals and our nation as a whole are becoming more aware of the importance of addressing mental health issues before they become problematic, and the use of MVMs has shown promise for aiding many aspects of mental health and well-being.

In regards to the 2010 DGAC's findings that there was "limited" evidence for MVMs to help reverse chronic disease when used by special or "unhealthy" populations, there now appears to be "moderate" evidence suggesting that supplements containing combinations of certain nutrients are beneficial in reducing chronic disease incidence when used by special at-risk populations. Daily MVM supplement use with vitamin and mineral doses near the RDA and adequate intake have been reported to be extremely safe across the clinical studies to date. Taking all of these studies into account, it appears that MVMs may be considered a true ally for special populations in the fight against nutrient shortfalls.

Acknowledgments

The author thanks Dr. Taylor Wallace, Dr. Douglas MacKay, Dr. Jeffrey Blumberg, Dr. Roger Clemens, and Stephanie Saullo, for their insightful review and discerning suggestions of this document. All conclusions are the work of the author. The author read and approved the final manuscript.

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