EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 3
33-53
Year: 2024

# EFFECT OF RELATIVE ENERGY DEFICIENCY IN SPORT (RED-S) SYNDROME ON BONE MINERAL DENSITY, BONE IMAGING OUTCOME AND ASSOCIATED CLINICAL BIOMARKERS IN ATHLETIC MEN: A SYSTEMATIC REVIEW

**[1]Adinnu D. C., [2]Iwuamadi C. E., [1]Carroll S., [3]*Nwozor C. M., [4]Enwelum H. O. and [4]Azuoma K. E.**

[1]Department of Clinical Exercise Physiology, Faculty of Sport Health and Exercise Science, University of Hull, HU6 7RX, England, United Kingdom.
[2]Royal Bournemouth Hospital (University Hospital Dorset NHS Foundation Trust) Bournemouth, England, BH7 7DW United Kingdom.
[3]Department of Physiology, Faculty of Basic Medical Sciences, Chukwuemeka Odumegwu Ojukwu Universitty, Uli Campus, Anambra State. Nigeria.
[4]Department of Physiology, Faculty of Basic Medical Sciences, College of Medicine, Abia State University, Uturu, Abia State.

***Corresponding Author: Nwozor C. M.**
Department of Physiology, Faculty of Basic Medical Sciences, Chukwuemeka Odumegwu Ojukwu Universitty, Uli campus, Anambra State. Nigeria.

**Article Received on 07/01/2024** **Article Revised on 28/01/2024** **Article Accepted on 19/02/2024**

## ABSTRACT

**Objectives:** To systematically investigate the effect of RED-S syndrome on bone health with regards to the BMD, bone imaging and relevant biomarkers in adult male athletes. **Design:** Systematic Review. **Data sources:** Five databases (MEDLINE, Academic Search Premier, CINAHL plus, Sport Discus, Scopus) were searched for papers. **Eligibility criteria for selecting studies:** Eligible studies were those academic papers that measured at least one variable of interest, included adult male athletes, and were written in English. **Results:** Twenty-one studies of fair to good quality were identified and reviewed. There were variations in the methods of measuring energy intake and EEE among the study participants ranging from questionnaires to dietary and training logs. Twelve studies reported some level of LEA among the athletes ranging from 18.9 ± 6.9 to 27.6 ± 12.2 kcal/kg FFM/day. Sixteen studies measured and reported the DEXA BMD with mixed outcomes of low values in some and normal values in others. Regional BMD measurement revealed that the lumbar spine was the most susceptible bone site to stress injuries. Six studies investigated the biomarkers of bone turnover with results varying in relation to LEA. **Conclusion:** LEA negatively affects BMD and overall bone health of male athletes putting them at risk of injury and under performance however, biomarkers of bone turnover (formation and resorption) in certain conditions could possibly remain within physiological levels despite a low BMD.

**KEYWORDS:** Athletic men, BMD, biomarkers, LEA, RED-S syndrome, sports physiology.

## INTRODUCTION

It is well known that athletic men and women and those who engage in professional sports are potentially more at risk of energy insufficiency, a condition resulting from a mismatch between caloric intake and energy expenditure.[1] Energy availability (EA) is defined as Energy intake (EI) (kcal) minus Exercise energy expenditure (EEE) (kcal) divided by Fat-free mass (FFM) (kg); where EEE is calculated as the additional energy expended above that of daily living during the exercise bout,[2] and estimated using dietary and training logs.[3] Energy insufficiency is mostly seen in weight-sensitive sports where leanness is important for desired performance, and to meet a competition required weight category.[4] For instance, professional jockeys are required to keep their body mass within race limits and are therefore weighed before and after each race.[5] This potentially predisposes them to dangerous weight maintaining strategies and altered dietary behaviours such as calorie restriction, self-induced vomiting after eating, use of laxatives etc. leading to side effects including dehydration, electrolyte imbalance, anaemia, and other features of the RED-S syndrome.[6] It has also been reported in some other athletic groups such as endurance runners, cyclists, light weight rowers and weight class combat sports.[2, 7–11]

RED-S is a constellation of clinical symptoms characterized by a sub-optimal homeostatic balance involving multiple body functions such as bone health,

endocrine, immunologic, metabolic, haematological, gastrointestinal, cardiovascular, and even psychological state, caused by a relative energy deficiency.[2] Initially known as the Female Athlete Triad (an interrelationship between low energy availability, menstrual dysfunction, and poor bone health), this phenomenon was expanded by the International Olympic Committee (IOC) in 2014 to include male athletes[12] following the acceptance of low energy availability (LEA) as the major underlying problem.[2] In 2017, researchers convened in response to the call for research into energy deficiency in men, and the product of that meeting was firstly the renaming of the Female Athlete Triad Coalition as the Male and Female Athlete Triad Coalition in 2018 and secondly, a consensus statement on the Male Athlete Triad which was published in 2021.[13]

Although there is no standardized or universally accepted way to measure LEA, an experimental study on eumenorrheic previously sedentary women observed that many organ systems become substantially disturbed at an EA < 30 kcal/kg FFM/day.[2,6,14] LEA exists in both males and females and can result from different pathophysiological processes which include eating disorders (anorexia nervosa, bulimia nervosa and binge eating), involuntary decrease in caloric intake, and excessive or prolonged exercising.[9] Asides the reproductive suppression, menstrual disruption and poor bone health attributed to LEA, other reported clinical consequences include elevated levels of cortisol, decreased levels of triiodothyronine (T3), insulin-like growth factor 1(IGF-1), leptin, low resting metabolic rate (RMR) and diminished lower limb neuromuscular performance.[3,15] Others are, the risk of endothelial dysfunction, severe bradycardia, and arrhythmias[16] which impact negatively on sporting performance.

It is also believed that the type of sport is a contributing factor with greater prevalence in females, lean athletic and weight-bearing sports.[9] Hooper reported in his research that approximately one-third to half of the highly physically active women show menstrual disturbances.[17] A study conducted to examine the prevalence, the signs and symptoms of LEA on 13 elite female sprinters at the start and end of a 5-month indoor training season showed that four (31%) sprinters presented at pre-season testing with at least one primary and secondary indicator of LEA, which increased to seven sprinters (54%) at the end of the season.[18] Additionally, five (39%) of the athletes had a previous history of stress fracture.[18] In male athletes, it has been reported to range from 25% to 40%; identified as LEA, low levels of testosterone and thyroid hormone (T3), and a 4.5 times higher incidence of bone injury.[4]

BMD is negatively impacted by prolonged periods of LEA increasing the risk of stress fractures and delaying the repair process due to insufficient nutrients and energy.[19] Bone metabolism can be assessed indirectly by determining the levels of bone biomarkers which give useful information on the bone formation or resorption in the long or short term.[20] A study which explored the short-term (5 days) effects of LEA, at 15 kcal kg LBM−1 day−1 on bone biomarkers in physically active women and men, compared to a balanced EA at 45 kcal kg LBM−1 day−1 showed that marker of bone formation (Carboxyl-terminal propeptide of type 1 procollagen (P1CP)) was significantly reduced, while biomarker of bone resorption [urinary amino-terminal cross-linked telopeptide of type I collagen (NTX)] increased significantly from baseline levels.[21] Furthermore, studies have shown a positive correlation between low body mass index (BMI ≤ 17.5 kg/m2) and an increased risk of low BMD[22,23] with females generally more susceptible. Early detection of athletes at risk of developing energy deficiency is vital to prevent negative health consequences in the long term.[16] In recent times, questionnaires such as the LEA in Female Questionnaire (LEAF-Q) and Clinical Assessment Tool (CAT) which are designed to assess the physiological features of the Female Athlete Triad or RED-S respectively are being used to screen athletes for symptoms of LEA.[3] It is recommended that these assessment tools together with timely and accurate blood biochemistry of sex hormones and other relevant clinical biomarkers will represent a more accurate and objective indicator of EA.[24]

Despite the growing body of literature on the effect of LEA on bone health, male athletes have not been extensively studied as compared to their female colleagues.[25, 26] Furthermore, most of these studies have looked at general effects of LEA such as on the endocrine (menstrual irregularities in women and poor libido in men), metabolic and sports performance outcomes with only a few focusing on its impact on bone mineral integrity in men, where early research suggests that male exercisers appear less susceptible to adverse bone effects of RED than females (reproductive differences).[23, 27] Therefore, the primary outcome of this review is to systematically investigate the effect of RED-S on bone health with regards to the BMD, bone imaging and relevant bone biomarkers of adult male athletes and recreationally active men.

## METHODS

### Search Strategy

This systematic review was conducted in line with the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[28] The PROSPERO database and Cochrane library was searched to see if similar systematic review has been conducted on the area of investigation and to ensure originality of the research hypothesis. The population, exposure to be considered and outcome measure of interest (PICO),[29] was determined and used to determine the inclusion/exclusion criteria and coin the research question.

As earlier stated, the focus will be on male athletes and men who engage in high level regular exercise (> 3 hours

a week). It will also be on those >16 years of age because professional athletics has been reported to commonly begin around this age or earlier,[30] allowing us a broad age range.

To identify eligible studies, an extensive search of some databases was done. The databases searched were SPORT Discus, Academic Search Premier, CINAHL plus and MEDLINE through EBSCOHost and Scopus. These databases were chosen because they contain journals on sport science, health, exercise, fitness, and related medical journals. The full text was searched on Scopus and Google Scholar. EBSCOHost and Scopus were used to search for the title, abstract and keywords due to many studies found when searching the full text. The search criteria were refined to get a manageable number of hits by limiting it to academic papers and to those published in English language.

The search terms were outlined to cover all aspects of the research focus. Synonyms, phrase searching, and related terms were listed for the main areas of the research focus. Truncations were used for terms which could be plural or used different endings in the literature. The following search terms were used for the database searches: ("RED-S" OR "relative energy deficiency in sport*" OR "low energy availability") AND ("bone mineral density" OR "bone mineral content" OR "bone strength index" OR BMD OR "bone imaging" OR biomarker* OR "biological marker*" OR "bone density" OR "bone mass" OR "bone health" OR DEXA), with the Boolean phrase OR used between each search term to expand the search area. The Boolean phrase AND was used between each group of terms to focus the search and cover all aspects of the research question. Additionally, the search did not limit study inclusion by the year of publication but were limited to include only human subjects, and original articles in peer reviewed journals. The hits from each search are shown in table 1 below. The process was concluded by manually searching key journals and abstracts from the major annual meetings in the discipline of energy deficiency in male and female athletes and the RED-S syndrome.

Abstracts and references of all journals found in the search results were exported to Endnote X9.3.3 (Thomson Reuters, Philadelphia, PA, USA) where the duplicate references were deleted bringing the total number of titles to analyse to 1034.

**Table 1: Number of journals found from each data base search.**

| Database | Total Hits | Duplicates Removed | Articles to Review by Title and Abstract |
|---|---|---|---|
| **MEDLINE** | 352 | 134 | 218 |
| **Academic Search Premier** | 172 | 93 | 79 |
| **CINAHL plus** | 121 | 78 | 43 |
| **Sport Discus** | 109 | 40 | 69 |
| **Scopus** | 627 | 2 | 625 |
| **Total** | **1381** | **347** | **1034** |

**Selection Criteria**

The article titles were reviewed and those that did not meet the inclusion criteria, unrelated to the research focus or duplicated were removed. The inclusion and exclusion criteria of the studies were established in advance of the literature search according to the clinical inquiry, research question and study design. A study was included for the systematic review if it satisfied the criteria outlined in table 2.

**Table 2: Inclusion and exclusion criteria.**

| | Inclusion | Exclusion |
|---|---|---|
| **Population** | Male elite or non-elite athletes and para-athletes, high level exercising men (adolescents, adults, and older adults) | Female only studies, athletes < 16 years of age. |
| **Exposure to be considered (intervention)** | Relative energy deficiency, LEA, Disordered eating, low calorie intake | Adequate energy intake, athletic or high-level exercising men + adequate caloric intake, caloric and exercise balance. |
| **Outcome of interest** | BMD, Bone biomarkers and, Radiological state of bone (DEXA, CT, pQCT, MRI), bone health, osteopenia, osteoporosis | Other unrelated physiological or pathological outcomes, sport performance |
| **Type of studies** | Cohort, randomized controlled trials (RCT), non-RCT, cross-sectional, descriptive, longitudinal evaluating the outcome of interest | Reviews, non-human studies, non-original studies, case reports, case studies, commentaries |

Although LEA threshold is not yet universally standardized,[8] emerging research suggests that the threshold may be lower in male and be between 20 – 25 kcal/kg FFM signalling the onset of physiological

changes.[1,15,24,31] Because of this and to be as inclusive as possible in the eligibility criteria, a relatively low and common threshold for LEA (< 30 kcal/kg FFM/day (125 kJ/kg FFM/day)[2,6] was used in this review. Psychological outcomes of LEA and RED-S would not be focused on or discussed as this is primarily a pathophysiological systematic review. Studies that met the inclusion criteria but compared outcome measures of athletes with a control group were also included however, the data from the control group would not be extracted for analysis. A total of 87 journal articles were included to be read in full. Four (4) full journal articles that were not found through online searches were requested for through the university inter-library loan services and obtained. Manual searching of the references within the selected articles was screened to find additional relevant articles and to ensure no important article was omitted from the initial database search. An additional 7 journal articles were obtained and included for analysis.

A few abstracts that were initially left in because of the uncertainty of their relevance to the research focus were removed from the analysis later. Articles that studied non-bone biomarkers or had no bone related outcome measure which were also initially added were removed after reading the full text. This also applied to review articles and updates where the extent of detail it contained was unclear from initially reading the abstract. Others were excluded due to incomplete relevant anthropometric and participant details, absent data on relative energy availability or energy expenditure.

**Data Extraction**

From the included studies, the following data (table 3) were extracted and double checked.

**Table 3: Information extracted from reading full journal article.**

| Study characteristics | Population characteristics | Energy status characteristics | Outcome measures |
|---|---|---|---|
| First author<br>Year of publication<br>Title<br>Study design<br>Sample size<br>Duration of study | Number of athletes/participants<br>Type of performing sport<br>Mode of exercise<br>Exercise intensity<br>Age<br>Height<br>Body mass<br>BMI<br>Percentage body fat | Mean daily energy intake<br>Mean daily exercise energy expenditure<br>Free fat mass (FFM)<br>Energy availability levels<br>Method of determining LEA | BMD measured by DEXA<br>Levels of relevant bone biomarkers<br>• serum pro-peptide of type 1 collagen (P1NP)<br>• serum β-carboxyl-terminal/N-terminal cross-linked telopeptide of type 1 collagen (β-CTX or NTX)<br>• osteocalcin<br>• alkaline phosphatase (ALP)<br>• bone specific alkaline phosphatase (BAP)<br>Radiological outcome such as CT, pQCT and/or MRI |

**Quality Assessment**

Articles were assessed for quality based on the type of study and using two quality assessment tools. The National Institutes of Health (NIH) Quality Assessment Tool[32] was used to assess the observational, cohort and cross-sectional studies while, the Cochrane Risk of Bias (RoB) 2 Tool[33] was used to evaluate the quality of randomized controlled trials. Studies assessed using the (NIH) Quality Assessment Tool were assigned a yes, no, or other to each of the fourteen criteria outlined in the appraisal tool. Then by considering each criterion, the overall quality of the study was determined and assigned 'good', 'fair', or 'poor' rating.[32] Using the RoB 2 assessment tool, RCT studies were judged based on answers to the signalling questions in each domain. This can be 'Low' or 'High' risk of bias or can be expressed as 'Some concerns'.[33] A table of methodological quality assessment with individual scores for each included study is attached as an appendix.

No further statistical analysis was undertaken on the included journal articles due to limited number of articles (six) included in the systematic review that had bone related biomarkers as outcome measure. More so, only two of the included journals used CT, MRI or pQCT to assess radiological outcome of bone health. Although most studies reported the BMD using Z-score, some scores had to be calculated, while few others reported BMD using $g/cm^2$ leading to non-uniformity of data so no further statistical analysis could be completed.

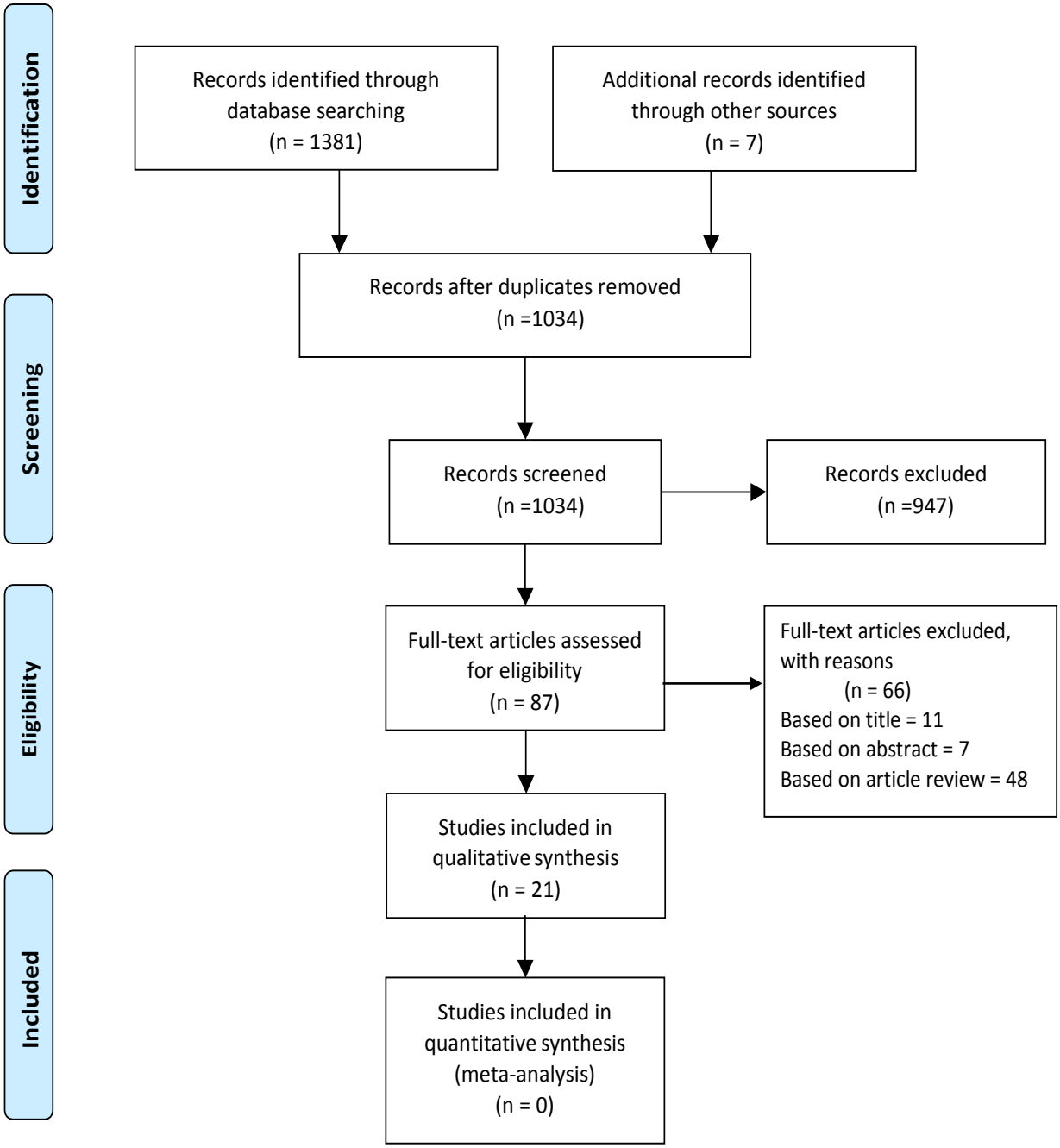


**Figure 1: Article identification and inclusion using PRISMA 2009 flow diagram.**

## RESULTS

The PRISMA flow diagram of the systematic review results are shown in figure 1.

### Study Characteristics

From full text article reviews, 21 studies were included in the systematic review. A total of 861 athletic and para-athletic men from various sporting backgrounds such as running, jockey, soccer, basketball, boxing, varsity athletes etc. participated in the included studies with an age range of 16-72years. The selected journal articles consist of thirteen cross-sectional studies,[4,10,23,24,31,34-41] five cohort studies,[14,27,42,43,44] two Randomized controlled trials (RCT),[21,45] and one descriptive study.[46] Ten of the studies included female participants however, the result of male only participants are considered in this review.

Three studies[35,37,39] compared their outcome measures with that of non-exercising controls mostly matched for age and body size. Regarding BMD, all but five studies[4,21,34,42,44] reported the total body DEXA BMD, while seven studies[10,14,21,27,38,40,43] had no report made on anatomical site-specific BMD as an outcome measure. Furthermore, only six studies[10,21,23,27,42,45] investigated different bone related biomarkers. Two studies[42,45] measured the serum level of alkaline phosphatase (ALP), while three studies[10,23,27] measured the level of serum

bone-specific alkaline phosphatase (BAP). Serum biomarkers of bone resorption (ß-CTX and ß-NTX) were measured and reported by three studies,[10,21,27] while Papageorgiou et al were the only study to investigate P1NP a biomarker of bone formation.[21] Radiological outcome such as bone stress injuries (BSI) or fracture was reported by two studies.[14,43] The summary of the studies and participant characteristics are shown in table 4.

**Quality of studies**

Assessment of quality was applied to all studies selected for this systematic review. Of the observational, cross-sectional and cohort studies that were assessed using the NIH quality assessment tool, only three studies[4,21,38] estimated a sample size apriori or justified their sample size. Similarly, the participation rate of eligible athletes was less than 50% in three studies.[14,40,46] Furthermore, it was not specified in most studies whether the outcome assessors were blinded to the exposure status of participants, and one of the studies was found to have more than 20% loss to follow-up after baseline. Overall, the RCT[20,45] showed a low risk of bias following assessment and were rated as high-quality studies (see appendix 2 and 3). For the NIH assessment, six studies[23,34,37-39,44] were rated 'good' while the other thirteen studies were all rated 'fair'.

**Energy Availability**

There were variations in the methods of assessing EA and the threshold for LEA among the selected studies. The more popularly used method of EA measurement which reflects the difference in EI and EEE in relation to FFM was used by twelve studies to indirectly calculate EA in their participants, three studies[4,36,44] calculated the resting metabolic ratio ($RMR_{ratio}$) from the predicted RMR ($_{p}RMR$) [using the Cunningham equation [RMR = 500 + (22 × FFM) etc],[47] and measured RMR ($_{m}RMR$) as a measure of EA. five studies[14,41,42,43,45] assessed the EA of their participants by using different questionnaires [eating disorder examination questionnaire (EDEQ), Female Athlete Triad Screening Questionnaire (FATSQ), Triad Consensus Panel Screening Questionnaire, Sport-specific Energy Availability Questionnaire and Interview (SEAQ-I), modified Female Athlete Triad Coalition Consensus Statement Cumulative Risk Assessment tool, and the Eating disorder inventory (EDI)]. As shown in table 5, twelve studies[10,21,23,24,27,31,34,38-40,44,46] measured EI using carefully evaluated participants dietary logs, while eight studies[14,35-37,41-43,45] estimated the participants EI by using questionnaires. EI was not recorded in one study.[4] Furthermore, in fourteen studies,[10,21,23,24,27,31,34,35,37-40,44,46] EEE was obtained and calculated using average participants training log and exercise record [including measurement of heart rate (HR) and maximum oxygen consumption ($VO_2$ max)], while six studies[14,36,41-43, 45] utilized questionnaires to obtain and estimate energy expenditure of their participants. Two studies[31,40] out of the twelve that calculated EA from EI – EEE, utilized < 20 and ≤ 25 kcal/kg FFM/day respectively as their thresholds for LEA. Table 5 also depicts the energy status of the different studies and their threshold for LEA.

**Table 4: characteristics of studies and participants with outcome measures included in the systematic review. Where available values are mean ± SD.**

| Study Characteristics | | | | Participant Characteristics | | | | Outcome Measures |
|---|---|---|---|---|---|---|---|---|
| **Author (Year)** | **Type of study** | **Duration** | **study design** | **Number of Participants** | **Age** | **Anthropometric data** | **Sport type and intensity** | |
| Brook et al (2019) | Retrospective cohort | 1 month | Electronic survey to assess the prevalence of factors associated with LEA, and low BMD in elite para-athletes and to describe the differences among sex, disability type, and sport type in health issues caused by LEA. | 260 (150 males) | 31.7 ± 11.5 years | □ | Para-athletes with spinal cord injury or lower extremity amputation. | EA, BMD, history of stress fracture, awareness of FAT and RED-S |
| Heikura et al (2018) | Cross-sectional | 7 days | cross-sectional report of EA measurements, metabolic and reproductive hormonal function, BMD, rates of injury, and body composition during | 59 (24 males) | 27.15 ± 4.0 years | Height= 1.82m ± 0.06; weight= 69.15 ± 6.45 kg; % body fat = 6.9 ± 1.5; FFM = N/R | Multinational world-class long-distance runners/race walkers | Body composition, BMD, oestradiol, total TES, IGF-1, T3, insulin, bone injuries |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | a high-intensity pre-competition training period and to investigate the efficacy of Triad and RED-S diagnostic tools to identify athletes at risk of LEA | | | | | |
| Høeg et al (2022) | Cross-sectional | 2 years | To determine the prevalence of Triad risk factors and low BMD in 100-mile ultramarathon runners. To explore the associations between sex hormones with BMD. | 123 (72 males) | 46.2 ± 10.3 years | Height = N/R; weight = N/R; BMI = 22.9 ± 2.6 kgm2; % body fat = N/R; FFM = N/R | Professional and competitive ultra-marathon runners. Participants ran an average 57.3 miles/week | Triad Cumulative Risk Assessment Score was calculated for each participant: - LEA, BMI, BMD, BSI, oestradiol, free T3, total T3, ferritin, 25-OH-D3 |
| Hooper et al (2017) | Cross-sectional | 24 hours | Cross-sectional between group design to assess men exhibiting features of exercise hypogonadal male condition (EHMC) and investigate a possible role of inadequate nutrition to the condition | 9 | 36.3 ± 9.2 years | Height = 180.0 ± 8.8cm; weight 77.7 ± 6.8kg; BMI = 23.98 ± 3.5 kg/m$^2$#; % body fat= N/A; FFM = 63.8 ± 5 kg | long distance runners. Participants ran an 81 ± 14 km average distance/week within 12 months | EA status, BMD, FSH, LH, cortisol, |
| Kalpana et al (2022) | Cross-sectional | N/S | Cross-sectional observational study to determine LEA among Indian national male Kho-Kho players, and its association with their health and performance related to RED-S. | 52 | 23.14 ± 3.71 years | Height = 165.84 ± 6.43 cm; weight = 59.1 ± 6.25 kg; BMI= 21.67 ± 6.28 kg/m$^2$#; % body fat = 11.81 ± 3.35 | National level kho-kho players. Been in the sport > 2 years with regular training | RED-S prevalence, EA status, metabolic indices, BMC, BMD, calcium, Vit-D3, |
| Keay et al (2018) | Cohort | 1 month | To evaluate the efficacy of a sport-specific EA questionnaire and use of clinical interview (SEAQ-I) to identify male cyclists at risk of developing consequences of RED-S. | 50 | 35.0 ± 14.2 years | Height = 1.81 ± 0.06m, Weight = 72.3±6.7 kg, BMI = 22.6±1.5 kg/m2; % body fat = 14.1 ± 3.2; FFM = N/R | International, national, and regional cyclists at ≥ level 2 British Cycling (BC) category for over 12 months (prior to cycling season). Average training hours on bike/week = 12.5 ± 4.4. Years of | Cyclists at risk of RED-S, BMD, body composition, AP, albumin, TES, free T3, T3, 25-OH-Vit D, electrolytes |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | cycling training = 11.2 ± 9.2 | |
| Keay et al (2019) | Randomized controlled trial (RCT) | 6 months | RCT to investigate the efficacy of an educational intervention, specific to competitive cyclists, to ensure adequate EA, bone health and performance during a race season | 45 | 36.2 ± 14.3 (18.5 - 72.0) years | Height = 1.80 ± 0.06m; weight = 73.2 ± 6.6 kg; BMI = 22.5 ± 1.5 kg/m2; % body fat = N/R; FFM = N/R | Competitive cyclists (equivalent to BC category 2 or above). Average training on bike = 11.2 ± 4.0 hours/week | EA, BMD, AP, albumin, TES, free T3, T3, 25-OH-Vit D, electrolytes |
| Kraus et al (2019) | Mixed (retrospective and prospective) cohort | 7 years | Mixed cohort design to determine if a modified Female Athlete Triad Cumulative Risk Assessment tool would predict BSI in male distance runners | 156 [historic (80) and prospective (76)] | 19.5 ±1.3 years | BMI = 20.9 ±1.6 kg/m2 | University middle and long-distance runners (cross-country and/or track ≥ 800m) | EA, BMI, BMD, BSI |
| Lane et al (2021) | Cross-sectional | 7 days | To investigate EA and the risk factors for RED-S, and their potential associations in non-elite male endurance athletes | 60 | 43.4 ± 11.6 years | Height = 1.78 ± 0.06 m; weight = 76.6 ± 9.6 kg; BMI = N/A; % body fat = 17.9 ± 5.0; FFM = 62.7 ± 6.2 kg | Competitive endurance athletes (runners, cyclists, triathletes, combined modes). Average training duration = 10.9 ± 2.7 hours/week; Average training years = 7.1 ± 8.8 | EA status, metabolic status, BMD, BAP, SHBG, LH, GH, free T3/T4, free TES, bioavailable TES. |
| Lee et al (2020) | Observational cohort | 1 month | To investigate the EA status of Korean university soccer players during training period and to evaluate its association with metabolic status, bone health and hormonal status | 12 | 19.1 ± 0.7 years | Height = 175.8 ± 5.1 cm, weight = 69.61 ± 5.79 kg, BMI = 22.5 ± 1.2 kg/m2, % body fat = 13.6 ± 2.6; FFM = 60.1 ± 4.5 kg | University soccer players. Exercising for 7-12 years | EA status, metabolic status, BMD, s-BAP, s-CTX, FSH, LH, TES, oestradiol, GH, IGF-1, T3, cortisol, leptin |
| McCormack et al (2019) | Cross-sectional | N/S | To evaluate and compare the BMD of university cross-country runners with like-sized non-running controls and estimate EA, disordered eating and eating attitude among them | 60 (27 males) | 19.7 ± 1.2 years | Height 176.4 ± 5.5 cm; weight 64.8 ± 4.4 kg; BMI = 20.8 ± 1.2 Kg/m2; % body fat = 15.4 ± 2.3; FFM = 52.7 ± 4.0 kg | Cross country runners. Participants put in >100 km/week across 9-10 running sessions. | Energy indices, EA, disordered eating attitudes and behaviours, BMD, minerals |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Moore et al (2021) | Cross-sectional | 2 weeks | Within subject cross-sectional design to examine male athlete triad (MAT) components; [LEA, ± eating disorder risk (ED), testosterone and BMD] in endurance-trained male athletes during different training periods. | 14 | 26.4 ± 4.2 years | Height = 179.5 ± 4.3 cm; weight = 70.6 ± 6.4 kg; BMI = 21.9 ± 1.8 (kg/m2); % body fat = ≤ 12%; FFM = 65.7 ± 5.4 kg | Endurance athletes (distance runners, triathletes, and obstacle racers) actively training and competing ≥10 h/week. | Energy indices, features of MAT, BMD, TES, minerals |
| Moris et al (2022) | Cross-sectional | N/S | To report the prevalence of the MAT conditions: [LEA, low BMD, and low testosterone] in male athletes from different sports. | 44 | 20.4 ± 0.2 years | Height = 180.5 ± 3.5 # cm; weight = 82.4 ± 5.2 kg; BMI = 25.3 ± 1.3 kg/m2; % body fat = 15.7 ± 1.7; FFM = 69.5 ± 3.8 kg | University athletes from 7 (cross country, soccer, wrestling, basketball, track, golf, and baseball) different sports. Actively participating in season games during testing | Prevalence of MAT features (LEA, low BMD, low free TES), SHBG, LH, leptin, insulin. |
| Õnnik et al., (2022) | Cross-sectional | N/S | To determine the prevalence of select Triad–RED–S components/risk factors in Kenyan runners to corresponding control groups with special interest on examining and comparing energy intake (EI), bone indices, and hormonal markers commonly associated with RED–S | 56 (30 male) | 28.0 ± 3.75 years | Weight = 57.7 ± 6.07 kg; BMI= 19.5 ± 1.84 kg/m2 | High-level middle-and long-distance runners. All athletes were actively training and competing at time of study | Energy indices, CBC, BMD, TSH, T3/T4, FSH, LH, cortisol, insulin, prolactin, TES, oestradiol, GH, IGF-1 |
| Papageorgiou et al (2017) | Randomised crossover | 2 x 9 days | RCT to investigate the effects of short-term LEA, at 15 kcal/kg LBM/day achieved via diet restriction and exercise on markers of bone turnover in physically active women and men, and to compare the effect between both sexes. | 22 (11 male) | 26 ± 5 years | Height = 1.78 ± 0.07m; weight = 73.1 ± 8.0 kg; BMI = 23.0 ± 1.6 kg/m2; % body fat = 18.3 ± 3.4; FFM = 60.33 ± 7.58 kg | Recreationally active moderate - vigorous physical activity > 3 hours/week. | Body composition, B-CTX, P1NP, leptin, insulin, IGF-1, T3, PTH, GLP-2, minerals |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pritchett et al (2021) | Exploratory descriptive | 7 days | Exploratory investigation to examine the symptoms of LEA and risk of RED-S symptoms in para-athletes using a multi-parameter approach. | 18 (9 male) | 27 ± 8 years | Height = 166 ± 5 cm; weight = 64.5 ± 8.7 kg; % body fat = 25.4 ± 7 | National and international level para-athletes. Participants underwent their regular training during period of study | BMD, EA status. testosterone (TES), IGF-1, progesterone, free T3 (fT3), and oestradiol. |
| Staal et al (2018) | Cross-sectional | N/S | To study the impact of using different equations to predict RMR on the prevalence of suppressed RMR and to explore associations with conditions related to energy deficiency in professional ballet dancers. | 40 (20 male) | 25.1 ± 4.8 (21.0–28.5) years | Height = 183.0 ± 4.4 cm; Weight = 72.8 ± 4.6 kg; BMI = 21.7 ± 1.3; % body fat = 8.0 ± 1.6; FFM = 66.7 ± 4.7 kg | Professional ballet dancers. Hours of training/week = 35.0 ± 11.3. Years of dancing = 14.0 (12.8–18.8) | Body composition, BMD, BP, disordered eating (DE) |
| Stenqvist et al (2020) | Cohort | 4 weeks | A prospective interventional study to determine how a 4 weeks mesocycle of intensified endurance training designed to increase aerobic performance, would affect RMR, body composition, energy intake, Hormone levels in well trained male cyclists. | 20 | 33.3 ± 6.7 years | Height: 180.8 ± 4.9 cm, Weight = 75.8 ± 7.3 kg; BMI = 23.2 ± 1.9 kg/m2; % body fat = 14.9 ± 5.2; FFM = 65.5 ± 5.2 kg | Regional and national cyclists. Participants underwent 3 HIIT intervals/week of 32 mins/session. Exercise hours/year = 395 ± 171; Active cycling years = 12.9 ± 9.7 | Body composition, bone health, EI, aerobic performance, TES, SHBG cortisol, T3, insulin, IGF-1 |
| Stenqvist et al (2021) | Cross-sectional | 2 months | To investigate RED-S in a Norwegian cohort of male athletes using surrogate markers, such as suppressed RMR, impaired bone health, and altered metabolic and endocrine variables | 44 | 24.8 ± 3.8 years | Height = 181.3 ± 8.4 cm; weight = 81.3 ± 15.9 kg; BMI = 24.7 ± 4.4 kg/m2; % Body fat = 14.7 ± 6.9; FFM = 69.4 ± 11.2 kg | Olympic level athletes (cyclists, runners, boxers, triathlon etc.). Training volume = 76.1 ± 22.9 hours/month | Body composition, RMR, BMD, TES, free T3, cortisol, lipids. |
| Taguchi et al (2020) | Cross-sectional | 7 days | To reveal the energy status of Japanese male runners, and to examine the association between energy deficiency and physiological characteristics such as energy metabolism, bone health, and hormonal status. | 6 | 19–21 years | Height = 171.7 ± 2.8 cm, weight = 56.4 ± 2.1 kg; BMI = 19.2 ± 1.1 kg/m2; % body fat = 9.5 ± 1.4; FFM = 51.0 ± 1.5 kg | University long distance runners. Weekly running distance = 132.2 ± 27.3 km; Athletic duration = 8.2 ± 2.7 years. Measurements were done | Energy metabolism, BMD, BAP, NTX, 25(OH)D, T3, IGF-1, LH, TES, oestradiol, electrolytes. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | during active training season | |
| Viner et al (2015) | Cross-sectional longitudinal | Once/month all through season (10 months) | To examine EA of competitive cyclists across the cycling training and competition season, analyse eating behaviours that may contribute to LEA, and compare EA of male versus female cyclists. | 10 (6 males) | 42.0 ± 7.7 years | Height = 177.9 ± 4.2 cm; weight = 72.4 ± 6.8 cm; % body fat = 11.9 ± 4.5; FFM = 63.8 ± 3.8 kg | Competitive cyclists. Daily exercise duration = 1.6 ± 0.6 (cycling: 1.4 ± 0.6) hours/day. Average racing experience = 13 ± 5 years | BMD, EA, eating behaviours contributing to LEA |

**Prevalence of low energy availability**

Although five studies reported a normal or subclinical EA status in their subjects, LEA was common among the athletic population in the RCT and most of the cross-sectional and cohort studies. Heikura et al in their study found that 25% of male athletes (long distance runners and race walkers) had LEA.[24] Hooper et al studied nine male long distance runners exhibiting symptoms of exercise hypogonadal male condition (EHMC) and found that mean EA in these athletes was 27.2 ± 12.7 kcal/kg FFM/ day as against 45.4 ± 18.2 kcal/kg FFM/ day in the non-exercising control group.[35] This is similar to the findings of Lane et al and Moore et al in their separate studies on competitive endurance runners where they reported that mean EA in the athletes was 28.7 ± 13.4 and 27.6 ± 12.2 kcal/kg FFM/day respectively.[23, 38] Additionally, the Taguchi et al study revealed a greater decline in mean EA (18.9 ± 6.8 kcal/kg FFM/day) among the six varsity long distance runners they studied and reported a severe negative energy balance [(range: −1444 to −722 kcal/d) Energy balance (EB)= EI minus estimated total energy expenditure (TEE)].[24] In their research, 20 kcal/kg FFM/day was reported by Viner et al as the mean EA of the six male cyclists across the competitive season.[34]

As an acceptable surrogate marker, RMR was calculated in some studies and used to determine EA. The study by Stenqvist et al yielded the same result as the previous ones. They undertook a 4-week intensified endurance training intervention on twenty male athletes including runners and cyclists without any apparent increase in their EI and reported a state of reduced energy among the athletes with a 3% reduction in their RMR.[44] Furthermore, they studied the prevalence of RED-S surrogate markers in forty-four male Norwegian Olympic level athletes and found seven (16%) of them to have reduced RMR, with five out of the seven athletes also having additional one or more markers of RED-S present.[24] Keay and colleagues recruited fifty competitive cyclists and studied the efficacy of combining a sport-specific EA questionnaire with clinical interview, in identifying male athletes at risk of developing RED-S. They observed that fourteen cyclists (28%) had LEA ten of whom were reported to be in a chronic state.[42] In a RCT that followed by the same researchers, they observed that cyclists with improved EA and skeletal loading had better outcome of bone health.[45]

**Low energy availability and bone health**

**Bone mineral density**

Asides from endocrine influence, studies have shown that bone strength, bone volumetric mineral density and geometry are greatly determined by energy status especially in the long term.[1,16,48] All studies that analysed the whole body and, in some cases, regional BMD of their athletes did so with the DEXA scan and adjusted their findings to age and sex-matched controls (Z-score) as recommended by the International Society for Clinical Densitometry (ISCD) for men aged between 18 to 49 years[49] within which most of the population in this review fall into. Brook et al in their study of one hundred and fifty para-athletes, found that eight (5.3%) had a low BMD Z-score while eleven (7.3%) had history of BSI and twenty-four (16%) presented with sport related stress reaction or fracture.[14] Similarly, Viner et al evaluated the prevalence of LEA in cyclists and its impact at different times during a training and competition season on BMD observed that 40% and 10% of participants had low BMD (Z score <−1) at the lumbar spine and femoral neck respectively.[34] In a more recent cross-sectional study by Høeg et al to determine the prevalence of the Female and Male Athlete Triad risk in ultra-marathon runners, more than a third (35%) of the male athletes had low BMD and 20.5% had a history of BSI.[49] Another recently published observational cross-sectional study by Kalpana et al to determine the prevalence of LEA and associated RED-S health and performance outcomes among Indian national male Kho-Kho players, observed that the BMD Z-scores were significantly lower in the LEA group [− 0.60 ± 0.71 (range = − 2.0 to + 0.80;23) ($p \leq 0.05$)], compared to the optimal EA group [1.07 ± 0.11 (range = 0.929–1.344;27).[49] As shown in table 5, the regional site-specific DEXA BMD among the participants of different studies in this review depict that the lumber spine was

the most affected anatomical bone site compared to other regions such as the hip and femoral neck.

**Biomarkers**

Interestingly, two studies by Keay and colleagues revealed that mean ALP remained within the physiological reference range in their participants despite a reduction in BMD Z-score in a combined 32% of participants across both studies.[42, 45] Two studies[10, 23] of the three that screened for s-BAP in their participants, observed that this osteo-metabolically important biomarker remained within the normal physiological reference range. Conversely, an observational cohort study by Lee et al to investigate the EA, metabolic status and bone metabolism including biochemical analysis in twelve Korean male soccer players observed that s-BAP was elevated without a change in BMD.[27] They also reported a significant rise in CTx well above the reference range (ng/mL) = 0.93 ± 0.18 (p = 0.920, ref. range = 0.05−0.45) without any association between EA and bone markers.

Papageorgiou et al in their RCT investigated the effects of low EA on BMD and markers of bone turnover (ß-CTX and P1NP) in recreationally trained males and females for nine days when LEA was reduced to (<15 kcal/kg LBM) and reported no significant change from baseline values in men.[21]

**Table 5: Characteristics of Energy status in the studies included in the systematic review. Where available values are mean ± SD.**

| Author (Year) | Characteristics of Energy Status | | |
|---|---|---|---|
| | **Method of Energy assessment** | **Threshold of low energy availability** | **Outcome of energy assessment** |
| Brook et al (2019) | Eating disorder examination questionnaire (EDEQ) for 28 days period, self-reported history of diagnosed eating disorder, BMI | < 30 kcal/kg.FFM/day | Elevated EDE-Q dietary restraint (≥3) 21 (14%); Elevated EDE-Q pathologic behaviour (>1) 55 (36.7%); History of diagnosed eating disorder 1 (0.7%). |
| Heikura et al (2018) | 7-day EI (via dietary recording) and EEE (via training recording and calculated using Cunningham equation) | < 30 kcal/kg.FFM/day | Categorized into 2 groups [LEA (6) = 21 ± 6; and Normal EA (18) = 37 ± 4]. 25% of males with LEA |
| Høeg et al (2022) | Female Athlete Triad Screening Questionnaire (FATSQ), the Triad Consensus Panel Screening Questionnaire, and the Eating Disorder Examination Questionnaire (EDEQ) | □ | Low risk = 46 (55.4%); Moderate risk = 29 (34.9%); High risk = 8 (9.6%) |
| Hooper et al (2017) | EI via food frequency questionnaire (FFQ). EE estimated by assuming a 10 min/mile average pace with caloric expenditure data | < 30 Kcal kg FFM/day | EEE (Kcal/day) 914.1 ± 143.5. EI (Kcal/day) 2623.0 ± 796.1. EA) 27.2 ± 12.7 |
| Kalpana et al | EA = EI - EEE; where EI obtained from 1-day direct weighment + dietary recall; EEE obtained from 1-day activity record of athlete + duration of activity corrected for basal metabolic rate (BMR). BMR predicted via Cunningham equation and found to be suitable for population of study. | ≤ 25 kcal/kg FFM/day | EI (kcal/day) 3550 ± 713.70 # EEE (kcal/day) 1902.5 ± 389.99 # EA (kcal/kg FFM/day) 33.16 ± 9.45 #. |
| Keay et al (2018) | Sport-specific Energy Availability Questionnaire and Interview (SEAQ-I) | □ | LEA = 14 (chronic LEA: 10) |
| Keay et al (2019) | SEAQ-I | □ | Positive change in EA (12); No change in EA (22); Negative change in EA (11) |
| Kraus et al (2019) | modified Female Athlete Triad Coalition Consensus Statement Cumulative Risk Assessment tool that excluded questions on menstrual history. | Low - high risk score from (0-2) | low risk = 0 |
| Lane et al (2021) | EA: EI - EEE - resting metabolic | < 30 kcal/kg FFM/day | EA (kcal/kg FFM) 28.7 ± 13.4, EI |

| | | | |
|---|---|---|---|
| | rate (RMR); where EI gotten via 4 days dietary log and EEE obtained via 7 days daily training record | | (kcal/day) 3073.8 ± 777.1, EEE (kcal/day) 1296.0 ± 466.7, Resting metabolic rate (RMR) (kcal/day) 1795.5 ± 209.4. |
| Lee et al (2020) | EA: EI (kcal/d) – net EEE (kcal/d)/FFM kg; EI assessed via 7-day food record and EEE determined via FLEX-HR method | < 30 kcal/kg FFM/day | EI (kcal/day) 3,456 ± 435<br>EEE (kcal/day) 1,747 ± 334<br>EA (kcal/kg FFM/day) 31.9 ± 9.9 |
| McCormack et al (2019) | EA: EI (kcal/d) - EEE (kcal/d)/FFM kg. EI derived from Block FFQ as total calorie intake. FFM derived from whole-body DXA scans. Training and physical activity logs (intensity and duration) over the previous 3 months used to calculate EEE | < 30 kcal/kg FFM/day | EI ($kcals/day^{-1}$) 2662.0 ± 788.1<br>EEE ($kcals/day^{-1}$) 1188.8 ± 179.5<br>EA ($kcals \cdot kgFFM^{-1}$) 35.6 ± 15.10 |
| Moore et al (2021) | EA: (EI – EEE) $kcal/kgFFM \cdot d^{-1}$. EI was assessed via participants record of their food and fluid intake (estimated) for 7 consecutive days during 2 separate weeks. EEE calculated using Individual VO2max – HR regression slopes via exercise logs and HR monitors. | < 30 kcal/kg FFM/day | EI (kcals/day) 2,658 ± 887; EEE (kcals/day) 865 ± 566; EA (kcal/kg.FFM/day) 27.6 ± 12.2 |
| Moris et al (2022) | EA: (EI – EEE)/ kg FFM. EI assessed via three, 24-hour food recalls based on the 5-step multiple-pass method; EEE was measured by as accelerometer worn on the dominant hip for 7 days | < 20 kcal/kg FFM/day | EI and EEE: N/R<br>EA (kcals·kgFFM−1): N/R |
| Õnnik et al., (2022) | EI obtained via 3 highest energy-intake days from a 7-day dietary diary. EEE obtained via 7 days training diary | □ | EI (kcal/day) 1581.46 ± 439.6 (Respective relative value = 2313.1 ± 642.7); EEE and EA: N/R |
| Papageorgiou et al (2017) | EA: (EI – EEE) kcal/kgFFM·d−1. EI assessed via participants record of food and fluid intake (estimated) for 7 consecutive days during 2 separate weeks. EEE via daily exercise (x 2 days) with duration (65 ± 7 mins) determined by $O_2$ uptake and RER | < 30 kcal/kg FFM | 1. Limited EA period [EI = 1720 ± 235 (kcal/day); EEE = 856 ± 110 (kcal/day); EA = 829 ± 125 (kcals·kgFFM−1)]. 2. Balanced EA period [EI = 3383 ± 393 (kcal/day); EEE = 856 ± 110 (kcal/day); EA = 2527 ± 283 (kcals·kgFFM−1}. |
| Pritchett et al (2021) | EA: EI — EEE kcal/kg.FFM/day. EI obtained via 7-day consecutive food log completed by all participants to reflect dietary intake most representative of typical diet. EEE obtained from 7-day training log with record of exercise description, training duration, and intensity. | < 30 kcal kg FFM/day | EI = 2566 ± 651 Kcal/day; EEE = 198 ± 47Kcal/day; EA = 41 ± 12 kcal kg FFM/day. |
| Staal et al (2018) | Eating disorder inventory (EDI) and, RMR (via 3 different methods) | $RMR_{ratio}$ < 0.90. | $RMR_{ratio}$ was calculated as ${}_{m}RMR/{}_{p}RMR$; Predicted RMR = 1,967 ± 104 Kcal/day (via Cunningham equation); measured RMR = 1,692 ± 103 Kcal/day; ${}_{m}RMR$ = 25.3 ± 1 kcal kg |

| | | | |
|---|---|---|---|
| | | | FFM/day $p = 0.02$ |
| Stenqvist et al (2020) | EI (pre and post-test) measured via weighed and submitted dietary log and, RMR (using Cunningham equation). EE via training log of 3 interval session a week for 4 weeks | RMRratio < 0.90 using the Cunningham (1980) equation | EI = [pre-test (3,015), post-test (3,021), mean ± SD (5.6 ± 560.6)]; absolute pre-test RMR = 1,768 Kcal/day; absolute post-test RMR = 1,716 Kcal/day (−52 ± 81); Relative pre-test RMR = 26.9 kcal/kg.FFM/day; relative post-test RMR 26.2 kcal kg FFM/day (−0.8 ± 1.2) |
| Stenqvist et al (2021) | Predicted RMR (using Cunningham equation) and measured RMR (via indirect calorimetry) | RMRratio < 0.90 using the Cunningham equation | RMR: [Relative RMR = 29.4 ± 4.1 (low = 23.6 ± 1.8, normal = 30.4 ± 3.3) kcal kg FFM/day. |
| Taguchi et al (2020) | EA= EI - EEE where, EI assessed using 3-day dietary records with food pictures; EEE was determined by the HR-$VO_2$ method | < 30 Kcal kg FFM/day | EI (kcals/day) 2,482 ± 124; EEE (kcals/day) 1,516 ± 386; EA (kcal/kg.FFM/day) 18.9 ± 6.9 |
| Viner et al (2015) | EA = EI – [EEE – (RMR/min × exercise min)] FFM kg/day, where EI was assessed via Training Peaks software to record dietary intake and exercise activity. EEE [calculated from METs, RMR and exercise duration (hr)]. RMR calculated via Cunningham equation | < 30 kcal kg FFM/day | EI (kcals/day) 2311 ± 485; EEE (kcals/day) 1424 ± 491; EA (kcal/kg.FFM/day) 19.5 ± 8.5. |

# Calculated values, min: minutes, FFM: free fat mass, METs: metabolic equivalent,

## DISCUSSION

With the understanding that LEA is the primary predisposing factor to the development of features of the RED-S syndrome, this systematic review of literature examined the effects of LEA on bone health and metabolism of male athletes with focus on the BMD, risk of bone stress injuries and anatomical sites of most impact. The twenty-one articles included in this review were carefully assessed using the NIH quality assessment tool and Cochrane RoB 2 tool and was found to be of 'moderate to good' quality, although in most of the cross-sectional and cohort studies, the investigators and technicians were not blinded to the research group or category of the participants; however, that was mostly unavoidable considering the type and nature of those studies. The major finding of this review is that male athletes just like their female counterparts are at risk of developing LEA and RED-S albeit at a lower threshold and are observed to be less susceptible to the adverse effect on bone. This perhaps could be due to reproductive and endocrine differences in men where an even suppressed level of testosterone could still fall within clinically normal range and maintain its protective and anabolic effect on bone.[16, 48] The participants within the studies chosen for this review took part in different sporting activities such as long-distance running (mostly), race-walking, cycling, soccer, triathletes, basketball, boxing, dancing etc. This review found that studies which reported a LEA in their participants are those whose sports type were mostly endurance running, cycling and triathletes strengthening the need for further research on other sport types. The prevalence of LEA in these athletic population is also largely dependent on the method and tool used for its assessment. For instance, the $RMR_{ratio}$, a recognised marker for the prediction of energy availability,[47] was adopted by three studies[4, 36, 44] and is derived from dividing the $_{m}$RMR by $_{p}$RMR where $_{p}$RMR can be calculated using different equations such as Harris–Benedict, Cunningham, Mifflin–St. Jeor, Owen, and WHO/FAO/UNU.[50] The $_{m}$RMR is obtained from an indirect calorimetry while in the supine position and after a minimum of 12 hours of fasting and 8 hours of sleep.[26] A $RMR_{ratio}$ of < 0.9 has been recognised as a surrogate marker and threshold for LEA although the research that yielded that value was done on female athletes.[4, 47]

A cross-sectional study by Staal et al included in this review which evaluated the prevalence of suppressed RMR as a surrogate marker for LEA by using different methods to calculate $_{p}$RMR and exploring its associations with other markers of energy deficiency in professional male and female ballet dancers,[36] observed that although low $RMR_{ratio}$ was generally prevalent among the dancers, it was dependent on the method used to determine the $_{p}$RMR (Cunningham, Harris–Benedict and DEXA) with values ranging from 25% to 85% in males.[36] Similarly, Stenqvist et al in their study on the prevalence of RED-S surrogate markers on forty-four male Norwegian Olympic athletes observed that seven

(16%) of the athletes had a low $RMR_{ratio}$ and subsequently showed other markers of the RED-S syndrome such as reduced testosterone level.[4] On the contrary, seven of twelve athletes who had two or more RED-S markers had a normal $RMR_{ratio}$ (from Cunningham equation and indirect calorimetry).[4] Because of the differences in the predictive equations of RMR, an error might be generated which is large enough to impact outcome and wrongly classify an athlete energy status. Furthermore, different questionnaires have been developed as tools for assessing EI and EEE, most of which were following research on female participants. The accuracy of these questionnaires has not been universally established as a standardised tool and are dependent on the response from the participants and therefore leading to a possible over or under classification of an athlete's energy status.[51] This can explain the variation in energy status observed among the participants of different sports in this review where some studies observed a LEA while other studies reported a normal EA.

Regarding BMD, it has been established that LEA has a demineralizing effect especially in the long term[2,19,52] however in this review, Moore et al in their study of 14 athletes of different sports reported a normal BMD in athletes who were observed to have LEA (27.6 ± 12.2 kcal/kg. FFM/day).[38] They also found an EA level ranging from ~25 and 29 kcal/kg FFM/day during the 2 weeks of training, without any evidence of low BMD.[38] Similarly, Lane et al investigated the EA and risk factors for RED-S among 60 male non-elite endurance athletes and reported an average LEA of 28.7 ± 13.4 kcal/kg. FFM/day, but their whole body BMD was observed to be within physiological normal levels [Z-score: 0.73 ± 0.95 (CI = 0.49, 0.97)].[23] They additionally reported that the LEA group (n=37) had a significantly higher BMD Z-score (0.98 ± 0.82, P =0.015) when compared to the adequate EA group [n=23 (0.33±1.03)] although no proof of physiological significance was established.[23] This provides support and strengthens the belief that although males may sustain lower EA levels, their endocrine and metabolic function remain maintained.[38] The term 'Low BMD' is defined by the American College of Sports Medicine (ACSM) as a Z-score between -1 and -2, and 'osteoporosis' as a Z-score $\leq -2$ in the presence of secondary risk factors of fracture.[53] In this review, whole body BMD of the participants was examined by sixteen studies and yielded a mixed outcome of low BMD in some and normal scores in others. As shown in table 6, Taguchi et al in their cross-sectional study, reported a significantly low mean BMD (Z-score of -1.1 ± 0.6).[10] Conversely, BMD was low In only one male participant out of the thirty that was investigated by Õnnik et al in their cross-sectional study of high level Kenyan male and female runners.[39] They reported that although EI was low among the participants, there was less tendency to a low BMD or any other RED-S related abnormality leading to their questioning of the applicability of the current Triad/RED-D criteria to the African athlete.[39] As most of the evidence is cross-sectional, the discrepancies could be due to the differences in assessment method, duration and severity of LEA between participants. Additionally, table 6 depicts the outcome of regional analysis of BMD in fourteen studies and reveal that although most of them were within physiological range, the lumbar spine (vertebrae) was the most susceptible anatomical site of low BMD and BSI among the participants when compared with other regions such as the hip and femoral neck. The femoral neck, hip and vertebrae are cancellous bone rich in trabecular network with more soft tissues compared to the compact or cortical rich bones of the limbs (femoral shaft, tibia, etc.)[54] Although trabecular bone is always surrounded by a cortical shell, the strength and thickness of the cortical shell depends on the location; being lesser in the spine. The presence of more trabecular network in the lumbar spine microarchitecture and composition plays a significant role in its ability to resist repetitive axial compression forces, however at the expense of strength.[54,55] This is consistent with the findings of Tenforde et al in their study of 28 male athletes where they observed that compared to athletes with a history of BSI in anatomic locations rich in cortical bone, athletes who sustained ≥1 BSI in an anatomic location with greater trabecular bone content, had a higher prevalence (4.6-fold) of low BMD.[19]

In this review, six studies (2 RCTs, 2 cross-sectional, and 2 observational cohort) reported findings on biomarkers of bone formation and resorption. The RCT by Papageorgiou et al to investigate the effects of deliberately induced short-term (5days) LEA, at 15 kcal/kg LBM/day on markers of bone turnover reported no change in ß-CTx or P1NP from baseline values.[21] ALP was observed to be within physiological normal levels in another RCT by Keay et al despite having eleven athletes (24%) out of forty-five with low BMD.[45] On the contrary, the Lee et al study to investigate the EA status of varsity soccer players during training period and evaluate its association with metabolic status, bone health and hormonal status, reported that mean bone formation (s-BAP) and resorption (CTx) biomarkers were both raised (see table 6).[27] More so, in the cross-sectional study by Taguchi et all, bone resorption biomarker NTx was high while BAP was observed to be low; therefore suggesting that further research is needed in this area.[10]

**Table 6: Outcome measures of bone health. Where available values are mean ± SD.**

| Author (Year) | Key Findings (Bone Health) | | | | |
|---|---|---|---|---|---|
| | **Total body BMD (DXA)** | **Bone Biomarkers** | **Radiological outcome** | **Site specific BMD** | **Site of most impact** |
| Brook et al (2019) | Low in 8 (5.3%) athletes. 11 (7.3%) with history of bone stress injury (BSI) | □ | 24 para-athletes with sport related stress reaction or fracture | □ | □ |
| Heikura et al (2018) | 1.316 ± 0.088 g/cm$^2$ (0.197 SD #) in LEA group and 1.279 ± 0.072 g/cm$^2$ (0.191 SD #) in Moderate EA group | □ | | Z-score: Spine = [0.1 ± 0.8 in LEA group and 0.4 ± 0.8 in moderate EA group] | Lumbar Spine |
| Høeg et al (2022) | Low in > 35% of participants. | □ | 20.5% had a history of BSI | Z-score: Lumbar =−0.2 (1.3%); Femur = 0.3 (0.9%); Total hip = 0.0 (0.8%) | Lumbar Spine |
| Hooper et al (2017) | Z - score = 1.5 (95% CI) | □ | □ | Z-score: Lumber = 0.5; Femur 1.0 # | Lumbar Spine |
| Kalpana et al | Z-score = [− 0.60 ± 0.71 (− 2.0 to + 0.80;23)] in LEA group, and 0.048 ± 0.99 (− 1.5 to + 2.7;27) in optimal EA group ($p \leq 0.05$) | □ | □ | □ | □ |
| Keay et al (2018) | □ | Alkaline phosphatase (ALP) (0–129 IU/L) = 65.0 ± 24.7 (range = 32.0–161.0) | □ | Z- score: Lumbar = − 0.8 ± 1.2 (range = −3.2 to 1.6); Femoral neck - 0.6 ± 0.9 (range =−2.6 to 1.0) | Lumbar Spine |
| Keay et al (2019) | Z-score: Negative change in EA (11) = −2.3; No change in EA (22) = −0.4; positive change in EA (12) = 2.2 | ALP (0–129/149 IU/L) = 64.4 ± 23.5 (33.0 to 156.0); −0.62 change in mean | □ | Z-score: Lumbar − 0.91 | Lumbar Spine |
| Kraus et al (2019) | Z-score: < −1.0 In 8 (14.8%) of participants | □ | 42 (27%) with radiological finding of bone stress injury (BSI) | □ | □ |
| Lane et al (2021) | Z-score: 0.73 ± 0.95 (CI = 0.49, 0.97) | s-BAP (µg/L) = 10.68 ± 0.30 (CI = 10.60, 10.75) (Ref range < 20.1) | □ | Z-score: Lumbar = 1.46 ± 1.36 (CI = 1.11, 1.80); Femoral neck = 1.59 ± 1.33 (CI = 1.25, 1.93) | Lumbar Spine |
| Lee et al (2020) | 1.384 ± 0.075 g/cm$^2$ (0.2076 SD #) $p$ = 0.677 | s-BAP (µg/L) = 23.9 ± 6.5 ($p$ = 0.289, Ref range = <20.1); s-CTx (ng/mL) = 0.93 ± 0.18 ($p$ = 0.920, Ref range = 0.05−0.45) | □ | □ | □ |
| McCormack et al (2019) | Z-score: 0.048 ± 0.743 (p ≤ 0.05) | □ | □ | Z-score: Antero-posterior (AP) spine = −0.800 ± 0.895; Femoral neck = 0.316 ± | Spine |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 0.667; Total hip = 0.500 ± 0.655 | |
| Moore et al (2021) | 1.3 ± 0.9 g/cm$^2$ (0.195 SD #) $p$ = 0.34; 4 participants (29%) ranged from −0.4 to 0.9 | □ | □ | □ | □ |
| Moris et al (2022) | Z-score: 1.66 ± 0.5 # ($p$ < 0.05) | □ | □ | Z-score: Femoral neck = 1.24 ± 0.26 #; Lumbar = 1.20 ± 0.41 # ($p$ < 0.05) | Lumbar Spine |
| Õnnik et al (2022) | Z-score: > − 1 (29 participants)<br>Z -score: − 1 to − 2 (1 participant)<br>Z-score: < − 2 (nil) | □ | □ | Lumbar<br>Z-score: > − 1 (14 participants)<br>Z -score: − 1 to − 2 (5 participants)<br>Z-score: < − 2 (1 participant)<br>Right Femur<br>Z-score > − 1 (18 participants)<br>Z-score: − 1 to − 2 (2 participants)<br>Z-score: < − 2 (nil) | Lumbar Spine |
| Papageorgiou et al (2017) | □ | No significant change observed from baseline values after restricted EI | □ | □ | □ |
| Pritchett et al (2021) | 1.22 ± 0.16 g/cm$^2$ (0.183 SD #) | □ | □ | Z-score (Hip) −1.7 + 0.7 | □ |
| Staal et al (2018) | Z-score: 1.30 ± 0.7 (p= 0.07) | □ | □ | Z-score: Lumbar = 0.37 ± 0.7; Femur neck = 1.70 ± 0.8; Total hip = 1.30 ± 0.7 | Lumbar Spine |
| Stenqvist et al (2020) | □ | □ | □ | Z-score: Lumbar spine = 0.1 ± 1.1; femoral neck = 0.2 ± 1.0; Total hip = 0.3 ± 0.9 | Lumbar Spine |
| Stenqvist et al (2021) | □ | □ | □ | Z-score: Lumbar = 0.59 ± 1.62 (p = 0.083); Femur = 0.96 ± 1.14 (p = 0.280) | Lumbar Spine |
| Taguchi et al (2020) | Z-score: −1.1 ± 0.6 (Ref > −1.0) | BAP (µg/L) = 17.9 ± 5.8 (ref 3.7–20.9); NTX (nmol/L) = 28.5 ± 7.1 (ref 9.5–17.7) | □ | □ | □ |
| Viner et al (2015) | □ | □ | □ | Lumbar spine: low in 40% of participants<br>Femoral neck: low in 10% of participants | Lumbar Spine |

Currently, the sports medicine position statement regarding RED-S recognises nutrition as the major determinant to promoting optimal bone health and prevention of injury in male and female athletes.[22] Treatment of athletes is primarily to increase daily EA, educate and support them through a multidisciplinary approach.[56] A multidisciplinary team (MDT) of health care professionals including but not limited to sport physicians, exercise physiologists, sport dieticians and clinical psychologists should be involved in the management of RED-S with the aim of increasing caloric intake to match expenditure, and therefore maintain energy balance.[57] Treatment can be grouped into pharmacological and non-pharmacological. Non-

pharmacological therapy is the recommended first line approach to treatment.[2] Educating athletes on risk factors, long-term consequences along with psychological implication and performance shortcomings of reduced EA should be the core of this management protocol. They should be made aware of available help with practical strategies in place to facilitate prompt treatment of injuries and overcome future challenges.[20] Psychosocial support and nutritional counselling are key to the achievement and restoring of adequate EA especially in those with disordered eating.[20] Counselling should include recommendations on daily intake of essential nutrients and vitamins such as calcium and vitamin D.[58] Dominguez et al, in 2007, helped participants in their study regain 90% of their ideal body weight, which resulted in increases in hip and spine BMD by 3.77% and 4.38%, respectively over 2.2 months.[58] Finally, although pharmacological therapy is rarely needed, it may be necessary in certain cases to treat low BMD and increased fracture risk, hypogonadism, low libido, and possibly infertility in male athletes.[59] For patients who did not respond to standard non-pharmacologic treatment, other medical treatment may include antipsychotics, antidepressants, or administration of leptin.[57]

The main strength of this review is that following a thorough search of major sport health related scientific databases, a relatively good number of articles that reported the BMD and other bone related outcome measures in athletic men was considered, most of which were of high quality. Additionally, unlike other studies previously conducted on this subject, this review was specific to bone health bone ranging across different sport type including endurance and weight class. The major limitation of this review is that only 3 of the 21 studies reported an outcome on the radiological effect of RED-S/LEA on bone therefore limiting the validity of that outcome measure. The application of different questionnaires in the measurement of athlete energy intake and expenditure will possibly affect the accuracy of the outcome in different studies therefore, efforts should be made to harmonize or standardize these methods.

In conclusion, this systematic review strengthens the already existing evidence that male athletes are susceptible to LEA and RED-S syndrome however, the threshold for LEA and at which level the clinical symptoms begin to manifest is yet to be universally established. Furthermore, biomarkers of bone turnover in certain conditions could possibly remain within physiological levels despite a low BMD. Awareness should be increased among professional sporting bodies, clubs, and athletic federations on this subject to minimize the risk of developing the syndrome among athletes and as such maintain optimal performance.

**REFERENCES**


1. Melin AK, Heikura IA, Tenforde A, *et al.* Energy Availability in Athletics: Health, Performance, and Physique. *International Journal of Sport Nutrition and Exercise Metabolism*, 2019; 29: 152–64. doi:10.1123/ijsnem.2018-0201.
2. Mountjoy M, Sundgot-Borgen J, Burke L, *et al.* The IOC Consensus statement: beyond the Female Athlete Triad—Relative Energy Deficiency in Sport (RED-S). *British Journal of Sports Medicine*, 2014; 48: 491–7. doi:10.1136/bjsports-2014-093502.
3. Logue DM, Madigan SM, Melin A, *et al.* Low Energy Availability in Athletes 2020: An Updated Narrative Review of Prevalence, Risk, Within-Day Energy Balance, Knowledge, and Impact on Sports Performance. *Nutrients*, 2020; 12: 835. doi:10.3390/nu12030835.
4. Stenqvist TB, Melin AK, Garthe I, *et al.* Prevalence of Surrogate Markers of Relative Energy Deficiency in Male Norwegian Olympic-Level Athletes. *International Journal of Sport Nutrition and Exercise Metabolism*, 2021; 31: 497–506. doi:10.1123/ijsnem.2020-0368.
5. Poon ET-C, O'Reilly J, Sheridan S, *et al.* Markers of Bone Health, Bone-Specific Physical Activities, Nutritional Intake, and Quality of Life of Professional Jockeys in Hong Kong. *International Journal of Sport Nutrition and Exercise Metabolism*, 2018; 28: 440–6. doi:10.1123/ijsnem.2016-0176.
6. Wasserfurth P, Palmowski J, Hahn A, *et al.* Reasons for and Consequences of Low Energy Availability in Female and Male Athletes: Social Environment, Adaptations, and Prevention. *Sports Medicine – Open*, 2020; 6. doi:10.1186/s40798-020-00275-6.
7. Barrack MT, Fredericson M, Tenforde AS, *et al.* Evidence of a cumulative effect for risk factors predicting low bone mass among male adolescent athletes. *British Journal of Sports Medicine*, 2017; 51: 200–5. doi:10.1136/bjsports-2016-096698.
8. Fagerberg P. Negative Consequences of Low Energy Availability in Natural Male Bodybuilding: A Review. *International Journal of Sport Nutrition and Exercise Metabolism*, 2018; 28: 385–402. doi:10.1123/ijsnem.2016-0332.
9. Skarakis NS, Mastorakos G, Georgopoulos N, *et al.* Energy deficiency, menstrual disorders, and low bone mineral density in female athletes: a systematic review. *Hormones* Published Online First: 22 April 2021. doi:10.1007/s42000-021-00288-0.
10. Taguchi M, Moto K, Lee S, *et al.* Energy Intake Deficiency Promotes Bone Resorption and Energy Metabolism Suppression in Japanese Male Endurance Runners: A Pilot Study. *American Journal of Men's Health*, 2020; 14: 155798832090525. doi:10.1177/1557988320905251.
11. Gillbanks L, Mountjoy M, Filbay SR. Lightweight rowers' perspectives of living with Relative Energy Deficiency in Sport (RED-S). *PLOS ONE*, 2022; 17: e0265268. doi:10.1371/journal.pone.0265268.

12. Elliott-Sale KJ, Tenforde AS, Parziale AL, *et al.* Endocrine Effects of Relative Energy Deficiency in Sport. *International Journal of Sport Nutrition and Exercise Metabolism*, 2018; 28: 335–49. doi:10.1123/ijsnem.2018-0127.
13. De Souza MJ, Strock NCA, Ricker EA, *et al.* The Path Towards Progress: A Critical Review to Advance the Science of the Female and Male Athlete Triad and Relative Energy Deficiency in Sport. *Sports Medicine* Published Online First, 19 October 2021. doi:10.1007/s40279-021-01568-w.
14. Brook EM, Tenforde AS, Broad EM, *et al.* Low energy availability, menstrual dysfunction, and impaired bone health: A survey of elite para-athletes. *Scandinavian Journal of Medicine & Science in Sports*, 2019; 29: 678–85. doi:10.1111/sms.13385.
15. Koehler K, De Souza MJ, Williams NI. Less-than-expected weight loss in normal-weight women undergoing caloric restriction and exercise is accompanied by preservation of fat-free mass and metabolic adaptations. *European Journal of Clinical Nutrition*, 2016; 71: 365–71. doi:10.1038/ejcn.2016.203.
16. Mountjoy M, Sundgot-Borgen J, Burke L, *et al.* International Olympic Committee (IOC) Consensus Statement on Relative Energy Deficiency in Sport (RED-S): 2018 Update. *International Journal of Sport Nutrition and Exercise Metabolism*, 2018; 28: 316–31. doi:10.1123/ijsnem.2018-0136.
17. Hooper DR. The Application of Heavy Strength Training in Relative Energy Deficiency in Sport. *Journal of Science in Sport and Exercise* Published Online First, 6 November 2019. doi:10.1007/s42978-019-00043-3.
18. Sygo J, Coates AM, Sesbreno E, *et al.* Prevalence of Indicators of Low Energy Availability in Elite Female Sprinters. *International Journal of Sport Nutrition and Exercise Metabolism*, 2018; 28: 490–6. doi:10.1123/ijsnem.2017-0397.
19. Tenforde AS, Parziale AL, Popp KL, *et al.* Low Bone Mineral Density in Male Athletes Is Associated with Bone Stress Injuries at Anatomic Sites with Greater Trabecular Composition. *The American Journal of Sports Medicine*, 2017; 46: 30–6. doi:10.1177/0363546517730584.
20. Papageorgiou M, Dolan E, Elliott-Sale KJ, *et al.* Reduced energy availability: implications for bone health in physically active populations. *European Journal of Nutrition*, 2017; 57: 847–59. doi:10.1007/s00394-017-1498-8
21. Papageorgiou M, Elliott-Sale KJ, Parsons A, *et al.* Effects of reduced energy availability on bone metabolism in women and men. *Bone* 2017; 105: 191–9. doi:10.1016/j.bone.2017.08.019.
22. Nose-Ogura S, Harada M, Hiraike O, *et al.* Management of the female athlete triad. *Journal of Obstetrics and Gynaecology Research*, 2018; 44: 1007–14. doi:10.1111/jog.13614.
23. Lane AR, Hackney AC, Smith-Ryan AE, *et al.* Energy Availability and RED-S Risk Factors in Competitive, Non-elite Male Endurance Athletes. *Translational medicine and exercise prescription*, 2021; 1: 25–32. https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC8294781/
24. Heikura IA, Uusitalo ALT, Stellingwerff T, *et al.* Low Energy Availability Is Difficult to Assess but Outcomes Have Large Impact on Bone Injury Rates in Elite Distance Athletes. *International Journal of Sport Nutrition and Exercise Metabolism*, 2018; 28: 403–11. doi:10.1123/ijsnem.2017-0313.
25. Torstveit MK, Fahrenholtz I, Stenqvist TB, *et al.* Within-Day Energy Deficiency and Metabolic Perturbation in Male Endurance Athletes. *International Journal of Sport Nutrition and Exercise Metabolism*, 2018; 28: 419–27. doi:10.1123/ijsnem.2017-0337.
26. McGuire A, Warrington G, Doyle L. Low energy availability in male athletes: A systematic review of incidence, associations, and effects. *Translational Sports Medicine* Published Online First, 4 February 2020. doi:10.1002/tsm2.140.
27. Lee S, Kuniko M, Han S, *et al.* Association of Low Energy Availability and Suppressed Metabolic Status in Korean Male Collegiate Soccer Players: A Pilot Study. *American Journal of Men's Health*, 2020; 14: 155798832098218. doi:10.1177/1557988320982186.
28. Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Medicine*, 2009; 6: e1000100. doi:10.1371/journal.pmed.1000100.
29. Tawfik GM, Dila KAS, Mohamed MYF, *et al.* A step by step guide for conducting a systematic review and meta-analysis with simulation data. *Tropical Medicine and Health*, 2019; 47: 1–9. doi:10.1186/s41182-019-0165-6.
30. Maffulli N. At what age should a child begin regular continuous exercise at moderate or high intensity? *Western Journal of Medicine*, 2000; 172: 413. https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC1070938/ (accessed 15 Apr 2020).
31. Moris JM, Olendorff SA, Zajac CM, *et al.* Collegiate male athletes exhibit conditions of the Male Athlete Triad. *Applied Physiology, Nutrition, and Metabolism*, 2022; 47: 328–36. doi:10.1139/apnm-2021-0512.
32. NIH. Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI). Nih.gov. 2009. https: //www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
33. Cochrane. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. Cochrane.org. 2011.https: //methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials.
34. Viner RT, Harris M, Berning JR, *et al.* Energy Availability and Dietary Patterns of Adult Male and

Female Competitive Cyclists With Lower Than Expected Bone Mineral Density. *International Journal of Sport Nutrition and Exercise Metabolism*, 2015; 25: 594–602. doi:10.1123/ijsnem.2015-0073.
35. Hooper DR, Kraemer WJ, Saenz C, *et al.* The presence of symptoms of testosterone deficiency in the exercise-hypogonadal male condition and the role of nutrition. *European Journal of Applied Physiology*, 2017; 117: 1349–57. doi:10.1007/s00421-017-3623-z.
36. Staal S, Sjödin A, Fahrenholtz I, *et al.* Low RMRratio as a Surrogate Marker for Energy Deficiency, the Choice of Predictive Equation Vital for Correctly Identifying Male and Female Ballet Dancers at Risk. *International Journal of Sport Nutrition and Exercise Metabolism*, 2018; 28: 412–8. doi:10.1123/ijsnem.2017-0327.
37. McCormack WP, Shoepe TC, LaBrie J, *et al.* Bone mineral density, energy availability, and dietary restraint in collegiate cross-country runners and non-running controls. *European Journal of Applied Physiology*, 2019; 119: 1747–56. doi:10.1007/s00421-019-04164-z.
38. Moore EM, Drenowatz C, Stodden DF, *et al.* Examination of Athlete Triad Symptoms Among Endurance-Trained Male Athletes: A Field Study. *Frontiers in Nutrition*, 2021; 8. doi:10.3389/fnut.2021.737777.
39. Õnnik L, Mooses M, Suvi S, *et al.* Correction to: Prevalence of Triad–RED–S symptoms in high-level Kenyan male and female distance runners and corresponding control groups. *European Journal of Applied Physiology*, 2021; 122: 209–9. doi:10.1007/s00421-021-04836-9.
40. Kalpana K, Cherian KS, Khanna GL. Energy availability and RED-S risk assessment among Kho-Kho players in India. *Sport Sciences for Health* Published Online First: 30 August 2022. doi:10.1007/s11332-022-00996-z.
41. Høeg TB, Olson EM, Skaggs K, *et al.* Prevalence of Female and Male Athlete Triad Risk Factors in Ultramarathon Runners. *Clinical Journal of Sport Medicine*, 2021; Publish Ahead of Print. doi:10.1097/jsm.0000000000000956.
42. Keay N, Francis G, Hind K. Low energy availability assessed by a sport-specific questionnaire and clinical interview indicative of bone health, endocrine profile and cycling performance in competitive male cyclists. *BMJ Open Sport & Exercise Medicine*, 2018; 4: e000424. doi:10.1136/bmjsem-2018-000424.
43. Kraus E, Tenforde AS, Nattiv A, *et al.* Bone stress injuries in male distance runners: higher modified Female Athlete Triad Cumulative Risk Assessment scores predict increased rates of injury. *British Journal of Sports Medicine*, 2018; 53: 237–42. doi:10.1136/bjsports-2018-099861.
44. Stenqvist TB, Torstveit MK, Faber J, *et al.* Impact of a 4-Week Intensified Endurance Training Intervention on Markers of Relative Energy Deficiency in Sport (RED-S) and Performance Among Well-Trained Male Cyclists. *Frontiers in Endocrinology*, 2020; 11. doi:10.3389/fendo.2020.512365.
45. Keay N, Francis G, Entwistle I, *et al.* Clinical evaluation of education relating to nutrition and skeletal loading in competitive male road cyclists at risk of relative energy deficiency in sports (RED-S): 6-month randomised controlled trial. *BMJ Open Sport & Exercise Medicine*, 2019; 5: e000523. doi:10.1136/bmjsem-2019-000523.
46. Pritchett K, DiFolco A, Glasgow S, *et al.* Risk of Low Energy Availability in National and International Level Paralympic Athletes: An Exploratory Investigation. *Nutrients*, 2021; 13: 979. doi:10.3390/nu13030979.
47. Schofield KL, Thorpe H, Sims ST. Resting metabolic rate prediction equations and the validity to assess energy deficiency in the athlete population. *Experimental Physiology*, 2019; 104: 469–75. doi:10.1113/ep087512.
48. Popp KL, Cooke LM, Bouxsein ML, *et al.* Impact of Low Energy Availability on Skeletal Health in Physically Active Adults. *Calcified Tissue International* Published Online First: 16 February 2022. doi:10.1007/s00223-022-00957-1.
49. Carey JJ, Delaney MF, Love TE, *et al.* Dual-Energy X-ray Absorptiometry Diagnostic Discordance Between Z-Scores and T-Scores in Young Adults. *Journal of Clinical Densitometry*, 2009; 12: 11–6. doi:10.1016/j.jocd.2008.11.001.
50. Hasson RE, Howe CA, Jones BL, *et al.* Accuracy of four resting metabolic rate prediction equations: Effects of sex, body mass index, age, and race/ethnicity. *Journal of Science and Medicine in Sport*, 2011; 14: 344–51. doi:10.1016/j.jsams.2011.02.010.
51. Lundy B, Torstveit MK, Stenqvist TB, *et al.* Screening for Low Energy Availability in Male Athletes: Attempted Validation of LEAM-Q. *Nutrients*, 2022; 14: 1873. doi:10.3390/nu14091873.
52. Ackerman KE, Putman M, Guereca G, *et al.* Cortical microstructure and estimated bone strength in young amenorrheic athletes, eumenorrheic athletes and non-athletes. *Bone*, 2012; 51: 680–7. doi:10.1016/j.bone.2012.07.019.
53. Dimitriou L, Weiler R, Lloyd-Smith R, *et al.* Bone mineral density, rib pain and other features of the female athlete triad in elite lightweight rowers. *BMJ Open*, 2014; 4: e004369. doi:10.1136/bmjopen-2013-004369.
54. Monier-Faugere M-C, Chris Langub M, Malluche HH. Bone Biopsies: A Modern Approach. *Metabolic Bone Disease and Clinically Related Disorders*, 1998; 237–80e. doi:10.1016/b978-012068700-8/50009-8.
55. Osterhoff G, Morgan EF, Shefelbine SJ, *et al.* Bone mechanical properties and changes with osteoporosis. *Injury*, 2016; 47: S11–20. doi:10.1016/s0020-1383(16)47003-8.

56. Briggs C, James C, Kohlhardt S, *et al.* Relative energy deficiency in sport (RED-S) – a narrative review and perspectives from the UK. *Deutsche Zeitschrift für Sportmedizin/German Journal of Sports Medicine*, 2020; 71: 243–8. doi:10.5960/dzsm.2020.459.
57. Boutari C, Pappas PD, Mintziori G, *et al.* The effect of underweight on female and male reproduction. *Metabolism*, 2020; 107: 154229. doi:10.1016/j.metabol.2020.154229.
58. Chu SM, Gustafson KE, Leiszler M. Female Athlete Triad. *American Journal of Lifestyle Medicine*, 2013; 7: 387–94. doi:10.1177/1559827613483441.
59. Fredericson M, Kussman A, Misra M, *et al.* The Male Athlete Triad—A Consensus Statement From the Female and Male Athlete Triad Coalition Part II: Diagnosis, Treatment, and Return-To-Play. *Clinical Journal of Sport Medicine*, 2021; 31: 349–66. doi:10.1097/jsm.0000000000000948.