HHS Public Access

Author manuscript

Med Sci Sports Exerc. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

Med Sci Sports Exerc. 2019 August ; 51(8): 1791. doi:10.1249/MSS.0000000000001954.

Response

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We believe that Loucks (1) has inaccurately represented our randomized controlled trial (RCT) designed to test the effects of 3 months of controlled exercise and diet at varying degrees of energy deficit on the induction of menstrual disturbances (MD) (2). Like Bullen et al. (3), we studied 35 previously untrained, eumenorrheic women who were screened to rule out existing organic, endocrine, and psychological causes of MD. Inclusion criteria included 2 screening cycles and one baseline eumenorrheic cycle with no MD as confirmed with serum (progesterone) and urinary (luteinizing hormone, estrogen, progesterone) measures. Our design allowed for a dose response analysis with a control and three non-overlapping energy deficit groups. We demonstrated a dose response relationship between the % energy deficit and the incidence of MD (2). We confirmed this dose response relationship in a follow up analysis (4) where energy balance data were re-analyzed as "energy availability" in a manner similar to Loucks (5). We reported overall significant declines in T3 and IGF-1 with energy deficiency and weight loss relative to our weight-stable exercising control group (2). Dose response related changes in metabolic hormones, but not body weight, were demonstrated by Loucks' 5 day studies, but notably all participants were not exposed to all treatments (semi-cross over design) and the data were analyzed using single-sided, one sample t-tests, providing more power in a single direction (5). As such, the assertion that our 3 month RCT should produce similar dose response relationships in endocrine biomarkers between our deficit groups should be considered in light of several factors: 1) our RCT was not powered to detect differences among deficit groups in biomarkers or urinary E2; it was powered to detect MD as per our hypothesis of a dose-response relationship between MD and energy deficiency, 2) sources of variability affecting endocrine biomarkers include exercise training effects, the different combinations of diet and exercise among groups to achieve the prescribed energy deficit, individual variability in compensatory reductions in weight, body fat, and RMR (6) and, 3) subject compliance to the fed diet outside the 2 supervised daily meals. These factors are more easily accounted for over 5 days as in Loucks et al. (5) than over 3 months. We reject Loucks' suggestion that our findings reflect age related menstrual instability. Any predisposition to MD due to non-intervention related causes was spread evenly among groups given our RCT design. The stability of our subjects' 3 pre-intervention cycle lengths is demonstrated by a within person standard deviation of 1.2 days. Our intervention induced significantly more MD as energy deficiency increased i.e., 35% of cycles in up to 88% of women, whereas our exercising control group experienced MD in 16% of cycles in up to 13% of subjects. In summary, we have demonstrated dose response relations between energy deficiency and MD in two different papers from the same RCT (2, 4). We have not observed

a threshold effect of energy availability in these analyses and we do not support the assertion that a critical threshold of energy availability is associated with MD in exercising women.

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