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Current Opinion in Physiology

Supplements for Optimal Sports Performance

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There is an enthusiastic market for the multitude of sports foods and supplements which claim to enhance sports performance. Despite a lengthy history of antipathy towards this industry, many peak sporting bodies and expert groups now support a pragmatic acceptance of the use of products which have passed a risk:benefit analysis of being safe, effective and legal, as well as appropriate to the athlete's age and maturation in their sport. Sports supplements can be grouped: sports foods which provide a practical form of nutrients to meet sports nutrition goals; medical supplements which may be needed to prevent or correct nutrient deficiencies that occur in athletes, and the larger category of performance supplements which claim either to directly enhance exercise capacity or to support activities that allow the athlete to train hard, recover, achieve physique goals or reduce the risk of illness and injury. Gaining an evidence base for this latter group is challenged by the scarcity of research in relation to the number of products on the market, as well as limitations or poor quality of some of the available studies. While controlled scientific trials and meta-analyses help to provide information about the general use of performance supplements, most high performance athletes are more interested in real-life issues that are hard to encapsulate (e.g. detecting benefits that are meaningful to the outcomes of sporting competition, accounting for the use of several supplements in combination or the use of same supplement over successive events). Strategies to isolate and explain the variability of benefits to individual athletes is also a topic demanding investigation.

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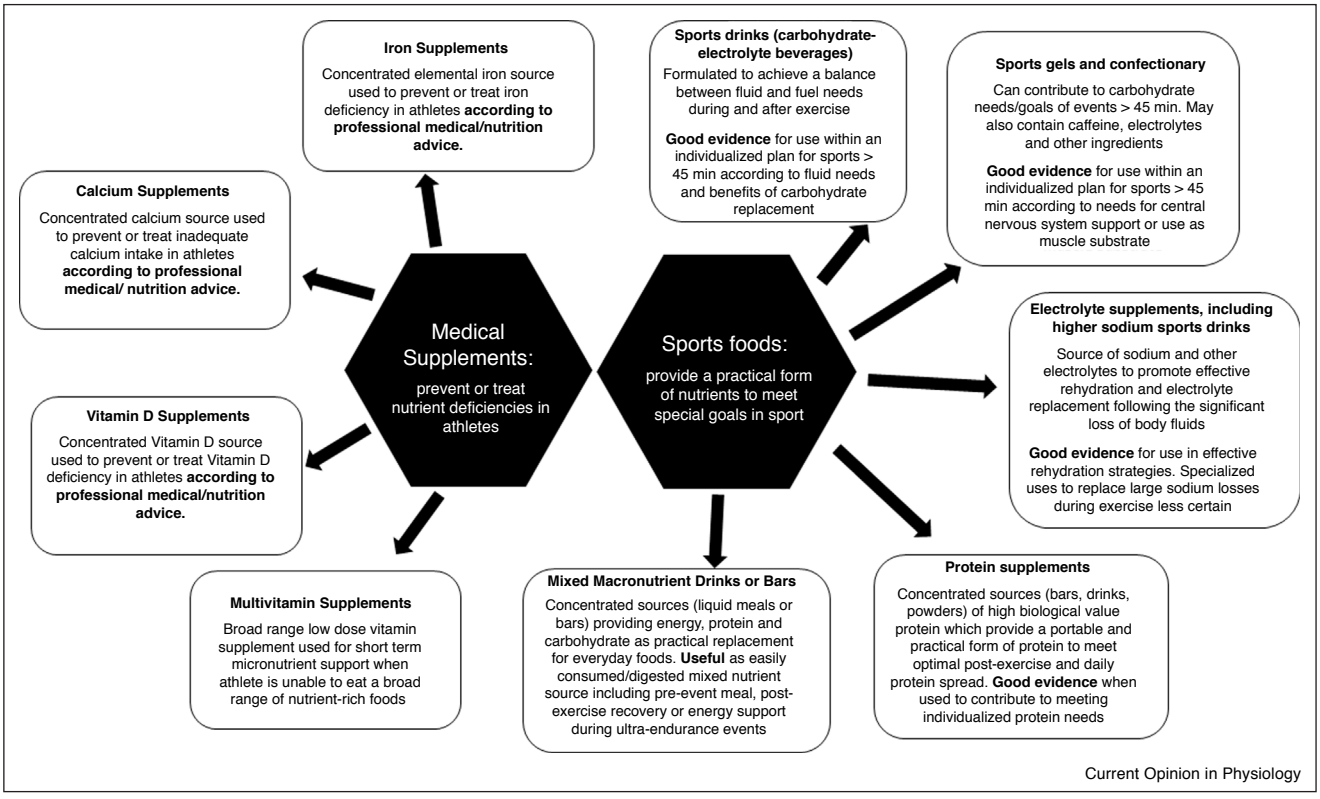
Introduction

According to recent business analyses, the sports supplement industry contributes a substantial market share of $US11.6 billion dollars within the more extensive health/wellness supplement portfolio, with projected growth forecast to reach 24.4 billion by 2025 [1]. Traditionally, peak bodies for sport or sports medicine have regarded supplement use by athletes with antipathy and conservative messaging that optimal performance is achieved through a 'well-balanced diet". Meanwhile, surveys confirm the high prevalence of sports food and supplement use among athletes, including greater use at higher levels of competition and different motivations of use [2•]. However, evolving awareness of the benefits of some products, and the need to better connect with athletes and coaches, have led to recent changes in this attitude. Indeed, several influential bodies now extend a pragmatic acceptance to products that have passed a risk: benefit analysis of being safe, effective and legal, while also being appropriate to the athlete's age and maturation in their sport [3••,4]. Although the number of commercially available supplements is overwhelming, three different categories can be recognized: 1. Medical supplements; 2. Sports foods; and 3. Performance supplements that either directly enhance exercise capacity or provide indirect benefits. This brief review provides an overview of these categories with topical updates on key products within each. In addition, it identified the challenges of developing the evidence base needed to allow the athlete to make an informed decision when contemplating supplement use.

Sports foods and medical supplements

Products within the categories of sports foods and medical supplements are arguably the most credible sports supplements, at least when manufactured by mainstream companies and used according to best-practice protocols adapted to the specific athlete and their scenario of use. As illustrated in Figure 1, medical supplements can be used to treat or prevent nutrient deficiencies; these often occur in increased prevalence in some athletic groups or have a detrimental effect on adaptation and performance, even at levels considered to be sub-clinical in sedentary populations. For example, iron deficiency may occur more frequently due to exercise-associated increases in the iron-regulatory hormone, hepcidin [5], which reduces dietary iron absorption and macrophage recycling. Meanwhile, sports foods provide a convenient way to consume specific nutrients targets, especially in exercise-related scenarios where consumption of everyday foods may be impractical. Although products in these categories may appear well-established, knowledge and practice continue to evolve. For example, it has been recently established that daily iron supplementation, commencing in advance of altitude training, is needed to augment existing iron

Figure 1



Summary of evidence-based uses of sports foods and medical supplements by athletes.

stores to maximize the desired hematological adaptations to this protocol, even in non-anemic athletes [6•].

In regard to the use of sports drinks, gels and confectionary, newer guidelines around carbohydrate intake during exercise [7] have expanded the range of benefits and valuable scenarios of use to include central nervous system effects from the oral sensing of carbohydrate in events of 45-75 min where its contribution as a muscle substrate is not limiting to performance [8,9]. They also note additional benefits of carbohydrate intake in amounts greater than the previous targets (i.e. 30-60 g/h), in scenarios of dwindling muscle glycogen stores (e.g. events of ~2 h and above) [10]. Here, targets of ~90 g/h [11•] are made possible by products with higher concentrations than standard sports drinks and the use of "multiple transportable carbohydrate" formula to include glucose-based and fructose sugar which increase intestinal carbohydrate absorption by utilizing different transport mechanisms [11•,12•,13]. Furthermore, there is evidence that practicing carbohydrate intake during exercise can adapt the gut, potentially by up-regulating the activity of sodium-dependent glucose transporters (SGLT1), to better absorb exogenous carbohydrate uptake [12•], with potential performance benefits [14•] coming from increased muscle carbohydrate use [15] as well as reductions in gut discomfort [14•]. However, these benefit seems specific to the form of exogenous CHO to which the athlete has adapted [14•]. Although intestinal absorption is currently considered the limiting factor in transferring exogenous carbohydrate into a substantial muscle fuel source [12•], there has been a renewed interest in strategies to increase the gastric emptying of concentrated carbohydrate solutions during exercise. A newly commercialized sports drink claims such an advantage by combining a concentrated (~15 g/100 ml) multiple transportable carbohydrate formula with added alginate and pectin [16]. This is apparently transformed from liquid to a hydrogel in the acidic gastric environment, for enhanced emptying via the lowering of net osmolality, but then reconverted in the duodenum for absorption [16]. Although the technology, employed in the better resourced areas of targeted drug delivery, has hypothetical appeal, the marketing and testimonial support [17] for this product has occurred ahead of the publication of robust investigations of its pharmacokinetics, gut tolerance and performance characteristics, particularly in the high performance scenarios and populations for which it is focused. While such research is eagerly awaited, some caution is warranted since negative feedback on gastric emptying from osmoreceptors in the duodenum may occur as the gel breaks down and increases intestinal lumen osmolality and energy content.

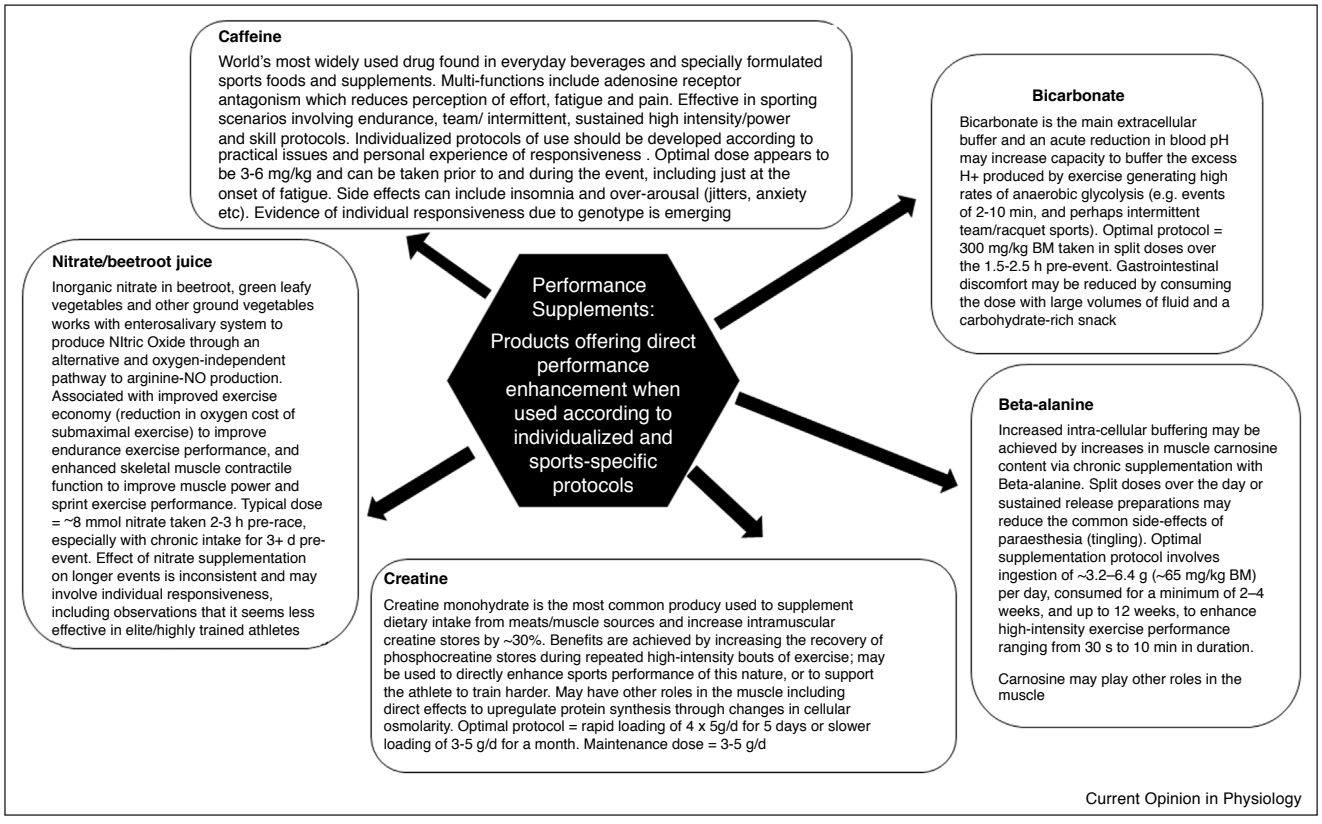
Performance supplements

The majority of sports supplements are marketed with claims of directly enhancing performance, or providing an indirect benefit via support for the athlete to train hard, recover or adapt optimally, stay free from illness or injury, or achieve optimal body composition. Figure 2 summarizes a number of products which enjoy substantial evidence of direct benefits of performance; further discussion can be found in recent reviews [3••,18•,19,20]. It is beyond the brief nature of this paper to cover the vast multitude of products in this category; however, some commentary around the oldest and one of the newest performance compounds will be provided as an example of the continued evolution of this field. Despite progress in identifying real or potential performance aids, it should be noted that the commercial presentation of many supplements involves multi-ingredient formula, often with undeclared "proprietary blends", which place the athlete at particular risk of unknown, variable [21], and potentially hazardous intakes of ingredients [22]. Indeed, supplements may contain deliberate or unintentional/contaminant content of substances that are banned under the anti-doping codes under which high performance athletes compete; these include stimulants, anabolic agents, selective androgen receptor modulators, diuretics, anorectics and β2 agonists [23•]. Strict liability codes mean that a positive urine test can trigger an Anti-Doping Rule Violation with potentially serious impact on the athlete's career, livelihood and reputation, despite unintentional intake or minute (ineffective) doses. Third-party auditing of products can help elite athletes to make informed choices about supplement use but cannot provide an absolute guarantee of product safety [22]. For this reason, athletes are guided to make systematic and informed decisions about supplement use that balance the potential benefits against the expense and potential harm (see Figure 3 [24•])

New thoughts on an old product

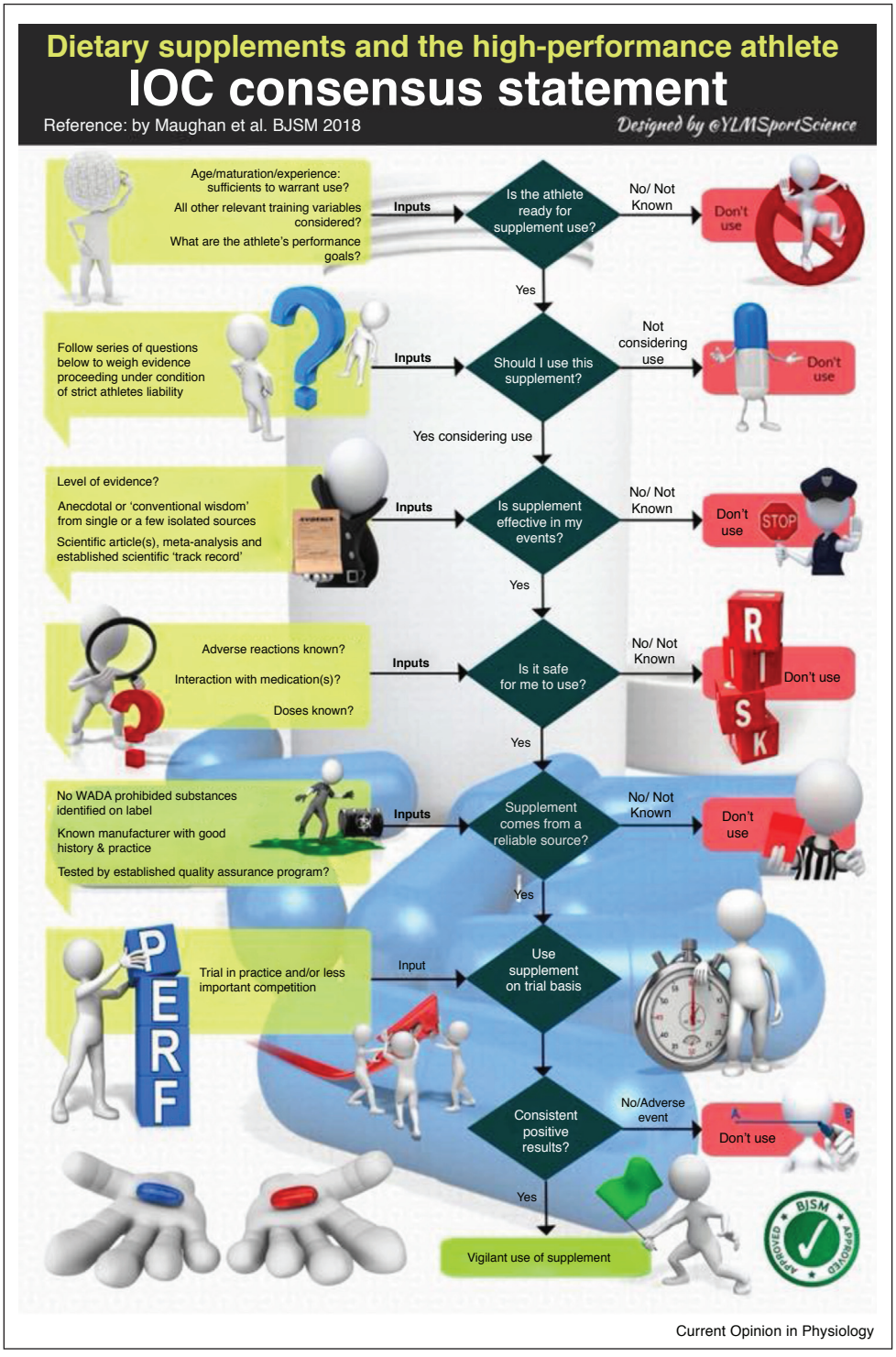
Caffeine is one of the oldest performance supplements, but also one of the few with robust evidence of performance benefits and the unusual trait of being ergogenic across a wide variety of exercise modes and protocols [18•]. The layers of current information span an umbrella analysis of 21 previous meta-analyses [25], drilling down to meta-analyses of its effects on groups of sports (e.g. team sports [26]) and even further to specific events (e.g. soccer [27]) and forms of intake (e.g. energy drinks [28•]). Although caffeine has numerous effects on various body tissues and systems, antagonism of adenosine receptors and direct effects on muscle contractility via calcium handling are the main mechanisms of action. Attenuation

Figure 2



Summary of evidence-based performance supplements achieving direct enhancement of exercise activities/sporting events.

Figure 3



Infographic providing a decision tree approach to making an informed decision about the intended use of a performance supplement according to the IOC Statement on the Use of Dietary Supplements by High Performance Athletes [24•].

of fatigue and enhanced perception of effort translates into performance improvements across a range of sporting activities, which explains its ubiquitous use by athletes. Indeed, its change in status in 2004, from a controlled substance on the List of Prohibited Substances to the Monitoring program of the World Anti-Doping agency, has provided a means of tracking its use by athletes, albeit with various limitations, by inspecting trends in urinary caffeine concentrations from samples taken at post-competition Anti-Doping Control stations [29•]. An analysis of nearly 7500 samples collected from 2004-2015 suggests that caffeine is used in moderate amounts, the prevalence of use and size of doses has increased over this time, and athletes in endurance/aerobic sports have the highest urinary concentrations [29•].

While the pioneering studies of caffeine and performance in the 1960s-1980s used doses of ~6 mg/kg body mass (BM), consumed an hour prior to exercise, to provide benefits in laboratory based exercise protocols, contemporary studies have shown that caffeine is ergogenic in smaller doses (~3 mg/kg) when consumed in a variety of protocols, pre- and during exercise, including just before the onset of fatigue [30]. This allows athletes to consume caffeine in similar doses and for similar purposes as the everyday consumer (i.e. to preserve their ability to undertake daily activities) [31], with encouragement to experiment to find a judicious use of this widely available drug (i.e. the lowest effective dose), according to their logistics of their sport, while minimizing any side-effects such as sleep disturbances and overstimulation of mood or metabolic response [31]. Intervention studies investigating real-world scenarios using high caliber athletes, in a simulated competition in field conditions [32•,33], actual competition [34,35] or as a laboratory simulation of an actual event [36] are welcomed. Future interests [37•] include comparison of the many currently used forms of caffeine intake (e.g. caffeine tablets, coffee, sports foods, energy drinks) as well as alternative forms such as chewing gum, mouth rinses and aerosols [38•]. There is also interest in the tolerance to habitual use of caffeine and the need for a "withdrawal period" to optimize the ergogenic effect of caffeine [39•]. While such withdrawal has been an expected component of intervention studies and cultural patterns of competition use by some athletes, other studies have shown that it is unnecessary for an effect to be seen [40]. Indeed, the apparently heightened performance effects of caffeine following several days of "de-adaptation" to normal caffeine intake prior to a trial might simply reflect the reversal of the negative effects of withdrawal (fatigue, headache etc) added to the true ergogenic effect. Nevertheless, a recent study which serially measured performance effects over a 20 day period of daily caffeine dose of 3 mg/kg reported that the greatest performance benefit was seen on the first day, and although there was a continued ergogenic effect, changes in the magnitude of this effect suggested progressive tolerance [41•].

Opportunities for a new product

Performance of exercise of > ~40 min is often determined by the availability of oxidative substrates for the muscle with various sports nutrition strategies targeting opportunities to increase carbohydrate availability or capacity for fat oxidation [42••]. A third option involves the increased use of ketone bodies (β-hydroxy-butyrate [BHB], acetoacetate and acetone) which are produced in the liver during starvation and a ketogenic diet to provide an alternative fuel source for peripheral tissues including brain, heart and skeletal muscle, with the latter having an enhanced ability to oxidize ketone bodies in endurance-trained individuals [43,44••]. Metabolic effects during exercise include attenuation of glucose utilization in peripheral tissues and anti-lipolytic effects on adipose tissue, while in post-exercise recovery, there may be enhancement of glycogen synthesis, attenuation of proteolysis in skeletal muscle and inhibition of histone deacetylases which regulate adaptive responses [43,44••]. The acute consumption of ketone salts and the recently developed ketone ester supplements [45••] has emerged as an alternative to chronic ketogenic diets, with benefits including the lack of need for strenuous and restrictive dietary changes and the opportunity to integrate this strategy into a range of other dietary manipulations of fat and carbohydrate availability [42••]. A landmark paper [45••] detailed the range of metabolic changes caused by the achievement of circulating ketone bodies within the potentially beneficial range of 1-3 mmol/L [44••] by a novel ketone ester as well as an observation of enhanced time-trial performance in well-trained cyclists who consumed it with a carbohydrate-rich drink before a 90 min protocol [45••]. Despite this promise, other studies using exogenous ketone supplements have failed to find performance benefit [46,47,48•], and issues such as gastrointestinal discomfort [48•], achievement and measurement [49•] of adequate but not excessive blood ketone body concentrations, and finding the "right" exercise/sports activity in which ketone bodies can provide a valuable fuel source without impairing the utilization of others [42••,43,44••] need to be overcome.

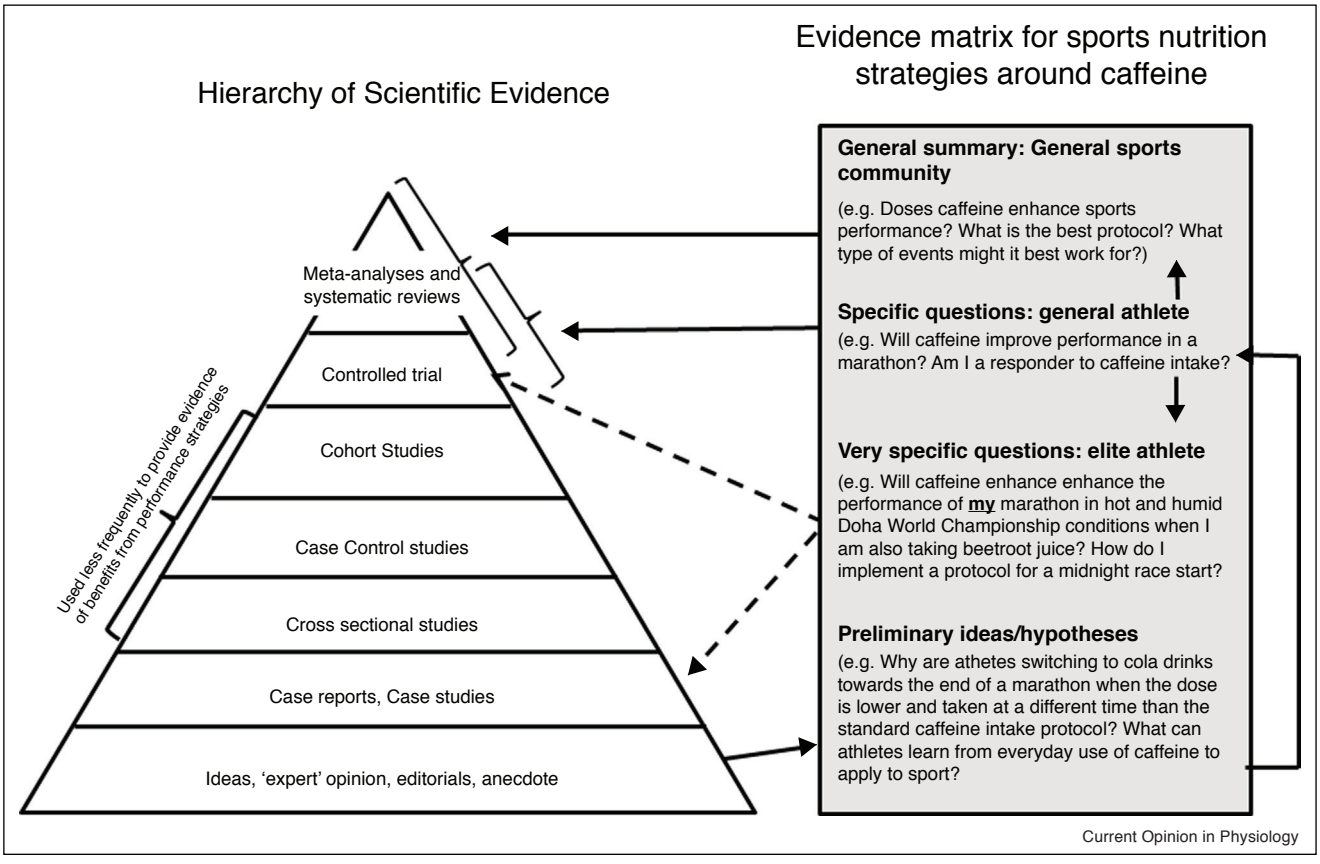
Finding an evidence base for performance supplements

Substantiating the claims made about performance supplements is a challenging process. This author has previously noted that the requirements and processes of sports science research, particularly as they relate to high performance athletes, are often misunderstood by mainstream researchers [50••], with the specific issues around performance supplements exemplifying the difference between the generalizable truths sought in many areas of scientific research and the intricate questions for which elite athletes seek answers. However, she has also stated

that this area of sports nutrition is probably the most effected by poor research methodologies, a low bar for publication and publication bias [51•]. Figure 4 provides a hierarchical model of the suggested strength of the evidence provided by different information sources, with specific examples continuing to be viewed through the prism of caffeine and sports performance. The most common types of information around supplement efficacy presented to athletes and coaches come from models with the lowest rigor: anecdotes/observations from athletes [51•]. Despite some hesitancy about the scientific credibility of this type of information, science has sometimes come to support supplement practices observed among athletes which were earlier dismissed as being incorrect or unlikely to achieve performance benefits. Indeed, some of the first trials of the lower doses of caffeine and its use during, rather than an hour prior to exercise, were undertaken to confirm and explain the persistent observations of the use of cola drinks (providing caffeine doses of 1-2 mg/kg) in the last 25% of prolonged endurance/ultra-endurance races [52]. However, caution is also advised due to the slow and non-systematic pathway of learning via experience, as well as the lack of transparency around the commercial involvement of athletes and scientists with the supplement industry [51•].

The controlled scientific trial remains the gold standard of investigative research but an understanding of key issues in sports performance research is needed to design and implement such studies [51•], especially to mimic the scenarios in which the product is targeted for use, and to control issues that can alter performance such as environmental conditions, background training and nutrition status, familiarization with the protocol and motivation [51•]. As summarized in Figure 4, few studies interrogate the specific and personalized scenarios in which athletes, particularly the highest caliber performers wish to apply supplement use; indeed, the complexity of the intended application of the supplement demonstrated in Figure 4 overwhelms the opportunity to undertake a scientific trial, both on methodological and economic grounds. There are four main themes in which the current performance supplement literature fails to address the specific needs of high performance athletes; interaction of evidence-based supplements that are used concurrently, the ability to repeat supplement use in a critical period,

Figure 4



Hierarchy of evidence sources for making decisions about performance supplements, comparing traditional approach with the appropriate protocols for use in sport; the specific requirements of athletes are exemplified by issues around caffeine use.

consideration of true individual differences in response, and the judgement of the magnitude of a performance difference that will be meaningful in competitive sport in which the margins of winning and losing are measured in decimal points [51•]. The last issue ignites debate about statistical analysis that is beyond the scope of this paper. However, caffeine has been involved in the emerging literature that attempts to address the other concerns.

Even though there are few evidence-supported performance supplements, they are often suited to the same type of event and may therefore be used concurrently. The development of the optimal protocol of use requires examination of the surprisingly numerous combinations and themes in which their separate and additive effects might interact [51•,52]. Current research endeavors have typically limited the focus to the single and/or combined use of two products, with the variation in results highlighting the need for such research. In the case of caffeine, studies have shown that bicarbonate and caffeine supplementation combined to increase the performance benefits of another judo simulation [53], but bicarbonate counteracted the benefits of caffeine on rowing ergometer performance due to gut disturbances [54]. A Latin Squares application of treatments in a crossover designed study can provide a robust and practical framework for investing the single and combined effect of two acutely administered products. Meanwhile, the integration of larger numbers of products into the athlete's program might be practically managed using single case and small group observations, with intuition and experience also guiding the process. In many sports, competition outcomes are decided through a series of heats and finals, stages in a race or games in a tournament. In some cases, the interval between bouts is measured in hours and may fall within the half-life of a supplement or the body's return to normal physiological status or homeostasis following the event. At least three different issues might need to be considered in terms of repeat use; subsequent use might require a different protocol to restore the physiological advantage or to meet the logistical requirements of competition spacing; desensitization of physiological systems may render the subsequent use of a supplement less effective; residual fatigue left from enhanced performance in the first event may carry over to the subsequent event [51•]. The corollary to these possibilities include an altered protocol (timing and dose), the decision not to use the supplement on all occasions, or the need to modify pacing strategies for earlier events. The sparse literature on repeated use of well supported performance supplements includes evidence that caffeine supplementation was equally effective when repeated, 24 hours apart, to enhance the performance of two cross-country ski time trials [55], despite increased muscle damage and soreness from the first bout, attributed to the greater effort made possible by caffeine use.

Finally, against a background of variability in day to day sports performance, worsened in size and outcome by poor study design/control, and small sample sizes [51•] is the likelihood that there are true individual responses to a supplement due to specific characteristics such as caliber [56] or sex, or to genetic differences. This requires effortful approaches around larger sample sizes and co-variate analysis, clever matching of subjects in cohort studies to isolate the characteristic of interest, and enhancement of "personalized medicine" research so that its outcomes are able to match its potential and industry marketing. Newer research around some of the issues is emerging, with studies on caffeine use reporting that females may be equally responsive to caffeine use in at least some scenarios of use [57]. Futhermore, single nucleotide polymorphisms (SNPs) of at least two different genes may account for true variability in the performance response to caffeine; CYP1A2, a gene associated with cytochrome P450 and hepatic metabolism of caffeine, and ADORA2A, a gene associated with the activity of the adenosine receptors [58•,59•]. Although studies of the effects of SNPs of these genes on metabolism and sports performance following caffeine use is emerging, it is likely to be more complex than identifying true responders and minimal responders or altering the characteristics of supplementation protocols to suit the specific activity of the genotype. Indeed, in terms of the CYP1A2 gene, there are various studies reporting a greater benefit in athletes with the AA allele rather than CC [60•], AC over others [61] and no difference between groups [62•]. Although this is an area of great interest, it is likely to be confused by issues of poor study design as well as specific effects of the rate of caffeine metabolism on the caffeine dose and sporting protocol.

Conclusion

Sports nutrition research should address the important questions that athletes and coaches need to consider to make evidence-based decisions about if and how to use a specific supplement. Medical supplements and sports foods can be chosen according to well-supported information about nutrient needs and nutritional goals. Unfortunately, the opportunity to undertake high quality investigations of performance supplements is dwarfed by the number of products on the market (even when these are limited to those with some evidence base) and the complexities of real-life scenarios of use that might make a difference to performance outcomes. Nevertheless, models to conduct and interpret studies of performance supplements are available. Caffeine provides a handy illustration of the way that knowledge and practice evolve in sports nutrition, with the likelihood that there is always something new or better to learn.

Conflict of interest

Nothing declared

Acknowledgements

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- • of special interest
- •• of outstanding interest

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This review translates the decision tree protocol for making evidence-based decisions about supplement use into an infographic.

25. Salinero JJ, Lara B, Del Coso J: **Effects of acute ingestion of caffeine on team sports performance: a systematic review and meta-analysis**. *Res Sports Med.* 2019, **27(2)**:238-256 http://dx.doi.org/10.1080/15438627.2018.1552146.

26. Mielgo-Ayuso J, Calleja-Gonzalez J, Del Coso J, Urdampilleta A, León-Guereño P, Fernández-Lázaro D: **Caffeine Supplementation and Physical Performance, Muscle Damage and Perception of Fatigue in Soccer Players: A Systematic Review**. *Nutrients* 2019, **11(2)** http://dx.doi.org/10.3390/nu11020440 pii: E440.

27. Souza DB, Del Coso J, Casonatto J, Polito MD: **Acute effects of caffeine-containing energy drinks on physical performance: a systematic review and meta-analysis**. *Eur J Nutr.* 2017, **56(1)**:13-27.

28. • Grgic J, Grgic I, Pickering C, Schoenfeld BJ, Bishop DJ, Pedisic Z: **Wake up and smell the coffee: caffeine supplementation and exercise performance-an umbrella review of 21 published meta-analyses**. *Br J Sports Med.* 2019 http://dx.doi.org/10.1136/bjsports-2018-100278. pii: bjsports-2018-100278 [Epub ahead of print].

This paper presents an umbrella review of 21 meta-analyses of caffeine and exercise/sports performance, rating the methodological processes and integrating the findings in terms of effects on different types of exercise.

29. • Aguilar-Navarro M, Muñoz G, Salinero JJ, Muñoz-Guerra J, Fernández-Álvarez M, Plata MDM, Del Coso J: **Urine Caffeine Concentration in Doping Control Samples from 2004 to 2015**. *Nutrients.* 2019, **11(2)** http://dx.doi.org/10.3390/nu11020286 pii: E286.

Although there are limitations with the translation of urinary caffeine concentrations following competition to caffeine intake practices, this study provides some interesting information on secular changes in the apparent use of caffeine as a competition performance aid since it was removed from the WADA List of Prohibited Substances in 2004.

30. Spriet LL: **Exercise and sport performance with low doses of caffeine**. *Sports Med.* 2014, **44 Suppl. 2**:S175-84 http://dx.doi.org/10.1007/s40279-014-0257-8.

31. Burke LM, Desbrow B, Spriet LL: *Caffeine for Sports Performance 2013*. Champaign, Illinois: Human Kinetics Inc.; 2013.

32. • Puente C, Abián-Vicén J, Salinero JJ, Lara B, Areces F, Del Coso J: **Caffeine Improves Basketball Performance in Experienced Basketball Players**. *Nutrients* 2017, **9(9)**:E1033 http://dx.doi.org/10.3390/nu9091033.

This study continues the pioneering work of this group in undertaking studies of caffeine and sports performance with real-world characteristics including the recruitment of high performance athletes, use of moderate caffeine doses, and simulated or actual competition measurements of performance in the field.

33. Del Coso J, Pérez-López A, Abian-Vicen J, Salinero JJ, Lara B, Valadés D: **Enhancing physical performance in male volleyball players with a caffeine-containing energy drink**. *Int J Sports Physiol Perform.* 2014, **9(6)**:1013-1018 http://dx.doi.org/10.1123/ijspp.2013-0448.

34. Portillo J, Del Coso J, Abián-Vicén J: **Effects of caffeine ingestion on skill performance during an international female rugby sevens competition**. *J Strength Cond Res.* 2016 http://dx.doi.org/10.1519/JSC.0000000000001763.

35. Del Coso J, Portillo J, Muñoz G, Abián-Vicén J, Gonzalez-Millán C, Muñoz-Guerra J: **Caffeine-containing energy drink improves sprint performance during an international rugby sevens competition**. *Amino Acids.* 2013, **44(6)**:1511-1519 http://dx.doi.org/10.1007/s00726-013-1473-5.

36. Lane SC, Hawley JA, Desbrow B, Jones AM, Blackwell JR, Ross ML, Zemski AJ, Burke LM: **Single and combined effects of beetroot juice and caffeine supplementation on cycling time trial performance**. *Appl Physiol Nutr Metab.* 2014, **39(9)**:1050-1057 http://dx.doi.org/10.1139/apnm-2013-0336.

37. • Pickering C, Grgic J: **Caffeine and Exercise: What Next?** *Sports Med.* 2019 http://dx.doi.org/10.1007/s40279-019-01101-0. [Epub ahead of print].

Even though caffeine has been studied for more than 60 years in relation to sports performance, there are still new issues to investigate to isolate better protocols that are specific to the sport and the individual athlete.

38. • Wickham KA, Spriet LL: **Administration of Caffeine in Alternate Forms**. *Sports Med.* 2018, **48(Suppl. 1)**:79-91 http://dx.doi.org/10.1007/s40279-017-0848-2.

This is an insightful review from a laboratory which has undertaken more than 30 years of research on metabolic and performance outcomes of caffeine research, on new forms of caffeine such as mouth rinses, gums and aerosols.

39. • Pickering C, Kiely J: **What Should We Do About Habitual Caffeine Use in Athletes?** *Sports Med.* 2019, **49(6)**:833-842 http://dx.doi.org/10.1007/s40279-018-0980-7.

This review identifies the issues underpinning individual tolerance to caffeine intake, and whether habitual caffeine intake should be considered, controlled or manipulated both in research efforts and in the implementation of caffeine supplementation protocols in sport.

40. Irwin C, Desbrow B, Ellis A, O'Keeffe B, Grant G, Leveritt M: **Caffeine withdrawal and high-intensity endurance cycling performance**. *J Sports Sci.* 2011, **29(5)**:509-515 http://dx.doi.org/10.1080/02640414.2010.54148.

41. • Lara B, Ruiz-Moreno C, Salinero JJ, Del Coso J: **Time course of tolerance to the performance benefits of caffeine**. *PLoS One.* 2019, **14(1)**:e0210275 http://dx.doi.org/10.1371/journal.pone.0210275 eCollection 2019.

This study involved a serial investigation of the effect of caffeine on performance over a 20 day span while receiving a placebo or 3 mg/kg daily dose around the exercise protocol. The findings confirmed that the effect of caffeine is diminished by habitual intake, but still remains ergogenic.

42. •• Burke LM, Hawley JA, Jeukendrup A, Morton JP, Stellingwerff T, Maughan RJ: **Toward a Common Understanding of Diet-Exercise Strategies to Manipulate Fuel Availability for Training and Competition Preparation in Endurance Sport**. *Int J Sport Nutr Exerc Metab.* 2018, **28(5)**:451-463 http://dx.doi.org/10.1123/ijsnem.2018-0289.

There is much confusion about the terminology, methodology and goals of various strategies that acutely or chronically manipulate carbohydrate and fat availability during training sessions (to promote adaptive responses or to support high quality training) or competition (to optimize performance). This review provides a summary of these strategies to enable a shared understanding between scientists, coaches and athletes.

43. Pinckaers PJ, Churchward-Venne TA, Bailey D, van Loon LJ: **Ketone Bodies and Exercise Performance: The Next Magic Bullet or Merely Hype?** *Sports Med.* 2017, **47(3)**:383-391 http://dx.doi.org/10.1007/s40279-016-0577-y.

44. •• Evans M, Cogan KE, Egan B: **Metabolism of ketone bodies during exercise and training: physiological basis for exogenous supplementation**. *J Physiol.* 2017, **595(9)**:2857-2871 http://dx.doi.org/10.1113/JP273185.

This is an exemplary review of the metabolism of ketone bodies in humans, and the potential role for exogenous intakes of ketone supplements. It presents an interesting theory of a range in which blood levels of circulating ketones is optimal for exercise metabolism.

45. •• Cox PJ, Kirk T, Ashmore T, Willerton K, Evans R, Smith A, Murray AJ, Stubbs B, West J, McLure SW, King MT, Dodd MS, Holloway C, Neubauer S, Drawer S, Veech RL, Griffin JL: **Clarke K. Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes**. *Cell Metab.* 2016, **24(2)**:256-268 http://dx.doi.org/10.1016/j.cmet.2016.07.010.

This investigation involves 5 separate studies of the effect of a novel ketone body product (a patented ketone ester produced by the authors)

on exercise metabolism, with the final study showing a benefit to the performance of endurance cycling when undertaken with a carbohydrate drink by well-trained cyclists. It is unusual for a sports supplement to be so extensively studied within a single paper, and to receive the attention of such a high impact journal.

46. Scott BE, Laursen PB, James LJ, Boxer B, Chandler Z, Lam E, Gascoyne T, Messenger J, Mears SA: **The effect of 1,3-butanediol and carbohydrate supplementation on running performance**. *J Sci Med Sport* 2018 http://dx.doi.org/10.1016/j.jsams.2018.11.027. pii: S1440-2440(18)30553-X [Epub ahead of print].

47. Evans M, Egan B: **Intermittent Running and Cognitive Performance after Ketone Ester Ingestion**. *Med Sci Sports Exerc.* 2018, **50(11)**:2330-2338 http://dx.doi.org/10.1249/MSS.0000000000001700.

48. • Leckey JJ, Ross ML, Quod M, Hawley JA, Burke LM: **Ketone Diester Ingestion Impairs Time-Trial Performance in Professional Cyclists**. *Front Physiol.* 2017, **8**:806 http://dx.doi.org/10.3389/fphys.2017.00806 eCollection 2017.

This study tried to replicate the results of the Cox et al. 2016 paper on supplementation with a ketone ester, using a protocol that was more specific to real life sport (professional cyclists, simulation of the upcoming world championship time trial course, integration with real world conditions of pre- and during time trial nutrition). The study was commissioned by the professional cycling team to allow them to decide whether to invest in the use of a ketone ester supplement. The lack of availability of the original supplement force the authors to trial a different di-ester; the lack of performance benefit and presence of a performance impairment was explained by gastrointestinal side-effects from the product.

49. • Stubbs BJ, Koutnik AP, Poff AM, Ford KM, D'Agostino DP: **Commentary: Ketone Diester Ingestion Impairs Time-Trial Performance in Professional Cyclists**. *Front Physiol.* 2018, **9**:279 http://dx.doi.org/10.3389/fphys.2018.00279 eCollection 2018.

This commentary, in response to the study of Leckey et al. 2017, provided valuable insights from experts working with ketone ester supplements (with one author having commercial interests in the original ketone monoester) of the difficulties of undertaking studies of exogenous ketone products.

50. •• Burke LM, Hawley JA: **Swifter, higher, stronger: What's on the menu?** *Science* 2018, **362(6416)**:781-787 http://dx.doi.org/10.1126/science.aau2093.

This was a commissioned paper which provided the authors with the opportunity to summarize key issues in sports nutrition, including some misunderstandings about the goals and protocols of sports nutrition research related to elite athletes within the wider science community.

51. • Burke LM, Peeling P: **Methodologies for Investigating Performance Changes With Supplement Use**. *Int J Sport Nutr Exerc Metab.* 2018, **28(2)**:159-169.

This paper summarizes the challenges of undertaking reliable and valid research on the performance effects of supplements. Protocols that address these challenges are provided. It serves as an underpinning paper for the IOC Consensus Statement on Dietary Supplements and the High Performance Athlete.

52. Burke LM, Practical: **Issues in Evidence-Based Use of Performance Supplements: Supplement Interactions, Repeated Use and Individual Responses**. *Sports Med.* 2017, **47 (Suppl. 1)**:79-100 http://dx.doi.org/10.1007/s40279-017-0687-1.

53. Felippe LC, Lopes-Silva JP, Bertuzzi R, McGinley C, Lima-Silva AE: **Separate and Combined Effects of Caffeine and Sodium-Bicarbonate Intake on Judo Performance**. *Int J Sports Physiol Perform.* 2016, **11(2)**:221-226 http://dx.doi.org/10.1123/ijspp.2015-0020 Epub 2015 Jul 13.

54. Carr AJ, Gore CJ, Dawson B: **Induced alkalosis and caffeine supplementation: effects on 2,000-m rowing performance**. *Int J Sport Nutr Exerc Metab.* 2011, **21(5)**:357-364 Epub 2011 July 22.

55. Stadheim HK, Spencer M, Olsen R, Jensen J: **Caffeine and performance over consecutive days of simulated competition**. *Med Sci Sports Exerc.* 2014, **46(9)**:1787-1796 http://dx.doi.org/10.1249/MSS.0000000000000288.

56. Jonvik KL, Nyakayiru J, van Loon LJC, Verdijk LB: **Viewpoint: Can elite athletes benefit from dietary nitrate supplementation?** *J Applied Physiol.* 2015, **119**:759-761 http://dx.doi.org/10.1152/japplphysiol.00232.2015.

57. Skinner TL, Desbrow B, Arapova J, Schaumberg MA, Osborne J, Grant GD, Anoopkumar-Dukie S, Leveritt MD: **Women Experience the Same Ergogenic Response to Caffeine as Men**. *Med Sci Sports Exerc.* 2019 http://dx.doi.org/10.1249/MSS.0000000000001885. [Epub ahead of print].

58. • Pickering C, Kiely J: **Are the Current Guidelines on Caffeine Use in Sport Optimal for Everyone? Inter-individual Variation in Caffeine Ergogenicity, and a Move Towards Personalised Sports Nutrition**. *Sports Med.* 2018, **48(1)**:7-16 http://dx.doi.org/10.1007/s40279-017-0776-1.

This review identifies issues in the individual responsiveness to the performance effects associated with caffeine supplementation and discusses the role of genetic testing. It is noted that the lead author is involved with a commercial company that undertakes such genetic testing.

59. • Southward K, Rutherfurd-Markwick K, Badenhorst C, Ali A: **The Role of Genetics in Moderating the Inter-Individual Differences in the Ergogenicity of Caffeine**. *Nutrients* 2018, **10** http://dx.doi.org/10.3390/nu10101352 pii: E1352.

This is an additional and independent review of issues in the individual responsiveness to the performance effects associated with caffeine supplementation and the role of genetic testing.

60. • Guest N, Corey P, Vescovi J, El-Sohemy A: **Caffeine, CYP1A2 Genotype, and Endurance Performance in Athletes**. *Med Sci Sports Exerc.* 2018, **50(8)**:1570-1578 http://dx.doi.org/10.1249/MSS.0000000000001596.

This study investigated the effects of different doses of caffeine on the 10 km cycling time trial performance of a large group of cyclists and found that carriers of the AA variant of the CYP1A2 gene ("fast metabolisers") had a greater performance enhancement with 2 and 4 mg/kg doses, while carriers of the CC variant had performance decrements, and AC variants produced a neutral experience.

61. Pataky MW, Womack CJ, Saunders MJ, Goffe JL, D'Lugos AC, El-Sohemy A, Luden ND: **Caffeine and 3-km cycling performance: Effects of mouth rinsing, genotype, and time of day**. *Scan J Med Sci Sports.* 2016, **26(6)**:613-619 http://dx.doi.org/10.1111/sms.12501.

62. • Puente C, Abián-Vicén J, Del Coso J, Lara B, Salinero JJ: **The CYP1A2-163C&A polymorphism does not alter the effects of caffeine on basketball performance**. *PLoS One.* 2018, **13(4)**: e0195943 http://dx.doi.org/10.1371/journal.pone.0195943.

This study failed to find a correlation between the effects of caffeine supplementation on a range of basketball skills and a simulated basketball gale and variants of the CYP1A2 gene.