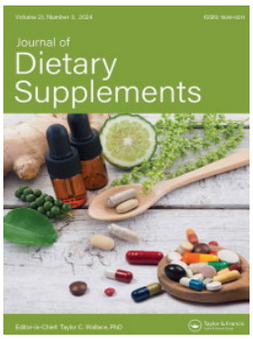

Taylor & Francis
Taylor & Francis Group

Journal of Dietary Supplements

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijds20

Revisiting the Definition of 'Healthy' Participants in Substantiation of Structure/Function Claims for Dietary Supplements

Malkanthi Evans, Erin D. Lewis, Joseph M. Antony, David C. Crowley, Andrew Charrette, Najla Guthrie, Jeffrey B. Blumberg & Gregor Reid

To cite this article: Malkanthi Evans, Erin D. Lewis, Joseph M. Antony, David C. Crowley, Andrew Charrette, Najla Guthrie, Jeffrey B. Blumberg & Gregor Reid (01 Feb 2024): Revisiting the Definition of 'Healthy' Participants in Substantiation of Structure/Function Claims for Dietary Supplements, Journal of Dietary Supplements, DOI: 10.1080/19390211.2023.2301383

To link to this article: https://doi.org/10.1080/19390211.2023.2301383

Published online: 01 Feb 2024.

JOURNAL OF DIETARY SUPPLEMENTS
https://doi.org/10.1080/19390211.2023.2301383

Taylor & Francis
Taylor & Francis Group

ARTICLE COMMENTARY

Revisiting the Definition of 'Healthy' Participants in Substantiation of Structure/Function Claims for Dietary Supplements

Malkanthi Evans, PhD[a], Erin D. Lewis, PhD[a**], Joseph M. Antony, PhD[a**], David C. Crowley, MD[a], Andrew Charrette, MSc[b], Najla Guthrie[c], Jeffrey B. Blumberg, PhD[d] and Gregor Reid, PhD[e,f]

[a]Clinical Trials Division, KGK Science Inc, London, Ontario, Canada; [b]Regulatory Division, KGK Science Inc, London, Ontario, Canada; [c]CEO, KGK Science Inc., London, Ontario, Canada; [d]Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA, USA; [e]Departments of Microbiology & Immunology and Surgery, Western University, London, Ontario, Canada; [f]Lawson Health Research Institute, London, Ontario, Canada

ABSTRACT

Concepts and definitions of 'healthy' have been evolving within clinical treatment algorithms as well as reference standards such as Body Mass Index and Dietary Reference Intakes. Consumers' perception of the word 'healthy' is also changing to reflect longer life span, need to stay active and in a good state of mental well-being while managing multiple diseases. Guidelines from the US Food and Drug Administration indicate that substantiating evidence for support of Structure/Function (S/F) claims for dietary supplements is best derived from clinical research conducted in a 'healthy' population. S/F claims cannot be represented to diagnose, treat, cure or prevent any disease. However, in this context, the term 'healthy' is non-descriptive and largely interpreted as an absence of disease. Guidelines for treatment of disease have been broadened to include biomarkers of disease risk such that the pool of 'healthy' volunteers eligible to be enrolled in clinical trials for S/F claim substantiation is greatly diminished. This perspective presents the challenges faced by the food and dietary supplement industry and by researcher efforts designed to substantiate S/F claims and suggest the phrase 'physiologically stable' or 'apparently healthy' as descriptions better suited to replace the term 'healthy.'

KEYWORDS

Apparently healthy; claims; clinical trials; dietary supplements; food and drug administration; healthy; physiologically stable; regulatory; structure/function

Introduction

Few, if any, individuals meet the World Health Organization (WHO) definition of health as "a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity" (WHO 2022). In the United States (US), 69% of adults between 40 and 79 years are prescribed at least one medication and 22.4% use at least five prescription medications (Hales et al. 2019). Recommended diagnostic

CONTACT Malkanthi Evans PhD mevans@kgkscience.com KGK Science Inc. London, ON, Canada
**EDL and JMA contributed equally.

thresholds have expanded, allowing for early risk reduction or treatment of chronic diseases, decreasing the population not on prescription medication (Moynihan et al. 2013; 2019; Schwartz and Woloshin 1999). As well, consumers' perception of the word 'healthy' has changed to reflect longer life span and their ability to be active and in a good state of mental well-being while managing multiple diseases with optimized medication regimens (Fallon and Karlawish 2019). Between 2009 and 2016, only 27.3 million (12.2%) American adults were deemed to have optimal metabolic health (Araújo et al. 2019). The traditional classification of 'healthy' using the Body Mass Index (BMI) has been challenged by new definitions (Zembic et al. 2021) and the committees responsible for Dietary Reference Intakes (DRI) are revising the definition of healthy populations (National Academies of Sciences 2022).

In accordance with the Dietary Supplement Health and Education Act of 1994, the labels of dietary supplements may present a statement of nutritional support, termed a Structure/Function (S/F) claim, which characterizes the effect a dietary ingredient has on the structure or function of the human body (FDA 2022a). S/F claims may not reference or infer treatment or reduction in the risk of disease; in contrast, health claims (HC) and qualified health claims (QHC) address reductions in risk of a disease or a state leading to disease. Health claims about a reduction in risk of disease by a food or food component are permitted but must be pre-approved by the US Food and Drug Administration (FDA). Health claims and QHC require varying levels of scientific evidence drawn from studies conducted in disease populations. QHC are supported by scientific evidence but do not meet the more rigorous "significant scientific agreement" standard required for an authorized HC (FDA 2022a). The FDA defines competent and reliable scientific evidence as the basis for S/F claims substantiation but holds randomized, controlled clinical trials as a 'gold standard' (FDA 2018). The 2022 Health Products Compliance Guidance by the Federal Trade Commission (FTC) reiterates the requirement that the population from which the groups are drawn must be appropriate for the purposes of the study (FTC 2022a). Currently, clinical research conducted in a 'healthy' population provides the most relevant evidence for support of S/F claims to be marketed for any general population or subgroup, e.g. older adults, women in menopause, etc., that is considered healthy or otherwise free from disease (FTC 2022a). Considering new research suggesting appropriate descriptions for the term 'healthy,' we present evidence that support the perspective of allowing the inclusion of populations that are 'physiologically stable' and/or 'apparently healthy' in clinical trials for S/F claim substantiation, so that the national population is better represented, and the findings more widely generalized.

The definition of disease has broadened

Evolving and expanding clinical treatment algorithms (Margolis 1983) present practical challenges for conducting research in generally healthy people. Current US demographics can be viewed as calling into question the real-world applicability of data derived from such a highly restricted sample. Broadening disease definitions, while potentially helping some people, also creates a larger population defined as having a disease (Herndon et al. 2007). For example, the recommended diagnostic thresholds for hypertension have substantially increased the prevalence of this condition (Lamprea-Montealegre

et al. 2018) with the largest increase among adults with a low risk for cardiovascular disease (CVD). Redefining hypertension by changing systolic blood pressure (BP) ≥140 mmHg instead of ≥160 mmHg or diastolic BP ≥90 mmHg instead of ≥100 mmHg creates 13 million new hypertensive patients. Changing the threshold from a fasting glucose level of ≥140 mg/dL to ≥126 mg/dL for diabetes results in 1.7 million new cases. Redefining hypercholesterolemia (serum cholesterol ≥200 mg/dL instead of ≥240 mg/dL) and being overweight (BMI ≥24.9 kg/m^2 instead of ≥27 kg/m^2), increases the number of new cases to 42 million and 29 million, respectively. These new definitions result in 75% of the adult US population classified as having a chronic disease (Schwartz and Woloshin 1999).

Participants who were reclassified in the National Health and Nutrition Examination Survey (NHANES) as hypertensive (BP ≥130/80 mmHg and BP <140/90 mmHg for males and females, respectively) were younger and considered less likely to have diabetes mellitus or CVD, in contrast with the traditional classification of hypertension (BP ≥140/90 mmHg) (Lamprea-Montealegre et al. 2018). These observations are important since prior research has shown a net benefit to risk ratio of intensive BP reduction that is dependent on CVD risk, with individuals at highest CVD risk deriving most benefit (Lamprea-Montealegre et al. 2018). However, Lamprea-Montealegre et al. (2018) concluded that individuals recommended to start therapy for hypertension were not well represented and had a markedly lower CVD risk profile than participants in the Systolic Blood Pressure Intervention Trial (SPRINT 2015) and Action to Control Cardiovascular Risk in Diabetes-Blood Pressure study (ACCORD 2010).

Further concerns arise when at-risk individuals are classified as having a disease, with earlier pharmacological interventions being advocated (Moynihan et al. 2013; 2019; Schwartz and Woloshin 1999). Treatment for high serum cholesterol was transformed in 1998 when 240 mg/dL cholesterol was considered normal. When appropriate randomization was applied, those who had cholesterol levels ranging from 184-228 mg/dL appeared to have less risk for an acute coronary episode (Worrall 2007). Over a 5-year period, 5% of patients who did not receive statins had a cardiac episode versus 3% of the statin patients, showing a 40% reduction in coronary episodes in the latter group. However, only 2% of patients taking statins stand to benefit, and one has to consider the risk of side effects of drugs, lost time in prescribing, cost, etc. (Perros and Koumpos 2022). Overdiagnosis targets healthy, asymptomatic people. Further, the number of people who must undergo treatment in order for one patient to benefit (i.e. the 'number needed to treat') continues to be an issue requiring attention (Welch 2015).

When drugs to lower cholesterol or manage diabetes, with known side effects, are initiated early as preventive measures (Ziaeian et al. 2016) then potential alternative approaches are often not considered or advocated, such as supplementing with probiotic strains to reduce cholesterol (Jones et al. 2012) or delay the onset of diabetes (Isolauri et al. 2015) or promoting a Mediterranean dietary pattern (DuBroff and de Lorgeril 2015). Indeed, the efficacy of the Mediterranean diet (DuBroff and de Lorgeril 2015) has further raised the controversy over widespread use of statins as well as the debatable conclusions of the Framingham Study raised by Mahmood et al. (2014). Their conclusions were questioned by DuBroff and de Lorgeril (2015) who opined on the prevalence of coronary heart disease (CHD) despite the increase in statin use and

cholesterol-lowering campaigns that have reached "pandemic proportions." They suggest that after two decades of statin use it is best to concede the anomalies of the cholesterol hypothesis and recommend a refocus on proven benefits of healthy lifestyle and the incorporation of the Mediterranean diet for the prevention of CHD (DuBroff and de Lorgeril 2015). More recently, the Mediterranean diet was reviewed for its positive effects on multiple processes linked to glucose homeostasis, which is a CVD risk factor (Martín-Peláez et al. 2020). This supports the view that the Mediterranean diet, in the context of an overall healthy lifestyle could play a role in mitigating type 2 diabetes. The net effect of current medical practice is that healthy people with low risk for disease are being prescribed statin pharmacotherapy, narrowing the pool of 'healthy' participants that can be considered in evidenced-based studies for S/F claims unrelated to cardiovascular function. For studies on cardiovascular health, the bar for inclusion has been raised for those participants considered to be in a state of health leading to dysfunction and restricting the breadth of evidence that can be considered for a S/F claim.

The current algorithm of initiating early treatment for chronic disease should result in lower disease prevalence. However, chronic disease in the past decade has increased (Raghupathi and Raghupathi 2018). As well, reports suggest pitfalls with increased risks of overmedication, untoward drug interactions, adverse effects (Guthrie et al. 2015; Bytyçi et al. 2017), and increased healthcare costs (Herndon et al. 2007). Research on dietary supplement and health promotion appears to be impeded by the continuous need for a differential identification of healthy populations for enrollment in studies for S/F claims. The inclusion/exclusion criteria might be clearly stated in the protocol, but it is not relevant to the general healthy population to whom the product is marketed, which is a fundamental tenet of advertising law in the US. Thus, this approach limits feasible, innovative research studies and their application to the general public, particularly in the context of the current paradigm of early pharmacological interventions and expanding criteria for diseases.

Consumer's perception of the word 'healthy'

When consumers were polled, as to how they measured their health, by the Health and Wellness Survey 2023, the most popular response was how fit and active they felt, followed by those who scored their state of health by their mental well-being (FMCG 2023). Seventy-four percent rated their health as good but were on a journey to improve and maintain their good health with digestion, mental well-being, immunity, and sleep being pursued as key areas needing improvement (FMCG 2023).

Research also shows that consumers care deeply about wellness with growing interest in this concept. In a 2020 survey of nearly 7,500 consumers in six countries, Callaghan et al. (2021) found 79% of the respondents believed in the importance of wellness, and 42% considered it a top priority. Wellness, particularly that of physical and mental health, was a priority for millions of people across the globe and continues to show a substantial increase in consumers' prioritization (Callaghan et al. 2021). Respondents considered wellness to be inclusive of better health, nutrition, sleep, appearance, and mindfulness. Masterson (2023) states that "cognitive and emotional well-being are top of mind for global consumers, but in order to seize the opportunity, products need

to offer more". Fallon and Karlawish (2019) note that "managing multiple diseases is the norm for older Americans. Having disease and feeling healthy are no longer considered mutually exclusive" and many report being in good or very good health despite managing two or more diseases. Currently, almost two-thirds of adults over age 65 and more than three-quarters over age 85 manage multiple chronic diseases (Fallon and Karlawish 2019).

Diseases such as polio, diphtheria, measles, tuberculosis, and pertussis were rampant 70 years ago with global life expectancies of 48 years for men and 53 years for women. These are now preventable and treatable but chronic diseases such as CVD, cancer, and stroke are the top three causes of death in the US today. Regular access to medical care, and lifestyle management has made it possible for most chronic conditions such as hypertension, diabetes, hypercholesterolemia, arthritis, osteoporosis etc. to be managed well, allowing most to consider themselves in good health, sometimes, even without symptoms. Thus, instead of pursuing 'absence' of disease, a more innovative definition of health is required as the definition of 'healthy' needs to "work for a nation" (Fallon and Karlawish 2019). Fallon and Karlawash (2019) opine that this is relevant particularly for an aging population of more than 617 million people worldwide over the age of 65 years living with chronic disease. With preventative treatment being applied based on changing definitions, diagnoses, and management of chronic diseases over time, there is a need to evaluate how these revisions can affect the nature and characteristics of the general population.

Within the ambit of the definition of 'healthy' is its application in the context of nutrition. In September 2022, the FDA proposed updating the definition for the implied nutrient content claim 'healthy.' Their intent was to be consistent with current nutrition science and Federal dietary guidance, especially the Dietary Guidelines for Americans, to help consumers achieve healthy dietary practices. If finalized, this action will revise the requirements for when the term 'healthy' can be used as an implied claim in food product labeling (FDA 2022b). Recent reviews on approaches to defining a healthy diet have been published (de Ridder et al. 2017; Cena and Calder 2020).

Body mass index is a poor indicator of health

Under the existing guidelines for S/F claims, obesity is considered a disease (ICD code E66.9) and is defined by BMI. The use of BMI as an eligibility criterion for S/F claims is fraught with challenges. Notably, the FDA has taken a more nuanced approach to the handling of overweight vs. obesity and state that although obesity is a disease, being overweight is not (FDA. Fed Regist 2000). In the US, among adults ≥20 years of age, 41.9% are obese and 73.6% are overweight and obese, and eligible to be on medication (FDA 2023a). Under these conditions, evaluating weight loss supplements only in those who are normal or overweight and not on medication excludes participants with obesity (BMI ≥30 kg/m^2) who may best benefit from such interventions, highlighting some of the contraindications in the use of BMI as an eligibility criterion in S/F claims evidence.

To further probe into the use of BMI for S/F claims, data from NHANES III (2009 to 2016) comprising 8721 individuals reveal less than a third of the 'normal' weight adults, who were defined by using their waist circumference (male, <102 cm; female, <88 cm),

fasting plasma glucose (<100 mg/dL), hemoglobin A1c (<5.7%), BP (systolic <120 mmHg; diastolic <80 mmHg), triglycerides (<150 mg/dL), and high-density lipoprotein cholesterol (male, ≥40 mg/dL; female, ≥50 mg/dL) and not taking any medications intended to impact any of these conditions(s), were found to be 'metabolically healthy' (MH) (Araújo et al. 2019). Applying these criteria result in only 12.2% of Americans defined as MH (Zembic et al. 2021). The authors used NHANES III data comprising 38,642 people and showed that classifying individuals who are normal or overweight (ICD code E66.3) as 'healthy' does not meet the current definition of health. The authors reported mortality risks of people and provided three *a priori* definitions of MH, which contrasted with the current classification of obesity, i.e. BMI ≥30.0 kg/m^2, as a disease, and MH as those who are normal (18.5-24.9 kg/m^2) or overweight (25-29.9 kg/m^2) and free of disease. The authors proposed a definition of 'metabolically healthy obese' (MHO) consisting of "individuals who are obese based on their BMI classification but not at increased risk for CVD and whose total mortality does not differ from healthy non-obese controls." Of the participants studied, 40% with obesity were considered MH. Participants classified as 'metabolically unhealthy' (MU) were at increased risk of CVD and mortality, independent of their BMI status. Therefore, MHO serves to distinguish individuals at-risk and not-at-risk of CVD; however, only individuals with a BMI <40 kg/m^2 appear to fit within a low-risk MHO phenotype. This definition of MHO illustrates that overweight and normal weight individuals can be at risk of higher total mortality.

An atlas of changes in blood analytes of a cohort of 1,277 individuals showed multi-omic associations with polygenic risk scores and gut microbiome composition that could be linked to BMI variations (Watanabe et al. 2023). The authors highlighted the usefulness of blood multi-omic profiling using machine learning models to show that blood multi-omics were superior to BMI with implications for predictive and preventive medicine. These findings and those of Zembic et al. (2021) spotlight that the current FDA guidelines in identifying a BMI of 30 kg/m^2 as obese and that of 25.0-29.9 kg/m^2 as overweight (FDA 2022c) should be revisited. Current restrictions in BMI criteria and chronic medication use are impractical and costly for recruitment of volunteers (FDA 2007; Hsu et al. 2018).

Dietary supplements vs. drugs

Therapeutic drugs treat a disease while supplements are intended to promote health through the maintenance of the structure and function of body systems. The movement of a biomarker within an acceptable laboratory range, in a healthy person, even if statistically significant, is not typically considered a clinically (i.e. medically) meaningful effect. Thus, heterogeneous group differences within a clinical trial comparing a supplement intervention with a placebo in a healthy cohort will seldom achieve a clear benefit (Parikh and Thiessen-Philbrook 2014).

The application of evidence-based medicine guidelines, in their entirety, to dietary supplement research is challenging since they were designed for drugs, not nutrients or supplements (Heaney 2014). A randomized control trial (RCT) may provide the best estimate of a causal relationship between a dietary supplement with the specified outcome and value of at least one or more well-designed RCTs often considered to provide persuasive evidence of benefit (Blumberg et al. 2010).

Results of previous studies, for example, the Calcium Preeclampsia Prevention Trial of the Women's Health Initiative, have shown that baseline nutrient status or co-nutrient status of the individual must be accounted for to ensure that the test nutrient is the only nutrition-related limiting factor in the response. Thus, co-nutrient status is an important inclusion criterion for enrollment in nutrient/supplement trials (Jackson et al. 2006). This is due to a sigmoid physiological response that typically occurs with nutrient/supplement investigations, which depend on the biology of the participant and their previous exposure to the nutritional components of the test product (Lappe and Heaney 2012). The latter impacts both the test and control groups. In contrast, drug studies have a clear demarcation with zero exposure in the placebo group.

Factoring in participant variation due to previous exposure *via* diet and/or supplements is an important consideration when working with apparently healthy participants. Current consumer food and supplement intake trends suggest that the twenty first century consumer is educated and looking for products beneficial for health promotion (Callaghan et al. 2021). Thus, the term 'healthy' determined based on no medication use is less important than the nutritional status of the individual. If participants have been on a stable dose of a drug for a pre-identified period and it has been determined that participant safety is ensured, and the drug does not interact with the investigational supplement, then the use of a drug should not preclude enrollment in a supplement trial. As well, food history, co-nutrient status, diet, and exercise should certainly be a consideration for enrollment. Heaney (2014) emphasizes that co-nutrient status must be optimized in trials of nutrients and states "it is indeed surprising how often this rule is ignored or overlooked. It may be that importance and salience are simply not understood."

Reconceptualizing recommended dietary intake

In the context of DRIs, the Recommended Dietary Allowances (RDA) committees of the Food and Nutrition Board (National Academies of Sciences 2022) have defined the phrase "healthy populations" or "apparently healthy populations" as specifically excluding individuals who have i) a chronic disease that needs to be managed with medical foods, ii) are malnourished (undernourished), iii) have diseases that result in malabsorption or dialysis treatments, or iv) have increased or decreased energy needs because of disability or decreased mobility.

This approach was also used for dietary recommendations from the Canadian Council on Nutrition (CCNR 1949), the joint US and Canadian DRIs, the European Food Safety Authority and the Nordic Nutrition Recommendations (Christensen et al. 2020), among others. The RDA committees reviewed the DRI framework and stated that scientific evidence has evolved, which supports the association of dietary intakes with chronic disease risk and improving the availability of dietary guidance for reducing the risk of chronic diseases separate from the DRI process (National Academies of Sciences 2022). Recently, the Federal DRI Joint US-Canadian Working Group addressed several pertinent questions (National Academies of Sciences 2022), a summary of which has been provided in Table 1.

Table 1. Defining populations for dietary reference intakes National (National Academies of Sciences 2022). Summarized for the purposes of this perspective.

Q1: Who should be included in the 'healthy population' definition to adequately characterize the population covered by the DRIs?
The phrase "apparently healthy population" (or "general population" or "healthy population") has been used by DRI committees to define the population covered by the DRIs as mentioned above in the text.
Q2: Is it assumed that subpopulations with risk factors for chronic diseases (such as overweight or obesity, high blood pressure, hypercholesterolemia, or prediabetes) are considered to meet the current definition since they do not meet the exclusion criteria listed above?
Unless there is reason to specifically exclude certain subpopulations, those at risk of chronic disease should be included. Individuals within subpopulations that are at risk for, or who have, a chronic disease and are also taking medications that alter the absorption should be evaluated in light of their specific condition.
Q3: Should a different term be considered other than "apparently healthy" population since the DRIs are developed to determine the recommended intake of nutrients to meet the needs of the majority of the general population and the health status of this population has shifted?
The term "exception" should be used in place of "exclusion" to describe the characteristics in the subgroups not to be included in the general population for the DRIs.
Q4: How should overweight and obesity be considered given the high prevalence of obesity?
Recommendation is to include populations who are overweight or with obesity because they sometimes represent a large segment of the population. However, when these individuals also have severe comorbidities and other metabolic disorders, they may be excluded from the population if there is evidence that their condition or medications alter their energy or other nutrient requirements.
Q5: How should this definition inform the use of the DRIs for their various purposes?
Specific exceptions to the general population should be determined on a nutrient-by-nutrient basis. Exceptions would be based on evidence that a particular disease, health condition, disability, or medication is likely to alter the requirement for the nutrient under review.

Based on the current recommendations of the DRI, it appears reasonable to accept medication use that is stabilized in the condition for which it is prescribed. If so, then excluding these participants from enrollment in a clinical study should be based only on consideration of their safety and an outcome that could be compromised by that medication. For example, if statins have stabilized the serum cholesterol of a participant with mild hypercholesterolemia, then that individual should be considered healthy as their condition is well-controlled and maintained. Excluding such participants from a study investigating an indication of structure or function unrelated to lipid status is neither medically nor scientifically supported if there are no likely interactions between the investigational dietary supplement and the prescribed statin or lipid metabolism. This approach would greatly expand the available pool of volunteers for recruitment and increase the generalizability of the results. A search for such a 'healthy' participant identified under the existing clinical treatment algorithm seems futile when considering current demographics (Moynihan et al. 2019).

Regulations governing structure/function claim substantiation

Dietary supplements in the US are regulated as foods, not medicinal products, and, according to the Nutrition Labeling and Education Act of 1990, dietary supplements cannot make a claim to diagnose, treat, cure, or prevent any disease (FDA 2022a). The FDA imposes several requirements for S/F claims (FDA 2023b). The FDA Compliance Guide on S/F Claims states: "It may not be possible always to draw a bright line between structure/function and disease claims. You should look at the objective evidence in your labeling to assess whether a claim explicitly or implicitly is a disease claim" (FDA 2017). Thus, the burden of proof lies solely with the study

sponsor/investigator to prove that the supplement under review is backed by "scientific proof that is not deceiving of a reasonable consumer" (FTC 1994).

Clinical trials investigating the non-therapeutic effect of a dietary supplement are exempt from the submission of an Investigational New Drug (IND) application for an S/F claim. Proposed new rules on IND exemptions for drug studies of products lawfully marketed in the US as foods or cosmetics under the category of self-determined exemptions state that dietary supplements are exempt from IND requirements if they are not intended to support a drug development plan for the product. Also included are labeling changes that would cause the lawfully marketed product to become an unlawfully marketed drug, compliance with requirements for review by an Institutional Review Board and those for informed consent, and fulfillment of applicable criteria designed to protect the health, safety, and welfare of trial participants. Under the category of FDA-determined exemption, the study sponsor/investigator must submit a written request providing information on the sponsor, the investigation, the product, and reasons as to why the investigation does not present a potential for significant risk to the participants (FDA 2022d).

To assist in decision-making about whether a S/F claim is or is not a disease claim, the FDA provides a definition of disease as damage to an organ, part, structure, or system of the body such that it does not function properly (e.g. CVD), or a state of health leading to such dysfunction (e.g. hypertension) and diseases resulting from essential nutrient deficiencies (e.g. scurvy, pellagra) are not included in this definition (FDA 2023c). To help decide whether a statement is or is not a disease claim, FDA considers the context in which the claim is presented using 10 criteria that are summarized in Table 2. Statements about a product, claims to diagnose, mitigate, treat, cure, or prevent disease (other than a classical nutrient deficiency disease) must meet one or more of these criteria in determining disease claims. These criteria are not intended to classify S/F statements as disease claims unless the statement implies disease prevention or treatment. For example, a statement may not mention a disease but may refer to identifiable characteristic signs or symptoms of a disease such that the intended use of the product to treat or prevent the disease may be inferred. Salient issues are the context of the statement decided from information on the label and in other advertising, and explicit or implied disease claims unless the claim has undergone premarket review by FDA and has been authorized or approved under the rules for HC or drugs (FDA 2017).

Table 2. Criteria to determine if a claim is a structure/function claim or a disease claim FDA 2017: Ten criteria to assist in deciding whether a claim is or isn't a disease claim, the new regulation contains a definition for disease (National Academies of Sciences 2022): Summarized for the purposes of this perspective.

Disease claims should, explicitly or implicitly, state that the dietary supplement has an effect on the following:	
1	A specific disease(s)
2	Symptoms characteristic to a specific disease(s)
3	Consequence of a natural state of symptoms constituting a health abnormality,
4	Disease through the dietary supplement, the formulation including the claim that the product contains an ingredient that is regulated as a drug by FDA for preventing or treating a disease, citations that refer to its use for disease, use of the term disease, use of visuals
5	Belongs to a class of products intended to diagnose, mitigate, treat, cure, or prevent a disease
6	Is a substitute for a disease therapy
7	Augments a therapeutic action
8	A role in the body's response to a disease
9	Treats, prevents, or mitigates adverse events associated with a therapy for a disease with symptoms
10	Otherwise suggests an effect on a disease(s)

The FDA states what constitutes acceptable statements for S/F claims and highlights the need for the study population(s) and targeted consumer(s) of dietary supplements to be comparable (FDA. Fed Regist 2000; FDA 2018). The definition of dietary supplement S/F claims by the FDA includes their being marketed to the general healthy population. The FDA has statutory authority to inform a company that they cannot test a disease population or that a company is marketing unlawfully to groups other than a general healthy population. Therefore, if a company had enrolled patients with a diagnosed condition in a clinical trial but ensures that they do not make a disease claim on the label or in labeling, then there appears to be a mismatch of the criteria the FTC has laid out in their guidance policy (FTC 2022a). Substantiation by competent and reliable scientific evidence is necessary to avoid fines by the FTC for false label claims (FTC 2021; 2022b). To highlight this point, over 120 cases have been filed by the FTC during the past decade against supplement companies challenging health claims (FTC, 2022c); for example, Abbott Laboratories and POM Wonderful were charged with studying populations that did not reflect the intended target market and thus making false and unsubstantiated claims (FTC 1997; FTC 2016).

Drawing on the POM Wonderful decision, the recently revised 2022 guidance takes a deeper dive into the key elements of quality research for S/F claims (FTC, 2022a). The section on the requirement of "competent and reliable scientific evidence" has also been expanded to emphasize the quality of the required research. Claims against companies have resulted from the population from which the groups drawn not being appropriate for the purposes of the study and highlights that the inclusion and exclusion criteria for participants should be clearly stated in the protocol and be relevant to the population to which the product is marketed (FTC 2016).

The guidance also states: "although there is no requirement for a specific number of RCTs, the replication of research in an independently conducted study adds to the weight of the evidence. Replication in a second study by independent researchers reduces the chance that the results of a single RCT may be influenced by unanticipated, undetected, systematic biases that may occur despite the best intentions of sponsors and investigators. An additional, independently conducted study corroborating findings provide greater confidence in the validity of the initial results" (FTC, 2022a).

The latter is true regardless of the research approach, i.e. *in vitro*, animal model, observational, and/or interventional. The Bradford Hill criteria included nine viewpoints by which to evaluate human epidemiological evidence to determine if an observed association can proceed to a verdict of causation. The criteria suggest that consistent, coherent multiple approaches provide stronger evidence than replication of any single approach (Nowinski et al. 2022). Similar evaluation of human evidence is suggested by the Council for Responsible Nutrition (CRN) in their 2023 petition which argues the FTC's Health Products Compliance Guidance requiring RCTs to other forms of evidence to substantiate nutrient and S/F claims (Long 2023). CRN contends that other forms of evidence including uncontrolled clinical studies, laboratory analysis, animal testing and epidemiological evidence establish a connection between a nutrient and healthy function of the body.

Revisiting the definition of 'healthy'

In the absence of explicit guidance, clinical trials designed to substantiate S/F claims for dietary supplements are limited by the definition of 'healthy.' Without the identification of clear boundaries, the term 'healthy' may be restrictively identified by investigators stating stringent inclusion/exclusion criteria in protocols for S/F substantiation in order to ensure that one does not cross the 'thin' line between S/F and disease claims (FDA 2017).

Most Americans would not meet the FDA guideline for a 'healthy' person but could be considered as 'physiologically stable' in context of their clinical presentation and history validated by a clinician (Nowinski et al. 2022). The inferred FDA position is that clinical trials for substantiation of S/F claims avoid any potential that eligible participants were tested for treating, curing, or preventing disease. While the available guidelines do not explicitly refuse the use of 'patients' (with disease) in substantiating S/F claims for 'healthy' people, without greater clarification providing confidence to investigators, it is challenging to design protocols to produce generalizable results.

This perspective concerns the impact of broadening the definition of disease and the need for rethinking the term 'healthy' with reference to S/F claim substantiation. This approach is consistent with the Food and Nutrition Board that scientific evidence has evolved and established a new category of 'physiologically healthy' or 'apparently healthy' and acknowledging the use of medication but differentiating and excluding those on specific types of medications. A similar challenge to the definition of 'healthy' is found in the evolving research on the new concepts on BMI categories. We propose that under appropriate and predefined conditions, being on a drug treatment should not preclude an individual's participation in a study for S/F claim substantiation.

When comparing study populations in dietary supplement and drug clinical trials, it was found that such restrictive eligibility criteria pose recruitment challenges that could prolong study durations and reduce study generalizability to the real-world population (Lebel et al. 2014). Without some guidance around the term 'healthy,' results from research will continue to remain restricted to narrow and unrepresentative populations. This is a disservice to consumers seeking complementary or alternative solutions to pharmacotherapy to maintain or improve their health.

The FDA recently released draft guidance with updated recommendations for good clinical practices aimed at modernizing the design and conduct of clinical trials (He et al. 2019). This guidance, has been adopted from the ICH E6 (R3), which was recently updated and *encourages "thoughtful consideration and planning to address specific and potentially unique aspects of an individual clinical trial* and *includes evaluation of trial characteristics, such as the design elements, the investigational product being evaluated, the medical condition being addressed, the characteristics of the participants, the setting in which the clinical trial is being conducted, and the type of data being collected*." The E6 (R3) encourages attention to trial design to promote "*quality and meaningful trial outcomes* relevant to both *trial participants and future patients*." The draft further states: "*When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations. The participant selection process should be representative of the anticipated population who is likely to use the medicinal product in future clinical practice to allow*

for generalizing the results across the broader population" (FDA 2023d). When stakeholders were approached for their input on the implications of the draft guidance for the dietary supplement trials, they stated they would "*like to see real world examples* which would be *helpful and transparent for all stake holders*. Definitive *clear and concise* directives were required to ensure clarity with "*opportunities to consult with FDA or FTC on innovative trial designs for substantiating S/F substantiation claims similar to that which exists for health claims or qualified health claims*" (italic emphasis by the authors) (Daniells 2023).

We agree with the new draft guidance adopted from the E6 (R3) that the safety and effectiveness of dietary supplements would be best evaluated in the population intended for their use in the marketplace and the participant selection process should not unnecessarily exclude participant populations and allow for generalizing the results across the broader population. Therefore, we suggest that even without a revision of FDA's definition of disease claims, there is room for the inclusion of 'physiologically stable' or 'apparently healthy' as a description for participant enrollment thus promoting better scientific design of protocols so that the results of clinical studies for S/F claims can reach the greatest range of the general population who could benefit from such evidence-based science.

Acknowledgements

We would like to acknowledge Shivani Bhardwaj and Foram Patel for help with the reference list.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

About the authors

Malkanthi Evans, PhD is the Chief Scientific Officer at KGK Science and Adjunct Professor, Western University. Drawing on over 15 years of strategic leadership and experience in the nutraceutical industry, she is responsible for leading the scientific team at KGK Science Inc. to employ new and novel research designs better suited to the industry. Her work in chronobiology and nutraceutical science has been recognized internationally. She is a leading scientist in health and wellness and her expertise lies in developing clinical trials to advance nutraceutical science, and to position studies for success with regulators and conscientious consumers. She brings her experience in Evidence-Based Medicine into developing the evidence required for nutrition and have spearheaded unique and innovative research initiatives, creating a new model for nutraceutical research to replace the 'one-disease-one-drug' model currently used in the nutraceutical industry. She is a frequent speaker at conferences on optimizing clinical trial design and the need for a new paradigm in study design in identifying biomarkers for the dietary supplement industry. She has over 90 peer reviewed publications and contributed to over 100 clinical trial designs. She earned her master's and doctorate degrees in physiology from the University of Guelph and

received her D.V.M with distinction in physiology from the University of Sri Lanka. She pioneered research in chronobiology and her landmark work in this area was the first of its kind in North America. Her studies in chronobiology support research conducted in the US and Europe on the impact of cellular oscillatory systems on the microbiome, cognition, sleep-wake rhythms, shift work, chronic disease, etc. and into applications in the supplement industry.

Erin D. Lewis, PhD is the Scientific Director Nutritional Sciences at KGK Science Inc. With more than a decade of academic, industrial, and clinical experience, Erin works with research, regulatory and clinical operation teams, and study sponsors to prepare clinical trial protocols, Investigator's Brochures, study reports and manuscripts according to ICH guidelines. She earned a Bachelor of Science Honors degree in Nutritional and Nutraceutical Sciences from the University of Guelph, a Doctor of Philosophy in Nutrition and Metabolism from the University of Alberta and completed postdoctoral training from Jean Mayer United States Department of Agriculture, Human Nutrition Research Center on Aging at Tufts University. Erin has authored over 30 peer-reviewed publications and 45 protocols and clinical study reports in the areas of human and animal nutrition, natural health products and clinical trials for presentation to regulatory bodies for claims substantiation.

Joseph M. Antony, PhD has over 25 years of experience in microbiology and neurovirology research. He obtained his BFSc and MFSc degrees from the University of Agricultural Sciences, India, and MSc from the National University of Singapore. His PhD dissertation from the University of Calgary, Canada focused on the role of human endogenous retroviruses in Multiple Sclerosis. He received his postdoctoral training in stem cell biology, liver cancer, and therapeutic synthetic antibodies from the University of Toronto and was employed as a research associate in Microbiology at Mount Sinai Hospital in Toronto. At KGK Science, Dr. Antony wrote clinical study reports, clinical trial protocols, and published several clinical trial-based papers, including review papers, white papers for the dietary supplement industry, and perspectives on clinical trial design. Dr. Antony is presently employed at Health Canada.

Najla Guthrie is the President and CEO of KGK Science. Her original research, which was conducted at the Center for Human Nutrition at the University of Western Ontario, focused on the effects of citrus juices and their constituent flavonoids on breast cancer cells. Today, this study continues to generate media and scientific interest and has marked Ms. Guthrie as an expert within her field. She is the author of over 50 publications in the area of nutraceuticals and has 10 issued patents and 18 pending applications. Her dedication to ensure scientific validation of the proof of safety and efficacy of nutraceuticals challenged and spurred industry to engage in evidence-based human clinical research. Over the last 25 years, Ms. Guthrie has ensured that KGK Science, conducts gold standard randomized clinical trials setting a benchmark for the industry.

David C. Crowley, MD is the Medical Director and Qualified Investigator at KGK Science Inc. He earned his Bachelor of Science Honors degree in Chemistry from the University of Western Ontario and received his Doctor of Medicine from the University of Toronto. Dr. Crowley has been in general practice for over 30 years, with exposure to emergency, obstetrics, and pediatric medicine. He has been a Qualified Investigator for over 25 years as part of the DCTM Clinical Trials Group. Dr. Crowley's research experience spans indications related to cardiovascular disease, diabetes, gastroenterology, arthritis, and metabolism. He applies his clinical expertise and knowledge to lead the safe conduct of clinical trials for the nutraceutical industry.

Andrew Charrette, MSc leads the regulatory affairs division of KGK Science, Andrew Charette brings extensive experience in regulatory processes for clinical trial research and in-depth knowledge of the cannabis regulations in North America. Since joining KGK in 2013, Andrew has led over 50 submissions to Health Canada and consulted on numerous product claims, NDI notifications and GRAS submissions to the U.S. FDA. Andrew received his undergraduate degree in Pharmacology and Physiology from the University of Western Ontario and later obtained a master's degree in Neuroscience from the University of Ottawa.

Jeffrey B. Blumberg, PhD is a Research Professor in the Friedman School of Nutrition Science and Policy at Tufts University. His research has been focused on the biochemical basis for the role of antioxidant nutrients and their dietary requirements in promoting health and preventing disease during the aging process via changes in the status of oxidative stress, glucoregulation, and inflammation. He has participated in activities relevant to the incorporation of sound nutrition science into public health policy, including work as a member of the Workshop on Health Promotion and Aging in the Office of the U.S. Surgeon General, Sports Medicine Committee of the U.S. Olympic Committee, Consultation on Preparation and Use of Food-Based Dietary Guidelines for the FAO/WHO, Food Advisory Committee of the FDA, and other committees.

Gregor Reid, PhD is a Fellow of the Royal Society of Canada and Canadian Academy of Health Sciences, and Distinguished Professor Emeritus at Western University. He has produced 32 patents, 607 peer-reviewed publications cited over 60,000 times, has a Google Scholar H index of 118 and has given over 650 talks in 54 countries. He is ranked #3 in Canada and #59 in the world for Microbiology Scientists by *research.com*. In 2001, he chaired the UN/WHO Expert Panel that defined the term probiotic. He has received numerous awards including an Honorary Doctorate from Orebro University, Sweden, a Distinguished Alumni award from Massey University, New Zealand, a Canadian Society for Microbiologists Career Award and The Dr Rogers Prize for contributions to Complementary and Alternative Medicine.

References

ACCORD. 2010. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 362(17):1575–1585. https://www.nejm.org/doi/full/10.1056/NEJMoa1001286.

Araújo J, Cai J, Stevens J. 2019. Prevalence of optimal metabolic health in American Adults: National Health and Nutrition Examination Survey 2009-2016. Metab Syndr Relat Disord. 17(1):46–52. doi: 10.1089/met.2018.0105.

Blumberg J, Heaney RP, Huncharek M, Scholl T, Stampfer M, Vieth R, Weaver CM, Zeisel SH. 2010. Evidence-based criteria in the nutritional context. Nutr Rev. 68(8):478–484. doi: 10.1111/j.1753-4887.2010.00307.x.

Bytyçi I, Bajraktari G, Bhatt DL, Morgan CJ, Ahmed A, Aronow WS, Banach M, Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. 2017. Hydrophilic vs lipophilic statins in coronary artery disease: A meta-analysis of randomized controlled trials. J Clin Lipidol. 11(3):624–637. doi: 10.1016/j.jacl.2017.03.003.

Callaghan S, Losch M, Pione A, Teichner W. 2021. Feeling good: The future of the $1.5 trillion wellness market. https://www.mckinsey.com/industries/consumer-packaged-goods/our-insights/feeling-good-the-future-of-the-1-5-trillion-wellness-market.

CCNR. 1949. A new dietary standard for Canada, 1949: Canadian council on nutrition Ottawa, Ontario. Can J Public Health Rev Can Santee Publique. 40(10):420–426. http://www.jstor.org/stable/41980247.

Cena H, Calder PC. 2020. Defining a healthy diet: Evidence for the role of contemporary dietary patterns in health and disease. Nutrients. 12(2):334. https://www.mdpi.com/2072-6643/12/2/334. doi: 10.3390/nu12020334.

Christensen JJ, Arnesen EK, Andersen R, Eneroth H, Erkkola M, Høyer A, Lemming EW, Meltzer HM, Halldórsson PI, Þórsdóttir I, Schwab U, Trolle E, Blomhoff R. 2020. The Nordic Nutrition Recommendations 2022 - principles and methodologies. Food Nutr Res. 64:1–10.

Daniells S. 2023. FDA updates clinical trials guidance to align with ICH: What's the impact for supplements? Nutraingredients. https://www.nutraingredients-usa.com/Article/2023/06/14/fda-updates-clinical-trials-guidance-to-align-with-ich-what-s-the-impact-for-supplements?utm.

de Ridder D, Kroese F, Evers C, Adriaanse M, Gillebaart M. 2017. Healthy diet: Health impact, prevalence, correlates, and interventions. Psychol Health. 32(8):907–941. doi: 10.1080/08870446.2017.1316849.

DuBroff R, de Lorgeril M. 2015. Cholesterol confusion and statin controversy. WJC. 7(7):404–409. doi: 10.4330/wjc.v7.i7.404.

Fallon KC, Karlawish J. 2019. It's time to change the definition of 'health.' STAT. https://www.statnews.com/2019/07/17/change-definition-health/.
FDA. 2007. Guidance for industry: Developing products for weight management. https://www.fda.gov/media/71252/download
FDA. 2017. Small entity compliance guide on structure/function claims. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/small-entity-compliance-guide-structurefunction-claims
FDA. 2018. Guidance for industry: Substantiation for dietary supplement claims made under section 403(r) (6) of the federal food, drug, and cosmetic act. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-substantiation-dietary-supplement-claims-made-under-section-403r-6-federal-food
FDA. 2022a. Structure/Function Claims. https://www.fda.gov/food/food-labeling-nutrition/structurefunction-claims?msclkid=e4fd12b6a61c11ec80961d2a07f7232d.
FDA. 2022b. Food labeling: Nutrient content claims; Definition of term "'healthy'". https://www.regulations.gov/document/FDA-2016-D-2335-1152.
FDA. 2022c. Weight-Loss and Weight-Management Devices. https://www.fda.gov/medical-devices/products-and-medical-procedures/weight-loss-and-weight-management-devices#:~:text=Overweight%20and%20Obesity,-Overweight%20and%20obesity&text=A%20BMI%20of%2030%20kg,that%20are%20associated%20with%20obesity.
FDA. 2022d. Investigational new drug applications; exemptions for clinical investigations to evaluate a drug use of a product lawfully marketed as a conventional food, dietary supplement, or cosmetic. FDA; A Proposed Rule by the Food and Drug Administration on 12/09/2022 https://www.federalregister.gov/documents/2022/12/09/2022-26728/investigational-new-drug-applications-exemptions-for-clinical-investigations-to-evaluate-a-drug-use.
FDA. 2023a. Obesity and overweight. https://www.cdc.gov/nchs/fastats/obesity-overweight.htm.
FDA. 2023b. CFR - Code of Federal Regulations Title 21. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312.
FDA. 2023c. Specific requirements for descriptive claims that are neither nutrient content claims nor health claims. FDA; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?fr=101.93#:~:text=Disease%20claims.,in%20this%20definition.
FDA. 2023d. FDA announces additional steps to modernize clinical trials 2023. https://www.fda.gov/news-events/press-announcements/fda-announces-additional-steps-modernize-clinical-trials.
FDA. Fed Regist. 2000. Regulations on statements made for dietary supplements concerning the effect of the product on the structure or function of the body. Food and Drug Administration, HHS. Final rule. https://www.federalregister.gov/documents/2000/01/06/00-53/regulations-on-statements-made-for-dietary-supplements-concerning-the-effect-of-the-product-on-the
FMCG. 2023. Consumer perceptions on health and wellness. https://fmcggurus.com/blog/fmcg-gurus-consumer-perceptions-on-health-and-wellness/#:~:text=Health%20benefits/claims%2C%20price%20and,term%20health%20and%20mental%20wellbeing.
FTC. 1994. Enforcement policy statement on food advertising. https://www.ftc.gov/legal-library/browse/enforcement-policy-statement-food-advertising.
FTC. 1997. Abbott settles FTC charges of deceptive claims for its "ensure" nutritional products. https://www.ftc.gov/news-events/news/press-releases/1997/01/abbott-settles-ftc-charges-deceptive-claims-its-ensure-nutritional-products.
FTC. 2016. POM Wonderful LLC, et al. https://www.ftc.gov/legal-library/browse/cases-proceedings/pom-wonderful-llc-et-al.
FTC. 2021. Nordic clinical, Inc. and Encore Plus Solutions, Inc. https://www.ftc.gov/legal-library/browse/cases-proceedings/172-3132-172-3143-nordic-clinical-inc-encore-plus-solutions-inc
FTC. 2022a. Health products compliance guidance. https://www.ftc.gov/system/files/ftc_gov/pdf/Health-Products-Compliance-Guidance.
FTC. 2022b. FTC proposed order stops marketers from continuing to promote supplements using baseless health claims. [cited 2023 Apr 5]. https://www.ftc.gov/news-events/news/press-releases/2022/03/ftc-proposed-order-stops-marketers-continuing-promote-supplements-using-baseless-health-claims.

FTC. 2022c. Health and fitness claims. https://www.ftc.gov/news-events/topics/truth-advertising/health-claims

Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. 2015. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Med. 13(1): 74. http://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-015-0322-7. doi: 10.1186/s12916-015-0322-7.

Hales CM, Servais J, Martin CB, Kohen D. 2019. Prescription drug use among adults aged 40-79 in the United States and Canada. NCHS Data Brief. No. 347 August 2019. https://www.cdc.gov/nchs/products/index.htm.

He Z, Rizvi RF, Yang F, Adam TJ, Zhang R. 2019. Comparing the study populations in dietary supplement and drug clinical trials for metabolic syndrome and related disorders. AMIA Jt Summits Transl Sci. 2019:799–808.

Heaney RP. 2014. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutr Rev. 72(1):48–54. doi: 10.1111/nure.12090.

Herndon MB, Schwartz LM, Woloshin S, Welch HG. 2007. Implications of expanding disease definitions: the case of osteoporosis. Health Aff (Millwood). 26(6):1702–1711. doi: 10.1377/hlthaff.26.6.1702.

Hsu M, Harper C, Gibson A, Sweeting A, McBride J, Markovic T, Caterson I, Byrne N, Sainsbury A, Seimon R, 2018. Recruitment strategies for a randomised controlled trial comparing fast versus slow weight loss in postmenopausal women with obesity-the TEMPO diet trial. Healthcare Basel Switz. 6(3):76. doi: 10.3390/healthcare6030076.

Isolauri E, Rautava S, Collado MC, Salminen S. 2015. Role of probiotics in reducing the risk of gestational diabetes. Diabetes Obes Metab. 17(8):713–719. doi: 10.1111/dom.12475.

Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SAA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D. 2006. Calcium plus Vitamin D supplementation and the risk of fractures. N Engl J Med. 354(7):669–683. http://www.nejm.org/doi/abs/10.1056/NEJMoa055218. doi: 10.1056/NEJMoa055218.

Jones ML, Martoni CJ, Prakash S. 2012. Cholesterol lowering and inhibition of sterol absorption by Lactobacillus reuteri NCIMB 30242: a randomized controlled trial. Eur J Clin Nutr. 66(11): 1234–1241. doi: 10.1038/ejcn.2012.126.Lamprea-Montealegre JA, Zelnick LR, Hall YN, Bansal N, de Boer IH. 2018. Prevalence of hypertension and cardiovascular risk according to blood pressure thresholds used for diagnosis. Hypertension. 72(3):602–609. doi: 10.1161/HYPERTENSIONAHA.118.11609.

Lappe JM, Heaney RP. 2012. Why randomized controlled trials of calcium and vitamin D sometimes fail. Dermatoendocrinol. 4(2):95–100. doi: 10.4161/derm.19833.

Lebel V, Alderson M, Aita M. 2014. Physiological stability: a concept analysis. J Adv Nurs. 70(9):1995–2004. doi: 10.1111/jan.12391.

Long J. 2023. CRN petition to FTC: RCTs aren't required to substantiate 'health-benefit' claims. Natural Products Insider. https://www.naturalproductsinsider.com/supplement-regulations/crn-petition-to-ftc-rcts-aren-t-required-to-substantiate-health-benefit-claims

Mahmood SS, Levy D, Vasan RS, Wang TJ. 2014. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet. 383(9921):999–1008. doi: 10.1016/S0140-6736(13)61752-3.

Margolis CZ. 1983. Uses of clinical algorithms. JAMA. 249(5):627–632. doi: 10.1001/jama.1983.03330290049028.

Martín-Peláez S, Fito M, Castaner O. 2020. Mediterranean diet effects on type 2 diabetes prevention, disease progression, and related mechanisms. A review. Nutrients. 12(8):2236. https://www.mdpi.com/2072-6643/12/8/2236. doi: 10.3390/nu12082236.

Masterson D. 2023. Mood is the name and multifunctionality is the game. Nutraingredients. Jul 17; https://www.nutraingredients-usa.com/Article/2023/06/29/Mood-is-the-name-and-multifunctionality-is-the-game#.

Moynihan R, Brodersen J, Heath I, Johansson M, Kuehlein T, Minué-Lorenzo S, Petursson H, Pizzanelli M, Reventlow S, Sigurdsson J, Stavdal, A Treadwell, J and Glasziou P. 2019. Reforming disease definitions: a new primary care led, people-centred approach. BMJ Evid Based Med. 24(5):170–173. https://ebm.bmj.com/content/ebmed/24/5/170. doi: 10.1136/bmjebm-2018-111148.

Moynihan R, Cooke GP, Doust JA, Bero L, Hill S, Glasziou PP. 2013. Expanding disease definitions in guidelines and expert panel ties to industry: a cross-sectional study of common conditions in the United States. PLoS Med. 10(8):e1001500. doi: 10.1371/journal.pmed.1001500.

National Academies of Sciences, Engineering, and Medicine. 2022. Defining populations for dietary reference intake recommendations: A letter report. Washington, DC: The National Academies Press; p. 50. https://nap.nationalacademies.org/catalog/26733/defining-populations-for-dietary-reference-intake-recommendations-a-letter-report.

Nowinski CJ, Bureau SC, Buckland ME, Curtis MA, Daneshvar DH, Faull RLM, Grinberg LT, Hill-Yardin EL, Murray HC, Pearce AJ, Suter CM, White AJ, Finkel AM, Cantu RC. 2022. Applying the Bradford Hill criteria for causation to repetitive head impacts and chronic traumatic encephalopathy. Front Neurol. 13:938163. https://www.frontiersin.org/articles/10.3389/fneur.2022.938163/full. doi: 10.3389/fneur.2022.938163.

Parikh CR, Thiessen-Philbrook H. 2014. Key concepts and limitations of statistical methods for evaluating biomarkers of kidney disease. J Am Soc Nephrol. 25(8):1621–1629. https://journals.lww.com/00001751-201408000-00007. doi: 10.1681/ASN.2013121300.

Perros F, Koumpos A. 2022. Overdiagnosis: The silent pandemic of the West? Public Health Toxicol. 2(1):1–4. http://www.publichealthtoxicology.com/Overdiagnosis-The-silent-pandemic-of-the-West-,145733,0,2.html. doi: 10.18332/pht/145733.

Raghupathi W, Raghupathi V. 2018. An empirical study of chronic diseases in the United States: A visual analytics approach. Int J Environ Res Public Health. 15(3):431. doi: 10.3390/ijerph15030431.

Schwartz LM, Woloshin S. 1999. Changing disease definitions: implications for disease prevalence. Analysis of the Third National Health and Nutrition Examination Survey, 1988-1994. Eff Clin Pract. 2(2):76–85.

SPRINT. 2015. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 373(22):2103–2116. https://www.nejm.org/doi/full/10.1056/NEJMoa1511939.

Watanabe K, Wilmanski T, Diener C, Earls JC, Zimmer A, Lincoln B, Hadlock JJ, Lovejoy JC, Gibbons SM, Magis AT, Hood L, Price ND, Rappaport N. 2023. Multiomic signatures of body mass index identify heterogeneous health phenotypes and responses to a lifestyle intervention. Nat Med. 29(4):996–1008. https://www.nature.com/articles/s41591-023-02248-0. doi: 10.1038/s41591-023-02248-0.

Welch G. 2015. Less medicine, more health: 7 assumptions that drive too much medical care. Beacon Press. https://www.beacon.org/Less-Medicine-More-Health-P1095.aspx

WHO. 2022. WHO definition of health, 1946. WHO. https://www.who.int/about/governance/constitution.

Worrall J. 2007. Why there's no cause to randomize. Br J Philos Sci. 58(3):451–488. https://www.journals.uchicago.edu/doi/10.1093/bjps/axm024. doi: 10.1093/bjps/axm024.

Zembic A, Eckel N, Stefan N, Baudry J, Schulze MB. 2021. An empirically derived definition of metabolically healthy obesity based on risk of cardiovascular and total mortality. JAMA Netw Open. 4(5):e218505. doi: 10.1001/jamanetworkopen.2021.8505.

Ziaeian B, Dinkler J, Guo Y, Watson K. 2016. The 2013 ACC/AHA cholesterol treatment guidelines: Applicability to patients with diabetes. Curr Diab Rep. 16(2):13. doi: 10.1007/s11892-015-0703-5.