NRC Research Press

REVIEW

Research in nutritional supplements and nutraceuticals for health, physical activity, and performance: moving forward[1]

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Abstract: This Horizons is part of a series that identifies key, forward-thinking research questions and challenges that need to be addressed. Specifically, this Horizons paper discusses research in nutritional supplements and nutraceuticals for health, physical activity, and performance, and is the product of a discussion by an expert panel that took place in January 2018 prior to the Canadian Nutrition Society Thematic Conference "Advances in Sport Nutrition from Daily Living to High Performance Sport". The objective of this Horizons paper was to identify core considerations for future studies for this research area, and how scientists can be leaders in the field to ensure the best quality science is available for decision makers. It is strongly recommended that the various elements highlighted throughout this Horizons paper will increase the awareness of the significant before-, during-, and after-research due-diligence required to produce research of the highest quality. While it is recognized that many scientists will not be able to meet all of these aspects, it is nonetheless important to consider the points outlined and to recognize that those elements that are not met in studies may be significant limitations.

Highlights

- Research questions that are hypothesis-driven are the strongest, and when combined with careful planning of the study, the result will often be of the best quality.
- Studies with a strong experimental design help discern between evidence-based findings and those that have not been substantiated.

Key words: aging, athlete performance, data analysis, diet, exercise, nutrition.

Résumé : Le document *Horizons* fait partie d'une série identifiant des questions clés de recherche avant-gardiste et des défis à relever. De façon spécifique, ce document *Horizons* traite de la recherche sur les suppléments nutritionnels et les nutraceutiques pour la santé, l'activité physique et la performance; il est le fruit d'une discussion tenue par un groupe d'experts en janvier 2018 avant la réunion thématique de la Société canadienne de la nutrition intitulée : « Progrès de la nutrition sportive, du quotidien au sport de haut niveau ». L'objectif de ce document *Horizons* est de déterminer les considérations fondamentales pour des études ultérieures dans ce domaine de recherche ainsi que la manière pour les scientifiques de devenir des chefs de file dans ce domaine afin de fournir aux décideurs une production d'une grande qualité scientifique. Il serait souhaitable que les différents éléments mis en évidence tout au long du document *Horizons* renforcent la prise de conscience de l'important devoir de diligence requis avant, pendant et après la recherche pour produire une recherche de la plus haute qualité. On admet que plusieurs scientifiques ne sont pas en mesure de répondre à tous ces aspects, néanmoins il est important de prendre en compte les points exposés et de reconnaître que les facteurs non pris en compte dans les études peuvent constituer des limitations importantes. [Traduit par la Rédaction]

Point fort

- Les questions de recherche basées sur des hypothèses sont les plus fortes et, lorsqu'elles sont combinées avec une planification minutieuse de l'étude, le résultat est souvent de la meilleure qualité.
- Les études avec un plan expérimental fort permettent de faire la distinction entre les résultats basés sur des données probantes et ceux qui ne le sont pas.

Mots-clés : vieillissement, performance des athlètes, analyse de données, régime alimentaire, exercice, nutrition.

Received 8 November 2018. Accepted 28 January 2019.

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*Wendy Ward currently serves as Co-Editor-in-Chief and Philip Chilibeck, Elena Comelli, and Lindsay Robinson currently serve as Associate Editors; peer review and editorial decisions regarding this manuscript were handled by Audrey Hicks and Terry Graham.

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[1]This paper is a part of the Horizons subcategory, which summarizes important achievements in the field and identifies key, forward-thinking research questions and challenges that need to be addressed.

A correction was made to the e-First version of this paper on 2 April 2019 prior to the final issue publication. The current online and print versions are identical and both contain the correction.

The challenge

Nutritional supplements including specific food components such as botanicals have been used to benefit human health and performance for centuries. While common terms such as nutritional or dietary supplements or nutraceuticals are used globally, there is no unifying singular definition and associated regulatory laws and evidence needed for health claim substantiation are unique to each country or region. The objective of this Horizons paper is to identify core considerations for future studies for this research area and to highlight how scientists can be leaders in the field to ensure the best quality science is available for decision makers. These decision makers may be health care or exercise performance professionals, industry leaders, government regulatory agencies, scientific journal editors, and consumers motivated to base decisions on findings from the highest quality studies. This Horizons paper specifically focuses on practical aspects for conducting high-quality studies rather than the next step of implementing findings from such studies.

The research field of nutritional supplements and nutraceuticals is relatively new to Western society, but it is becoming increasingly important to consider their efficacy within unique populations, such as older adults and those engaged in sport performance, as well as those who are taking them for a general emphasis on health and well-being. Indeed, there is widespread interest in supplements among many stakeholders that includes consumers, industry members, and scientists. Consumer motivations for use of supplements are broad, and usually relate to the perceived belief of efficacy, and can include general well-being, aesthetic pursuits, prevention or management of chronic disease, longevity, fitness, sport performance, and/or any combination of such factors (Dickinson and MacKay 2014; Knapik et al. 2016). There are substantial financial gains for industry in developing and selling such products as it is estimated that the global market of dietary supplements will be 278 billion USD by 2024 (Grand View Research 2018). We believe that the field of nutritional supplements and nutraceuticals is vulnerable to over-interpretation of findings and that specific effects are sometimes based on information that has been over-extrapolated from the basis of the actual information. Studies with a strong experimental design help discern between evidence-based findings and those that have not been substantiated. However, weak, descriptive studies with indirect and correlative measures can lead to misleading conclusions for efficacy.

In line with the goals of the Horizons series, it is hoped that this paper will be particularly useful to new investigators. Although many of the raised themes are universal to any field of research, they are important to emphasize to improve the quality of the growing literature on supplements. There is a current need to reinforce important considerations for future studies where research publications proliferate, and it may become more difficult to discern the quality of the evidence. The following is a discussion of how such investigations should ideally be planned for, conducted, analyzed, and evaluated during the peer-review publication process (Tables 1 and 2).

Developing the research plan

Research question

Critical first steps for any study include the development of a research question and careful planning. This includes a thorough literature review to ensure that the research question is unique and relevant, to ultimately confirm that the study is novel and fills a knowledge gap. Identifying a specific mechanism of action is also important to guard against wasted resources and/or over-interpretation of off-label or serendipitous findings. With ever-increasing time demands, the value of conducting sufficient pre-study due diligence is critical to study success. Furthermore, research questions that are hypothesis-driven are the strongest, and when combined with careful planning of the study (including the actual conduct of the experimentation through to data interpretation) the result will often be of the best quality.

Assembling a team

Planning may involve collaboration and assembling a team to ensure that all facets of the study can be expertly conducted. Depending on existing expertise of an investigator and whether conducting a study in humans or using an animal model, a team may include a food scientist/product developer; animal nutritionist; scientists with specific expertise in unique methods or analyses of metabolites of interest in biological samples; an exercise performance testing expert; and a statistician. Development and/or characterization of the product to be tested may involve a food scientist or biological chemist for in vitro analysis, and they can also provide insight into acceptability of the product if incorporated into a food or food product. Practical aspects such as finding a company that can assist with intervention development and packaging with blinded labelling is also a consideration. Similarly, for animal-based studies, colour-coded diets can be used to reduce bias that may be introduced by those providing the diet during the in vivo trial. Incorporation of the test component should be carefully considered, particularly for animal diets, such that levels of nutrients, other than a potential nutrient(s) under study, are identical among test diets. If energy content is altered per unit of diet, nutrients should be adjusted for the differing energy content. This step is achievable by working with a nutritional scientist at the diet company to develop ideal study diets with correspondingly appropriate control diets. The AIN-93 diet is an established control diet from which intervention diets can be based through modification of the level and/or source of 1 or more nutrients (Reeves 1997; Reeves et al. 1993). Moreover, specific expertise with analyses of metabolites in serum or urine resulting from consumption of the product in biological samples is essential to determine appropriate timing of sampling after consumption. An understanding of the metabolism of the test compound, as comprehensive as possible, is also important to ensure that appropriate markers that identify biological activity are evaluated. As with any study, preplanning of statistical analyses is ideal and may warrant direct involvement of a statistician from the planning stage onwards.

Other considerations

Planning also involves consideration of how sex and/or gender will be integrated in a study design and how the results will be interpreted. Granting agencies in Canada and the United States, as well as globally, are including such aspects in the review process (Canadian Institutes of Health Research 2018; National Institutes of Health 2018). A feasibility or pilot study may be warranted and essential for securing adequate funding for a larger clinical trial. Moreover, a well-designed feasibility or pilot study, which answers a novel research question, should not be underestimated. For example, a pilot study to show a bioactive compound is detectable in blood after oral human consumption, prior to a full-scale clinical trial with a health and/or performance outcome, can help guide next steps with novel ingredients. Moreover, scientists must take every step to ensure the safety of human research participants. During the design of the study, the true contents of the supplement must be considered and perhaps determined independently, with each ingredient considered for possible health effects and these need to be addressed. Also, if an investigation only examines acute ingestion of the supplement, there should be discussion of potential adverse health effects for long-term use of the supplement.

For human studies, Good Clinical Practice (GCP) guidelines provide guidance for conducting trials albeit the focus is for pharmaceutical-based products (https://www.ich.org/products/guidelines.html). Researchers planning a clinical trial can also

Table 1. Human studies: essential "must have" and optional "good to have" aspects that contribute to a high-quality study in the field of nutritional supplements or nutraceuticals.

Essential "must have" aspects	Optional but "good to have" aspects
• Assemble a team with required expertise • Ethics approval • Power calculation • Register trial within a clinical trial registry (e.g. www.clinicaltrials.gov) • Follow CONSORT guideline for reporting of randomized controlled trials (including inclusion of a comparator group) • Characterize the level of component(s) of interest in the supplement • Include as much detail as possible about preparation of product, and its composition, including analyses performed, to ensure no cross-contamination and to understand the safety of ingredients and potential adverse health effects • Justification for participants studied (e.g. age, ethnicity, health status, athletes) • Measure of participant compliance • Identification of primary outcome measure linked to appropriate power calculation • Justify choice of outcome measures and clearly define terminology related to them (e.g. inflammatory response) • Appreciation of lab-specific technical error of measurement for key outcome measures linked to power calculation • Assessment of background diet and exercise • Assessment of exercise with trial replication • Determine if there are inter-individual differences that are clinically meaningful and warrant further investigation • Post-trial questionnaire confirming double blinding of intervention, with code blinding that is not broken until statistics are completed (if no double blinding, justification as to why it was not possible)	• Biochemical markers of compliance • Understand how the product is metabolized, including metabolites • Examine sex-specific responses to the supplement

Note: CONSORT, Consolidated Standards of Reporting Trials (http://www.consort-statement.org/).

Table 2. Studies using animal models: essential "must have" and optional "good to have" aspects to contribute a high-quality study in the field of nutritional supplements or nutraceuticals.

Essential "must have" aspects	Optional but "good to have" aspects
• Assemble a team with required expertise • Ethics approval • Power calculation • Follow ARRIVE guideline • Detailed information about preparation of product • Complete diet composition • Diets that are balanced for nutrients not being studied, with adjustment of nutrients per energy level • Justification for dose studied • Justification for route of administration • Description of how age of animals studied relates to human lifespan	• Evidence that product is metabolized similar in humans and the animal model • Accurate measure of intake • Examine sex-specific responses to the supplement

Note: ARRIVE, Animal Research: Reporting of In Vivo Experiments.

refer to the Consolidated Standards of Reporting Trials (CONSORT; http://www.consort-statement.org/) statement and related resources to ensure their study can produce high-quality evidence (Moher et al. 2012). When studying the effect of a nutritional supplement or a nutraceutical in a human intervention study, there are also common considerations beyond those described in GCP guidelines that will strengthen the quality of a study (Table 1). Moreover, many of these aspects also apply to studies using animal models.

Preparing and characterizing a nutritional supplement or nutraceutical

Ideally, the complete composition of a nutritional supplement or nutraceutical would be characterized. However, if this is not possible because of a complex composition and/or cost, determining the level of the purported active component can be a focus and should almost be a requirement. Commercially available products may be accompanied by a certificate of analysis for specific aspects of a product from the company. Verification of the level of the active component under study by a third-party, certified laboratory to provide confidence regarding purity and composition significantly strengthens the quality of a study. One example is a company called LGC, based in the United Kingdom, that routinely tests for quality and compliance of products, and with respect to performance supplements, is experienced with testing for banned substances in products (https://www.informed-choice.org/what-lgc). Details regarding preparation of the product should be included. The temperature of preparation and the form of the supplement are key aspects to report and to understand the changes in bioavailability that may result. Some studies will use supplements in powder (pill) or liquid form. In studies testing a supplement, it is important to have a control that resembles the appearance and taste of the supplement as closely as possible for adequate blinding, considering aspects such as additional nutrients and/or energy provided. Also, the form of product may alter biological activity in vivo. Detailed reporting of both the composition of the supplement and its preparation will strengthen the repeatability of findings with future studies.

Metabolism of the nutritional supplement or nutraceutical

Understanding the metabolism or mechanism of action of a supplement can help inform the study design. For example, this information can be used to determine if an effect is likely to be acute and/or if the supplement should be taken before or after exercise to have the greatest potential biological effect. Another consideration may be the half-life and the frequency by which the supplement needs to be taken. However, it is important to acknowledge that for many nutritional supplements and nutraceuticals, some or many aspects of metabolism will be unknown. If that is the case, this should be acknowledged in any publication arising from the work. Metabolism of a nutritional supplement or nutraceutical is complex, and for some, a multitude of metabolites may result, and may make it impossible to fully characterize all aspects. Another aspect to consider is if changes in gut microbiome due to illness or antibiotics may alter metabolism. For example, the bioactive lignans resulting from flaxseed consumption are synthesized by gut bacteria and use of antibiotics is associated with lower enterolactone plasma concentration (Bolvig et al. 2016). Disease state may also alter metabolism because of differences in inflammation and oxidative stress. Reporting and replication of background diet prior to intervention trials is also important to understand potential additive or synergistic effects that may manifest with the consumption of a supplement. Moreover, baseline nutritional status, including dietary intakes, may impact outcomes. For example, beetroot (high in nitrates) supplementation to improve endurance performance is less effective in individuals who have a high natural background diet of nitrates, which are abundant in green leafy vegetables (Govoni et al. 2008), and is further compounded by the fact that antibacterial mouthwash can attenuate the effectiveness of nitrates (Jones 2014). Thus, it is good practice to explicitly describe baseline diet and nutritional status, as well as background exercise, and other confounding factors, of all participants.

Participant compliance

It is important to consider the approach to measuring participant compliance. Ideally, self-reported compliance will be supported by biomarkers that may include measurement of specific urinary or serum markers of intake. Moreover, elucidating markers that are strictly elevated by the test product may be challenging as many supplements and nutraceuticals may have overlapping metabolites that result from consumption of foods. Furthermore, as previously discussed, if the product has not been fully characterized in terms of its metabolism, a precise measure of compliance may be problematic. Some studies will have a design where participants can consume the product in the presence of an investigator and thus mitigate the challenges of having a biomarker of intake to ensure compliance. At the very least, electronically confirmed daily compliance reminders (texts, emails) from researchers to participants are necessary and should be reported in the subsequent paper. Use of an exit survey that asks participants to identify which intervention they thought they received and the level of confidence in their answer can provide insight into whether an observed benefit may be altered by a placebo effect. A placebo effect has been reported to be particularly strong in studies of supplement use in high-performance sport (McClung and Collins 2007).

Choice of outcome measures

Nutritional supplements and nutraceuticals will be studied in relation to a wide variety of outcome measures that may span from biochemical markers through to changes in body composition, as well as performance outcomes. Regardless of the primary outcome of interest, it is important that the method and variability for the measurement of this outcome are considered and a priori power calculations completed to guide participant recruitment requirements. In particular, a primary outcome should be identified and a power calculation a priori based on that outcome should be conducted to ensure statistical errors are minimized. Also, the expected or clinically significant effect size should be reported to provide context for the biological and not solely the statistical significance of results. Moreover, in human performance studies, there can be scientific disagreement on the best performance outcome to be measured. An example is whether a time trial or time to exhaustion protocol should be used. Both have merit depending on the research question (Laursen et al. 2007). Thus, considerable thought and justification are required. Inherent within the discussion of outcome measures is that the variability of a specific methodology be known and considered when conducting power calculations and interpreting differences due to treatment. It is essential to know the variability of a methodology or test to evaluate whether a difference due to a product is sufficiently large to be real. Such a change, for example in dual energy X-ray absorptiometry-measured fat- and bone-free lean tissue mass would have to exceed normal day-to-day as well as time-dependent variability in this measure if the measure were made, for example, 12 weeks apart. As such, it would be important to include in-house estimates of variability and a control group to account for this possibility.

Many nutritional supplements and nutraceuticals are studied for their purported anti-inflammatory or anti-oxidant activity and yet choice of biomarkers to demonstrate this activity can be confusing and debated in the literature. Moreover, it may be difficult to have biomarkers in preventative research and for such studies it may not be appropriate to use biomarkers provided the study is of high quality. In addition, terms such as "inflammatory response" are often used loosely without specific reference to how it is defined, which can greatly cloud the interpretation of outcome measures. Keeping abreast of current acceptable outcomes for assessing inflammation and anti-oxidant activity is important to make the best choices for measuring and reporting within a study. Choice of tissue to measure is also important as it can restrict the accuracy and/or applicability of the data. Furthermore, clear statements in a paper about the working definitions for such terms and a brief rationale for the choice of markers is encouraged and can contribute positively to the field.

Responders versus nonresponders

There has been ever-increasing interest in responders and nonresponders to an intervention, particularly with reference to performance outcomes. Repeated serial trials are helpful to determine if an individual is consistently a nonresponder but such repeated trials are not always feasible. Rather, there should be a priori considerations for defining a nonresponse, with a link to a measure of variability of the outcome measurement. A conceptual framework for quantifying true inter-individual differences in response to an intervention has been discussed extensively in the literature (Atkinson and Batterham 2015, 2017; Atkinson et al. 2018; Williamson et al. 2017, 2018) with specific examples from studies investigating weight change or maximal oxygen uptake in response to exercise interventions (Williamson et al. 2017, 2018). This framework includes a comparison of the standard deviation of the change in the intervention group with the same change in the comparator (control or untreated) group to make an informed decision regarding whether an observed inter-individual difference is of clinical relevance. Importantly, this comparison provides an essential justification for whether or not consideration of potential modulators or mediators that explain an individual response should be pursued (Atkinson and Batterham 2015). Genetics should also be considered in the interpretation of study data even if it may not be feasible to genotype participants. The issue of participant variation is also important to consider when processing

and presenting the data. Researchers are encouraged to consider the extent of inter-individual variation in the study outcomes and if appropriate (and if ethical approval for reporting individual data points is obtained) consider presenting not only the mean responses but information on the response variability and the potential for responders and nonresponders. Also, reporting of individual responses is useful within animal studies.

Use of animal models to understand the human response

Findings obtained using animal models can contribute to the totality of the evidence regarding the efficacy of a nutritional supplement or nutraceutical, or even a food component that is being studied at a higher dose than exists naturally in a food. These interventions can be tested in the context of unique physiological states created through a specific surgical procedure. Examples of these procedures include ovariectomy, to accelerate and mimic the physiological response observed in women after menopause, while synergist ablation can induce significant muscle hypertrophy. Surgical procedures such as these are useful to focus on a specific mechanism, but it is important to acknowledge that the resultant state does not fully mimic the human situation. In general, whenever reporting findings from an animal model, it is critical to address any specific challenges that can be unique to a given species or outcome regarding translatability to humans. Findings should be interpreted in this context and the implications for translatability to humans explicitly discussed in the publication.

Testing nutritional supplements in animal models allows the investigator to control for many confounders including diet. Also, there is the opportunity to use an inbred and/or outbred strain to either control for genetic variation or to study a heterogeneous population, respectively. An appropriate animal model can also provide unique opportunities to test previously untested compounds during particularly sensitive stages of the lifespan such as pregnancy and early postnatal life that would not be possible to study in humans. But careful consideration of how to study littermates must be considered in a study design; sharing the same uterine environment will bias results and thus a litter should typically represent an n of 1. Also, rodent models can be used to study longitudinal responses over a period of months rather than studying humans over many years. With advanced imaging it is possible to study changes due to aging or responses to specific interventions in multiple tissues and organs throughout the lifespan, studies that are simply not feasible in humans. Not only can such findings provide a rationale or hypothesis for clinical trials, but these studies can also investigate safety aspects that may be challenging to study in humans. In the case of compounds with potential hormonal activity, safety aspects such as histology and function of reproductive tissues can be assessed. However, there are important considerations to integrate in a study design using animals to maximize the potential translation of findings to humans (Table 2).

The ARRIVE guidelines – Animal Research: Reporting of In Vivo Experiments – were developed to improve the quality of research resulting from use of animals, keeping in mind best practice, and with the long-term goal of reducing the numbers of animals used in research (Kilkenny et al. 2010). The reduction in numbers of animals used for research is also a mandate of many organizations throughout the world that oversee ethical treatment of animals in research, such as the Canadian Council on Animal Care, which also supports the "3 Rs" (replacement, reduction, refinement) (Canadian Council on Animal Care). ARRIVE guidelines are increasingly endorsed by many scientific organizations, including journals, societies, and funding agencies. When testing nutritional supplements or nutraceuticals using animal models, there are additional aspects that must also be considered in addition to the ARRIVE guidelines. Some of these aspects have been discussed previously, including characterization of the test material, accurate production of diet containing precise levels of test component, and choice of outcome measures. While knowing the exact composition of the product tested is vital to ensure repeatability between and among studies, additional considerations include the following: dose, route of administration, and metabolism of the test component as well as the stage of the development when administration occurs.

Dose

When considering the dose of a nutritional supplement or nutraceutical there are key questions to answer, such as: Could the dose be studied in humans? What is the basis for the calculation of the dose? Is the investigation aimed at studying physiology or pharmacology?

Route of administration

Daily oral administration, and potentially without requiring oral gavage that may cause distress to the animal, is ideal to truly mimic how the component will be consumed by humans. However, oral consumption via diet or water can sometimes be challenging or not feasible. One example is at an early stage of development when sole food source may be through mother's milk. Also, compounds that are expensive or available only in small quantities and/or at extreme financial costs may not allow incorporation into the diet or water source, and necessitate oral gavage. In situations where components are incorporated into animal diet, accurate measurement of dietary intake is also needed and requires specialized housing for most exact measurements of food intake. Given ethical considerations regarding single housing of animals, particularly rodents, it is essential to consider best practice for accurate measurement of intake.

Metabolism

Related to both the dose as well as the route of administration is whether the test component is metabolized similarly in the animal model compared to humans. If, for example, a compound requires delivery via injection, how does that alter the availability of the active compound and overall metabolism? Moreover, an important consideration is whether there are age- or sex-specific differences in how a supplement or nutraceutical is metabolized.

Stage of the life cycle

The stage of development when the intervention is introduced may modulate the strength and/or permanence of an effect. For nutritional programming studies in which the maternal or early life exposure is manipulated to determine the permanent effect at adulthood, the length of time to see an effect and safety aspects are key considerations. While such studies may be many months in duration or longer, measurement of a relevant biomarker or longitudinal measure, in the same animal, can strengthen the study design by reducing inter-animal variation. Moreover, longitudinal measures may capture differences with a test component that may not be present at endpoint but at one or more key developmental stages prior to endpoint. Nutritional programming effects may not always be permanent but may change throughout different stages of the life span.

As mentioned earlier, granting agencies require consideration of sex and gender within study designs in response to an intervention (Canadian Institutes of Health Research 2018; National Institutes of Health 2018). Inherent in such animal studies is also the need to understand age equivalency in humans, and may depend on specific outcomes of interest when establishing at what age a mouse, for example, represents a young or an aged adult. For example, in terms of bone development, trabecular bone structure in mice has been shown to peak at approximately 2 months of age in both an inbred strain (C57BL/6J) and outbred

stock (CD-1) and is thus an age that is representative of peak bone mass that occurs by early adulthood in humans (Glatt et al. 2007; Sacco et al. 2017). With respect to aging models, particularly in mice, it is important to consider differences in mechanisms of aging (Demetrius 2005). In summary, reporting how dose, route of administration, metabolism, and stage of life-cycle have been considered and/or controlled for in a study will strengthen the applicability of the findings to humans. Since many researchers use the same or similar models repeatedly to test various products, defining and characterizing the model system becomes more feasible.

High-quality studies with null or equivocal findings are publishable (and should be published)

It is important to be in the habit of trying to publish findings from all high-quality studies, regardless of the results. An example could include studies in which the effect of a supplement has been studied in terms of enhancing physical performance. While many poster presentations at scientific meetings that never actually get published may report no significant effect of the specific supplement, published papers may consistently report that the supplement does enhance performance. While such a situation is an example of publication bias, it is important to not contribute to this phenomenon. It is equally important that reviewers and journal editorial boards recognize that a novel and high-quality study should be published regardless of whether the study had equivocal findings.

Concluding remarks

Following the aspects discussed in this paper and highlighted in Tables 1 and 2 will lead to best practices, and most importantly, high-quality findings for use by relevant stakeholders. In the end, we strongly recommend that the various elements highlighted throughout this Horizons paper will increase the awareness of the significant before-, during-, and after-research due-diligence required to produce research of the highest quality. It is recognized that many scientists will not be able to meet all of these aspects, but researchers need to consider the points outlined throughout this Horizons paper and to recognize that those elements that are not met in their studies may be significant limitations.

Conflict of interest statement

The authors have no conflicts of interest to report.

Acknowledgements

Wendy E. Ward holds a Canada Research Chair in Bone and Muscle Development at Brock University; Elena M. Comelli holds the Lawson Family Chair in Microbiome Nutrition Research at the University of Toronto; and Stuart M. Phillips holds a Canada Research Chair in Skeletal Muscle Health in Aging at McMaster University.

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