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IOC consensus statement: dietary supplements and the high-performance athlete

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Dietary Supplements and the High-Performance Athlete

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Abstract

Nutrition usually makes a small but potentially valuable contribution to successful performance in elite athletes, and dietary supplements can make a minor contribution to this nutrition program. Nonetheless, supplement use is widespread at all levels of sport. Products described as supplements target different issues, including the management of micronutrient deficiencies, supply of convenient forms of energy and macronutrients, and provision of direct benefits to performance or indirect benefits such as supporting intense training regimens. The appropriate use of some supplements can offer benefits to the athlete, but others may be harmful to the athlete's health, performance, and/or livelihood and reputation if an anti-doping rule violation results. A complete nutritional assessment should be undertaken before decisions regarding supplement use are made. Supplements claiming to directly or indirectly enhance performance are typically the largest group of products marketed to athletes, but only a few (including caffeine, creatine, specific buffering agents and nitrate) have good evidence of benefits. However, responses are affected by the scenario of use and may vary widely between individuals because of factors that include genetics, the microbiome and habitual diet. Supplements intended to enhance performance should be thoroughly trialled in training or simulated competition before implementation in competition. Inadvertent ingestion of substances prohibited under the anti-doping codes that govern elite sport is a known risk of taking some supplements. Protection of the athlete's health and awareness of the potential for harm must be paramount, and expert professional opinion and assistance is strongly advised before embarking on supplement use.

Keywords: ergogenic aid, performance, sport nutrition, banned substance

Introduction

Dietary supplements are used by athletes at all levels of sport, reflecting the prevalence of their use in the wider society. About half of the adult US population uses some form of dietary supplements (Bailey et al., 2011) and, though there are regional, cultural and economic differences, a similar prevalence is likely in many other countries. Athletes describe a range of different reasons for their supplement choices (Fennell, 2004), and products that fit the description of "supplement" can target various roles within the athlete's performance plan. These include the maintenance of good health by contributing to the required intake of specific nutrients, the management of micronutrient deficiencies and the provision of energy and macronutrient needs that might be difficult to achieve through food intake alone. Other specific uses of supplements reported by athletes include direct performance enhancement or the indirect benefits that arise from the provision of support for hard training, the manipulation of physique, the alleviation of musculoskeletal pain, rapid recovery from injury, and enhancement of mood.

Some sporting bodies now support the pragmatic use of supplements that have passed a risk-vs-benefit analysis of being effective, safe and permitted for use, while also being appropriate to the athlete's age and maturation in their sport. This review summarises the issues faced by high performance athletes and their support team (coach, trainer, nutritionist, physician) when considering the use of supplements, with the goal of providing information to assist them to make informed decisions.

What is a supplement?

There is no single definition, either legal or within nutritional science, of what constitutes a dietary supplement. The US Congress, for example, in framing the 1994 Dietary Supplements Health and Education Act (DSHEA; https://ods.od.nih.gov/About/DSHEA_Wording.aspx), described a dietary supplement as:

> " . . . a product, other than tobacco, which is used in conjunction with a healthy diet and contains one or more of the following dietary ingredients: a vitamin, mineral, herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients."(supplements, 1994)

This definition is unsatisfactory, as it depends on whether or not a "healthy diet" is consumed. For the purposes of this overview, we define a dietary supplement as:

> A food, food component, nutrient, or non-food compound that is purposefully ingested in addition to the habitually-consumed diet with the aim of achieving a specific health and/or performance benefit.

Furthermore, we recognise that dietary supplements come in many forms, including:

a) Functional foods: foods enriched with additional nutrients or components outside their typical nutrient composition (e.g., mineral- and vitamin-fortified, as well as nutrient-enriched foods)

b) Formulated foods and sports foods; products providing energy and nutrients in a more convenient form than normal foods for general nutrition support (e.g. liquid meal replacements) or for targeted use around exercise (e.g., sports drinks, gels, bars)
c) Single nutrients and other components of foods or herbal products provided in isolated or concentrated forms
d) Multi-ingredient products containing various combinations of those products described above that target similar outcomes

Prevalence of, and rationale for, use by athletes

With such widespread use of supplements in the general population and with the specific focus of athletes on achieving peak performance, it is not surprising that a high prevalence of supplement use is reported in most surveys of athletes (Maughan et al., 2007). Comparisons between surveys are confounded by numerous factors: these include differences in the definition of what constitutes a dietary supplement; ability to capture irregular use; inappropriate sample selection; and the use of non-validated and non-standardized survey instruments (Garthe et al., 2017). Nevertheless, surveys generally suggest that supplement use:

a) Varies across different sports and activities
b) Increases with level of training/performance
c) Increases with age
d) Is higher in men than in women
e) Is strongly influenced by perceived cultural norms (both sporting and non-sporting)

Although athletes often consume supplements to take advantage of intended/claimed effects or benefits, a range of motives underpins supplement use (Garthe et al., 2017). For example, athletes use supplements:

a) To correct or prevent nutrient deficiencies that may impair health or performance
b) For convenient provision of energy and nutrients around an exercise session
c) To achieve a specific and direct performance benefit in competition
d) To gain a performance improvement indirectly accrued from outcomes such as allowing more effective training (i.e., higher intensity, greater volume), better recovery from training sessions, optimising mass and body composition, or reducing risks of injury and illness
e) For financial gain (sponsorship) or because products are provided free of charge
f) As a 'just in case' insurance policy
g) Because they know or believe that other athletes/competitors are using the supplement(s)

Some supplements may be used for multiple functions. Zinc, for example, may be taken with the aim of promoting wound healing and tissue repair (Prasad, 2014) or reducing the severity and duration of the symptoms of an upper respiratory tract infection (Solomons, 1998). Carbohydrate supplements are used to enhance performance in many events via the provision of fuel substrate (Stellingwerff et al., 2014), to support the immune system (Peake et al., 2017), or to improve bioavailability of other supplements, e.g., creatine (Steenge et al., 2000). Similarly, creatine supplementation may directly enhance performance in strength and power events, and can assist in training harder, gaining lean body mass or maintaining lean mass during periods of immobilisation after injury (Branch, 2003;

Gualano et al., 2012; Heaton et al., 2017). Decisions on supplement use therefore need to consider both the context of use and the specific protocol employed.

Assessing the evidence base for supplement use

Supplements target a range of scenarios of use, so different approaches are needed to assess their effectiveness. Supplements aimed at correcting nutrient deficiencies need to be judged on their ability to prevent or treat sub-optimal nutrient status, with the benefit accruing from the removal of the associated impairment of health, training capacity or performance. The effectiveness of sports foods might be hard to isolate when they are used within the general diet to meet everyday energy needs and nutrient targets. However, benefits may be more easily detected when they are specifically consumed before, during or after an event or training session to provide nutrients that are limiting for performance (e.g., to provide fuel for the muscle or brain) or to defend homeostasis (e.g., by replacing water and salt losses). Performance-enhancing supplements which are claimed to achieve direct or indirect benefits pose a greater challenge in terms of a sound evidence base. With only a few exceptions, there is a scarcity of research, and many of the available studies are not of sufficient quality to warrant their application to elite athletes.

Substantiating the claims made about performance supplements and sports foods is difficult (Burke et al., 2017). To various audiences, 'proof' comes in different forms. Figure 1 provides a proposed hierarchical model of the relative strength of the evidence provided by different information sources. However, most of the information around supplement efficacy in sport comes from models with the lowest rigour: anecdotes/observations from athletes; and scientific or mechanistic hypotheses that explain how a supplement might target a critical/limiting factor in performance, but with little-to-no evidence. Systematic reviews and meta-analyses, which synthesize the outputs of many studies to yield a conclusive statement of efficacy in a broad sense are at the top of the evidence hierarchy. While these summaries help to provide information about the general use of performance supplements, scientific trials that are properly controlled and well-conducted provide the basis for these reviews as well as an opportunity to address more specific questions about supplement applications. Thus, meta-analyses are a reflection only of the quality and quantity of the studies that are available for review, and may also be influenced by the inclusion and exclusion criteria applied to the available data.

The 'gold standard' for investigating the effects of supplements on sports performance is the prospective, randomised, controlled scientific trial, in which subjects are randomly allocated to receive either an experimental or placebo treatment (ideally in a double-blind manner) or crossed over to receive both treatments in counterbalanced order, under standardized conditions. Practical issues may cause some variations to ideal design, but sports scientists are encouraged, if they wish their results to be applicable to athletes in competition, to ensure that their studies include:

a) An adequate sample size and appropriate participant characteristics (e.g., event, training status, calibre) to allow the results to have statistical power and to be applicable to high performance athletes
b) Mimicking, as far as possible, the conditions (e.g., environment, nutrition preparation, event strategies) that exist in real-life competition
c) Standardization, to the extent that is possible, of variables that might influence the results

(e.g., pre-trial exercise and diet, environmental conditions, external encouragement or distraction). It is recognised that this conflicts to some extent with b above, and will limit the situations in which the results can be applied

d) Use of a protocol of supplement use (e.g., specific product, dose and timing of intake) that is likely to optimize any effects
e) An independent verification of the contents of the supplement under investigation to ensure that the product is truly unadulterated, both to ensure the integrity of the study and to avoid inadvertent doping positives if the subjects are athletes
f) Verification that the supplement was taken and induced a biological response (e.g., via muscle, blood, urine, or saliva sampling)
g) A performance protocol that is valid and sufficiently reliable to detect small but potentially meaningful changes/differences in performance outcomes.
h) Interpretation of results in light of the limitations of the study design and the change that would be meaningful to real-life sport

Given the specificity of the information that is required by some athletes and their support staff to assess the effectiveness of a supplement (e.g., related to a targeted event and its conditions, the specific individual, the combination with other performance strategies) it is unreasonable to expect that definitive evidence will always be available. Issues that are particularly under-researched and should be considered of high priority include measurement of performance in the field or under "real-life" conditions, investigation of the combined use of a number of supplements, and the repeated use of supplements as might occur in multi-day competition or when heats and finals occur close together. Scenarios that fall outside the scope of the available literature or practical research design may need to be interrogated by individual or small group case studies. Recommended methodologies for these studies include repeated baseline performances before the introduction of the supplement, or an alternating series of presentation and absence of the supplement (Maughan et al., 2017).

For the purposes of this overview, we rely primarily on studies of healthy adults that are relevant to athletes. We recognise that data from studies of elite athletes are almost entirely absent. We also recognise that mechanistic studies on animal and cell culture models are useful in identifying mechanisms, but a mechanism is not necessary to demonstrate an effect that may be meaningful to an athlete: what we think today to be the mechanism by which enhancement of performance or health occurs might be proved wrong by later studies. It must also be recognised that an individual's habitual diet can affect gene expression and their microbiota and these, in turn, can affect response to supplementation. While the variation in the genome between individuals is less than 0.01%, the variation in microbiota is significant (80-90%) and emerging data suggests that both these factors could affect athletic performance (Clark et al., 2017; Ribeiro et al., 2013). The following sections present an overview of the use of supplements to address different roles in sports nutrition, first by identifying the principles of use and then by examining some of the specific products that have a good or emerging evidence base to support this situation-specific use by athletes.

Supplements used to prevent or treat nutrient deficiencies

Many micronutrients play an important role in the regulation of processes that underpin sports performance, ranging from energy production to the manufacture of new cells and proteins. A frank

deficiency of one or more of these nutrients may lead to a measurable impairment of sports performance – either directly or by reducing the athlete's ability to train effectively (e.g., iron deficiency anaemia) or to stay free from illness or injury (e.g., impact of vitamin D deficiency on bone health). Athletes are not immune to the inadequate eating practices or the increased nutrient loss/requirements found in some members of the general population and may even be at greater risk of deficiencies because of increased nutrient turnover or increased losses. A further challenge is the occurrence of sub-clinical deficiencies that may be both hard to assess (i.e., they lack a clear metric or universal threshold of what is "adequate") as well as being subject to debate about whether there is an "optimal" level for performance that differs from the usual classification systems of nutrient status (deficiency/sub-clinical deficiency/normal). When sub-optimal nutritional status is diagnosed, the use of a nutrient supplement to reverse or prevent further deficiencies can contribute to the overall treatment plan.

Nutritional assessment of an athlete involves systematic protocols that obtain, verify and interpret evidence of nutrition-related problems, as well as their causes and significance. A complete assessment should ideally include a detailed medical and nutritional history, diet evaluation, anthropometry and body composition analysis, and biochemical testing (Larson-Meyer et al., 2017). Unlike the *ad hoc* use of nutrient supplements taken by athletes as an insurance policy, this nutritional assessment should ensure that the athlete:

a) Can address the factors that led to the nutrient deficiency, including ensuring that the athlete's nutrition plan is adequate in energy, macro- and micronutrients
b) Would benefit from an acute or chronic period of supplementation to correct and/or prevent a nutrient deficiency and can understand the appropriate supplementation protocol
c) Is not at risk for health issues associated with supplement use, including interactions with prescription or over-the-counter medications
d) Has a baseline assessment against which future measures to assess progress can be compared

Nutrients that often need to be supplemented under these circumstances include iron, calcium, and Vitamin D (Table 1). Iodine (for those living in areas with low levels of iodine in foods or not using iodised salt), folate (for women who might become pregnant) and vitamin B12 (for those following a vegan or near-vegan diet) supplementation may be warranted in these population groups, but these considerations do not apply specifically to athletes.

Supplements (sports foods) used to provide a practical form of energy and nutrients

Sports nutrition guidelines provide clear recommendations for targeted intake of energy and nutrients in a variety of contexts. In some situations, it is impractical for an athlete to consume "everyday" or normal foods to meet their nutrition goals due to issues around preparation or storage, ease of consuming the foods due to training schedules, gut comfort, or the challenge of meeting nutrient targets within the available energy budget. In these cases, sports foods can provide a convenient, albeit usually more expensive, alternative option for meeting these nutrient goals. Table 2 provides an overview of products that fit this description and their more common evidence-based uses.

Supplements that directly improve sports performance

A few performance-enhancing supplements might, at the present time, be considered to have an adequate level of support to suggest that marginal performance gains may be possible. These supplements include: caffeine, creatine (in the form of creatine monohydrate), nitrate, sodium bicarbonate, and possibly also β-alanine. The mechanisms of action, typical dose, potential performance benefits, and known side-effects of each of these supplements are summarised in Table 3. Performance-enhancing supplements should be considered only where a strong evidence-base supports their use as safe, legal and effective and, ideally, after adequacy of sports nutrition dietary practices is ensured. Whenever possible, supplements should be trialled thoroughly by the athlete in training that mimics the competition milieu as closely as possible before committing to use in a competition setting. Athletes should do a careful risk analysis to see if the marginal gains would outweigh the risk of inadvertent doping due to contamination.

Supplements that improve performance indirectly

Many dietary supplements claim to enhance performance indirectly – by supporting the athlete's health, body composition, and their ability to train hard, recovery quickly, adapt optimally, avoid or recover from injury, and tolerate pain or soreness. Illness is a major problem for athletes if it interrupts training or occurs at a critical time, such as during a selection event or a major competition. Susceptibility to illness is increased in situations where athletes are involved in a high volume of training or competition and either intentionally or unintentionally experience deficits in energy intake (e.g., weight-loss diets), macronutrient intake (e.g. train-low or sleep-low-carbohydrate) and micronutrient status (e.g., vitamin D insufficiency in the winter) (Bermon et al., 2017). Athletes might benefit from nutritional supplements to support immunity in these scenarios and at other times when they are either susceptible to infection (e.g., during the common cold season and after long-haul travel) or suffering from an infection. Table 4 summarises evidence for some of the commonly promoted "immune supportive" supplements, noting that the most promising candidates to assist in the prevention or treatment of upper respiratory symptoms are vitamin D and probiotics. Vitamin C during periods of heavy exertion and zinc lozenges at the onset of symptoms may be useful, but high doses of single antioxidants, particularly vitamin C and E, may blunt exercise-induced training adaptations (Nikolaidis et al., 2012; Paulsen et al., 2014; Powers et al., 2011). Probiotic supplementation may reduce the incidence of travellers' diarrhoea and gastrointestinal infection. Cochrane reviews have noted the low quality of many studies on nutritional supplements that are claimed to support immunity; specifically, small samples, poor controls and unclear procedures for randomisation and blinding were commonplace (Hao et al., 2015; Singh et al., 2013). Clearly, there is a pressing need for randomized controlled trials in high-level athletes with sufficient participant numbers, rigorous controls and procedures, appropriate supplementation regimens, and clinically meaningful measures of immunity.

Supplements that assist an athlete to train harder, recover more quickly and prevent injury or accelerate return to play when injury does occur can obviously enhance the athlete's preparation and, indirectly, their competition outcomes. Many products claim to provide benefits of this nature; Table 5 summarises the evidence for some of the most popular compounds. Finally, the manipulation of body composition, including gaining lean (muscle) mass and reducing body fat levels, can contribute to performance in many events. This explains the large number of "weight gainers" and "fat burners" in the general and sports supplement market, though many of these are

prohibited in sport. Protein is considered to be the premier ingredient in weight gain-promoting supplements and evidence-based reviews conclude that protein is effective at promoting lean mass gain when combined with resistive exercise (Hector et al., 2017). Evidence of efficacy for 'fat burning' supplements is far from conclusive, however, and there is a complete absence of evidence for the effectiveness of the vast majority of supplements marketed in this category. Table 6 summarizes the evidence for some of the most common ingredients or products of this type (Hector et al., 2017).

Adverse effects

Adverse effects from the use of supplements may arise from a number of factors, including the safety and composition of the product *per se* and inappropriate patterns of use by athletes. Poor practices by athletes include the indiscriminate mixing and matching of many products without regard to total doses of some ingredients or problematic interactions between ingredients. Even commonly-used products may have negative side-effects, especially when used outside the optimal protocol. For example, iron supplementation in those with already adequate iron stores can result in symptoms that may begin with vomiting, diarrhoea, and abdominal pain and develop to haemochromatosis and liver failure (Mettler et al., 2010). Bicarbonate may cause gastrointestinal distress when ingested in amounts sufficient to enhance performance; this can impair rather than improve performance and may counteract the benefits of other supplements taken at the same time (Carr et al., 2011a). The "more is better" philosophy, when applied to caffeine, may result in side effects, including nausea, anxiety, accelerated heart rate and insomnia, that outweigh the performance benefits (Peeling et al., 2017). Unwanted outcomes become more common with caffeine doses ≥ 9 mg/kg body mass, but maximal benefits are usually achieved with intakes of 3-6 mg/kg (Burke, 2008). The possibility of more serious outcomes is illustrated by adverse, and potentially fatal, responses in two separate incidents in which very large doses (up to 30 grams) of caffeine were administered to healthy volunteers participating in laboratory studies (http://www.telegraph.co.uk/news/2017/01/25/university-fined-400k-students-taking-part-caffeine-experiment/). These incidents were due to errors in the dose calculation: if this can happen in a University research environment with supposed oversight by experienced staff, the potential clearly exists for similar errors by athletes and coaches.

Athletes and members of their support team should be aware of the regulations that govern the manufacture and marketing of supplements. According to the Dietary Supplements Health and Education Act 1994 (DSHEA; https://ods.od.nih.gov/About/DSHEA_Wording.aspxhttps://ods.od.nih.gov/About/DSHEA_Wording.aspx) passed by US Congress, nutritional supplements sold in the US that do not claim to diagnose, prevent or cure disease are not subject to regulation by the Food and Drugs Administration (FDA). Similar regulations apply in most other countries, where supplements are regulated in the same way as food ingredients and are therefore not subject to the stringent regulations that are applied to the pharmaceutical industry. This means that there is no requirement to prove claimed benefits, no requirement to show safety with acute or chronic administration, no quality assurance of content, and liberal labelling requirements. It is well recognised that there are problems with some of the dietary supplements on sale, but the options open to those responsible for food safety are limited by the legislation that applies. The FDA regularly uses its powers to recall products in breach of the regulations, though they fully admit that their resources are insufficient for comprehensive

monitoring, and recalls generally occur only after many people are harmed (https://www.fda.gov/food/recallsoutbreaksemergencies/recalls/default.htm): they have recently recalled supplement products containing excessive doses of Vitamins A, D, B6 and selenium because of potentially toxic levels of these components. Examples of product complaints have included the presence of impurities, including lead, broken glass and metal fragments, because of the failure of the producers to observe good manufacturing practice. The risk of gastrointestinal upset because of poor hygiene during the production and storage of products is also of concern. Although this may seem a minor inconvenience, and of similarity to food safety issues, the coincidence of problems around a crucial training period or competitive event may significantly interfere with athlete's performance goals. It should be noted, though, that all of these problems are also regularly reported in normal foods.

Some supplements may actually cause harm to health, but these can be difficult to identify, and products are usually withdrawn only after a significant number of adverse events have occurred. For example, a range of products containing hydroxycitric acid was withdrawn from sale, but only after they were linked with the death of one consumer and with a substantial number of other cases of liver toxicity, cardiovascular problems and seizures (https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm155817.htm). The extent of the problem is illustrated by the fact that, in the US in 2015 approximately 23,000 emergency department visits annually are reported to be associated with dietary supplement use (Geller et al., 2015). This figure can be viewed as substantial, or it can be seen as small compared to the total number of adverse responses associated with the use of medications (Maughan et al., 2017). However, minor problems that do not require acute medical aid may still be sufficient to interrupt training or prevent participation, so this statistic probably underestimates the risk for athletes.

The biggest concern for athletes who compete under an anti-doping code (usually the World Anti-Doping Code, as published by the World Anti-Doping Agency [WADA]) is that supplements can contain prohibited substances that result in an anti-doping rule violation (ADRV). Athletes - and their support teams - may be at risk for an ADRV if there is evidence that they have used or attempted to use products containing ingredients on the Prohibited List (www.wada.ama.org). A common problem is the recording of an adverse analytical finding (AAF) of a prohibited substance in a urine sample ("positive drug test") as a result of supplement use (Maughan, 2005). Millions of athletes may be subject to anti-doping testing, although these are mostly professional, national or international level athletes. For these athletes in particular, even if the ingestion of the prohibited substance was unintentional, the rules of strict liability within the World Anti-Doping Code mean that an AAF will be recorded, and may mean the loss of medals won or records set and financial sanctions as well as temporary or permanent suspension from competition. It also damages the athlete's reputation and may lead to loss of employment and income through failed sponsorship opportunities. Where there has been deliberate cheating or benefit accrued from the use of a prohibited substance, these penalties seem entirely appropriate, but it is undoubtedly true that some ADRVs can be attributed to the innocent ingestion of prohibited substances in dietary supplements, with catastrophic results for the athlete.

One cause of an AAF arising from supplement use relates to an athlete's failure to read product labels to recognize the presence of prohibited substances. Many athletes consider supplements to be "natural" or "regulated" and therefore safe. Other athletes are confused by the number of

chemical names for some prohibited substances and thus fail to recognise them on the product label. However, the most worrying cause of an inadvertent AAF is the use of supplements that contain prohibited substances as an undeclared ingredient or contaminant. Since the publication of the seminal study on the presence of undeclared prohibited substances in supplements (Geyer et al., 2004), there have been numerous reports of supplement contamination (Maughan, 2005). Recent reviews suggest that this problem remains (Martinez-Sanz et al., 2017)(http://www.informed-sport.com/news/australian-supplements-survey-highlights-need-testing). It is difficult to gain a perspective of the true prevalence of supplement contamination. Although the original study reported that ~15% of more than 600 products acquired from around the world contained undeclared prohomones (Geyer et al., 2004), this and other investigations rarely include a truly random sample of the supplements and sports foods used by athletes. Some individual products or categories of products can be considered inherently more at risk of contamination due to the country of origin, the manufacturer, the type of product and the range of declared ingredients (https://www.usada.org/substances/supplement-411/). Nevertheless, it should also be recognised that common supplements, including Vitamin C, multivitamins and minerals, have also been found, albeit rarely, to contain prohibited substances (Geyer et al., 2008). The range of prohibited substances found as undeclared ingredients in supplements now includes products from many sections of the World Anti-Doping Code, including stimulants, anabolic agents, selective androgen receptor modulators, diuretics, anorectics and β2 agonists (Martinez-Sanz et al., 2017).

In some cases, the amount of the prohibited substance in a supplement may be high, even higher than the normal therapeutic dose. For example, Geyer et al (Geyer et al., 2002) reported the analysis of metandienone (commonly known as methandrostenolone or Dianabol) in high amounts in a "body building" supplement from England. The recommended amount of the supplement would have supplied a dose of 10-43 mg; in comparison, the typical therapeutic dose of this drug was 2.5-5 mg/d (Goodman et al., 1975), though its medical use has been discontinued in most countries for many years. This amount would certainly have a potent anabolic effect, but would likely produce serious side effects, including psychiatric and behavioural effects and significant damage to a range of body systems including the liver (Solimini et al., 2017). Unlike many of the earlier cases involving steroids related to nandrolone and testosterone, this is not a trivial level of contamination and raises the possibility of deliberate adulteration of the product with the intention of producing a measurable effect on muscle strength and muscle mass. Most reports of adverse health outcomes resulting from supplement use have focussed on liver problems of varying degrees of severity, but other organs are also affected. One epidemiological case-control study (Li et al., 2015) examined the association between use of muscle-building supplements and testicular germ cell cancer (TGCC) risk, with 356 TGCC cases and 513 controls from the Eastern United States. The odds ratio (OR) for the use of muscle-building supplements in relation to risk of TGCC was elevated (OR=1.65, 95% confidence interval (CI): 1.11–2.46) with significantly stronger associations for early users and longer periods of use.

Ironically, supplements that are contaminated with extremely small amounts of prohibited substances – too low to have any physiological effect – may still cause a positive doping outcome. For instance, ingestion of 19-norandrostenedione, a precursor of nandrolone, will result in the appearance in the urine of 19-norandrosterone, the diagnostic metabolite for nandrolone. If the urinary concentration of 19-norandrosterone exceeds 2 ng/mL, an AAF is recorded (Baume et al.,

2004). The addition of as little as 2.5µg of 19-norandrostenedione to a supplement, can result in a urinary concentration of 19-norandrosterone that exceeds this threshold (Watson et al., 2009). These amounts are close to the limits of detection of the analytical methods currently applied to the analysis of dietary supplements, and are far below the levels of contamination deemed acceptable from a health and safety perspective.

Various efforts are being made to address the problems including the use of third-party auditing activities to identify products that athletes may consider to be at "low risk" of containing prohibited substances. There can be no absolute guarantee that any product is entirely safe, but these schemes do help the athlete to manage the risk. Athletes contemplating the use of dietary supplements should consider very carefully whether the possible benefits outweigh the risks of a doping offence that might end their career.

Practical implications and decision tree

Dietary supplements are an established part of the landscape of modern sport and are likely to remain so. Athletes who take supplements often have no clear understanding of the potential effects of supplements they are using, but supplements should be used only after a careful cost-benefit analysis has been conducted. On one side of the decision tree are the rewards, the most obvious of which are correction of nutrient deficiencies, achievement of nutritional goals, or enhancement of one or another physiological/biochemical function to directly or indirectly improve performance. On the other side lie the costs, the possibility of using an ineffective supplement, the possible risks to health, and the potential for an ADRV. A flow of questions that could be posed in reaching an informed decision is shown in Figures 2 and 3.

In deciding whether to use a supplement, athletes should consider all aspects of their maturation in, and preparation for, their event to ensure that the supplement under consideration provides an advantage that no other strategy can address. Whether the supplement is practical to use should also be assessed: is the product available, affordable, tolerated and compatible with the athlete's other goals? The input of the athlete's coaching team and medical/science support network is important. Athletes who do not have regular access to such a network should consider decisions around supplement use as an important reason to consult an independent sports nutrition expert as well as a physician. Analysis of the evidence around the effectiveness of supplements and their safety is often difficult. A complete nutritional assessment may provide an appropriate justification for the specific use of nutritional supplements and sports foods. For a small number of sports supplements, there is good evidence of a performance effect or indirect benefit for some athletes in some specific situations with little or no risk of adverse outcomes (Peeling et al., 2017; Rawson et al., 2017b). Professional advice is often important in ensuring that the athlete is sufficiently knowledgeable about the appropriate protocol for use of these supplements, but individual athletes may respond very differently to a given supplement, with some exhibiting a markedly beneficial effect while others experience no benefit or even a negative effect on performance. Furthermore, the situation in which the athlete wishes to use the supplement may differ in important ways from its substantiated use. Repeated trials may be necessary to establish whether a true effect, rather than just random variation, is seen in response to use of any novel intervention. Some trial and error may also be involved in fine tuning the supplement protocol to suit the needs of the specific situation of use or the individual athlete.

Evidence to support the effectiveness and safety of many of the supplements targeted at athletes, however, is largely absent. There seems to be little incentive for those selling supplements to invest the substantial sums needed to undertake detailed scientific evaluation of their products. Even where some evidence does exist, it may not be relevant to the high-performance athlete because of limitations in the study design (such as the specificity of the exercise tests), the study population, or the context of use. Failure to verify the composition of the supplements used may also give misleading results. It seems sensible to exercise caution when using supplements, as any compound that has the potential to enhance health or exercise performance by altering physiological function must also have the potential for adverse effects in some individuals. Athletes should see good evidence of a performance or other benefit, and should be confident that it will not be harmful to health, before accepting the financial cost and the health or performance risks associated with any supplement. Finally, the athlete should be sure, if supplements or sports foods are to be used, that they have undertaken due diligence to source products that are at low risk of containing prohibited substances (https://www.usada.org/substances/supplement-411/).

Conclusion

Dietary supplements can play a small role in an athlete's sports nutrition plan, with products that include essential micronutrients, sports foods, performance supplements and health supplements all potentially providing benefits. Some supplements, when used appropriately, may help athletes to meet sports nutrition goals, train hard, stay healthy and injury free. A few supplements can directly enhance competition performance. However, it takes considerable effort and expert knowledge to identify which products are appropriate, how to integrate them into the athlete's sports nutrition plan, and how to ensure that any benefits outweigh the possible negative side-effects, including the potential for an ADRV. A strict risk-benefit analysis involving a decision tree approach to the effectiveness, safety and risks should identify the small number of products that may benefit the athlete. Such an analysis requires the input of a well-informed sports nutrition professional.

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Table 1. Examples of micronutrients often requiring supplementation in athletes (see Larson-Meyer et al (2018) for additional information).

Micronutrient	Overview	Diagnosis and outcomes of insufficiency	Protocols and outcomes of supplementation
Vitamin D	Important in regulation of gene transcription in most tissues so insufficiency/deficiency affects many body systems (Hossein-nezhad et al., 2013). Many athletes are at risk of insufficiency at various times throughout the year (Larson-Meyer et al., 2010).	No consensus over the serum 25-hydroxyvitamin D concentration (the marker of vitamin D status) that defines deficiency, insufficiency, sufficiency and a tolerable upper limit (UL). The need to supplement depends on UVB exposure and skin type.	Supplementation of between 800 IU and 1,000-2,000 IU/day is recommended to maintain status for the general population. Supplementation guidelines are not yet established in athletes. Short-term, high dose supplementation which include 50,000 IU/week for 8-16 weeks or 10,000 IU/day for several weeks may be appropriate for restoring status in deficient athletes. Careful monitoring is necessary to avoid toxicity (Heaney, 2008).
Iron	Suboptimal iron status may result from limited iron intake, poor bioavailabiity and/or inadequate energy intake, or excess iron need due to rapid growth, high-altitude training, menstrual blood loss, foot-strike haemolysis, or excess losses in sweat, urine or faeces (Thomas et al., 2016).	Several measures performed simultaneously provide the best assessment and determine the stage of deficiency. Recommended measures: Serum Ferritin, Transferrin saturation, Serum Iron, Transferrin receptor Zinc protoporphyrin, Haemoglobin, Haematocrit,	Athletes who do not maintain adequate iron status may need supplemental iron at doses > than their RDA (i.e., >18 mg/d for women and >8 mg/d for men). Athletes with Iron deficiency requires clinical follow-up which may include supplementation with larger doses of oral iron supplementation along with improved dietary iron intake (Thomas et al., 2016). Numerous oral iron preparations are available and most are equally effective as long as they are taken (Moretti et al., 2015). High dose iron supplements, however, should be not taken unless iron deficiency is present.

		Mean corpuscular volume (Gibson, 2005).	
Calcium	Avoidance of dairy products and other calcium-rich foods, restricted energy intake and/or disordered eating increases risk of suboptimal calcium status (Thomas et al., 2016).	No appropriate indicator of calcium status. Bone mineral density scan may be indicative of chronic low calcium intake but other factors including suboptimal vitamin D status and disordered eating are also important.	Calcium intakes of 1,500 mg/day and 1,500 to 2,000 IU vitamin D are recommended to optimize bone health in athletes with low energy availability or menstrual dysfunction (Thomas et al., 2016).

Note: indiscriminate supplementation with any of the above nutrients is not recommended. Deficiencies should first be identified through nutritional assessment, which includes dietary intake and the appropriate blood or urinary marker, if available.[17]

Table 2. Summary of common sports foods and functional foods used by athletes. Add reference to Currell et al here

Sports Food	Form	Typical composition	Common sports-related use
Sports drink	Powder or ready to drink liquid	5–8 % CHO 10–35 mmol/L sodium 3–5 mmol/L potassium	Simultaneous delivery of fluid + CHO during exercise Post-exercise rehydration and refuelling
Energy drink	Ready to drink liquid or concentrated shot	Carbohydrate, especially in typical ready to drink varieties Caffeine Note: May contain taurine, B vitamins and other ingredients with variable supporting evidence and some level of concern	Pre-exercise caffeine supplement Carbohydrate and caffeine intake during exercise
Sports gel or sports confectionery	Gel: 30–40 g sachets Confectionery: Jelly–type confectionary (generally in pouch of ~ 40–50 g)	~25 g CHO per sachet or ~ 5 g CHO per confectionery piece Some contain caffeine or electrolytes	Carbohydrate intake during exercise
Electrolyte replacement supplements	Powder sachets or tablets	50–60 mmol/L sodium 10–20 mmol/L potassium Typically, low carbohydrate (2-4 g/100 mL)	Rapid rehydration following dehydration undertaken for weight-making Replacement of large sodium losses during ultra-endurance activities Rapid post-exercise rehydration following moderate to large fluid and sodium deficits
Protein supplement	Powder (mix with water or milk) or ready to drink liquid Protein-rich bar, usually low in CHO	Provides 20-50 g protein in a single serve from high quality types of animal (whey, casein, milk, egg) or vegetable (e.g., soy) origin	Post-exercise recovery following key training sessions or events where adaptation requiring protein synthesis is desired Achievement of increase in lean mass during growth or response to resistance training Portable nutrition for busy schedule or travel

		Note: may contain other ingredients, some of which are not evidence based and may increase the risk of contamination	
Liquid meal supplement	Powder (mix with water or milk) or ready to drink liquid	1–1.5 kcal/mL: 15–20% protein and 50–70% CHO Low to moderate fat Vitamins/minerals: 500–1000 mL supplies RDI/RDAs	Supplement high-energy diet (especially during heavy training/competition or weight gain) Low-bulk meal replacement (especially pre-event meal) Post-exercise recovery (CHO and protein) Portable nutrition for busy schedule or travel
Sports bar	Bar	40–50 g CHO 5–10 g protein Usually low in fat and fibre Vitamins/minerals: 50–100% of RDA/RDIs Note: may contain other ingredients, some of which are not evidence-based and may increase the risk of contamination	CHO source during exercise Post-exercise recovery—provides CHO, protein and micronutrients Portable nutrition for busy schedule or travel
Protein-enhanced food	Milk, yoghurt, ice cream, cereal bars and other food forms	Increased protein content from normal food variety achieved by adding protein sources or filtration of water from product Typically allows normal portion to provide ~ 20 g protein to meet sports nutrition target	Value added food able to achieve protein target for post-exercise use or to improve protein content of other meals and snacks in athlete's diet

Table 3. Supplements with good to strong evidence of achieving benefits to performance when used in specific scenarios.

Caffeine	
Overview	Caffeine is a stimulant that possesses well-established benefits for athletic performance across endurance-based situations, and short-term, supramaximal and/or repeated sprint tasks.
Mechanism	Adenosine receptor antagonism; increased endorphin release; improved neuromuscular function; improved vigilance and alertness; reduced the perception of exertion during exercise (Burke, 2008; Spriet, 2014).
Protocol of use	3-6 mg/kg of body mass (BM), in the form of anhydrous caffeine (i.e., pill or powder form), consumed ~60 min prior to exercise (Ganio et al., 2009). Lower caffeine doses (<3 mg/kg BM, ~200 mg), provided both before and during exercise; consumed with a CHO source (Spriet, 2014).
Performance Impact	Improved endurance capacity such as exercise time to fatigue (French et al., 1991), and endurance-based time-trial (TT) activities of varying duration (5-150 min), across numerous exercise modalities [i.e., cycling, running, rowing, and others; (Ganio et al., 2009)]. Low-doses of caffeine (100-300 mg) consumed during endurance exercise (after 15-80 min of activity) may enhance cycling TT performance by 3-7 % (Paton et al., 2015; Talanian et al., 2016). During short-term, supramaximal and repeated sprint tasks, 3-6 mg/kg BM of caffeine taken 50-60 min before exercise results in performance gains of > 3% for task completion time, mean power output, and peak power-output during anaerobic activities of 1-2 min in duration (Wiles et al., 2006), and of 1-8% for total work output and repeat sprint performances during intermittent team game activity (Schneiker et al., 2006; Wellington et al., 2016).
Further considerations and potential side-effects	Larger caffeine doses (≥9 mg/kg BM) do not appear to increase the performance benefit (Bruce et al., 2000), and are more likely to increase the risk of negative side-effects, including nausea, anxiety, insomnia and restlessness (Burke, 2008). Lower caffeine doses, variations in the timing of intake before and/or during exercise, and the need for (or lack thereof) a caffeine withdrawal period should be trialled in training prior to competition use Caffeine consumption during activity should be considered concurrent with carbohydrate (CHO) intake for improved efficacy (Talanian et al., 2016). Caffeine is a diuretic, promoting increased urine flow, but this effect is small at the doses that have been shown to enhance performance (Maughan et al., 2003).
Creatine	

Overview	Creatine loading can acutely enhance the performance of sports involving repeated high-intensity exercise (e.g. team sports), as well as the chronic outcomes of training programs based on these characteristics (e.g., resistance or interval training), leading to greater gains in lean mass and muscular strength and power (Rawson et al., 2007; Volek et al., 2004).
Mechanism	Supplementation increases muscle creatine stores, augmenting the rate of PCr resynthesis; thereby enhancing short-term, high-intensity exercise capacity (Buford et al., 2007) and the ability to perform repeated bouts of high-intensity effort
Protocol of use	Loading-phase: ~20 g/day (divided into 4 equal daily doses), for 5-7 days (Lanhers et al., 2017) Maintenance-phase: 3-5 g/day (single dose) for the duration of the supplementation period (Hultman et al., 1996a). Note: concurrent consumption with a mixed protein/CHO source (~50 g of protein and CHO) may enhance muscle creatine uptake via insulin stimulation (Steenge et al., 2000).
Performance Impact	Enhanced maximum isometric strength (Maganaris et al., 1998) and the acute performance of single and repeated bouts of high-intensity exercise (<150 s duration); most pronounced effects evident during tasks <30 s (Branch, 2003; Lanhers et al., 2017). Chronic training adaptations include lean mass gains and improvements to muscular strength and power (Rawson et al., 2007; Volek et al., 2004). Less common: Enhanced endurance performance resulting from increased/improved protein synthesis, glycogen storage and thermoregulation (Cooper et al., 2012; Kreider et al., 2017). Potential anti-inflammatory and anti-oxidant effects are noted (Deminice et al., 2013).
Further considerations and potential side-effects	No negative health effects are noted with long-term use (up to 4 years) when appropriate loading protocols are followed (Schilling et al., 2001). A potential 1-2 kg body mass increase after creatine loading [primarily as a result of water retention (Deminice et al., 2013; Powers et al., 2003)], may be detrimental for endurance performance or in events where the body mass must be moved against gravity (e.g., high jump, pole vault) or where athletes must achieve a specific body mass target.
Nitrate	
Overview	Dietary nitrate (NO_3^-) is a popular supplement that has been commonly investigated to assess any benefits for prolonged submaximal exercise (Bailey et al., 2009) and high-intensity, intermittent, short-duration efforts (Thompson et al., 2015; Wylie et al., 2016).
Mechanism	Enhances Nitric Oxide (NO) bioavailability via the NO_3^--nitrite-NO pathway, playing an important role in the modulation of skeletal muscle function (Jones, 2014a).

	Nitrate augments exercise performance via an enhanced function of type II muscle fibres (Bailey et al., 2015); a reduced ATP cost of muscle force production; an increased efficiency of mitochondrial respiration; an increased blood flow to the muscle; a decrease in blood flow to VO_2 heterogeneities (Bailey et al., 2010).
Protocol of use	High nitrate containing foods include leafy green and root vegetables, including spinach, rocket salad, celery and beetroot Acute performance benefits are generally seen within 2-3 h following a NO_3^- bolus of 5-9 mmol (310-560 mg) (Hoon et al., 2014). Prolonged periods of NO_3^- intake (>3 days) also appear beneficial to performance (Thompson et al., 2016; Thompson et al., 2015), and may be a positive strategy for highly-trained athletes, where performance gains from NO_3^- supplementation appear harder to obtain (Jones, 2014b).
Performance Impact	Supplementation has been associated with improvements of 4-25% in exercise time to exhaustion and of 1-3% in sport-specific time trial performances lasting <40 min in duration (Bailey et al., 2015; McMahon et al., 2016). Supplementation is proposed to enhance type II muscle fibre function (Bailey et al., 2015), resulting in the improvement (3-5%) of high-intensity, intermittent, team-sport exercise of 12-40 min in duration (Thompson et al., 2015; Wylie et al., 2016). Evidence is equivocal for any benefit to exercise tasks lasting <12 min (Reynolds et al., 2016; Thompson et al., 2016).
Further considerations and potential side-effects	The available evidence suggests there appear to be few side-effects or limitations to nitrate supplementation There may exist the potential for GI upset in susceptible athletes, and should therefore be thoroughly trialled in training There appears to be an upper limit to the benefits of consumption [i.e., no greater benefit from 16.8 mmol (1,041 mg) vs. 8.4 mmol (521 mg); (Wylie et al., 2013)]. Performance gains appear harder to obtain in highly-trained athletes (Jones, 2014b).
Beta Alanine	
Overview	Beta Alanine augments intracellular buffering capacity, having potential beneficial effects on sustained high-intensity exercise performance.
Mechanism	A rate-limiting precursor to the endogenous intracellular (muscle) buffer, carnosine; the immediate defence against proton accumulation in the contracting musculature during exercise (Lancha Junior et al., 2015). Chronic, daily supplementation of beta-alanine increases skeletal muscle carnosine content (Saunders et al., 2016).
Protocol of use	Daily consumption of ~65 mg/kg BM, ingested via a split-dose regimen (i.e. 0.8-1.6 g every 3-4 h) over an extended supplement time frame of 10-12 weeks (Saunders et al., 2016).
Performance Impact	Small, but potentially meaningful performance benefits (~0.2-3%) during both continuous and intermittent exercise tasks of 30 s to 10 min in duration (Baguet et al., 2010; Chung et al., 2012; Saunders et al., 2016).

Further considerations and potential side-effects	A positive correlation between the magnitude of muscle carnosine change and performance benefit remains to be established (Saunders et al., 2016). Large inter-individual variations in muscle carnosine synthesis have been reported (Nassis et al., 2016). The supplement effectiveness appears harder to realise in well-trained athletes (Bellinger, 2014). There is a need for further investigation to establish the practical use in various sport-specific situations (Hobson et al., 2012; Saunders et al., 2016). Possible negative side-effects include skin rashes and/or transient paraesthesia.
Sodium Bicarbonate	
Overview	Sodium Bicarbonate augments extracellular buffering capacity, having potential beneficial effects on sustained high-intensity exercise performance.
Mechanism	Acts as an extracellular (blood) buffer, aiding intracellular pH regulation by raising the extracellular pH, and HCO3- concentrations (Katz et al., 1984; Lancha Junior et al., 2015). The resultant pH gradient between the intracellular and extracellular environments leads to efflux of H+ and La- from the exercising muscle (Katz et al., 1984; Mainwood et al., 1975).
Protocol of use	Single acute NaHCO3 dose of 0.2-0.4 g/kg BM, consumed 60-150 min prior to exercise (Carr et al., 2011b; Siegler et al., 2012) Alternative strategies include: Split doses (i.e., several smaller doses giving the same total intake) taken over a 30-180 min time period (Lambert et al., 1993). Serial-loading with 3-4 smaller doses per day for 2-4 consecutive days prior to an event (Burke, 2013; Douroudos et al., 2006; Mc Naughton et al., 2001).
Performance Impact	Enhanced performance (~2%) of short-term, high-intensity sprints lasting ~60 s in duration, with a reduced efficacy as the effort duration exceeds 10 min (Carr et al., 2011b)
Further considerations and potential side-effects	Well-established GI distress may be associated with this supplement Strategies to minimise GI upset include: Co-ingestion with a small, carbohydrate rich meal (~1.5 g/kg BM carbohydrates) (Carr et al., 2011c); The use of sodium citrate as an alternative (Requena et al., 2005) Split dose or stacking strategies (Burke, 2013; Douroudos et al., 2006; Mc Naughton et al., 2001) Given the high potential for GI distress, thorough investigation into the best individualised strategy is recommended prior to use in a competition setting.

Table 4. Nutritional supplements for immune health in athletes: proposed mechanism of action and evidence for efficacy.

Supplement	**Proposed Mechanism of Action**	**Evidence for Efficacy**
Vitamin D	An essential fat-soluble vitamin known to influence several aspects of immunity, particularly innate immunity (e.g., expression of antimicrobial proteins). Skin exposure to sunlight accounts for 90% of the source of vitamin D.	Moderate support. Evidence for deficiency in some athletes and soldiers, particularly in the winter (decreased skin sunlight exposure). Deficiency has been associated with increased URS. Recommend 1,000 IU/day D_3 autumn-spring to maintain sufficiency. Further support required (He et al., 2016).
Probiotics	Probiotics are live microorganisms which when administered orally for several weeks, can increase the numbers of beneficial bacteria in the gut. This has been associated with a range of potential benefits to gut health, as well as modulation of immune function.	Moderate support in athletes with daily dose of ~10^{10} live bacteria; Cochrane review of 12 studies (n=3720) shows ~50% decrease in URS incidence and ~2 d shortening of URS; minor side effects. More evidence is required supporting efficacy to reduce gastrointestinal distress and infection, e.g., in a travelling athlete. (Gleeson et al., 2011; Hao et al., 2015).
Vitamin C	An essential water-soluble antioxidant vitamin that quenches ROS and augments immunity. Reduces interleukin-6 and cortisol responses to exercise in humans.	Moderate support for 'preventing URS'. Cochrane review of 5 studies in heavy exercisers (n=598) shows ~50% decrease in URS taking vitamin C (0.25–1.0 g/day). Further support required. Unclear if antioxidants blunt adaptation in well-trained. Relatively small effects on cortisol compared with carbohydrate; immune measures no different from placebo. No support for 'treating URS'. Cochrane reviews show no benefit of initiating vitamin C supplementation (> 200 mg/day) after onset of URS (Hemila et al., 2013; Nieman et al., 2002).

Carbohydrate (drinks, gels)	Maintains blood glucose during exercise, lowers stress hormones, and thus counters immune dysfunction.	Low-moderate support. Ingestion of carbohydrate (30-60 g/h) attenuates stress hormone and some, but not all, immune perturbations during exercise. Very limited evidence that this modifies infection risk in athletes (Bermon et al., 2017; Walsh et al., 2011).
Bovine colostrum	First milk of the cow that contains antibodies, growth factors and cytokines. Claimed to improve mucosal immunity and increase resistance to infection.	Low-moderate support that bovine colostrum blunts the decrease in saliva antimicrobial proteins after heavy exercise. Some evidence in small numbers of participants that bovine colostrum decreases URS. Further support required (Brinkworth et al., 2003; Davison et al., 2010).
Polyphenols e.g., Quercetin	Plant flavonoids. *In vitro* studies show strong anti-inflammatory, anti-oxidant, and anti-pathogenic effects. Animal data indicate an increase in mitochondrial biogenesis and endurance performance.	Low-moderate support. Human studies show some reduction in URS during short periods of intensified training and mild stimulation of mitochondrial biogenesis and endurance performance; albeit, in small numbers of untrained subjects. Limited influence on markers of immunity. Putative anti-viral effect for Quercetin. Further support required (Gleeson, 2016; Nieman et al., 2007).
Zinc	An essential mineral that is claimed to reduce incidence and duration of colds. Zinc is required for DNA synthesis and as an enzyme cofactor for immune cells. Zinc deficiency results in impaired immunity (e.g., lymphoid atrophy) and zinc deficiency is not uncommon in athletes.	No support for 'preventing URS'. High doses of zinc can decrease immune function and should be avoided. Moderate support for 'treating URS'. Cochrane review shows benefit of zinc acetate lozenges (75 mg) to decrease duration of URS; however, zinc must be taken < 24 h after onset of URS for duration of cold only. Side effects include bad taste and nausea (Singh et al., 2013).
Glutamine	Non-essential amino acid that is an important energy substrate for immune cells, particularly lymphocytes. Circulating glutamine is lowered after prolonged	Limited support. Supplementation before and after exercise does not alter immune perturbations. Some evidence of a reduction in URS after endurance events in competitors receiving glutamine supplementation (2 x 5 g). Mechanism for therapeutic effect

	exercise and very heavy training.	requires investigation (Castell et al., 1996; Walsh et al., 1998).
Caffeine	Stimulant found in a variety of foods and drinks (e.g., coffee and sports drinks). Caffeine is an adenosine receptor antagonist and immune cells express adenosine receptors.	Limited support. Evidence that caffeine supplementation activates lymphocytes and attenuates the fall in neutrophil function after exercise. Efficacy for altering URS in athletes remains unknown (Dulson et al., 2016; Walker et al., 2007).
Echinacea	Herbal extract claimed to enhance immunity via stimulatory effects on macrophages. There is some *in vitro* evidence for this.	Limited support. Early human studies indicated possible beneficial effects but more recent, larger scale and better controlled studies indicate no effect of Echinacea on infection incidence or cold symptom severity (Karsch-Volk et al., 2015; Linde et al., 2006).
Omega-3 PUFAs	Found in fish oil. May influence immune function by acting as a fuel, in their role as membrane constituents or by regulating eicosanoid formation, e.g., prostaglandin. Prostaglandin is immunosuppressive. Claimed to exert anti-inflammatory effects post-exercise.	Limited support for blunting inflammation and functional changes after muscle damaging eccentric exercise in humans and no evidence of reducing URS in athletes (Jakeman et al., 2017; Mickleborough, 2013).
Vitamin E	An essential fat-soluble antioxidant vitamin that quenches exercise-induced ROS and augments immunity.	No support. Immune enhancing effects in the frail elderly but no benefit in young, healthy humans. One study actually showed that vitamin E supplementation increased URS in those under heavy exertion. High doses may be pro-oxidative (Hemila et al., 2003; Meydani et al., 2004).
β-glucans	Polysaccharides derived from the cell walls of yeast, fungi, algae, and oats that stimulate innate immunity.	No support in humans. Effective in mice inoculated with influenza virus; however, human studies with athletes show no benefits (Nieman et al., 2008; Volman et al., 2008).

URS = upper respiratory symptoms; ROS = reactive oxygen species. PUFA = polyunsaturated fatty acids.

Table 5. Supplements that may assist with training capacity, recovery, muscle soreness and injury management

Supplement	**Proposed Mechanism of Action**	**Evidence for Efficacy**
Creatine monohydrate Creatine is a naturally occurring nutrient, consumed in the diet, and synthesized in the body. Recommended supplement dose is 20 g/d for 5 d followed by 3 to 5 g/d to increase and maintain elevated body creatine levels (Harris et al., 1992; Hultman et al., 1996b).	Enhanced adaptive response to exercise via increased growth factor/gene expression, increased intracellular water Reduced symptoms of or enhanced recovery from muscle damaging exercise (e.g., DOMS) Enhanced recovery from disuse or immobilization/ extreme inactivity Improved cognitive processing Decreased risk/enhanced recovery from mTBI	Many studies demonstrate improved training adaptations, such as increased lean mass or strength, indicating an enhanced adaptive response to exercise (Branch, 2003; Heaton et al., 2017; Rawson et al., 2003). Reduced symptoms of, or enhanced recovery from, muscle damaging exercise (e.g., DOMS) have been reported in some, but not all studies (reviewed in (Rawson et al., 2017a). Enhanced recovery from disuse or immobilization/ extreme inactivity has been reported in some, but not all studies (reviewed in (Heaton et al., 2017)). Improved cognitive processing is reported in most studies, especially when volunteers were fatigued by sleep deprivation or mental/physical tasks (reviewed in (Gualano et al., 2016; Gualano et al., 2012; Rae et al., 2015; Rawson et al., 2011). The effects in athletes have not been well characterized, and only one group attempted to translate these effects into to athletic performance, albeit with a positive result. (Cook et al., 2011) Decreased damage and enhanced recovery from mTBI is supported by open label trials in children (Sakellaris et al., 2006; Sakellaris et al., 2008) and using animal models.(Sullivan et al., 2000) These data are not conclusive and more research is warranted. However, athletes at risk for concussion, who already ingest creatine supplements for performance or muscular benefits, may receive important brain benefits as well. A small increase in body mass is common with supplementation. This may be relevant for sports with

		weight classes/restrictions or where increased body mass may decrease performance.
Beta-hydroxy Beta-methyl-butyrate (HMB) HMB is a metabolite of the amino acid leucine. Manufacturer recommended dosage is 3 g/d	Enhanced adaptive response to exercise via decreased protein breakdown increased protein synthesis. Increased cholesterol synthesis, increased growth hormone and IGF I mRNA, increased proliferation and differentiation of satellite cells, and inhibited apoptosis (reviewed in (Szczesniak et al., 2015)).	Beneficial effects of HMB on strength and fat free mass are small, while the effects on muscle damage are unclear (Rowlands et al., 2009). Recent reports of "steroid like" gains in strength, power, and fat free mass, and reductions in muscle damage from HMB-free acid (HMB-FA) supplementation (Lowery et al., 2016; Wilson et al., 2014; Wilson et al., 2013) have not been reproduced and seem unlikely.(Phillips et al., 2017) Potential use for HMB during extreme inactivity/disuse or recovery from injury, but these effects have only been described in older adults following 10 days of bed rest (Deutz et al., 2013). Benefits of HMB supplementation could most likely be obtained from normal dietary protein or whole protein supplements (Wilkinson et al., 2013), so HMB supplements may not be more effective than adhering to the current protein intake recommendations
Omega 3-Fatty Acids About 2 g/d	Improved cognitive processing. Decreased risk/enhanced recovery from mTBI. Increased muscle protein synthesis. Reduced symptoms of or enhanced recovery from muscle damaging exercise (e.g., DOMS)	Improved cognitive processing following omega 3-fatty acid supplementation shown in healthy older adults those with mild or severe cognitive impairment (reviewed in (Barrett et al., 2014)). It is not known if these benefits would occur in young, healthy athletes, or how this would translate to athletic performance. Animal data show that the structural damage and cognitive decline associated with mTBI are reduced/attenuated with omega-3 fatty acid supplementation when ingested either before or after the injury (reviewed in (Barrett et al., 2014; Erdman et al., 2011; Tipton, 2015). Two case studies support these

		findings (Lewis et al., 2013; Roberts et al., 2008) and large, double-blind, placebo-controlled trials are currently under way (clinicaltrials.gov NCT101903525, NCT01814527). In muscle, omega-3 fatty acid supplementation can increase muscle protein synthesis (Smith et al., 2011a, 2011b), but this may not occur when protein is ingested after exercise in recommended amounts (Smith et al., 2011a, 2011b). Anti-inflammatory effects of omega-3 fatty acid intake may reduce muscle damage or enhance recovery from intense, eccentric exercise (e.g., decrease DOMS), but this is not a consistent finding (Gray et al., 2014; Jouris et al., 2011). No indication that decreased omega 3-fatty acids in the body impair performance, and high dose supplements can cause some adverse effects (reviewed in (Erdman et al., 2011; Mickleborough, 2013), so the best recommendation may be to include rich sources of omega-3 fatty acids, such as fatty fish, in the diet instead of supplements. Low risk but unclear if supplementation should be pursued by athletes, in lieu of including fatty fish in the diet as a source of omega-3 fatty acids. Fish oil or omega-3 fatty acid supplement consumption could include heavy metal contaminants, or cause bleeding, digestive problems, and/ or increased LDL.
Vitamin D An essential fat-soluble vitamin. Skin exposure to sunlight normally accounts for 90% of the source of vitamin D.	Enhanced adaptive response to exercise Decreased stress fractures	Data on the effects of vitamin D supplementation on muscle function and recovery are equivocal, with discrepancies likely explained by differences in baseline vitamin D concentrations prior to supplementation (Close et al., 2016; Close et al., 2013; Owens et al., 2015; Owens et al., 2014). Collectively, these data strongly suggest a role for adequate vitamin D in the adaptive process to stressful exercise.

		Low vitamin D status is associated with a 3.6X higher stress fracture risk in Finnish military recruits (Ruohola et al., 2006). US Naval recruits supplemented with 800 IU/d of vitamin D3 and 2000 mg calcium reduced stress fracture incidence by 20% (Lappe et al., 2008). More data are needed, but it appears that vitamin D status, relates to stress fracture risk, and supplementation, when warranted, may reduce this risk.
Gelatin and vitamin C/collagen Recommended dose is 5 to 15 g gelatin with 50 mg vitamin C (Shaw et al., 2017). Collagen hydrolysate dose is about 10 g/d (Clark et al., 2008; McAlindon et al., 2011)	Increased collagen production Thickened cartilage Decreased joint pain	Gelatin and collagen supplements appear to be low risk. Few data available, (Clark et al., 2008; McAlindon et al., 2011; Shaw et al., 2017) but increased collagen production and decreased pain seem possible. Functional benefits, recovery from injury, and effects in elite athletes are not known.
Anti-inflammatory supplements: Curcumin (a constituent of the spice turmeric) is often ingested for anti-inflammatory effects at a dose of about 5 g/d. Tart cherry juice at a dose of about 250-350	Anti-inflammatory effects Reduced symptoms of or enhanced recovery from muscle damaging exercise (e.g., DOMS)	Decreases in inflammatory cytokines and/or indirect markers of muscle damage with anti-inflammatory supplements such as curcumin (McFarlin et al., 2016; Nicol et al., 2015; Sciberras et al., 2015) and tart cherry juice (reviewed in (Bell et al., 2014; Coelho Rabello Lima et al., 2015)) have been reported Anti-inflammatory effects may be beneficial, although benefits may be sport/training specific. More research is

mL (30 mL if concentrate) twice daily for 4 to 5d before an athletic event or for 2 to 3 d afterwards to promote recovery.		needed before these compounds can be recommended to athletes.

DOMS=delayed onset muscle soreness, mTBI-mild traumatic brain injury (concussion)

Table 6. Supplements promoted to assist with physique changes: Gain in lean mass and loss of body fat mass

Supplement	**Proposed Mechanism of Action**	**Evidence for Efficacy**
Gaining LBM*		
Protein Usually comprised of isolated proteins from various sources (whey and soy most common) **Recommended daily dose:** 1.6 g protein/kg/d optimal (up to 2.2 g/kg/d with no adverse effects) **Recommended per-meal doses:** 0.3-0.5 g protein/kg (3-4 times per day and in close temporal proximity to exercise, with post-exercise being consistently shown to be effective)	Enhances lean mass gains when ingested during programs of resistance training due to increased provision of building blocks (amino acids) and leucine as a trigger for a rise in muscle protein synthesis and suppression of muscle protein breakdown.	Meta-analyses focussing on younger and older participants have shown positive effects enhancing gains in muscle mass (Cermak et al., 2012; Morton et al., 2017), but effects are not large.
Leucine	Stimulates muscle protein synthesis and supresses protein breakdown (possibly through insulin)	Short-term mechanistic data available,(Wilkinson et al., 2013) but no long-term trials showing efficacy (Aguiar et al., 2017)
Losing fat mass**		
Protein From increased dietary sources or supplemental isolated proteins	Enhance fat mass loss and promotes retention of lean mass	Meta-analyses confirm small but significant effects of greater dietary protein in weight loss to enhance fat mass loss and promote lean mass retention (Krieger et al., 2006; Wycherley et al., 2012)
Pyruvate	No data	Small-to-trivial effect (Onakpoya et al., 2014a)

Chromium	Potentiates biological actions of insulin	No effect (Tian et al., 2013)
Green tea (polyphenol catechins and caffeine)	Thermogenic agent and/or lipolytic enhancing agent	Small-to-trivial effect (Jurgens et al., 2012)
α-Lipoic acid	No clear role, but possible antioxidant	Small-to-trivial effect (Kucukgoncu et al., 2017)
Conjugated linolenic acid (CLA)	Changes membrane fluidity favouring enhanced fat oxidation	Small-to-trivial effect (Onakpoya et al., 2012)
Konjac fibre (glucomannan)	Water-soluble polysaccharide - dietary fibre	Small-to-trivial effect (Onakpoya et al., 2014b)
Omega-3 Polyunsaturated fatty acids	No clear role, but possible appetite suppression, improved blood flow, and/or modulator of gene expression	Small-to-trivial effect (Zhang et al., 2017)
Chitosan	Lipid-binding agent to reduce lipid absorption	Small-to-trivial effect (Jull et al., 2008)

* In combination with a progressive resistance exercise programs.

** In combination with an exercise- and/or diet-induced energy deficit.

Figure legends

Figure 1. Hierarchy of evidence used to establish good practice.

Figure 2. Flow chart to guide informed decision making and reducing risk of ADRV during nutritional supplement use.

Figure 3. Flow chart to guide informed decision making and reducing risk of ADRV during ergogenic supplement use.

Figure 1

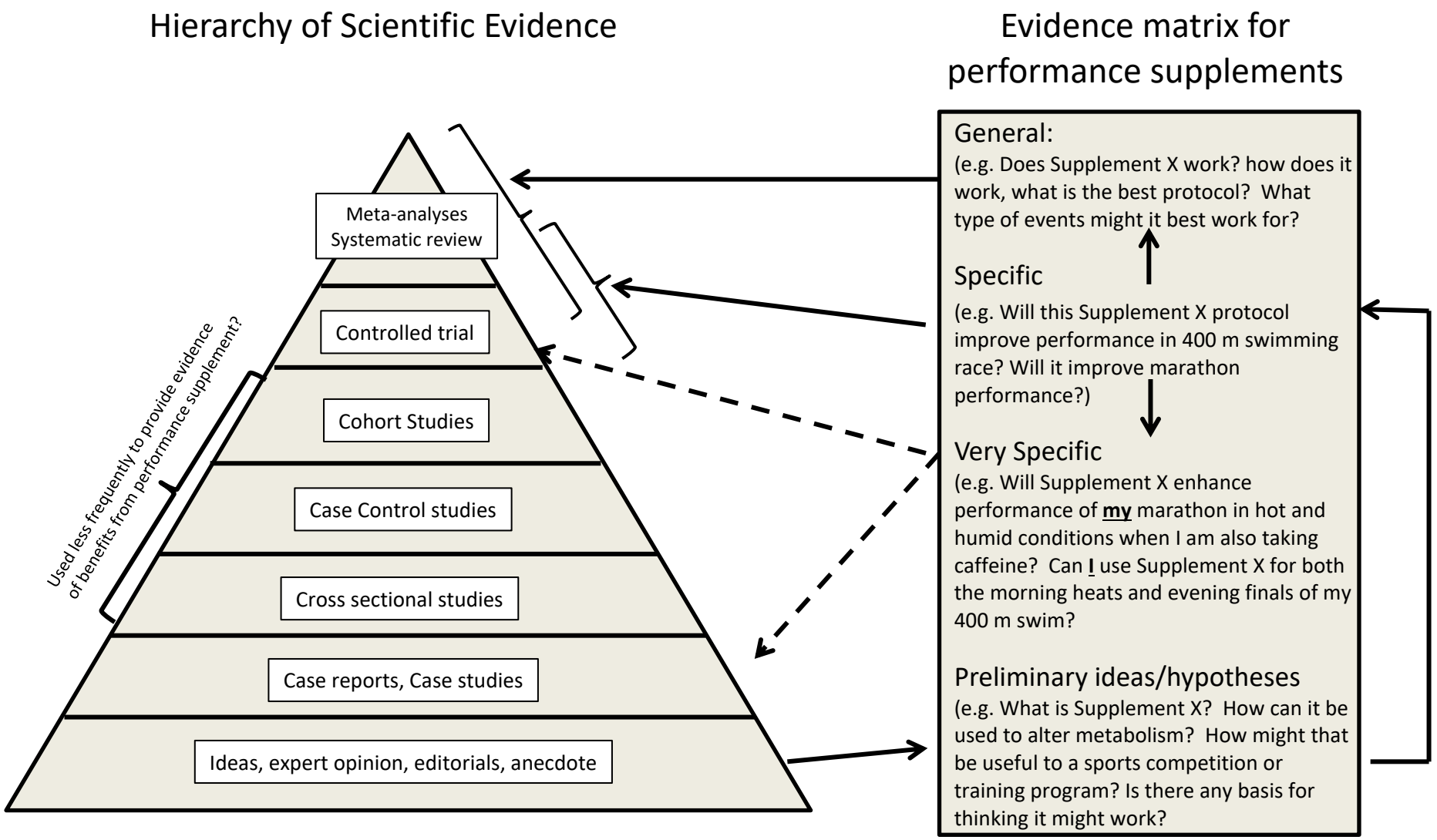

Hierarchy of Scientific Evidence
Meta-analyses
Systematic review
Controlled trial
Cohort Studies
Case Control studies
Cross sectional studies
Case reports, Case studies
Ideas, expert opinion, editorials, anecdote
Used less frequently to provide evidence of benefits from performance supplement?
Evidence matrix for performance supplements
General:
(e.g. Does Supplement X work? how does it work, what is the best protocol? What type of events might it best work for?
Specific
(e.g. Will this Supplement X protocol improve performance in 400 m swimming race? Will it improve marathon performance?)
Very Specific
(e.g. Will Supplement X enhance performance of my marathon in hot and humid conditions when I am also taking caffeine? Can I use Supplement X for both the morning heats and evening finals of my 400 m swim?
Preliminary ideas/hypotheses
(e.g. What is Supplement X? How can it be used to alter metabolism? How might that be useful to a sports competition or training program? Is there any basis for thinking it might work?

Figure 2.

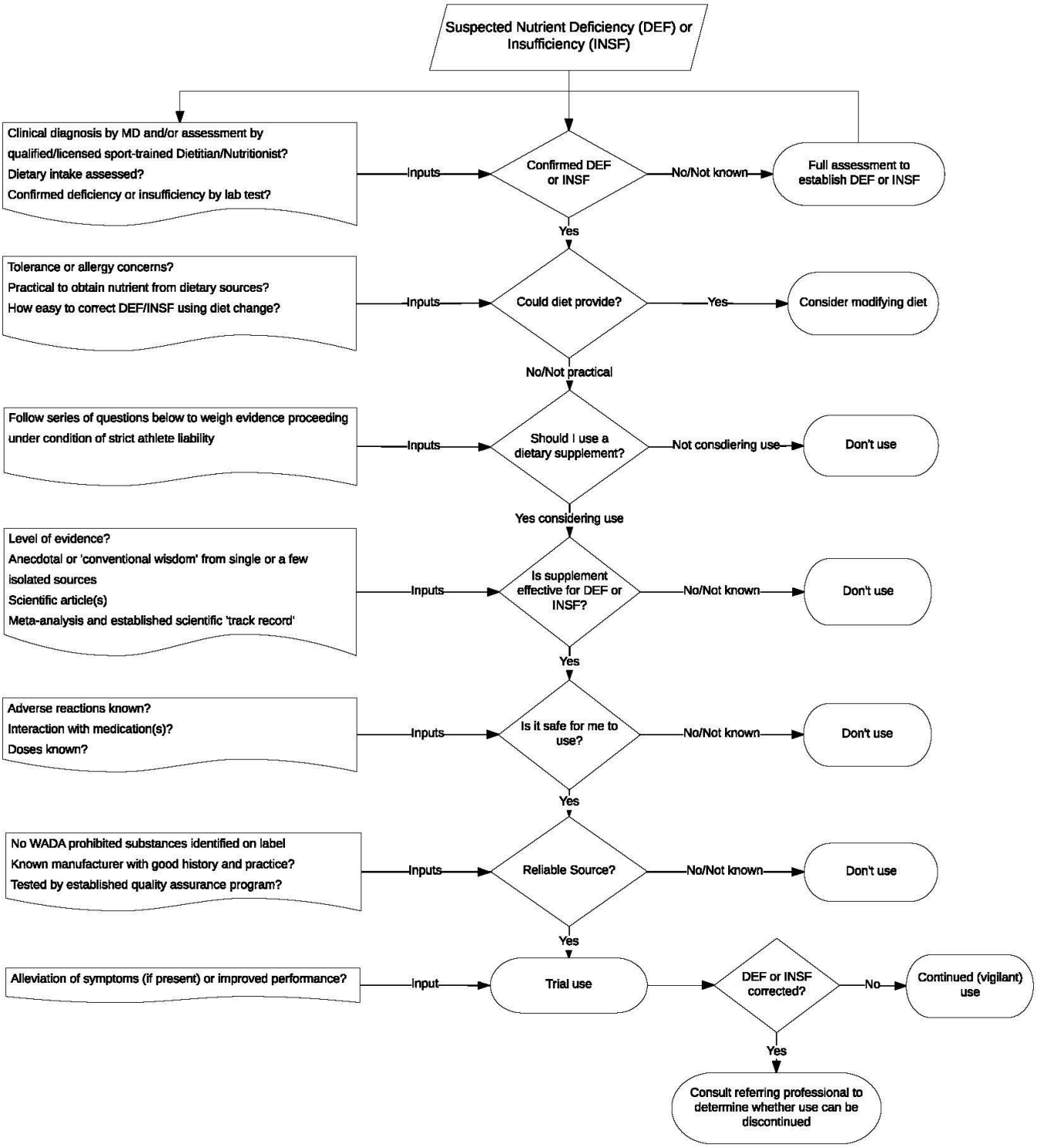
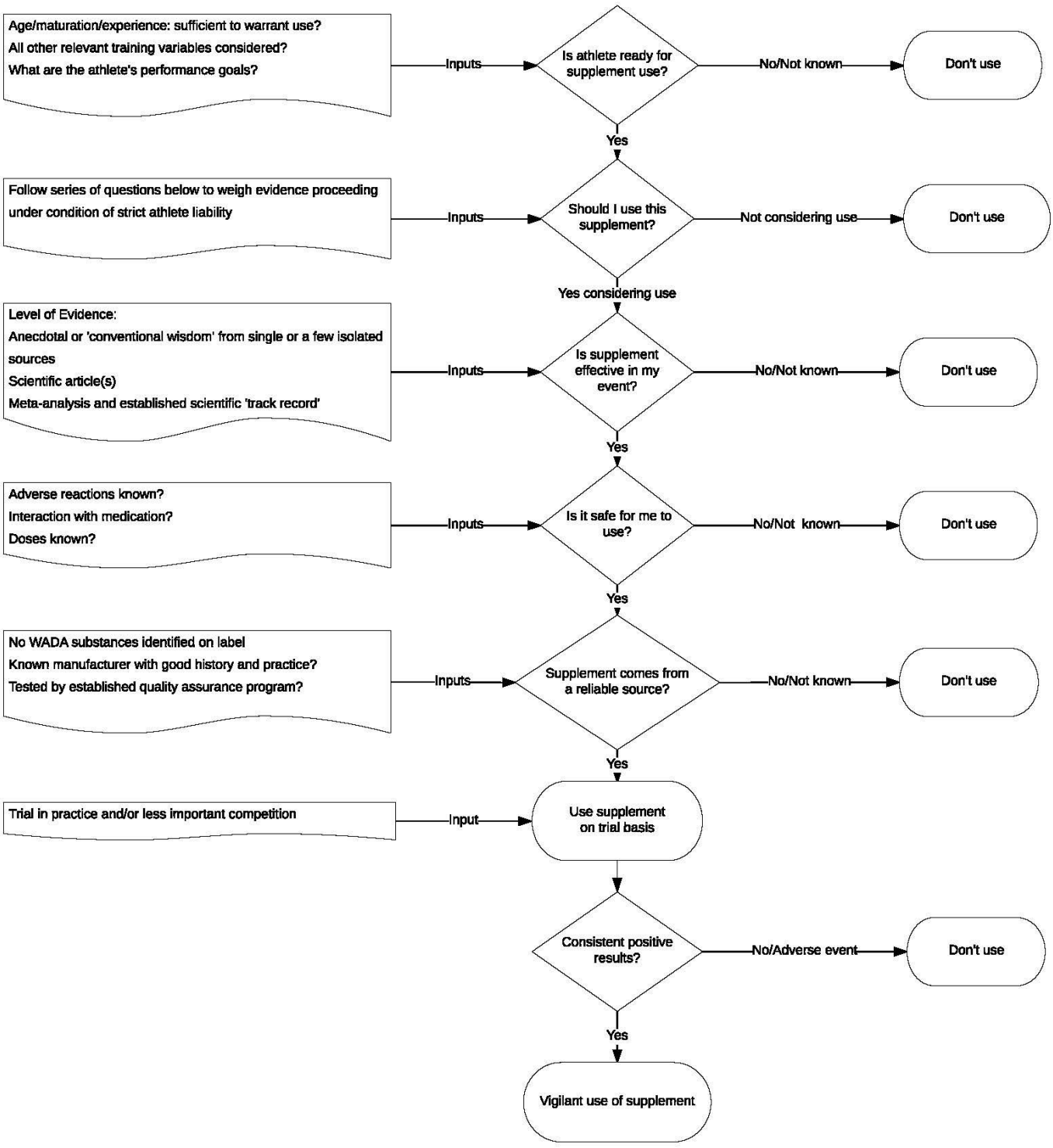

Suspected Nutrient Deficiency (DEF) or Insufficiency (INSF)
Clinical diagnosis by MD and/or assessment by qualified/licensed sport-trained Dietitian/Nutritionist?
Dietary intake assessed?
Confirmed deficiency or insufficiency by lab test?
Inputs
Confirmed DEF or INSF
No/Not known
Full assessment to establish DEF or INSF
Yes
Tolerance or allergy concerns?
Practical to obtain nutrient from dietary sources?
How easy to correct DEF/INSF using diet change?
Inputs
Could diet provide?
Yes
Consider modifying diet
No/Not practical
Follow series of questions below to weigh evidence proceeding under condition of strict athlete liability
Inputs
Should I use a dietary supplement?
Not consdiering use
Don't use
Yes considering use
Level of evidence?
Anecdotal or 'conventional wisdom' from single or a few isolated sources
Scientific article(s)
Meta-analysis and established scientific 'track record'
Inputs
Is supplement effective for DEF or INSF?
No/Not known
Don't use
Yes
Adverse reactions known?
Interaction with medication(s)?
Doses known?
Inputs
Is it safe for me to use?
No/Not known
Don't use
Yes
No WADA prohibited substances identified on label
Known manufacturer with good history and practice?
Tested by established quality assurance program?
Inputs
Reliable Source?
No/Not known
Don't use
Yes
Alleviation of symptoms (if present) or improved performance?
Input
Trial use
DEF or INSF corrected?
No
Continued (vigilant) use
Yes
Consult referring professional to determine whether use can be discontinued

Figure 3.


Age/maturation/experience: sufficient to warrant use?
All other relevant training variables considered?
What are the athlete's performance goals?
Inputs
Is athlete ready for supplement use?
No/Not known
Don't use
Yes
Follow series of questions below to weigh evidence proceeding under condition of strict athlete liability
Inputs
Should I use this supplement?
Not considering use
Don't use
Yes considering use
Level of Evidence:
Anecdotal or 'conventional wisdom' from single or a few isolated sources
Scientific article(s)
Meta-analysis and established scientific 'track record'
Inputs
Is supplement effective in my event?
No/Not known
Don't use
Yes
Adverse reactions known?
Interaction with medication?
Doses known?
Inputs
Is it safe for me to use?
No/Not known
Don't use
Yes
No WADA substances identified on label
Known manufacturer with good history and practice?
Tested by established quality assurance program?
Inputs
Supplement comes from a reliable source?
No/Not known
Don't use
Yes
Trial in practice and/or less important competition
Input
Use supplement on trial basis
Consistent positive results?
No/Adverse event
Don't use
Yes
Vigilant use of supplement