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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](https://doi.org/10.1080/19390211.2023.2301383)

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



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Published online: 01 Feb 2024.



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

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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

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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/m² instead of ≥ 27 kg/m²), 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 $\geq 130/80$ 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 $\geq 140/90$ 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 (Ziaieian 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 (Isolaauri 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 Karlawish (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 ($\text{BMI} \geq 30 \text{ kg/m}^2$) 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, $<102 \text{ cm}$; female, $<88 \text{ cm}$),

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/m², as a disease, and MH as those who are normal (18.5–24.9 kg/m²) or overweight (25–29.9 kg/m²) 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/m² 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/m² as obese and that of 25.0–29.9 kg/m² 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.

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