# Misunderstanding the Female Athlete Triad: Refuting the IOC Consensus Statement on Relative Energy Deficiency in Sport (RED-S)

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An IOC consensus group has recently introduced a new umbrella term, that is, 'Relative Energy Deficiency in Sport' (RED-S) to describe the physiological and pathophysiological effects of energy deficiency in male and female athletes.[1] The authors assert that "new terminology is required to more accurately describe the clinical syndrome originally known as the Female Athlete Triad" that is a "more comprehensive, broader term for the overall syndrome, which includes what has so far been called the 'Female Athlete Triad'."[1] This new terminology (RED-S) is insufficiently supported by scientific research to warrant adoption at this time. The Female Athlete Triad has more than 30 years of published evidence to support its existence in the scientific literature with strong evidence for its clinical sequelae and should remain a focus of scientific inquiry and translation.[2–6] Moreover, several major concerns and errors with the IOC consensus statement should give researchers and practitioners great pause before adopting the IOC's new terminology, its theoretical construct and its proposed recommendations for screening and return to play.

As stated by the IOC authors, the science of energy deficiency in the male athlete and in other groups is still in its 'infancy'.[1] In contrast, research on the Triad has been published since the early 1990s[4] and, in fact, even earlier. Reports of menstrual and other problems in athletes were becoming prevalent in the literature as early as the 1960s, but particularly in the 1970s and 1980s.[7–10] The first symposium related to the topic at the American College of Sports Medicine (ACSM) Annual Meeting was organised by Barbara Drinkwater in 1981 and was entitled 'Menstrual Irregularities in Female Athletes'. The term 'Female Athlete Triad' was introduced at a workshop in 1992.[4] The first position stand from the ACSM was published in 1997,[2] and a revised position stand was published in 2007.[3] In 2014, a comprehensive consensus paper on diagnosis, treatment and return to play on the Female Athlete Triad was published by the Female Athlete Triad Coalition,[5 6] which has been endorsed by the ACSM, the American Medical Society for Sports Medicine and the American Bone Health Alliance. The National Collegiate Athletic Association in the USA has been highlighting the Coalition's Triad Consensus paper in their Sports Science Institute Newsletter by publishing a four-part series to highlight the paper and to help with dissemination of the treatment and return-to-play guidelines.

While we appreciate the need for improved thinking in medical science, we strongly believe it is unwise and misleading to propose a new approach based on faulty science. We strongly believe that it is unwise to distract and mislead the medical community from the well-known term 'the Female Athlete Triad'.[11] The IOC paper lacks scientific integrity in two ways. First, the scientific evidence of RED-S as it applies to men, non-Caucasians and disabled individuals is in its infancy and is not sufficiently developed to warrant a new theoretical construct. We support the effort to call for more research in these populations; however, it should not be at the expense of a focus on and priority of the female athlete. Second, the IOC paper[1] is fraught with errors and misinterpretations of the scientific literature per se. The errors discussed in this paper include a flawed framework for the RED-S model, an incorrect representation of the Female Athlete Triad, applying data in women to make recommendations in men, frank errors in treatment recommendations, a return-to-play model that is ambiguous, does not accommodate cumulative risk and is difficult to apply in clinical practice, errors in presenting the physiology of energy deficiency and low energy availability and subsequent impact on reproductive function, errors in the diagnosis of low bone mineral density (BMD) in adolescents, errors in effects of oestrogen on bone and calcium, errors in calcium and vitamin D recommendations and many other errors as discussed below.

A unique feature of the IOC paper is the introduction of the 'hub and spoke' diagram.[1] However, this figure illustrates a poorly developed concept referred to as RED-S, and misrepresents three decades of Triad science. What are illustrated as 'spokes' on a wheel with a RED-S hub are the oversimplified listing of seemingly independent physiological systems, functions and mechanisms when in fact these physiological systems, functions and mechanisms are not independent of one another, but rather interact and exhibit synergistic and antagonistic effects. The complex interactions of physiological factors with a causal link to low energy availability have been described and experimentally manipulated in studies[12–19] that provide the scientific foundation for the most severe clinical outcomes identified in the triangle diagram illustrating the Female Athlete Triad. At the centre of the RED-S hub and spoke diagram is the term 'relative energy deficiency' which, according to the IOC authors, refers to the aetiological factor underpinning RED-S, that is, "an energy deficiency relative to the balance between dietary energy intake (EI) and the energy expenditure required to support homeostasis, health and the activities of daily living, growth, and sporting activities." This definition of the 'energy deficiency' component of RED-S in terms of energy balance is incongruent with the definition of 'energy availability' used throughout the rest of the IOC paper.[1] Energy balance and availability are not synonymous.[20] Careful work by Triad researchers has demonstrated that Triad conditions can be present in women who are in 'energy balance' and thus do not exhibit 'energy deficiency' as defined in the

IOC paper, but likely exhibit 'low energy availability' as defined and supported in work by Loucks and colleagues[15–17 20] and included (albeit defined incorrectly) in the IOC paper. The psychological portion of the diagram also appears independent of all other factors, another alarming misrepresentation, as decades of research in the field of eating disorders (ED) and the Triad would substantiate.[21–23]

Another error presented in the IOC paper and its figure is the simplistic and underdeveloped approach to understanding the Triad by implying that the Triad platform is limited to reproductive and skeletal issues, and that the IOC RED-S idea is more comprehensive. The 2007 position stand on the Triad[3] and the 2014 consensus paper[5 6] include a discussion of other medical issues, to include cardiovascular issues such as impaired endothelial vasodilation, impaired perfusion to working muscles, impaired skeletal muscle oxidative metabolism, lipid dysfunction, problems with the central nervous system, gastrointestinal system and renal system. Certainly the psychological concerns are highlighted in all of these publications on the Female Athlete Triad[2–6] when discussing disordered eating (DE) and ED. Stress fractures are a component of the Triad even though they are not specifically listed in the diagram of the Triad; likewise, metabolic and endocrine perturbations are mechanisms of the components of the Triad. Clearly, the most serious clinical sequelae of the Female Athlete Triad include ED, reproductive disorders and skeletal outcomes. In particular, negative bone outcomes are especially concerning since they are questionably irreversible,[2 3 5 6] and as such, are highlighted in the framing of the terminology of the Triad. Such a highlight on the most serious clinical sequelae benefits many athletes who suffer from these clinical outcomes, and does not exclude other outcomes. The Triad framework is also most favourable for knowledge translation to the most frequently affected population, namely young female athletes and exercising women. Alternatively, the introduction of a new term (RED-S), and a new (flawed) illustration of the physiology of the syndrome diffuses the messaging about the heightened susceptibility to and severity of effects of the Triad in girls and women, and places too much emphasis on 'sport', thus overshadowing the many recreational athletes that are similarly affected.[11 24 25]

The IOC paper incorrectly claims the recognition that energy deficiency can impact male athletes as something new; this is not new and Triad researchers and others have been alluding to this concern since 1993. The first 1993 ACSM workshop paper[4] and the 1997[2] as well as the 2007[3] versions of the ACSM Triad position stands indicate that further research is necessary to explore clinical outcomes in male athletes. Although several studies have documented the existence of Triad-like conditions in male cyclists,[26 27] judoists[28] and horse jockeys,[29] almost two decades later few data exist to support the existence of serious clinical sequelae in men relative to those in women that result from energy deficiency.

Meanwhile, there is good reason to suspect that sex differences protect men against the serious clinical consequences of energy deficiency that afflict women. Testosterone promotes bone as well as muscle growth, and effects of low testosterone on bone formation are different from the effects of low oestrogen on bone resorption.[30 31] Testosterone endows men with wider bones that are less susceptible to fracture.[32] Furthermore, the energetic costs of reproduction are much lower in men than in women.[33] Men do not have to 'fuel' ovarian and menstrual cycles, let alone gestation and lactation. Evidence of effects of low energy availability on sperm count and motility is largely non-existent, in part because egg cells mature by growing in size, whereas sperm cells mature by shrinking. Sperm do not store large quantities of energy derived from the male body, and inside women they derive their fuel for motility from the female body. For these and other reasons, reproductive and skeletal disorders may occur in men in extreme energy deficiency, but a prevalence as high as that in women at less severe levels of energy deficiency is doubtful.

Many more studies should document a concerning prevalence of physiological and clinical consequences of low energy availability in male athletes before a new term is introduced for those specific conditions in men. Moreover, the recent studies documenting ED and low bone density in men[34–36] deserve to be extended without bias stemming from existing literature in women. It has taken decades to learn that important sex differences exist in male and female physiology, and we should not repeat previous mistakes by establishing clinical guidelines for both sexes when there are data primarily only for one sex. It is misleading in this regard that the risk stratification and return-to-play guidelines in the IOC paper are developed mostly from studies in women,[1] include few male-specific end points and ignore that implementation problems will exist if applied to male athletes. The preceding concerns of lack of data and the errors in applying clinical guidelines to more than one population are magnified when other issues such as race, ethnicity and ability are considered. The point made by the IOC authors that low energy availability has serious consequences in male athletes, non-Caucasians and individuals with disabilities is important, but there is no evidence for their recommendation. Indeed, their recommendations should have stopped at advocating for more research and should not have extended to screening, treatment and return-to-play recommendations.

The IOC authors propose a new risk assessment and return-to-play model, 'Red Light-Yellow Light-Green Light', representing high-risk, moderate-risk and low-risk athletes, respectively.[1] Concerning is both the lack of evidence and lack of quantification behind some of the risk factors noted within this framework. For example, the lack of clarity and quantification of 'yellow light' risk factors, such as 'prolonged abnormally low per cent body fat', 'prolonged energy deficiency' and 'lack of progress in treatment', makes each one of them difficult to interpret in the return-to-play schema. Likewise, this framework does not take into account cumulative risk in a quantitative way that can be measured over time to assess improvement or decline. Similarly, the return-to-play categories noted in table 3 do not provide the clinician any guidance as to the number of risk factors within each category that warrant the return-to-play recommendations. As such, adopting the IOC return-to-play model will lead to ambiguous decision-making.

The IOC paper is also weakened by the authors' disregard for accuracy when referencing scientific literature. The IOC paper[1] is fraught with fundamental errors and misinterpretations of the literature. Several of these errors are described below. Generally speaking, the paper is poorly referenced throughout. There are many instances where inaccurate references are used, several instances where statements are not referenced and many instances where original research is not referenced. The most important and blatant errors are listed below.

## HORMONAL AND METABOLIC IMBALANCE SECTION

1. The authors state that "Abnormal levels of hormones, LH pulsatility, inadequate body fat stores, low energy availability (EA) and exercise stress may be aetiological factors in menstrual disorders in athletes. Marked reduction in EA

may disrupt the LH pulsatility by affecting the hypothalamic hormone gonadotropin-releasing hormone (GnRH) output which subsequently alters the menstrual cycle." These statements are incorrect. The hypothalamus can make GnRH in varying amounts or patterns (GnRH output) in different states of energy availability, but it is specifically abnormal GnRH *pulsatility* that impacts gonadotropin pulsatility, as opposed to GnRH output, and that leads to amenorrhoea.[37]

2. The authors state that "Subtle menstrual dysfunction, such as very light bleeding, mildly extended menstrual interval and premenstrual and postmenstrual spotting may occur, and may be underestimated by routine screening." De Souza *et al*[24] is cited for this statement.

   Although De Souza *et al*[24] reported that subtle menstrual disturbances are prevalent among physically active women, it was highlighted that these subtle menstrual disturbances are difficult to detect clinically. In addition, there is no mention of light bleeding or spotting in the De Souza *et al*[24] paper.

## HEALTH AND PERFORMANCE SECTION

1. The authors state that "hormonal and metabolic abnormalities caused by RED-S and carbohydrate deficiency can result in a decreased production of growth hormone." This statement is incorrect. Low EA is associated with an *increase* in growth hormone, which is most likely a result of reduced circulating insulin-like growth factor 1 (IGF1) concentrations and hepatic growth hormone resistance.[38 39]
2. The authors state that "Oestrogen increases uptake of calcium into blood and deposition into bone, while progesterone facilitates the actions of oestrogen through multiple complex mechanisms." This is also inaccurate. Oestrogen acts by inhibiting osteoclast activity, not by increasing uptake of calcium into blood and deposition in bone.[40] Calcium absorption from the gut is driven by 1,25(OH)2 vitamin D.[41] It is not clear what (if any) bone effects of oestrogen are facilitated by progesterone and how. No original research references are provided to support the proposed progesterone effects on bone in the IOC paper.
3. The authors state that testosterone stimulates osteoclast activity. Testosterone does not stimulate osteoclast activity. Testosterone directly stimulates osteoblast activity thereby upregulating bone formation,[30 42] and may inhibit osteoclast activity through its aromatisation to oestrogen (which has primarily antiresorptive effects).
4. The authors state that "DE/ED in male jockeys are associated with low BMD" and cite Dolan *et al*[29] as a reference for this statement. This is an inaccurate reference for this statement. Dolan *et al*[29] did not assess DE or ED in their study. Rather, Dolan *et al*[29] report that low BMD in jockeys was associated with low IGF-1 and elevated sex hormone-binding globulin concentrations.

## SCREENING AND DIAGNOSIS SECTION

### Bone health

The authors state that "In the adolescent, DXA should include the whole body (head excluded) in addition to the lumbar spine… A value below −2.0 SD is considered as osteoporosis with the presence of secondary clinical risk factors." This statement requires clarification. The International Society of Clinical Densitometry (ISCD) recommends assessment of lumbar spine or whole body sites for assessment of bone density in adolescents, and while it prefers the assessment of whole body less head (to whole body), when technically feasible, it does not indicate that whole body BMD assessment should not be performed.[43] In addition, the ISCD defines osteoporosis in adolescents as low bone density z-scores ( ≤−2) with a history of clinically significant fracture[43] and not a low bone density z-score alone. This stand has been reiterated in the 2013 position statement from the ISCD.[44 45] It is important to clarify this and to indicate what conditions constitute secondary clinical risk factors.

## TREATMENT SECTION

1. For the section regarding weight gain and improvement in bone density, the authors state "However, full recovery may not be feasible, as bone microarchitecture is also impaired." The reason for lack of full recovery is not that bone architecture is also impaired. Impaired bone architecture is a consequence of many of the same factors that lead to low bone density.[46 47] Lack of full recovery of bone parameters is likely consequent to incomplete recovery of certain hormonal changes (such as cortisol elevation) despite an improvement in energy status.[48]
2. The authors recommend that the "athlete diet should include 1500 mg/day of calcium." The reference that is cited for that statement[49] does not directly state that 1500 mg/day is the appropriate calcium intake for athletes. Rather, the article provides guidelines for how to counsel individuals about appropriate calcium intake, but does not recommend a certain intake. Furthermore, the appropriate calcium intake *for athletes* is not mentioned in the article.[49] The current recommended dietary allowance for calcium from the 2011 Institute of Medicine guidelines is 1300 mg/day for adolescents and 1000 mg/day for young adults.[50 51] According to the American Academy of Pediatrics Committee on Sports Medicine and Fitness,[52] and others,[53] it is recommended that *amenorrhoeic* athletes intake 1500 mg of calcium per day. As such, this is an example of a statement that uses imprecise wording and is not properly referenced.
3. The authors state that "Programmes of high-impact loading and resistance training should be implemented at least 2–3 days/week for athletes in non-weight bearing sports and/or those with decreased BMD." This statement is not supported by any reference. In fact, one may argue that high-impact loading activity may precipitate fractures in amenorrhoeic women with very low bone density. This issue is not discussed.
4. The authors state that leptin "can be used to stimulate appetite." On the contrary, leptin is an anorexigenic hormone and therefore suppresses appetite[54–56] and, in fact, recombinant leptin administration is associated with suppression of appetite and weight loss in women with functional hypothalamic amenorrhoea.[57 58]
5. The authors state that "The Endocrine Society Guideline (2011) recommends maintaining vitamin D [25(OH)D] blood levels above 32–50 ng/mL, with 1500–2000 IU/day of vitamin D." This is inaccurate. The guidelines are as follows[59]: "We recommend using the serum circulating 25(OH)D level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter), and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (525–725 nmol/liter)", and "We suggest that adults aged 19–50 yr require at least 600 IU/d of vitamin D to maximize bone health and muscle function. It is unknown whether

600 IU/d is enough to provide all the potential non-skeletal health benefits associated with vitamin D. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1500–2000 IU/d of vitamin D." The Endocrine Society guidelines do not provide a recommended target range for vitamin D.

6. The authors state that "use of the oral hormonal contraceptive pills in athletes with functional hypothalamic amenorrhea have been reported to have a detrimental effect on BMD through the suppression of androgen secretion and cause premature closure of the epiphyses compromising growth of the long bones in adolescents." The authors cite Scheid *et al*.[60] Scheid *et al*[60] is the wrong reference as that paper has nothing to do with any of these factors.
7. Throughout the treatment section, no critical analysis of randomised controlled trials versus prospective studies is presented and no source literature is referenced. This is a major flaw as treatment recommendations are included in the IOC paper. In addition, treatment recommendations for bone health in men are not based on studies in male athletes.

## SUMMARY

We are concerned that readers of the IOC paper will be confused and misled by the poorly referenced statements and frank (and sometimes dangerous) errors in the paper. The IOC authors should publish a correction of these and other errors noted. Broadening research of low energy availability in other groups, such as the male athlete, athletes of diverse ethnicities and the disabled athlete may help to advance science and may one day warrant introduction of a specific term for whatever serious clinical sequelae of energy deficiency may be discovered in future research on men.

Research on the 'Female Athlete Triad' has forged a platform from which a broad array of healthcare providers (eg, physicians, sport dietitians, mental health professionals and athletic trainers) have made great strides in learning how to manage and treat affected women. Research on the 'Female Athlete Triad' has also been translated to the lay public such that more and more affected female athletes and exercising women willingly seek education, prevention and treatment.

Meanwhile, subsuming the term 'Female Athlete Triad' under the umbrella of the term RED-S has the potential to confuse rather than enlighten, and undo decades of work educating and advocating for awareness, prevention and treatment for the Triad. The individual most impacted by the de-emphasis on the Triad will be the female athlete herself. The overwhelming clinical importance of the Female Athlete Triad compared with other conditions under the proposed RED-S umbrella will continue to make a specific reference for the Triad useful for those who deal with it, including physicians, coaches, sport dietitians, athletics trainers, parents and, most importantly, female athletes. As such, efforts promoting awareness, prevention and treatment of the Female Athlete Triad remain critically important and should not be overshadowed by an ill-conceived and poorly defended new construct.

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