Commentary in Response to “A Review of Nonpharmacological Strategies in the Treatment of Relative Energy Deficiency in Sport”

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A recently published review by Kuikman et al. (2021) focused on potential nonpharmacological treatments for relative energy deficiency in sport (RED-S) and aimed to highlight (a) interventions that improved energy availability (EA), (b) interventions that targeted factors known to exacerbate and/or *independently* affect the health outcomes of low EA (e.g., carbohydrate availability, fiber intake, and micronutrients), and (c) nonnutritional adjunct therapies (resistance training and cognitive behavioral therapy). Although we may be early career researchers who do not yet have decades of experience in this field, we do still have an appreciation for evidence-based research and the many steps that are necessary to accumulate evidence in support of a developing scientific model. As such, upon reading this review, several concerns were raised regarding the thoroughness and scope of the review that we hope can be appreciated.

As a necessary reminder, to date, the Female Athlete Triad (Triad) components of low EA, menstrual dysfunction, and bone health remain the most scientifically supported and clinically valid aspects of RED-S. RED-S is proposed to be an expansion of symptoms beyond menstrual dysfunction and impaired bone health. Therefore, the Triad is foundational to the RED-S model, and it remains an important point to stress that the Triad should be explicitly stated when discussing RED-S, particularly if one is focusing solely on energy, reproduction, and bone. A primary concern regarding Kuikman et al.'s (2021) review stems from the way in which content was framed and presented by the authors, wherein foundational research regarding the effects of EA, as it relates to menstrual and bone health, was omitted, and the purposes of previous investigations were rebranded to fit RED-S when the Triad was, in fact, the focus of the research. We understand that there has been historic disagreements between Triad and RED-S researchers (De Souza et al., 2014b; Mountjoy et al., 2015; Williams et al., 2019), but the complete absence of reference to the Triad in this manuscript is not accurate (Kuikman et al., 2021). Notably, every study cited within the “Improving EA” section (Cialdella-Kam et al., 2014; Dueck et al., 1996; Kopp-Woodroffe et al., 1999; Lagowska et al., 2014b; Mallinson et al., 2013), in addition to the other studies that were not referenced (Arends et al.,

2012; Lagowska et al., 2014a), was designed to assess whether improved energetic status (i.e., increased EA) specifically leads to recovery of menstrual function and/or improved bone health in exercising women with menstrual disturbances; that is, recovery from the Triad (De Souza et al., 2014a; Nattiv et al., 2007). To present the aforementioned studies as treatment for RED-S, a condition that did not yet exist at the time that the original research studies were conducted, without mention of the Triad, is misleading and historically inaccurate.

In line with the need for more evidence to support the additional proposed conditions of RED-S, another key omission of this paper is the failure to address nonpharmacological (i.e., nutritional) interventions that would specifically address proposed RED-S physiological impairments (i.e., hematological, gastrointestinal, and immune) that extend *beyond* the Triad conditions of energy deficiency, menstrual function, and bone health. Highlighting the lack of interventions to date would reinforce to researchers that more evidence-based investigations are needed to (a) causally link RED-S to each of the physiological impairments proposed in the RED-S model and (b) develop investigations to specifically explore nonpharmacological treatments of the latter conditions if directly identified with experimental evidence to be secondary to energy deficiency. Furthermore, the majority of this review (“Nutritional Interventions”) does not, in fact, describe prior nonpharmacological investigations to address the cause of RED-S (i.e., reverse energy deficiency/increase EA), rather it merely describes additional factors that may be contributing to RED-S related symptoms *independent of low EA*. For example, the effects of carbohydrate availability on bone turnover (Hammond et al., 2019) were stated to be independent of energy intake. Arguably, interventions that do not target energy status would not be sufficient to treat RED-S, unless the etiology of the symptoms attributed to RED-S is not, in fact, a direct result of energy deficiency/low EA. To summarize, while the Triad does not preclude the existence of other physiological effects of energy deficiency/low EA, as proposed in the RED-S model, more evidence is still required to support the effects of energy deficiency on the proposed physiological impairments and potential treatments (if experimentally identified to be secondary to RED-S).

Additional concerns arise in the sections about (a) EA and (b) stress management due to the exclusion of relevant literature. While the authors discuss concerns with the reliability of the EA measurement raised by our lab (De Souza et al., 2019) and others

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(Areta et al., 2021; Burke et al., 2018), it is equally important to discuss how the EA threshold of 30 kcal·kg FFM⁻¹·day⁻¹, established under laboratory-controlled conditions and applied to luteinizing hormone pulsatility (Loucks & Thuma, 2003; Loucks et al., 1998), may not translate to menstrual disturbances in free-living women. For example, experimental evidence in a 3-month randomized controlled trial demonstrated that the threshold of 30 kcal·kg FFM⁻¹·day⁻¹ is not related to the induction of menstrual disturbances (Lieberman et al., 2018; Williams et al., 2015) nor is it able to discriminate among a range of subclinical menstrual disturbances (Reed et al., 2015). These studies highlight efforts from those within the field to engage in critical appraisal of “accepted” concepts, allowing for scientific progress that advances our understanding of physiology. With respect to stress management, the failure to cite more recent research in exercising women demonstrating that underlying stress and depression are related to disordered eating behaviors and dysfunctional attitudes in exercising women with menstrual disturbances (Strock et al., 2020) is another example of excluding important data, particularly because these findings are potentially relevant targets for psychological intervention. It is important for reviews of this nature to comprehensively portray the science available to ensure an accurate and complete up-to-date understanding of the current state of knowledge. Failure to do so could be seen as a disservice to readers and the field.

Both the Triad and RED-S models can exist simultaneously, and manuscripts on topics such as nonpharmacological treatments for energy deficiency/low EA would benefit from acknowledging both conditions. The omission of Triad literature (Arends et al., 2012; Lagowska et al., 2014a; Lieberman et al., 2018; Strock et al., 2020; Williams et al., 2015) and exclusive of key experimental studies, draws attention to the noncomprehensive nature of the review and does not advance our understanding of RED-S. If science is to progress, authors should do their best to cite all relevant literature that may support or refute their perspectives. In addition, rewriting history by retroactively misrepresenting published research specifically involving energy deficiency, menstrual dysfunction, and poor bone health to characterize RED-S, with no mention of the Triad, is inaccurate and has the potential to hamper scientific and clinical advancements. After all, the Triad is foundational to RED-S. The importance of providing an unbiased review of literature with proper attribution and a comprehensive approach to citations cannot be understated, as this will help guide more informed decisions with respect to evidence-based RED-S medicine.

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