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What is the evidence for a Triad-like syndrome in exercising men?

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Recently, an expert panel under the leadership of the Female and Male Athlete Triad Coalition (Coalition) convened and determined that there was sufficient evidence to date to warrant an official consensus statement and naming of a Triad-like condition in exercising men which will be published in 2019. Our understanding of a Triad-like condition in men will be developed using an evidence-based medicine approach to ensure the accuracy of the component conditions and their physiological relationships, and with the understanding that it is clinically diagnosable and treatable. This review will present the current evidence on low energy availability, reproductive function, and bone health in exercising men to provide an overview of an initial working model of a similar Triad-like syndrome in male athletes. In male athletes, it appears that both the hypothalamic gonadal axis and the skeletal system are impacted by low energy availability and energy deficiency. The impact of energy deficiency on bone in male athletes appears to occur frequently with a relatively high incidence of bone stress injuries presenting in the presence of low bone mineral density, and the impact to the hypothalamic gonadal axis seems to be translated to both spermatogenesis and androgenic hormonogenesis with both oligospermia and low testosterone concentrations observed. Lastly, men appear to be robust and more resilient to the effects of low energy availability compared to women, requiring more severe energetic perturbations before alterations are observed and are more quickly reversible in men than in women.

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Introduction

The Female Athlete Triad (Triad), first named and presented to the public in 1997 [1] and adopted as an official position stand by the American College of Sports Medicine, was updated in 2007 [2] and represents the scientific foundation of the clinical conditions affecting the health of exercising women. The Triad was established using a scientifically rigorous evidence-based approach to develop its model, building upon decades of research [2]. The current model, as defined in the 2007 position stand, is built on the premise that low energy availability (energy deficiency) presenting with or without disordered eating directly causes menstrual disorders and poor bone health, and that menstrual disorders can also contribute to poor bone health [2]. The Female Athlete Triad Coalition (Coalition), an international organization of clinicians and researchers, and the American College of Sports Medicine have played primary roles in sheparding Triad research and allowing for scientific translation by developing guidelines for prevention and return to play [3,4].

The Female Athlete Triad Coalition underwent an official organizational name change in 2019 to become the Female and Male Athlete Triad Coalition as a way to emphasize and recognize the emerging data which support a similar Triad-like model in exercising men. Renaming the Coalition was one of the actionable outcomes of a roundtable meeting held in Denver, CO by Dr Aurelia Nattiv and Dr Michael Fredericson, and under the leadership of the Coalition, to bring together experts to assess and discuss the evidence available to date in support of a Male Athlete Triad model. The expert group concluded that sufficient evidence exists to warrant an official consensus statement and naming of a Male Athlete Triad. An official Consensus Statement will be published under the leadership of the Female and Male Athlete Triad Coalition in late 2019 to officially name and describe the current state of knowledge of a Male Athlete Triad. To date, several papers have addressed Triad-like issues in male athletes [5,6••,7,8,9••,10••] but much more research is needed to fill gaps in the literature and to develop an evidence-based model with scientific rigor in a manner similar to what has been done for the Female Athlete Triad model [1–4,11].

Recently, much attention has been directed to the concept of Relative Energy Deficiency in Sport (RED-S), largely due to its application to men [12]. While the attention around RED-S has been beneficial in garnering attention to the concept of a Triad-like condition in men, concerns regarding the accuracy and scientific validity of the RED-S model [13] have been documented. An analysis of the quality of supporting evidence of RED-S and of the Female Athlete Triad models has been recently evaluated [14] and we have highlighted the failure of the RED-S model to withstand the test of scientific rigor as a working model due to the lack of scientific evidence for many of the proposed associations between relative energy deficiency and the

physiological and performance outcomes of the model itself [14]. As a Male Athlete Triad model is developed over the next several years, scientific rigor and evidenced-based medicine will be fundamental to its development. Important considerations include the identification of each component condition, the accuracy behind the evidence supporting physiological relationships between conditions, and the focus on clinical relevance to ensure the condition is clinically diagnosable and treatable. We as a scientific community and consumer of medicine must continue to prioritize the importance of scientific rigor, quality of evidence, and attention to clinical relevance as a model for a Male Athlete Triad is developed.

This review will provide a report on the current knowledge for an initial working model of a similar Triad-like syndrome in male athletes based on available evidence to date. This review will present the evidence on low energy availability, reproductive function and bone health in exercising men. This paper will place an emphasis on the scientific evidence available to inform us of the physiology of each component of a Triad-like syndrome in men.

Energy availability associated with a Triad-like syndrome in male athletes

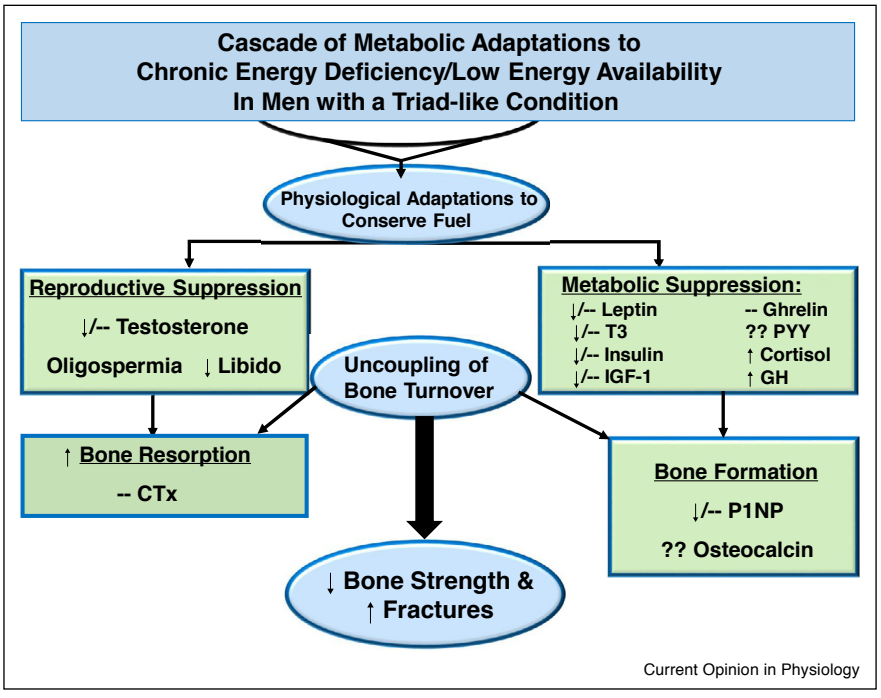
The model

Considering the evidence available to date, an initial working model of a Triad-like syndrome in men is likely to resemble the Female Athlete Triad model with three similarly themed inter-related components, which are likely to be described as a) low energy availability or energy deficiency with or without a disordered eating etiology, b) suppression of reproductive function that will include low testosterone concentrations and poor semen quality, and c) impaired bone health. With scientific evidence, the characteristics of each of these similarly themed inter-related components will need to be definitively described by way of directional arrows that inform the causal relationships among these components, whether the most severe clinical sequelae can be reversed, and if subclinical conditions are apparent in men. Notably, such a model will be published late in 2019 by the Female and Male Athlete Triad Coalition to formally describe and name the Male Athlete Triad.

Evidence of a Triad-like syndrome in male athletes

In male athletes, it appears that both the hypothalamic pituitary gonadal (HPG) axis and the skeletal system are impacted by low energy availability and energy deficiency in a manner presented in Figure 1. In fact, the preponderance of evidence to date demonstrates that the impact of energy deficiency on bone in male athletes appears to occur frequently with a relatively high incidence of bone stress injures presenting in the presence of low bone mineral density in particular subsets of male athletes [6••,15]. The impact to the HPG axis of low

Figure 1



Summary of the effects of low energy availability on metabolic, reproductive, and bone health in exercising men. EA, energy availability; T3, total triiodothyronine; PYY, peptide YY; IGF-1, insulin-like growth factor 1; GH, growth hormone; CTX, C-terminal telopeptide type I collagen; P1NP, N-terminal propetide of type I procollagen.

energy availability in male athletes seems to be translated to both spermatogenesis and androgenic hormonogenesis, with poor morphology of sperm, to include immature sperm and round cells, poor forward motility and poor penetration of cervical mucous and low testosterone concentrations observed in male athletes, particularly in athletes engaged in leanness sports and after very strenuous bouts of prolonged exercise [16–19]. The evidence available to date for each component of a Triad-like syndrome in male athletes will be discussed below.

The evidence for low energy availability in a Triad-like syndrome in male athletes

To date, cross-sectional reports of hypogonadotropic hypogonadism, including low testosterone [20–23] and poor semen quality/oligospermia [17,24], and an increased rate of bone stress injuries [6••,7,15] have been reported in male athletes, particularly in those sports that favor leanness. Leanness sports include: a) endurance/anti-gravitational sports such as long distance running, triathlons, road cycling, ski jumping, and high jumping where a high body weight tends to restrict performance, b) weight-class sports, such as wrestling, judo, boxing, light weight rowing, and taekwondo where specific weight requirements must be met prior to competition, and c) aesthetic sports, such as gymnastics, figure skating, and diving, where there is a subjective judging component; all of which prioritize a lean body type to lend a competitive advantage [48].

When examining energy availability and its impact on reproductive and bone health, both acute and long-term, chronic perturbations must be considered. Acute bouts of strenuous exercise, that is, ultra-endurance events, are associated with metabolic hormone alterations in exercising men including suppression of leptin and IGF-1 [19] and increases in cortisol [16,18] and GH [16]. Only two sets of investigators have manipulated short-term exercise and energy intake over 4–5 days to induce low energy availability in men in a manner similar to the studies conducted by Loucks *et al.* [25–27] which helped develop the Female Athlete Triad model and to underscore the causal role of energy availability on other Triad components. The first of these studies conducted in exercising men, by Koehler *et al.* [9••], set energy availability at either 45 or 15 kcal/kg FFM/day and observed reductions in both leptin and insulin concentrations, with no effect on TT_3 or IGF-1 concentrations. Energy availability was set through a combination of diet and exercise manipulations, or by manipulating diet alone, and the changes observed were independent of the manner in which low energy availability was achieved (i.e. via energy restriction or exercise energy expenditure). In a similar study from Papageorgiou *et al.* [10••], restricted energy availability, set at 15 kcal/kg FFM/day, failed to suppress TT_3, insulin, leptin, or IGF-1 concentrations. These findings are in stark contrast to the findings of Loucks *et al.* [26,27] in women exposed to varying levels of energy availability. Thus, further research is warranted to determine the factors and conditions that do, in fact, cause perturbations similar to that observed in the aforementioned acute ultra-endurance events versus short-term and long-term exposure to low energy availability in men and to compare between men and women. These details will be necessary to define the components of a Triad-like syndrome in men and to provide the appropriate scientific evidence in support of such a syndrome. Both the magnitude and the duration of low energy availability or energy deficiency on metabolic hormones and resting metabolic rate (RMR) also needs to be defined in men.

Some evidence for metabolic adaptations to energy deficiency in men is provided by the multi-stressor Army Ranger studies; that is the effects of chronic energy restriction on the induction of metabolic adaptations in men during an 8-week Army Ranger training course where energy deficiency was combined with additional stressors, including sleep deprivation and psychosocial stress [28•]. The 8-week Army Ranger training course resulted in significant energetic perturbations, including declines in total body mass, fat mass, and fat free mass, reductions in the concentrations of TT_3, IGF-1 and insulin, and increases in the concentrations of cortisol and GH [28•]. Notably, after 4–5 weeks of recovery, most metabolic perturbations returned to pre-exposure values. These findings provide scientific evidence in support of the suppressive effects of severe energy restriction and exercise during various stressful environments with respect to suppression of the metabolic hormonal profile in men.

The evidence for suppressed reproductive function in a Triad-like syndrome in male athletes

In the aforementioned short-term study which manipulated energy availability to 15 kcal/kg FFM/day [9••], no difference in testosterone concentration was observed compared to exposure to an energy availability of 45 kcal/kg FFM/day. This finding is somewhat surprising since perturbations as low as an EA of 15 kcal/kg FFM/day can be considered severely low energy availability [29]. However, when we consider observations in the Loucks *et al.* [26] experimental paradigms, estradiol was not suppressed until energy availability was severely low and set at 10 kcal/kg FFM/day. Thus, these data suggest that, in men, perturbations to reproductive function require reductions that are more aggressive (i.e. lower) in energy availability than 15 kcal/kg FFM/day, or must include chronic or repeated exposure for prolonged periods of time. Further testing is warranted to clarify this point in the literature.

Acute bouts of prolonged, strenuous, outdoor exercise, such as running and cycling races of ~160–1200 km and the multi-stressor Army Ranger studies do provide

evidence for the effects of low energy availability or energy deficiency on reproductive function in men (Table 1). For example, acute bouts of ultra-endurance exercise in trained men were, in fact, successful at the induction of a hypogonadal state characterized by reduced testosterone [16,18,19] and LH [18] concentrations. In the Army Ranger multi-stressor 8-week study, concentrations of testosterone were reduced, falling below the normative range of values, and mean LH concentration was reduced in a subgroup of soldiers who were not provided supplemental calories and thus exposed to more severe energy restriction [28•]. When examining the pulsatile secretion of LH, there is also evidence of reproductive suppression in endurance athletes, but only in cases of extremely high training loads. Runners averaging >125 km/wk displayed reduced LH pulse frequency [22], whereas runners with a training load of only ~80 km/wk demonstrated no changes in LH pulse frequency compared to controls [20,30]. In endurance trained men averaging >450 min/wk of training, there were no differences in LH pulse frequency or amplitude compared to sedentary controls [23]. Experimental models of energy restriction alone, however, demonstrate reduced LH pulse frequency in both men and male monkeys [31,32], suggesting that men participating in high training volumes are likely energy deficient and not supplementing their energy intake sufficiently to meet the energetic demands of training.

As a caveat, although testosterone concentrations in men participating in high volume training may have lower testosterone concentrations compared to what is observed in untrained men, oftentimes, the values are still within the normal physiological range [20,21,23]. Specifically, runners averaging 64–80 km/wk were at the lower end of normal testosterone concentrations, but still within range [20,21]. And, a group of endurance trained men, although not necessarily runners but averaging >450 min of exercise per week, had lower concentrations of total and free testosterone compared to sedentary controls, but were again within the normal range [23]. Data published from Hackney's group also support the findings of low resting testosterone concentrations in endurance trained athletes, but also emphasizes that while the testosterone concentrations observed are low (within 50–75% of normal), they are still within the low-normal range [33,34].

In the 1990s our lab proposed that a 'volume-threshold effect' was apparent in high mileage runners and effects to the reproductive axis were translated when exercise volumes were excessive. We reported (Figure 2) that high mileage runners (108.0 ± 4.5 km/wk) had lower testosterone levels, decreased sperm motility, an increased number of immature sperm, and decreased sperm penetration of bovine cervical mucus compared to moderate distance runners (54.2 ± 3.7 km/wk) and controls [17]. We concluded that in high mileage runners, decreased testosterone concentrations and abnormal semen profiles underscore the importance of meeting energy needs during periods of high exercise energy expenditure associated with high volumes of exercise training [17,24]. It is also notable that in our study, moderate mileage running (40–60 km/wk) was not associated with alterations to

Table 1

Testosterone concentrations in a subset of studies of exercising men. Data presented as mean ± SE (nmol/L)

Study	Pre	Post	Recovery	Control	Significance
Short term restricted EA					
Koehler *et al.* (caloric restriction)	18.72 ± 1.42	17.44 ± 2.95			NS
Koehler *et al.* (caloric restriction + exercise)	18.27 ± 1.59	15.46 ± 3.33			NS
Acute exercise bouts					
Kraemer *et al.* (Runners)	12.32 ± 1.41	6.96 ± 1.01			Pre versus Post
Kraemer *et al.* (Cyclists)	13.81 ± 1.30	5.59 ± 1.53			Pre versus Post
Kupchak *et al.*[a]	14.9	10.9	13.5		Pre versus Post Post versus Recovery
Multi-stressor environment					
Friedl *et al.*[b]	16.3 ± 1.6	2.2 ± 0.9	19.3 ± 3.2		Pre versus Post Post versus Recovery
Cross-sectional					
McColl *et al.*[a]	13.8 ± 1.0			29.4 ± 1.0	NS
Wheeler *et al.*[a]	24.0			28.0	Runners versus Controls
Hackney *et al.*	17.3 ± 1.6			25.1 ± 2.3	Trained versus Untrained

Conversion factor: ng/mL = nmol/L × 0.288.
NS: not significant.
[a] Approximations of concentrations based on available data and figures.
[b] Subset of completers who had a follow-up visit during recovery.

Figure 2

	High Mileage Runners (n = 11)	Moderate Mileage Runners (n = 9)	Controls (n = 10)	p
Totals				
Volume (ml)	4.1 ± 0.5	3.5 ± 0.6	2.5 ± 0.5	0.116
Sperm Density (× 10^6/ ml)	88.5 ± 14.8*	127.2 ± 32.2	175.5 ± 24.9	0.045
Sperm Count (× 10^6)	352.0 ± 69.6	317.8 ± 83.3	375.9 ± 58.9	0.858
Normal Motile Count (× 10^6)	58.5 ± 10.8°	118.8 ± 20.3	106.7 ± 22.3	0.052
Motile Count (× 10^6)	134.5 ± 23.9*	240.1 ± 45.3	224.7 ± 39.1	0.037
Motility				
Forward Progressive (%)	40.3 ± 4.3*	48.8 ± 4.5∞	58.7 ± 2.4	0.006
Non-Progressive (%)	6.1 ± 1.4**	7.3 ± 1.1**	2.0 ± 1.0	0.014
Non-Motile (%)	53.6 ± 4.4*	43.9 ± 3.8	39.3 ± 1.9	0.023
Morphology				
Normal (%)	40.9 ± 2.0	46.4 ± 4.4	47.0 ± 3.3	0.341
Large (%)	2.5 ± 0.8	1.7 ± 0.6	2.3 ± 1.0	0.760
Small (%)	3.9 ± 0.7	2.5 ± 1.1	2.3 ± 0.5	0.350
Amorphous (%)	34.5 ± 2.3	37.2 ± 2.2	37.4 ± 2.8	0.653
Immature(%)	16.8 ± 2.2°	10.1 ± 2.0	10.9 ± 1.2	0.031
Round Cells (million)	8.0 ± 1.6°	2.5 ± 1.1	2.5 ± 0.9	0.004
Sperm Penetration of Cervical Mucus				
Penetrak (mm)	26.8 ± 6.3*	37.5 ± 7.2	43.2 ± 7.0	0.024

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Semen characteristics of high mileage runners, moderate mileage runners, and sedentary controls. Reprinted with permission from De Souza *et al.* [17] © Georg Thieme Verlag KG.

testosterone or sperm quality and that the reproductive profile in these runners was indeed similar to that observed in the non-running sedentary control group. Taken together, our data suggest that high volumes of exercise training likely result in an energy deficient environment predisposing these athletes to reproductive suppression secondary to undernutrition [17,24] and the failure to fuel adequately to meet energetic needs.

The evidence for poor bone health in a Triad-like syndrome in male athletes

There are subsets of male athletes reported to have low bone mineral density (BMD) scores, such as male distance runners, and thus at high risk for poor bone health and bone stress injury in a manner similar to that reported in female athletes [35,36]. Specific risk factors for low BMD in exercising men include low body weight (<85% expected), average weekly running mileage >30, and previous stress fracture [7]. When the issue of categorizing low bone mineral density in male athletes is considered, the International Society for Clinical Densitometry recommends the use of a Z-score in men aged 20–50 of −2.0 or worse with the presence of risk factors, or in boys and young men aged up to age 19 a *Z*-score of −2.0 or worse with the presence of a fracture [37]. However, given that exercising men in weight bearing sports are exposed to mechanical loading some argue that it is more appropriate to draw concern when the *Z*-score is −1.0 or worse [2]. Certainly in non-weight bearing sports, such as cyclists and jockeys, low BMD scores have been reported in men [38,39]. However, leanness-sports that include a high-impact loading component may mitigate the effects of energy restriction on bone health. For example, comparisons between jockeys and boxers, both weight-class sports, found that jockeys had lower BMD at the total body, lumbar spine, and femoral neck compared to both boxers and non-athlete controls, and boxers actually had higher BMD at the lumbar spine compared to controls; a consistent pattern was also observed among groups with jockeys having the lowest value for each measurement, followed by controls, and then boxers with the highest values [40].

Interestingly, reports on bone quality and structure in exercising men with low bone mineral density and bone stress injuries is not yet available. In exercising women with amenorrhea, decreased volumetric trabecular density and number, increased trabecular spacing, and cortical thinning in amenorrheic athletes is observed compared to menstruating athletes and non-athlete

controls [41]. Changes in microarchitecture, such as the aforementioned findings, presumably place these women at increased risk for fractures. Studies that define microarchitecture of bone in at-risk male athletes are essential to further understand the effects of low energy availability and energy deficiency in men. We do know that in healthy men, participation in high-impact, bone-loading sports is protective and improves bone quality as a 20% higher trabecular bone mineral density, 22% higher trabecular number at the distal tibia, and 28–38% higher failure load, as assessed by HRpQCT, was observed in skiers and soccer players compared to low-impact swimmers [42].

We also know that a high incidence of bone stress injuries has been reported and is of great concern in male athletes. Among 80 collegiate runners followed prospectively for 2 years, 27% sustained at least one bone stress injury, and these injuries were predicted by a modified version of the Female Athlete Triad Cumulative Risk Assessment score for male athletes that included low energy availability, low BMI, prior bone stress injury and low BMD values [6••]. And, in adolescent male runners, previous fracture and participation in a greater number of competitive seasons were associated with an increased rate of stress fractures [43]. Importantly, a graded relationship was observed in adolescent male athletes suggesting a cumulative effect for risk factors on impaired bone health [7], similar to what has been observed in exercising women [35,36]. These studies highlight the importance of risk identification to screen athletes at high risk for poor health outcomes related to bone.

Lastly, there is evidence that bone turnover markers are influenced by periods of energy restriction [10••,44]. Short-term energy restriction, ~50% deficit over three days, did result in a decrease in bone formation in trained male runners [44]. However, when compared to women, similar to what was observed in the metabolic and reproductive systems, men appear to be more robust against the effects of low energy availability on bone turnover. Five days of restricted energy availability (15 kcal/kg FFM/day) was sufficient to reduce bone formation by 13% and increase bone resorption by 19% in women, as assessed by concentrations of P1NP and CTX, respectively but there was no significant effect in men [10••].

Reversibility of conditions

The Female Athlete Triad model of 2007 includes bi-directional arrows from the 'healthy' to 'unhealthy' extreme ends of the model, based on the evidence that women can progress or recover from each condition, and which can occur at varying rates. With respect to a Triad-like syndrome in men, the metabolic and reproductive perturbations observed appear to be quickly reversible upon refeeding, or cessation of exercise. For example, metabolic and reproductive hormones returned to normal, pre-training, values within a month of completing Ranger training, and most were reversed within one week. [28•]. Similarly, with respect to the acute endurance events, testosterone concentrations quickly rebounded towards baseline levels, and were significantly elevated from post-race values at 12 hours of recovery [19] and returned to pre-race values within 48 hours [18]. In one well controlled study of a single bout of exhaustive endurance exercise in endurance trained runners, testosterone concentrations were suppressed following the exhaustive exercise bout, but returned to baseline within 72 hours [45].

Interestingly, recovery of the HPG axis is likely due to an increase in central drive to the hypothalamus since refeeding after a single day of fasting successfully increased both LH pulsatility and testosterone in male monkeys, and, recovery occurred in a manner such that LH and testosterone progressively increased as the size of the refeed meal increased [46]. Additionally, a recent case study of an adolescent athlete provides further evidence that hypogonadotropic hypogonadism associated with excessive exercise and malnutrition is readily reversible with lifestyle modifications. Upon reducing the frequency and intensity of exercise, as well as increasing caloric intake, testosterone concentration was normalized within the one year follow-up period [47•].

Summary, conclusion, and future directions

According to the evidence to date, we propose the current thinking of the effects of energy availability on reproductive function and bone health in both female and male athletes. From the data reviewed, it appears that low energy availability in men can influence metabolism, reproduction, and bone. These systems in men, however, are robust and more resilient to the effects of low energy availability compared to those of women, requiring more severe energetic perturbations before alterations similar to that observed in women are present and which are more quickly reversible in men than in women. Although initial evidence supports a Triad-like syndrome in exercising men, the evidence available at this time is limited both in quantity and quality of design, that is, prospective versus observational, regarding the role of low energy availability and energy deficiency on reproduction and bone health in exercising men. As such, we encourage researchers to systematically conduct scientifically rigorous studies in men that will a) elucidate the magnitude of low energy availability, independent of additional stressors, required to induce metabolic and reproductive perturbations, b) demonstrate the direct causal effects of low energy availability on the HPG axis and bone health as well as the indirect effect of low energy availability on bone health through HPG axis suppression, and c) identify the 'intermediate' subclinical outcomes that may be present. Currently, the idea of a working model of a Triad-like syndrome in male athletes remains in the early

stages of development consistent with the limited evidence available. A full model for a Male Athlete Triad, based on available data to date, will be proposed later in 2019 by the Female and Male Athlete Triad Coalition.

Conflict of interest statement

Nothing declared.

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- • of special interest
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