

Scientific rigor and credibility in the nutrition research landscape

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ABSTRACT

Scientific progress depends on the quality and credibility of research methods. As discourse on rigor, transparency, and reproducibility joins the cacophony of nutrition information and misinformation in mass media, buttressing the real and perceived reliability of nutrition science is more important than ever. This broad topic was the focus of a 2016 plenary session, “Scientific Rigor and Competing Interests in the Nutrition Research Landscape.” This article summarizes and expands on this session in an effort to increase understanding and dialogue with regard to factors that limit the real and perceived reliability of nutrition science and steps that can be taken to mitigate those factors. The end goal is to both earn and merit greater trust in nutrition science by both the scientific community and the general public. The authors offer suggestions in each of the domains of education and training, communications, research conduct, and procedures and policies to help achieve this goal. The authors emphasize the need for adequate funding to support these efforts toward greater rigor and transparency, which will be resource demanding and may require either increased research funding or the recognition that a greater proportion of research funding may need to be allocated to these tasks. *Am J Clin Nutr* 2018;107:484–494.

Keywords: research methods, scientific rigor, nutrition, conflict of interests, transparency, trust

INTRODUCTION

Science is the best method we have of coming to an impartial knowledge about the world. Science derives its power to produce such knowledge from its methods and its power to influence persons to accept such knowledge from their trust that the methods will be implemented objectively and rigorously. Hence, if methods, or trust in those methods, are compromised, the knowledge generated by their application may be faulty or its acceptance eroded. Consequently, there is much interest in achieving ever greater rigor, reproducibility, and transparency in science (1–5). Various fields and parties have expressed such concerns and put forth efforts to strengthen the integrity of the scientific process, such as the American Statistical Association (6), the Center for Open Science (7), individual universities [e.g., (8)], and government funding agencies [e.g., (9, 10)]. Similar concerns

and efforts are evident in nutrition and obesity research (11–13) as areas of scientific work in which the importance of trust appears especially salient (14–18).

Both real and perceived threats to the credibility of nutrition science are often generated by research and communication processes that are biased by competing interests (i.e., interests other than the seeking of objective knowledge). This may be true of other sciences, but it is certainly true of nutrition science. As such, the ASN, the International Life Sciences Institute (ILSI) North America, and the Canadian Nutrition Society united in the opening symposium of the 2016 ASN Scientific Sessions to discuss the following topics: 1) maximizing scientific rigor and managing competing interests effectively, 2) research integrity in an era of competing interests, 3) the nature of competing interests, 4) uses of industry-funded research by federal agencies, 5) relations between funding source and quality of resultant research, 6) NIH guidelines for rigor and reproducibility, and 7) moving

This article is a summary of the ASN’s opening scientific session “Scientific Rigor and Competing Interests in the Nutrition Research Landscape” for the Annual Meeting at Experimental Biology in San Diego, CA, held 3 April 2016. The symposium was organized and sponsored by several partners, including the ASN, International Life Sciences Institute (ILSI) North America, and the Canadian Nutrition Society. The chair of the US National Academies of Science, Engineering, and Medicine’s Food and Nutrition Board was invited to participate. This summary describes and expands on the content presented during this session. The presentation titles and respective authors are as follows: “Maximizing Scientific Rigor and Managing Competing Interests” by Dr. Cutberto Garza; “Research Integrity in an Era of Conflict of Interest” by Sylvia Rowe; “The Nature of Competing Interests” by Dr. Arya M Sharma; “How Industry Funded Research Is Used by Federal Agencies” by Dr. Barbara O Schneeman; “The Relationship Between Funding and Quality of Research” by Dr. Esther Myers; “NIH Guidelines for Rigor and Reproducibility” by Dr. Christopher J Lynch; and “From Recognition to Mitigation: Paths Forward” by Dr. David B Allison. The opinions expressed are those of the authors and not necessarily those of their institutions or any other organizations.

Supported in part by National Institute of Diabetes and Digestive and Kidney Diseases grant F32DK107157 (to CMK).

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Received November 30, 2017. Accepted for publication December 4, 2017.

First published online March 16, 2018; doi: <https://doi.org/10.1093/ajcn/nqx067>.

from recognition of threats to rigor and trust in nutrition science to mitigation. Here, we summarize various perspectives on different kinds of threats to credibility in the nutrition research landscape, the role of competing interests in generating both real and perceived threats, and how to manage and reduce those threats in ways that both warrant and foster the public's confidence in the nutrition science community and disseminated public health research.

MAXIMIZING SCIENTIFIC RIGOR AND MANAGING COMPETING INTERESTS: SETTING THE STAGE

As in most areas of science, nutrition research faces challenges that affect critical areas of global public health concern and require both reliable science and society's trust in the research process and its results for progress to ensue. For instance, remarkable advances in biology and technology provide scientists with opportunities to examine interactions among environments, human behaviors, and genomes in ways that were unthought of even 10 y ago. These opportunities overlap with public health challenges that result from concurrent trends, such as ongoing demographic shifts due to aging, impaired health due to weight status, and global population growth due to economic improvements. These trends may amplify direct effects on nutrition by affecting additional dynamics. For example, economic growth may challenge environmental sustainability, and increasing abilities to manipulate food supplies may influence consumer behaviors in ways that prompt focus on undue manipulations of consumer choices and corporate responsibilities. Responsible management of these trends will largely depend on the conduct of science and the trust stakeholders engender in science.

Additional issues in nutrition science that face increasing demands for improvement include the following: reviewing the processes for updating the Dietary Guidelines for Americans (19–21) and international nutrient standards (22, 23), expanding the use of chronic disease endpoints in Dietary Reference Intake development (23, 24), examining nutritional requirements for medical foods (25–27), strengthening monitoring and assessment of food safety (28, 29), and addressing global food and nutrient security (30–32). The nature of these endeavors highlights both the importance and challenges of discerning opinion from fact. Succeeding in each of these endeavors is critical for the advancement of nutrition science and health promotion at the global level. Yet, the objectivity needed for success can be impeded by personal beliefs and other conflicts when they are not successfully managed (33).

To enhance trust in nutrition science, addressing issues of scientific rigor and managing competing interests successfully are key. In response to these needs, the ASN assembled an advisory committee (12) with a mission entitled, “Ensuring Trust in Nutrition Science.” Its charge is to identify best practices for optimizing rigor, transparency, and accountability in the conduct of science and in the realization of anticipated public benefits of nutrition research. The desired outcomes are the adoption of best practices by ASN and its nonprofit, for-profit, and government partners, to make those best practices available to all interested parties and to maintain the goal of equipping the public to objectively evaluate the rigor, transparency, and relevance of nutrition research. A major underlying component of this endeavor is thus to explore how to responsibly manage and mitigate both real and perceived biases within nutrition research that are created by competing interests.

RESEARCH INTEGRITY IN AN ERA OF COMPETING INTERESTS

Although various competing interests, such as the desire for fame and respect, the imperative to publish, or stakes in previous bodies of work, may increase bias within research and merit attention, financial interests often receive the most attention [e.g., (34, 35)]. The attention to financial interests is particularly relevant because of the substantial role that industry funding has in food science and nutrition research and the likelihood this role will continue to grow. There are several reasons for this. First, public sources of research funds (e.g., USDA, US Department of Health & Human Services, CDC, NIH, National Science Foundation, Horizon 2020, National Research Council, and German Research Foundation) are limited. Second, not all nutrition research fits into the NIH biomedical model—the most substantial source of public funds for biomedical research (36). Third, the food industries themselves are legally responsible for showing support of their claims with research and, in some cases, for proving the safety of their food products. Fourth, researchers with funding from nonprofit organizations have incentive to also partner with industry—for instance, to show their ability to obtain diverse research support when applying for tenure, test interesting questions not typically supported by nonprofit funds, and receive consulting income when their expertise may benefit research conduct. The high prevalence of privately funded research in nutrition science, coupled with the drive for investigators to work with industry (i.e., in public-private partnerships), results in both real, perceived, and potential dual interests and the need to ensure trust and transparency.

Concerns of this nature are not new (37). With regard to the role of scientists in government, a 1960 article in *Science* (38) states, “The situation is awkward, but it is also absolutely unavoidable. The government clearly needs the best scientific advice it can get, and it can get this advice only from men with the pertinent experience—that is, in most cases, precisely from the men who will find themselves in a conflict-of-interest situation,” which the article goes on to describe as associating with, consulting for, and investing in the intellectual centers doing business with the government in their area of expertise. Serious debate about the physician-industry relationship became prevalent within the US government and peer-reviewed scientific journals in the 1990s (39, 40) and persists today (41, 42). Conflicts related to food, nutrition, and agriculture shifted into focus soon after and remain of high public interest.

In the late 1990s, ILSI North America considered various ways to address competing interests in nutrition research. A publication (13) resulted in 2009 with 3 major scientific organizations—ASN, the then American Dietetic Association, and the Institute of Food Technologists—that urged putting systems in place to build trust through transparency, as well as developing a common understanding among all public and private parties. One principle pertains to the conduct of the research itself (i.e., from design to implementation and outcome) and maintains that the way to ensure trust in scientists and the entire scientific process is to show rigor. This includes having access to verifiable data, ensuring an intent to publish those data and following through on that intent, disclosing known limitations, and restricting ghost authorship (43). Trust and transparency are the critical elements to the public dialogue today; and as stated by *The New England Journal of Medicine*, “Transparency

becomes increasingly necessary in an environment with low trust" (44).

Although ideals, such as providing access to verifiable data, might help improve both rigor and trust, particularly when competing interests are present, it is worthwhile to point out that efforts to improve the current state of affairs are in progress. The determination of how to manage prevailing barriers might need to ensue before solutions can become common practice. For instance, proposals have been put forth to make data more accessible [e.g., (45)]. However, issues of data-access rights, platform, and funding might still need to be sorted out on a case-by-case basis to facilitate widespread implementation. The process's successful implementation requires changes at the institutional level, such as prioritization of funds allocated toward these tasks, as well as interested and qualified personnel to develop and implement them.

THE NATURE OF COMPETING INTERESTS: DISCLOSURE IS NOT ENOUGH

As described above, financial conflicts of interest perhaps receive the most attention and are prevalent within nutrition science as public-private research partnerships. The purpose of these partnerships is to share resources to obtain a mutual goal that could not be obtained independently. For instance, researchers provide industry with advice on how to test the efficacy of their products, and industry provides researchers with funds to conduct required evaluations. When competing interests are managed responsibly, all parties can then provide new information to the public. Although few would argue that these relationships, like all relationships, do not raise ethical concerns that must be managed, the extent to which these partnerships can benefit nutrition and public health research is noteworthy, as we show here with several examples.

The Sibutramine Cardiovascular Outcomes (SCOUT) Trial is one of the largest clinical trials on an antiobesity medication ever conducted. It included 400 centers, 16 countries, and a sample of 10,000 persons; had a 5-y duration; was a randomized, double-blind study; and was sponsored by Abbott for ~\$200 million (46). Research consultants advised the protocols, communicated with investigators at other centers, and had full access to the data. This study found that although the drug had an effect on weight loss, the incidence of noncardiovascular complications increased by 16%. Consequently, Abbott withdrew their compound from each of the 70 countries in which it was launched (47). As a net gain, the unique data set provided researchers with the first set of intervention data that indicate that losing weight, especially in high-risk groups, reduced the risk of cardiac events (48).

In another example, the randomized, case-controlled, A Study of Risk Factors for First Myocardial Infarction (INTERHEART) study consisted of 27,000 persons in 52 countries and investigated risk factors for those entering a hospital with a heart attack compared with matched controls. This study found waist-to-hip ratio to be a more reliable predictor of heart attacks than BMI (49). AstraZeneca, Novartis, Sanofi Aventis, Knoll Pharmaceuticals (now Abbott), Bristol-Myers Squibb, Sanofi-Synthelabo, Boehringer-Ingelheim, Sankyo, Banyu, Pfizer, Pharmacia & Upjohn, Warner-Parke-Davis, and King Pharma sponsored the study and worked in collaboration with the Population Health Research Institute at McMaster University in Canada; University of

Wisconsin Medical School; Instituto Mario Negri in Italy; the University of Cape Town; Ninewells Hospital and Medical School in the United Kingdom; the University of Split, Croatia; Gaborone Private Hospital in Botswana; the Cardiovascular Institute and Fu Wai Hospital in China; Ramathibodi Hospital in Thailand; and Nairobi Women's Hospital in Kenya. These are examples of highly powered, impactful studies that benefited from public-private partnerships and served the public.

Another example of a public-private partnership ultimately benefiting nutrition science is research conducted on *trans* fatty acids. *trans* Fatty acids were originally incorporated into foods by industry. They were anticipated to be a healthier alternative to SFAs by scientists, consumer advocates (e.g., the Center for Science in the Public Interest), and mass media through the late 1980s (50). After results from clinical trials challenged this view in 1990 (51), a study funded by industry (e.g., the Institute of Shortening and Edible Oils, Nabisco Foods Group, the National Association of Margarine Manufacturers, the Snack Food Association, and others) in collaboration with the USDA and George Washington University Medical Center (52) found evidence suggesting that *trans* fatty acids increase the risk of developing heart disease by adversely affecting plasma cholesterol. As argued by Schleifer in 2011 (50), corporations have a history of involvement in research to control their products' image [e.g., (53–56)]. Some members of the private sector stepped in to defend *trans* fats, presumably to protect their commercial interests; nonetheless, it was transparent reporting of the industry-funded findings that arguably provided the most compelling evidence against *trans* fatty acids (52). The private sector is, in some cases, legally required to show the safety and efficacy of their products via scientific research, which is discussed in more detail below. At its best, commercial funding relieves financial burdens from the public sector, which understandably prioritizes biomedical research, and provides reliable data on food products and supplements for use by the public, scientists, clinicians, and policy makers to inform decisions about optimal food intake. The degree of risk posed by these partnerships, coupled with their known benefits, suggests to their advocates that the preservation of these partnerships is optimal but only when results are from unbiased work and transparently documented by rigorous methods, contract terms, appropriate data analyses, and a clear intent and execution of noncensored publishing—standards that all science benefits from.

Although public-private partnerships create an invaluable opportunity to generate knowledge, competing financial interests may bias the research process when not managed responsibly, and thus many steps have been taken in attempt to reduce such bias and warrant trust. For instance, it is now the usual practice for peer-reviewed journals to require disclosure of financial interests when submitting articles for publication. This practice does help warrant trust in science via improved transparency. When considering biases (i.e., the degree to which a research process is biased or its results reliable), however, funding sources may not be the most important question. When breaking down conflicts of interest, 3 areas merit consideration: 1) someone has an interest in something, 2) this interest drives an agenda, and 3) the agenda may or may not affect the integrity of the goal-achieving process. When considering industry and commercial conflicts, the agenda often is straightforward and simple to document. The industry agenda is to sell a product or service and profit from the sale, and thus people look at industry-funded research data

carefully to ensure that products are not portrayed as better than the data support. Alternatively, people may opine, *a priori*, that because studies funded by industry or commodity groups are more likely to report beneficial results than a lack of harm (35), their findings should be considered biased (57). Similar to the simplicity of limiting conflict-of-interest disclosures to industry support, declaring the previous or anticipated publication of a book relevant to the topic at hand is a straightforward way for scientists to report another important source of competing commercial interest. Perhaps the relative ease of discerning and reporting commercial conflicts contributes to their focus in discussions about competing interests, even though other conflicts may be at least as prominent and threatening to the validity of results.

Reporting conflicts of interest becomes more complicated, for instance, with the agenda of making a living via career advancement. If academic researchers want tenure, they often must obtain grant support (often from both private and federal sectors, to show resource diversity) and publish. Both processes involve a level of “selling” research questions and results. This creates ample room for career-related conflicts of interest to bias messages of significance and the interpretation of results. Even after scientists achieve tenure, the desirability of obtaining publicity and speaking fees or further enhancing professional stature may result in substantial conflicts of interest. Such conflicts likely are commonly held and may or may not impede the integrity of the scientific process. This is likely also the case with commercial conflicts. Yet, the former variety often goes unacknowledged in disclosures and formal discussions of competing interests. Although redundant, disclosures of commercial and other conflicts may strengthen science, prime awareness of common potential causes of biases, influence the refinement of systems that help protect the scientific process from biases, and substantially enhance trust.

Matters become further complicated with ideological conflicts of interest, such as when the source of conflict is a person’s opinion or belief. In this case, the agenda may be to convince others of an idea or spread an opinion. One may ask whether a person’s research is unduly biased in the direction of his or her ideology. Such agendas could be very personal, in some cases perhaps subconscious, unreported in disclosure statements, and potentially just as critical a risk to credibility as financial and career conflicts. For instance, if a scientist loses a parent to a cancer that was missed due to lack of screening, that researcher may have an agenda to promote cancer screening. Could such a history bias research that seeks to elucidate the benefits of early cancer detection?

Our challenge is that professionals have competing interests beyond the commercial variety that may bias their research process and render findings invalid and untrustworthy. They can include career, ideological, and other interests based on personal histories—that is, a plethora of agendas that are unknown because they are not declared within scientific reports or, in some cases, known by those who hold them. Conflict-of-interest forms typically probe who scientists receive money from, but this is just one source of potential conflicts. Funding disclosures contribute to transparency and trust, and thus should be continued, but they are unlikely to eliminate bad science (e.g., unwarranted degrees of certainty). Ultimately, what matters when considering credibility is the quality of the research itself, and the most reliable evidence of research quality is the degree of transparency and

rigor of the underlying science. For every study, the following questions are likely the most important:

- 1) Is the research question important?
- 2) Does the study design address the question?
- 3) Was the study well performed?
- 4) Were steps taken to ensure objectivity?
- 5) Was the proper statistical analysis used?
- 6) Were the right conclusions drawn?
- 7) Is enough information reported to answer these questions?

Agendas may or may not be known, but regardless, the science must live up to expectations that center on robustness and replicability if the goal is to improve the credibility of nutrition research.

A FEDERAL PERSPECTIVE ON RESEARCH DATA

In the realms of food safety and health claims, one aspect that may help improve credibility is clarification of the degree of rigor involved in the policies by which federal agencies use research to make decisions. Thus, this section provides insight about how the Food and Drug Administration (FDA), particularly the Center for Food Safety and Applied Nutrition, uses a variety of resources to evaluate the safety of ingredients and food additives, as well as evidence to support claims about products. It describes the sources of information that are used by federal agencies, the nature of existing evidence, the processes of agency review in the context of safety and claims, and strengths and limitations of these processes.

Sources of information deemed useful to federal agencies include reports from authoritative scientific bodies (e.g., The National Academy of Sciences, Engineering, and Medicine), consensus reports produced by other government agencies (e.g., for the government to be consistent when making recommendations to the public), experimental studies published in peer-reviewed literature, and research conducted by federal agencies for use by those agencies [e.g., NHANES data (58) figured prominently in making decisions about updating the Nutrition Facts on food labels]. Several federal agencies, such as the FDA, employ consumer research groups to foster understanding of the ways in which information might be misleading to consumers (59). However, information sources used by agencies may not be published research in some cases; for instance, those with proprietary interest submit resources as part of a packet that are not in the publicly available peer-reviewed research literature.

Agencies such as the FDA make public, through guidance documents, the process for review and evaluation of scientific data. Generally, this process requires submission of all of the available evidence and the agency conducts an independent review of the data to determine whether the evidence is useful for making a scientific conclusion relevant to the issue under review. The FDA typically does not rely on the conclusions in the reports submitted but makes its own conclusions after careful review of the reported methods and results to evaluate the quality and relevance of the information. The FDA conducts evaluations of safety data to approve food additives for addition to the food supply and has a statutory requirement to review the identity of the additive, its proposed use, technical effect, and method of analysis, as well as to provide full reports on all safety investigations. The FDA provides guidance for petitioning companies (60) on its process to

review the evidence on the food additive to determine safety, an acceptable level of use of that product, or to deny the petition.

The use of claims or representations of health or nutritive benefits in food labeling is another example of the federal need for scientific research. By statutory requirement, it is the manufacturer's responsibility that all such claims be truthful and not misleading. However, certain types of claims require submission of data for review to the FDA before they can be used in food labeling. Under the Dietary Supplement Health and Education Act (61), structure-function claims, which are for maintaining the structure or function of the body in healthy individuals, can be used on dietary supplements, but the agency must be notified within 30 d of their use in marketing. If this type of claim is used in food labeling, it must be based on the nutritive value of the food, and the manufacturer must be able to substantiate the claim.

Health claims and qualified health claims (QHCs) are about a substance and disease risk reduction. Health claims are authorized through rule-making by the agency after scientific review to determine if significant scientific agreement supports the claim. QHCs are qualified based on the level of credible evidence that is available (i.e., those that do not meet the significant scientific agreement standard) and used under a letter of enforcement discretion from the FDA. In either case, a petition must be submitted to the agency for review to determine whether a claim is appropriate. The FDA provides guidance, which is publicly available (62), as to what kinds of evidence can substantiate claims and outlines their evidence-based review system to evaluate health claims. This guidance document is useful for understanding how the FDA reviews scientific evidence for all types of claims. This process entails obtaining all studies of the substance, including any proprietary studies from the manufacturer, as part of a complete petition packet; determining which studies are suitable from which to draw scientific conclusions; evaluating the quality of the evidence; and determining whether the evidence supports the proposed claim. Once its review is completed, the FDA can authorize the claim through rule-making, use enforcement discretion for a QHC, or deny the petition for the claim.

The types of evidence the FDA regards as suitable for review include intervention and observation studies conducted in humans that evaluate the substance-disease relation on which the claim is based. Review articles, book chapters, abstracts, animal studies, and in vitro studies may provide useful background or mechanistic information but are not used to substantiate proposed claims. The FDA will not consider studies with the following fatal flaws: studies that lack a control group, relevant statistics (e.g., compares baseline with endpoint instead of treatment with control), or control for key confounders; that use a nonvalidated disease biomarker as the endpoint; that do not isolate an independent effect (e.g., if the study is of a fruit and the claim is on a compound within that fruit); that provide observational data without any intake validation; that are conducted in a malnourished population that is not relevant to the US population, for which the claim would be used; and that are conducted in a diseased population (62).

DOES FUNDING SOURCE AFFECT RESEARCH QUALITY?

As described above, science generated with funds from for-profit companies represent some of the most-attacked findings

within nutrition research. The trustworthiness of research funded by industry is debated at research conferences, in peer-reviewed publications, public news, and social media. Investigators have aimed to address this question by reviewing the funding sources of published literature and categorizing them by quality of methods and direction of findings (35, 63–65). Some of these data are described below.

Lesser et al. (65) evaluated 256 reports of research on soft drinks, juice, and milk that were published between 1999 and 2003. Of those, 111 declared funding and were coded as 1 of 3 categories: 1) received all funds from industry, 2) received mixed funds (i.e., some from industry and some not), or 3) received no funds from industry. Report conclusions also were coded as falling in 1 of 3 categories: 1) beneficial to industry interests, 2) neutral relation to industry, or 3) against the industry position, assuming the industry's interests are in support of its product. When all industry-funded conclusions were compared with those from nonindustry support, industry-funded conclusions were more likely to be positive. Although published industry-funded research may be trustworthy, these findings raise questions as to whether nonpositive findings remain unpublished. Just as it is conceivable that this would distort the scientific record in favor of commercial interests, so too is it conceivable that the converse may be true for nonindustry-funded studies.

In another study, Wilde et al. (63) evaluated 79 obesity-related studies published between 2002 and 2005 that were either funded by the federal government's semipublic programs (66) for Fluid Milk and Dairy or the NIH. Results were classified into 1 of 4 categories: 1) favorable toward industry, 2) unfavorable, 3) neutral, or 4) undetermined. In summary, the authors found that although conclusions of NIH research were the only ones to state unfavorable findings, they also were more likely to favor industry. Again, these data do not provide insight on the quality of published industry reports but suggest that unfavorable findings may be withheld from publication. However, as reported previously in a different context (67), when compared with industry, academic and noncommercial funders are just as likely to withhold unfavorable findings. Furthermore, although withholding findings may present ethical issues (67), withholding findings in itself does not necessarily signal an intent to deceive. Results may go unpublished due to limited resources (e.g., time to follow-through) or reasonable competing interests (e.g., prioritization of publishing work that is of high quality or aids in the acquisition of the next grant or the belief of authors, editors, or reviewers that null findings would not be worthwhile to publish).

Myers et al. (64) aimed to determine whether funding source affects the overall quality rating for various types of research reports (e.g., interventional, observational, and review). The overall quality rating of positive, neutral, or negative is based on 10 major questions about the rigor of the research and reporting methodology and is intended to reflect the level of confidence the results merit. The authors used the ratings recorded in the Academy of Nutrition and Dietetics Evidence Analysis Library of 2539 systematic reviews of interest to dietitians. Funding source was classified as governmental, industry, university hospital, unreported, nonprofit, or multiple. Industry was further categorized by food and supplement companies, pharmaceutical companies, commodity groups, other, or multiple. Investigators found that most studies were funded by multiple sources, followed by government, university, hospital, nonprofit, and unreported. The criteria that statistically predicted overall quality ratings were

degree of objectivity in subject selection methods, comparability of study groups, blinding, detail in intervention description, clarity of the research question, and appropriateness of statistical analyses (64).

Review articles were more likely to receive a neutral or negative quality rating than interventional and observational studies. With regard to funding source, studies that did not report funding were nearly 5 times as likely to receive negative ratings and nearly 2 times as likely to receive neutral ratings. Studies that reported either university or hospital funding were more likely to receive neutral ratings. Significant differences in quality were not detected among government-, multiple, or industry-funded studies. In other words, this study found no evidence of apparent bias (specifically, for research design, conduct analyses, or reporting attributable to industry as a funding source) for the food and nutrition research examined. Instead, studies whose funding sources were characterized as university, hospital, or undisclosed or with lack of funding were more likely to receive lower-quality ratings. However, this study was conducted in 2009, when the reporting guidelines implemented in the early 2000s were coming into vogue. Thus, it is unknown whether these findings remain valid for reported current research.

It is important to point out, however, that other studies have shown inconsistent findings. For instance, Chartres et al. (68) found no significant difference in the number of conclusions reported as favorable to industry between industry- and nonindustry-sponsored nutrition studies (even though they unexpectedly conclude in the abstract that, “these findings suggest but do not establish that industry sponsorship of nutrition studies is associated with conclusions that favor the sponsors”). Furthermore, Krinsky (69) described how causality has not been established when scientists attribute such associations to conflicting interests and concluded that scientists should remain skeptical by not settling on a default hypothesis that, “bias is always or typically the cause.” Overall, it is not clear whether a relation between funding source and research quality or direction of findings is shown, or if it is, whether it means that industry-funded research is any less reliable than nonindustry-funded research. If associations between industry funding and outcomes suggesting bias are observed, it is more appropriate to draw attention to likely sources of bias and to identify practices designed to avoid or manage them rather than engaging in ad hominem arguments.

NIH GUIDANCE: RIGOR AND REPRODUCIBILITY IN GRANT APPLICATIONS

One way that threats to rigor and credibility in science have been managed is through changes that the NIH has made to their instructions for grant applications. These changes address a confluence of recent concerns raised by the biomedical community and were motivated by several findings directly relevant to issues of rigor and reproducibility. For instance, institute directors found that few preclinical studies were performed on female rodents and, in another context, that many cell lines used by researchers were identified incorrectly (70). A number of workshops followed to address such issues and led to the development of changes that now require more rigor and help ensure reproducibility in 4 key areas: 1) scientific premise, 2) rigorous experimental design, 3) consideration of key relevant biological variables such as sex, and 4) authentication of key biological and chemical resources.

Scientific premise

With regard to improving the rigor of background material when reviewing the scientific premise of proposed research, (e.g., strengths and weaknesses of previous research that is crucial to applications), applicants are instructed to consider whether the authors of articles included in the proposal’s review of previous work reported transparently, studies were rigorous, and methods were valid. Enhancing rigor in scientific premise is not meant to impede innovation or interfere with exploratory research (i.e., research that frequently requires less discussion of previous research) but instead to identify risks related to successfully addressing proposed questions and objectively evaluate research strategies designed to bolster the proposed work’s success. Reviewers are instructed to look for strict applications of the scientific method to ensure robust and unbiased experimental designs, methodologies, analyses, and reporting of results and their interpretation.

Rigorous experimental design

With respect to experimental design, applicants are now asked to describe how they will achieve robust and unbiased results. Aspects of design that are encouraged include the use of standards, sample size estimations, randomization, blinding approaches, control for interoperator variability, prespecified statistical analysis plans, documentation of statistical expertise, and the handling of missing data. These principles apply to clinical and preclinical and basic research.

Consideration of relevant biological variables

In consideration of relevant biological variables, such as sex, the Office on Research for Women’s Health developed 4 “Cs,” which are as follows: to “consider” taking sex into account when designing a study, “collect” and tabulate sex-based data, “characterize” and analyze sex-based data, and “communicate” and publish or report sex-based data in studies. Strong justifications based on scientific literature are expected in applications that propose studying only one sex.

Authentication of key biological and chemical resources

The last of these changes is to ensure authentication of key biological or chemical resources. Examples of resources that require authentication are cell lines, specialty chemicals, antibodies, and other biologics. Authentication guidelines are needed for numerous crucial resources. Their development is underway and likely to continue on an ongoing basis, because researchers are expected to transparently report how all key resources are authenticated. For example, university research affairs personnel are formalizing processes for verifying putative cell line identities by sequencing approaches. For nutrition science research, additional authentication to consider might be that of validating diets formulated in animal studies to verify whether essential and harmful components are unexpectedly missing or present, respectively (71).

A number of pilot studies were conducted to examine the ramifications and feasibility of making these changes to grant applications. For instance, the NIH tested whether page limits would need to be altered to accommodate likely changes. These

inquiries concluded that descriptions of key biological resource authentication would be provided most appropriately in separate attachments and that other likely changes would not affect the 12-page research plan limit. Instructions related to proposals' scientific premises will be addressed in the significance section, whereas scientific rigor and consideration of relevant biological variables will fall under separate sections that describe proposed approaches. Moreover, changes that relate to training programs, requested biographical sketches, other application sections, and evaluation guidelines were developed for program officers and are available to the research community on the NIH website (72).

FROM RECOGNITION TO MITIGATION: A PATH FORWARD

To address additional ways to improve scientific rigor and credibility in nutrition science, this section offers a taxonomy of the way research goes astray, discussion of the importance of focusing on the essence of science, and ways to move from recognition of some of the challenges the field faces to mitigation of straying from sound science. There are ≥ 3 ways that science sometimes goes astray: 1) fraud (i.e., fabrication, falsification, or plagiarism), 2) distortion (i.e., misleading reporting), and 3) gross error (i.e., mistakes). None of these sources of undesirable practices are new. Each has been noted throughout the history of science. We hope and believe that fraud is quite rare, and although it is practiced (73), it can be difficult to detect empirically (74, 75). Distortion and gross errors may arise intentionally or unintentionally. Overall, the latter may have an equivalent or greater distorting effect on the literature (76–78) and are found in nutrition science (79).

For instance, one study (80) estimated the potential effects that a policy limiting the calorie content of kids' meals would have on childhood obesity. The authors reported that for the average child eating fast food 2 times/wk, 2 pounds of weight gain/y could be avoided if kids' meals were restricted to 550 calories (80). The authors further noted that 3% of children "could theoretically expect to avert weight gain of 27 pounds per year" if calories in children's meals were limited to 550 kcal (81). One of us collaborated in using a validated model that controls for growth (82) to estimate effects on children aged 6–12 y who eat fast food several times per day. The validated model predicted that 6.5 pounds of weight gain could be avoided, whereas the alternative model (83, 84) inaccurately predicted the avoidance of a 27-pound weight gain (81). The original study's authors (85) acknowledged the correction and admirably retracted the original article (86). This is an example of an unintended misuse of mathematics and of a subsequent false inference, but nonetheless, the original publication had potential to detrimentally affect the scientific record.

Throughout various attempts to correct either misleading literature or reports containing errors, several barriers to seeing such corrections to fruition have been reported and arguably stunt science's self-correcting process (87). As we described in *Nature* (88), some journals charged a fee of ~\$2000 to publish a letter to the editor correcting errors published by them. One publisher required an up-front agreement to pay an additional fee to retract a follow-up correction letter should an error be found in the submitted letter. Such policies provide disincentives to report and admit errors, correct them, and build an improved culture of truth.

Although not all agree (89), a growing consensus suggests (90–93) that the way forward to improved credibility in the nutrition research landscape is to focus on the principles of science. Science does not look into the souls of people to determine who is a truth teller. Conflict disclosures are critical steps in warranting trust (and should remain a standard of transparent reporting), but such disclosures alone do not justify trust. Even when people are honest, biases may be subconscious (94) [as members of the public are aware (95)] and mistakes can be made. What can be done is rigorous research and transparent reporting in accordance with the scientific method. We assert that, in science, 3 things matter epistemologically: 1) the data; 2) the methods used to collect or produce those data, which give the data their evidential meaning; and 3) the logic by which the data are connected to conclusions. All else are distractions. If the goal is to improve the science—our efficiency in coming to knowledge—and trust in the scientific process, the needs are to adhere to the principles that support sound science and not focus solely on disclosures. It is here that we can engage in concrete ways to move from the recognition of the challenges we face to the mitigation of straying from sound science.

Many approaches have been suggested for assessing the soundness of science (4, 96–103). Approaches commonly fall under 3 concrete ways to meet that end: 1) data sharing, 2) development and use of checklists, and 3) methodologic training.

Data sharing

An example of a recent mistake made by one of us (104) concerns an analysis of publicly available NHANES data that could not be reproduced by another group. The work was checked, and 2 mistakes were uncovered: 1 in the analyses of the publicly available data and a second in the algorithm the analysis used. The algorithm was developed by the authors who attempted to replicate the flawed analysis. Both groups worked together to correct the 2 errors. These corrections were only possible because the raw data were available to others who noticed inconsistencies. This verification process is a critical step to the scientific method and is drastically limited when data are withheld (105–107).

Checklists

An article was recently retracted because the authors inadvertently published an analysis of the wrong data set (108). Any scientist can imagine making a mistake such as this if good practices are not in place. This is why surgeons and pilots use checklists—too much is at stake to not adequately prepare for easily avoidable errors. We need to develop and use checklists in our research. Various checklists have been developed [e.g., (109–111)], which help satisfy some needs of researchers; however, work remains to be done to help researchers ensure the use of valid methods of research and analysis.

Methodologic training

Both formal and informal (112) training are a cornerstone to science and integral to improving the scientific process. Statistical training in particular or, at the very least, training in the importance of collaborating with experienced biostatisticians is key.

Numerous avoidable errors are common within nutrition science (79). For example, a recent meta-analysis (113) that claimed to have found a significant effect of the fiber supplement glucomannan on weight loss contained inaccuracies that exaggerated the estimate. Upon collaboration with experienced biostatisticians, these issues were resolved, and a correction was published (114).

Furthermore, there is merit to the “Social Value of Public Information” perspective (115, 116), which, put simply, is that not all information is equally important. In other words, some studies warrant gold-standard levels of implemented rigor and others do not (117). Rather than waste valuable resources, variations in degree of rigor should be commensurate to the needs of each research question to optimize research payoff (97, 118). With respect to reporting, however, there should not be variation in rigor, because gaps can impede the value of research and lead to further waste of resources (119). The reader needs to know what was done in order to judge and verify the reliability of the reported science. Ensuring compliance to reporting guidelines [e.g., (109)] as well as depositing supplementary information online may serve to improve transparency while respecting understandable space limitations in printed academic journals. Improved reporting transparency also would benefit reproducibility (120). There have been reproducibility efforts in psychology (121) and cancer research (122), and one could ask whether we should sample subsets of studies within nutrition science for experimental reproduction.

Furthermore, as discussed by Sagner et al. (123), personal factors [i.e., independent from the science conducted (e.g., previous funding)] are often mistaken as grounds for ad hominem attacks, bullying, and harassment within science. This is particularly relevant to the field of nutrition. Although we are not aware of formal analyses of such matters, different fields seem to get disproportionate attention to concerns raised about conflicting interests. Anecdotally, we have observed far less concern and vitriol in engineering and computer science than in fields such as public health, nutrition, and pharmaceuticals. To the extent that our informal impression is accurate, a difference in concern may imply that fields in health and nutrition are ahead of the curve, because acts of questioning drive the self-correcting process of science. However, the very essence of science (i.e., pursuit of knowledge via scientific method) is abandoned in the case of ad hominem arguments, which often occur in the public eye and in the name of competing interests, such as political or financial gain. Such attacks on the essence of science and on individual scientists (124, 125) are rooted in logical fallacies (126), may confuse the message given to the public as to how to evaluate science rigorously and consider evidence for decision making, may foster mistrust of science without clear grounds, may give competing interests a persuasive power that is unjustified by logic or empirical evidence, are dehumanizing, and should not be tolerated.

Finally, it is important to improve the value of a culture of truthfulness. By a culture of truthfulness, we mean a culture in which people feel passionately about the importance and necessity of seeking and communicating truth. This implies not only an intent to speak truthfully but it presupposes a culture of carefulness, because one can speak many untruths unintentionally if one is not careful. In other words, sloppiness may reduce truthfulness. A culture of transparency warrants trust. If transparency is lacking in reporting by peer-reviewed journals and scientific presentations published as abstracts (127), how can other

scientists use reported results effectively, the media report results accurately, or the public trust science? A recent headline of press releases (128–130) affiliated with the CDC read, “New Study Shows That Combating Childhood Obesity in Schools Works,” with comments within stating, “as the Alliance celebrates its 10-year anniversary, a new peer-reviewed study confirms we are delivering on our mission of reducing the prevalence of childhood obesity.” However, the study abstract (131) states that, “analysis showed no difference between Healthy Schools Program (HSP) schools and control schools in overweight or obesity prevalence. Program exposure varied widely among participating schools, and each additional contact with onsite training and technical assistance or HSP national advisors was associated with a 0.3% decline in overweight and obesity prevalence.” The abstract’s conclusion reads as follows: “HSP appears to be an important means of supporting schools in reducing obesity. Although participation in HSP alone was not sufficient to improve weight status in California schools, there was a clear dose-response relationship to the program. HSP serves as an effective model for addressing childhood obesity among engaged schools.” The incongruity between the results and conclusion of an otherwise useful study and report does not serve science. Greater focus on adherence to the principles of science and renewed commitment to establishing systems that encourage the value of truth and safeguarding honesty (132) will benefit all members of society, scientists, and industry personnel who want to know and publish truthful answers to research questions.

We thank Gwen Twillman for coordinating the draft of this manuscript.

The authors’ responsibilities were as follows—CMK: drafted the manuscript; CG, SR, AMS, BOS, EM, CJL, and DBA: provided input via session presentations and editorial assistance with manuscript drafts; and all authors: read and approved the final manuscript. EM has received funding for research and evidence analysis projects from the government (e.g., NIH, CDC), nonprofit organizations (e.g., Academy of Nutrition and Dietetics, ILSI North America), and industry (e.g., National Dairy Council, Almond Board of California, Ajinomoto, The Coca-Cola Company). AMS has received research and other support from the Heart and Stroke Foundation of Canada, the Canadian Diabetes Association, and the Canadian Institutes of Health Research and additional government, nonprofit, and for-profit organizations (including pharmaceutical companies) with interests in obesity, nutrition, and health. DBA has received financial and other benefits from the following entities: The Frontiers Foundation, the State of Oregon Department of Justice, ASN, the Federal Trade Commission, the FDA, the Nutrition Science Initiative (NUSI), and numerous additional government, nonprofit, and for-profit organizations (including publishing, food, beverage, and pharmaceutical companies) with interests in obesity, nutrition, and health. The remaining authors had no conflicts of interest to declare.

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