**The cardiovascular disease risk indicators linked with low energy availability in physically active females: a systematic review**

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**Abstract**

Objective: To systematically review the literature on cardiovascular disease (CVD) risk indicators linked with low energy availability (LEA) in physically active females. Design: The Cochrane Collaboration Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol was used to capture articles related to CVD risk indicators linked with LEA in physically active females. Methods: A search of PubMed, SportDiscus (EBSCOhost), One Search, and Google Scholar was performed. Results: Nine studies were included. Eight studies were rated fair, and one study was of good quality. Most studies found no significant effect of LEA on lipid levels, except for one study which identified abnormal lipid levels. Physically active females with LEA had significantly lower levels of phosphatidylethanolamine (*p* = .030) and exhibited distinct triglyceride trajectories, including acute exercise-induced fluctuations in those with amenorrhea, a steady increase in those with functional hypothalamic amenorrhea, and varying patterns based on energy availability (False Discovery Rate-adjusted *p* value < .050). With regards to the impact of LEA on direct vascular indices, one study found no significant difference in brachial artery flow-mediated dilation, pulse wave velocity, carotid intima–media thickness, or carotid artery reactivity between elite long-distance runners and inactive women. Whereas, another study reported significantly reduced flow-mediated dilation (*p* = .016) in elite dancers with LEA. Higher energy availability had no link to heart rate variability, and LEA was significantly associated with 2.5-fold increased CVD risk (*p* = .001). Conclusion: LEA may elevate CVD risks in physically active females. However, larger scale longitudinal studies with robust study designs (e.g., blood biomarkers and vascular assessments) are necessary to validate these implications.

*Keywords*: Relative Energy Deficiency in Sport, vascular function, endothelial dysfunction, blood lipid profiles, women's health.

**Key Points**

Low energy availability was linked to several cardiovascular disease risk indicators, such as abnormal lipid profiles and endothelial dysfunction, though the effects were inconsistent across studies, highlighting the need for more conclusive evidence. Future research should prioritise longitudinal studies with larger sample sizes, utilising direct measures of vascular function and comprehensive lipidomic analyses to clarify the impact of low energy availability on cardiovascular disease risk indicators in physically active female populations.

**Introduction**

Low energy availability (LEA) is a physiological condition in which the body does not have sufficient energy to meet its physiological demands (Lee, 2024). LEA can result from either a deliberate or unintentional imbalance, where energy intake (EI) falls short of adequate supporting an athlete’s exercise energy expenditure (EEE; Melin et al., 2024). Practically, energy availability (EA) is calculated by subtracting EEE from total EI and is typically reported relative to fat-free mass (FFM) (i.e., kcal⋅kg FFM⋅day−1) (Tarnowski et al., 2023). LEA can be categorised based on its duration: Short-term LEA refers to inadequate EA lasting from days to weeks, medium-term LEA spans weeks to months, and long-term (prolonged) LEA extends from several months to years (Heikura et al., 2022). Traditionally, an EA value of ≤30 kcal·kg−1 FFM·day−1 has been widely recognised as the threshold for identifying LEA in athletes (Burke et al., 2018; De Souza et al., 2014; Maughan et al., 2018). However, more recent studies have questioned the reliability of this single cut-off, particularly in females, suggesting that adverse outcomes such as ovarian suppression and functional hypothalamic amenorrhea (FHA) are more likely to occur as EA decreases, even without reaching this specific threshold (De Souza et al., 2022; Lieberman et al., 2018; Reed et al., 2015).

It is important to recognise that LEA thresholds are influenced by several individual moderating factors, such as gynecological age, biological sex, sport-specific demands, the macronutrient composition of the energy deficit, and genetic predispositions (Heikura et al., 2022; Loucks, 2006). Moreover, the concept of an LEA “dose or load,” which considers both the severity and duration of energy deficiency (i.e., LEA level times by the number of days with LEA), may interact and influence (Areta et al., 2021; Heikura et al., 2022). Given these complexities, relying solely on threshold-based assessments from short-term studies may provide an incomplete picture of LEA (Melin et al., 2024). Consequently, it is believed that using a range of EA values, rather than a fixed single cut-off threshold, may offer a more accurate and comprehensive reflection of an athlete’s EA status (Melin et al., 2024).

In the early 1990s, the Female Athlete Triad was introduced, defined by three interrelated conditions: decreased bone mineral density (BMD), menstrual dysfunction (MD), and LEA (De Souza et al., 2014; Golden, 2002; Nattiv et al., 1994; Yeager et al., 1993). In 2014, the term Relative Energy Deficiency in Sport (RED-S) was introduced to describe LEA in athletes and to provide a framework for understanding the wide range of potential performance consequences (e.g., reduced training adaptations, diminished endurance capacity, and decreased muscle strength) and health effects (e.g., compromised bone health, reproductive irregularities, and gastrointestinal issues) associated with this condition (Mountjoy et al., 2014, 2018, 2023). Studies have shown that both the Female Athlete Triad and RED-S arise from LEA, with or without disordered eating (DE), can potentially lead to physiological impairments across multiple systems, including the cardiovascular, immune, and reproductive systems, as well as effects on BMD, metabolic rate, and protein synthesis (De Souza et al., 2014; Mountjoy et al., 2014). While the connections between LEA, MD, and reduced BMD have been extensively studied, largely due to the historical focus on the Female Athlete Triad (De Souza et al., 2007, 2008; Loucks and Thuma, 2003; Reed et al., 2015), certain aspects of the RED-S model remain less explored (Scheid et al., 2024), such as its link to cardiovascular disease (CVD). Despite limited research on the relationship between LEA and CVD, the 2023 International Olympic Committee consensus statement on RED-S emphasised a bidirectional link between impaired cardiovascular function and LEA (Mountjoy et al., 2023).

Disturbances in hormonal and cardiovascular health are among the key features of RED-S (Mountjoy et al., 2023). Restriction of caloric intake inhibits the hypothalamic–pituitary–ovarian axis, potentially leading to hypoestrogenism and FHA (Rickenlund et al., 2005). Estrogen provides several cardiovascular benefits, such as protecting blood vessels from atherosclerotic lesion formation and reducing low-density lipoprotein cholesterol (LDL-C) and lipoprotein (a) level (Meyer et al., 2006). As a result, the hypoestrogenism associated with problematic LEA may compromise cardiovascular health in young female athletes, predisposing them to early pathological changes (Silvennoinen et al., 2024). This is supported in research where MD in premenopausal women was linked to a higher risk of future CVD (Okoth et al., 2023). This is particularly concerning given that the prevalence of hypothalamic amenorrhea in female athletes can reach as high as 69% (Coelho et al., 2021). However, further research is needed to fully elucidate the mechanisms linking EA, hormonal regulation, and cardiovascular health.

LEA can negatively impact health and performance by inducing maladaptations such as hormonal imbalances, reproductive dysfunction, psychological disorders, thyroid suppression, and altered metabolic processes (Wasserfurth et al., 2020). Therefore, LEA, whether short- or long-term, can contribute to increased CVD risk. For instance, LEA-induced hormonal imbalances (e.g., reduced leptin, insulin, and insulin-like growth factor-1 [IGF-1], alongside elevated cortisol; Koehler et al., 2016; Loucks and Thuma, 2003; Wasserfurth et al., 2020), reproductive dysfunction (e.g., low estradiol and progesterone in females; Sale and Elliott-Sale, 2019), thyroid suppression (e.g., decreased triiodothyronine [T3]; Loucks and Heath, 1994), and metabolic alterations (e.g., hypercholesterolemia and electrolyte imbalances leading to arrhythmias; Melin et al., 2015; Walsh et al., 2000), exacerbate CVD risk.

Despite the increasing number of publications within the area of LEA and its physiological effects (Cabre et al., 2022), as well as the high prevalence of LEA among female athletes (Oxfeldt et al., 2023), there has been no review of the evidence regarding the CVD risk indicators linked with LEA in physically active females. Therefore, our review aims to address this gap by systematically reviewing the literature concerning the CVD risk indicators linked with LEA in physically active females.

**Methods**

**Search strategy**

The present systematic review achieved preregistration approval from Prospero (CRD42023402455). The Cochrane Collaboration Preferred Reporting Items for Systematic Reviews and MetaAnalyses protocol 2020 updates (Page et al., 2021) were adhered to when completing this review. A specific research question was developed as part of a search strategy that supported the identification of key search terms. Online databases PubMed, SportDiscus (EBSCOhost), and One Search were searched. Individual manual searches using Google Scholar were also used to find suitable articles relating to the key terms, with the final search being August 2024. The search keywords were divided into components using the PICO scheme (P = Population, I = Intervention, C = Comparisons, and O = Outcomes; Page et al., 2021). Therefore, our PICO framework was as follows: The Population included physically active to elite-level females across all sports and exercise disciplines. The Intervention was LEA risk or LEA status. The Comparator consisted of females at risk of LEA versus those not at risk, or females in an LEA state compared to females with adequate EA. The Outcome measures were CVD risk indicators.

Medical Subject Headings (MeSH) terms were predominantly used in the PubMed database, supplemented by other relevant key terms. Boolean logic was applied to search and filter through results, using terms including “OR” to identify articles containing any of the terms and “AND” to combine different terms. The following represents the search terms employed to generate articles: “cardiovascular disease” OR “cardiovascular abnormalities” OR “heart disease” OR “hypertension” OR “atherosclerosis” OR “coronary artery disease” OR “endothelial dysfunction” OR “cardiac output” OR “heart rate” OR “vascular function” OR “blood pressure” OR “cardiovascular function” OR “arteriosclerosis” AND “low energy availability” OR “energy defic\*” OR “energy restriction” OR “amenorrhea” AND “female” OR “women” OR “physically active” OR “trained” OR “sport” OR “exercise” OR “athlete” NOT “men” NOT “animals” NOT “pregnant” NOT “obese.” These filters were applied: Humans, English, Female.

**Eligibility criteria**

The eligibility criteria were physically active to elite trained female athletes using all tiers as defined by McKay *et al*. (2021; i.e., trained [local-level representation], highly trained [competing at the national level], and elite [competing at the international level]), studies assessing LEA risk or status, and CVD risk indicators.

No specific sport or type of exercise was excluded. For instance, dancers were included because dance and sport share key physical demands, such as fitness and strength (Koutedakis and Jamurtas, 2004). Additionally, dancers are a distinct group of elite artistic performers who frequently exhibit signs of LEA (Keay et al., 2020) and have been associated with a high prevalence of LEA (Sekulic et al., 2020; Statuta et al., 2017), placing them at risk of the negative health and performance consequences of RED-S (Keay et al., 2020).

Sedentary and physically inactive females were defined as those who fail to meet the World Health Organisation’s recommended physical activity guidelines for adults, which include engaging in more than 150 min of moderate-intensity activity or over 75 min of vigorous-intensity activity per week (Bull et al., 2020).

Since the intervention was LEA risk and LEA status, participants were classified as either at risk of LEA or in a state of LEA. LEA risk was measured using self-reported questionnaires such as the low energy availability in females questionnaire, where a score of ≥8 indicates a high risk of LEA in female athletes (Melin et al., 2014). Additionally, LEA risk was determined using the Low Energy Availability in Females Questionnaire in combination with at least one secondary marker of LEA, such as fasting blood glucose below 4 mmol/L, free T3 under 3.5 pmol/L, ferritin levels less than 25 μg/L, LDL-C exceeding 3.0 mmol/L, fasting insulin below 20 pmol/L, reduced IGF-1, or low blood pressure (BP) indicated by systolic BP under 90 mm Hg and/or diastolic BP under 60 mm Hg. Eating disorder (ED) and DE questionnaires were also used as surrogates for LEA risk, with LEA identified by a positive response to one or more of the three ED/DE screening tools (Ackerman et al., 2019). LEA status was either assessed by calculating EA using the formula: EA = Energy intake (EI; kcal/ day) − exercise energy expenditure (EEE; kcal/day) ÷ fat-free mass (FFM; kg), which then determined LEA status was confirmed when EA was measured as <30 or <45 kcal·kg FFM−1·day−1. Alternatively, EA was calculated as EI minus EEE expressed in kcal per day, with LEA defined as a negative value.

CVD risk indicators are factors that predict or contribute to CVD (Jenkins, 1988). These include measures of endothelial function (flow-mediated dilation [FMD] and carotid artery reactivity [CAR %]), vascular health (carotid intima–media thickness [cIMT}, and pulse wave velocity [PWV]), lipid metabolism (total cholesterol [TC], LDL-C, high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]). Systemic inflammation is assessed via C-reactive protein, interleukin-6, and tumor necrosis factor-alpha. Additional indicators include BP, heart rate variability (HRV), echocardiographic (ECG) data, and cardiorespiratory fitness (VO2max). Moreover, no specific time constraints were applied to the measurement of CVD risk indicators or the assessment of LEA risk or status. Participants could be assessed at a single time point or across multiple time points, depending on study design and data availability.

The exclusion criteria encompassed males, sedentary females, habitual smokers, animal studies, nonpeer-reviewed articles, and studies not written in English.

**Data extraction**

Articles from the online database search were exported into Rayyan software. Two authors screened the titles and abstracts of each retrieved article from the search strategy based on the inclusion and exclusion criteria. Manual searching of the references within relevant articles was checked to ensure no critical articles were ignored. Article data such as study design, population, outcome measures, and significant findings were extracted. The authors were blinded to each other’s decisions to reduce potential biases (Higgins et al., 2019). Following the searches, the authors convened to resolve any disagreements, with the third author assisting in reaching final confirmation.

**Quality assessment**

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies by the National Heart, Lung, and Blood Institute at the National Institutes of Health (2014) was used to assess the risk of bias and methodological quality of studies in this review The first and second authors independently conducted the quality assessment for each study to ensure objectivity. Studies were given a cumulative quality rating of good, fair, or poor based on responses to the questions. Any disagreements between the first and second authors were resolved through discussion between three authors until a consensus was reached.

**Results**

A total of 616 articles were identified from the online databases (supplementary materials S1). After removing duplicates, 457 articles remained from the literature search. Titles and abstracts of the 457 articles were screened resulting in 15 eligible studies. No review papers were deemed appropriate for inclusion. After quality assessment, the full texts were screened, leading to the exclusion of six for not meeting the inclusion criteria. A final total of nine studies were included in this review.

**Characteristics of the studies**

The studies selected in this review included a total of 1,230 physically active females, with sample sizes ranging from 14 to 1,000 physically active females. The studies used various designs including cross-sectional (Ackerman et al., 2019; Black et al., 2018; Clark et al., 2018; Kyte et al., 2022; Melin et al., 2014), prospective (Gifford et al., 2020; Hoch et al., 2011), experimental (Sygo et al., 2018), and observational approaches (Varga et al., 2020).

**Study Quality**

The included studies were rated as good, fair, or poor quality based on the National Institutes of Health quality assessment scores. A total score of 11–14 indicated good quality, a score of 5–10 indicated fair quality, and a score of 0–4 indicated poor quality. Responses categorised as “other, cannot determine (CD), not reported (NR), not applicable (NA),” were classified as “yes” in the scoring system and did not affect the overall quality rating (Rama et al., 2024). According to the National Institutes of Health quality assessment, eight studies were of fair quality (five to 10; Ackerman et al., 2019; Black et al., 2018; Clark et al., 2018; Hoch et al., 2011; Kyte et al., 2022; Melin et al., 2014; Sygo et al., 2018; Varga et al., 2020), and one was rated as good quality (11–14; Gifford et al., 2020; supplementary materials S2), indicating a moderate to low risk of bias. None of the included studies justified their sample sizes, and none of the studies employed blinding for the outcome measures. However, blinding was not feasible due to the nature of the methods used for assessing EI and EE, which made complete transparency difficult for both researchers and the participants. Blinding of participants and researchers was also not applicable, especially given eligibility was partly dependent on EI and/or EE. Five studies involved a single visit (Ackerman et al., 2019; Clark et al., 2018; Hoch et al., 2011; Kyte et al., 2022; Varga et al., 2020), three measured participants over 2 days, one on consecutive days (Melin et al., 2014), one a week apart (Black et al., 2018), one over 5 months (Sygo et al., 2018), and one measured participants on three occasions over 10 days within an 11-month period (Gifford et al., 2020).

**Methods of assessing cardiovascular risk**

Most of the studies included in this review (six out of nine) incorporated venous blood analysis to assess the CVD risks of LEA. More specifically, blood samples were analysed for TC LDL-C, HDL-C, and TG (Black et al., 2018; Clark et al., 2018; Kyte et al., 2022; Melin et al., 2014; Sygo et al., 2018; Varga et al., 2020), well-known blood biomarkers that represent increased CVD risk (Roeters van Lennep et al., 2023). One study measured Apolipoprotein A and Apolipoprotein B (Kyte et al., 2022), and another performed lipidomic analysis (Varga et al., 2020). Only two of the included studies directly assessed vascular function and morphology through brachial artery flow-mediated dilatation (FMD) and arterial stiffness via PWV (Hoch et al., 2011; Kyte et al., 2022). One of which also measured CAR% and cIMT (Kyte et al., 2022), and the other study measured electrical activity of the heart through electrocardiogram (Hoch et al., 2011). One study assessed HRV using a 5-min single lead ECG recorded with a 6 CheckMyHeart device (DailyCare Biomedical, Taoyuan, Taiwan). The metrics assessed included root-mean-square of successive differences (RMSSD), percentage of successive normal R-R intervals greater than 50 ms (pNN50), low-frequency (LF) power, high-frequency (HF) power, LF/HF ratio, nonlinear sample entropy, parasympathetic nervous system (PNS) index, and sympathetic nervous system (SNS) index. While RMSSD, pNN50, sample entropy, PNS index, and SNS index were directly derived from the ECG recordings, LF power, HF power, and the LF/HF ratio were computed using fast Fourier transformation (Gifford et al., 2020). Moreover, three studies assessed resting heart rates and brachial BP (Hoch et al., 2011; Kyte et al., 2022; Melin et al., 2014). In both studies that assessed PWV, central pressures were also evaluated using pulse wave analysis (Hoch et al., 2011; Kyte et al., 2022). One study assessed the CVD risk of female athletes subjectively using an adapted version of the Preparticipation Examination—Fourth Edition (American Academy of Family Physicians, American College of Sports Medicine and American Medical Society for Sports Medicine, 2010) where the heart health questions were utilised (Ackerman et al., 2019).

**The cardiovascular disease risk indicators linked with low energy availability**

The studies included in this systematic review assessing the CVD risks of LEA were categorised into the following categories: blood lipid profile, lipidomics, vascular function and morphology measures of cardiovascular health, HRV, and the quantitative assessment of CVD risks. Table 1 summarises the main findings of each study concerning the CVD risk indicators linked with LEA.

**Blood lipid profile**

Most studies (six out of nine) analysed blood lipid profiles to assess the CVD risk of LEA; however, the results were mixed. Clark et al. (2018) found no significant difference in blood lipid levels between cross-country, track-and-field athletes with clinical versus subclinical MD. Sygo et al. (2018) reported no change between pretraining and post training season in TC, LDL-C, and HDL-C levels, with all values remaining within normal ranges in elite-level track-and-field sprinters. Black et al. (2018) reported no significant difference in HDL-C concentration between recreationally active females at risk of LEA and those not at risk (*p* = .415), although a small number of females had plasma lipid concentrations indicative of elevated CVD risk. In contrast, Kyte et al. (2022) found significantly higher HDL-C levels in elite long-distance runners (44% of which were at LEA risk) compared to the control group of inactive women (*p* = .017). Furthermore, Melin et al. (2014) found among the elite endurance athletes with elevated TC, the majority had confirmed LEA, reduced EA and/or DE and/or ED (73%; Melin et al., 2014). “Melin et al. (2014) also reported that 25% of their sample of elite endurance athletes had hypercholesterolemia. However, the LDL-C/HDL-C ratio remained within normal limits due to concurrently elevated HDL-C levels. Additionally, 38% of the athletes had total cholesterol (TC) levels of ≥5 mmol/L. Varga et al. (2018) found smaller differences in lipid trajectories between elite endurance athletes with sufficient EA and those with LEA, but no significant differences were observed between these groups.

**Lipidomics**

One study (Varga et al., 2020) investigated the lipidomic profiles and their acute changes in response to acute bouts of exercise in female elite endurance athletes at risk of RED-S, revealing several significant associations with lipidomic features between fat mass percentage, HDL-C, TC, free testosterone and cortisol. During a fasting state, 20 lipidomic features showed significant associations (False Discovery Rate-adjusted *p* value < .050) with various clinical biomarkers such as HDL-C, testosterone, and fat mass percentage, while cortisol levels demonstrating an overrepresentation of associations with lysophosphatidylcholines and phosphatidylcholines. This overrepresentation indicates that cortisol had a disproportionately high number of statistically significant correlations with these lipidomic features compared to other clinical biomarkers assessed in the study. Visual inspection (a process of examining data trends) of the lipid trajectories over five time points revealed differences in lysophosphatidylcholines, phosphatidylcholines, sphingomyelins, and TGs (which are different classes of lipids; Jaspers et al., 2024) in relation to menstrual function status (amenorrhea vs. FHA) and energy EA status (Varga et al., 2020). TG exhibited reactive patterns in response to exercise in athletes with normal menstrual cycles, while those with MD showed blunted or abnormal responses (Varga et al., 2020). Similarly, some phosphatidylethanolamines and sphingomyelins displayed divergent trajectories depending on LEA or MD (Varga et al., 2020).

**Vascular function and morphology measures of cardiovascular health**

Two studies (Hoch et al., 2011; Kyte et al., 2022) assessed vascular function and morphology. One study (Hoch et al., 2011) found that 64% of elite dancers (77% of which had LEA) had abnormal brachial artery FMD (<5%), with FMD values significantly correlated with serum estrogen (*p* = .026) indicating increased CVD risk. In contrast, the other study (Kyte et al., 2022) found no significant difference in brachial FMD (*p* = .080), PWV (*p* = .342), carotid artery reactivity (CAR%; *p* = .227), cIMT (*p* = .063), or biomarkers reflecting endothelial activation between inactive females and the elite long-distance runner group (44% of the runners were at risk of LEA; *p* = .084 and *p* = .914, respectively).

**Heart rate variability**

Only one study examined the impact of LEA on autonomic nervous system activity as an objective measure of CVD risk. This study assessed HRV and found no significant association between higher EA and HRV (*p*> .10) in female officer cadets (Gifford et al., 2020). In the time domain, the RMSSD increased significantly from baseline across subsequent testing visits phases across the 11-month basic military training (η2 = .075, *p* = .036). Similarly, the pNN50 also increased significantly from baseline across visits (η2 = .079, *p* = .003). In the frequency domain, LF power remained stable across visits with no significant change (η2 = .002, *p* = .70), and HF power showed an initial upward trend, followed by a slight decrease and later recovery (η2 = .028, *p* = .11). Moreover, the LF/ HF ratio remained relatively consistent (η2 = .021, *p* = .17). Nonlinear HRV analysis revealed an increase in sample entropy over time across the visits (η2 = .149, *p* = .003). Additionally, the PNS index improved (η2 = .090, *p* = .001), while the SNS index decreased significantly from baseline and remained lower throughout (η2 = .083, *p* = .002).

**Table 1. Summary of findings on the cardiovascular disease risk indicators linked with low energy availability in physically active females from studies included in this review.**

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| **Study** | **Aims and Objectives** | **Study type** | **Study design** | **Participant Characteristics** | **CVD Outcome measures** | **CVD findings** |
| Ackerman *et* *al*. (2019) | To examine the association of low EA with RED-S health and performance consequences in a large clinical population of physically active females. | Cross-sectional. | Completed an online questionnaire to determine low or adequate EA using the BEDA-Q (Martinsen et al., 2014), ESP (Cotton, Ball and Robinson, 2003), LEAF-Q (Melin et al., 2014) and the Faecal Incontinence Questionnaire (Reilly et al., 2000). | *n*: 1000 females from the Division of Sports Medicine at Boston Children’s Hospital, USA.  Age: 18.9 ± 3.3 years  PA Level: ≥4 hours of self-reported PA per week for ≥6 months pre-participation. | Cardiovascular risk was assessed using adapting heart health questions from the Preparticipation Examination – Fourth Edition (AAOP, 2010).  Diet type not reported. | Physically active females with LEA were more than 2.5 times more likely to suffer cardiovascular issues (OR = 2.53, 95% CI: 1.49 to 4.32, *P* = 0.001). |
| Black *et* *al*. (2018) | To determine if recreationally active females at risk of LEA identified by the LEAF-Q have different plasma lipid and hormonal concentrations or nutrient intakes compared to those not at risk. | Cross-sectional. | Completed an online questionnaire with LEAF-Q and demographic details, reported daily exercise, submitted a 3-day diet record, provided blood and saliva samples, and had body composition assessed via bioelectrical impedance. | *n*:38 females from Dunedin, New Zealand and surrounding areas​.  Age: 22.6 ± 5.6 years  PA Level: Recreationally active, meeting New Zealand’s PA guidelines (150–300 minutes moderate or 75–150 minutes of vigorous activity per week, or a combination). | The lipid profile for the LEA risk group (N =24) and the non-LEA risk group (N =14) were as follows: TC (4.31 ± 0.15 vs. 4.80 ± 0.32 mmol/L, *P* = 0.128), HDL-C (1.31 ± 0.060 vs. 1.40 ± 0.10 mmol/L, *P* = 0.415), LDL-C (2.51 ± 0.150 vs. 2.93 ± 0.28 mmol/L, *P* = 0.163), TC/HDL-C Ratio (3.43 ± 0.18 vs. 3.57 ± 0.24 mmol/L, P = 0.667, TGs (1.07 ± 0.17 vs. 1.04 ± 0.10 mmol/L, *P* = 0.894).  Diet type not reported. | No significant difference in HDL-C concentration between the LEA and non-LEA risk groups (*P* = 0.415). A small number of recreationally active females had plasma lipid concentrations indicative of elevated CVD risk. |
| Clark et al., (2018) | To evaluate the prevalence of clinical MD and the association with LEA in NCAA Division I female distance runners, and to assess the efficacy of the LEAF-Q in this population and the association between menstrual function and indexes of health and performance. | Cross-sectional. | Completed the LEAF-Q and EAT-26 following a practice session. Over two assessment periods, on separate days: Day 1 included anthropometrics, blood samples, RMR, and body composition. Day 2 involved a VO2 max assessment. Dietary EI and EE were measured over 3 days. | *n*: 15 females  Age: 19-22 years (SD not reported)  PA Level: Division I cross-country and track-and-field student-athletes. | Participants with clinical MD (N =6), the lipid profile showed: TC (4.39 ± 0.33 mmol/L), LDL-C (2.27 ± 0.22 mmol/L), HDL-C (1.69 ± 0.19 mmol/L), and TG (0.72 ± 0.33 mmol/L). In comparison, the SC/EU group (N =9) has corresponding values of TC (4.63 ± 0.72 mmol/L), LDL-C (2.53 ± 0.61 mmol/L), HDL-C (1.68 ± 0.19 mmol/L), and TG (0.77 ± 0.29 mmol/L).  Diet type not reported. | No significant differences in blood lipids between NCAA Division I female distance runners with clinical or subclinical MD (TC: *P* = 0.470; LDL-C, *P* = 0.330; HDL-C, *P* = 0.900; TG, *P* = 0.770). |
| Gifford *et* *al*. (2020) | To compare EA measured from EEEmpva with EEEtpa using doubly labelled water in female British Army Officer Cadets. Additionally, to determine the relationship of EA with physical fitness, body composition, HRV, and EB. | Prospective. | Completed three consecutive 10-d assessments of EEEmvpa, EEEtpa and EI.  HRV was assessed using a 5-minute single-lead ECG, capturing time-domain measures (RMSSD and pNN50), frequency-domain metrics (LF and HF power), and nonlinear indicators (sample entropy). Fitness was measured via a 1.5-mile run test and body composition was monitored using DEXA scans. | *n*: 47 females  Age: 23.9 ± 2.6 years  PA Level: British Army Officer Cadets, Royal Military Academy, Sandhurst, meeting Ministry of Defence (2018) medical standards. | HRV time domain measures showed the following results: RMSSD median (IQR) values were 35.7 (23.5 - 56.4) at Visit 1, 51.4 (33.6 - 66.81) at visit 2, 45.9 (37.6 - 55.29) at Visit 4, and 47.2 (30.6 - 66.6) at visit 6 (P = 0.036). For pNN50 (%), the median (IQR) values were 14.7 (4.9 - 31.6) at Visit 1, 28.4 (11.1 - 43.8) at Visit 2, 24.4 (16 - 35.7) at Visit 4, and 27.6 (9.6 - 44.9) at Visit 6 (*P* = 0.003).  Diet type not reported. | Visit 1: participants EA (8 kcal/kg FFM/day), HRV RMSSD (35.7 ms), 1.5-mile run time (10:41 min), FM (15.6 kg), and FFM (49.6 kg). Visit 2: participants EA (-10 kcal/kg FFM/day), HRV RMSSD (51.4 ms), 1.5-mile run time (10:08 min), FM (14.4 kg), and FFM (50.2 kg). Visit 3: participants EA (9 kcal/kg FFM/day), HRV RMSSD (45.9 ms), 1.5-mile run time (10:20 min), FM (16.1 kg), and FFM (49.4 kg). Visit 4: participants EA (recovered), HRV RMSSD (47.2 ms), 1.5-mile run time (10:38 min), FM (15.6 kg), and FFM (49.4 kg). Visit 5: participants EA (further improved), HRV RMSSD (47.2 ms), 1.5-mile run time (10:29 min), FM (stable), and FFM (stable). Visit 6: participants EA (stable), HRV RMSSD (47.2 ms), 1.5-mile run time (10:29 min), FM (stable), and FFM (stable).  Higher EA was not associated with HRV (*P* > 0.10). |
| Hoch *et* *al*. (2011) | To determine the prevalence of the three components of the female athlete triad (DE, MD, low BMD) and their relationships with brachial artery FMD in professional dancers. | Prospective. | Completed the EDE-Q to evaluate eating habits and attitudes, self-reported menstrual status/history via a questionnaire, and provided a 3-day food record and 3-day accelerometer data to assess EA. Baseline serum concentrations of thyrotropin, prolactin, and other hormones were measured. BMD and body composition were assessed using a DEXA scan, and endothelial function was evaluated through FMD. | *n*: 22 females from a single ballet company in the Midwest, USA.  Age: 23.2 ± 4.7 years  PA Level: Professional dancers. | The prevalence of the female athlete triad among professional dancers: 32% had disordered eating, 36% experienced MD, 23% showed low BMD, and 14% exhibited all three components of the triad.  No significant differences were observed between professional dancers with abnormal FMD (<5%, N =14) and professional dancers with normal FMD (≥5%, N =8) in several key cardiovascular parameters.  Resting HR, SBP, and DBP showed no significant differences between the abnormal and normal FMD groups, with values of: HR (56.1 ± 9.9 vs. 54.9 ± 8.8 bpm, *P* = 0.78), SBP (101.2 ± 10.0 vs. 99.0 ± 5.3 mmHg, *P* = 0.57), and DBP (60.6 ± 8.9 vs. 62.1 ± 4.6 mmHg, *P* = 0.67).  No significant differences between the abnormal and normal FMD groups in baseline brachial artery diameter (2.8 ± 0.3 vs. 2.6 ± 0.4 mm, *P* = 0.21), peak brachial artery diameter (2.9 ± 0.4 vs. 2.8 ± 0.4 mm, *P* = 0.67), or peak change in flow velocity (67.2 ± 41.7 cm/s vs. 75.2 ± 30.3 cm/s, *P* = 0.64). However, FMD showed a significant (2.9 ± 1.6% vs. 7.9 ± 1.4% respectively, *P* = 0.001).  Diet type not reported. | Over half (64%) had abnormal brachial artery FMD (<5%). The FMD values significantly correlated with serum oestrogen (*P* = 0.026), whole-body BMD (*P* = 0.02) and lumbar BMD (*P* = 0.03). |
| Kyte *et* *al*. (2022) | To investigate vascular  function and morphology, including endothelial function, in Norwegian female elite long-distance runners, compared to inactive women. | Cross-sectional. | Data collection occurred in three phases: Phase 1: assessments of vascular function and morphology, including FMD, PWV, CAR %, and cIMT. Phase 2: blood samples for hormone analyses, metabolic parameters, lipids, and biomarkers of endothelial activation. RED-S risk was assessed using LEAF-Q. Phase 3: body composition assessments via DEXA scans and a VO2 max test. | *n*: 33 females Age: 16 Norwegian elite long-distance runners, mean age 27.0 years (24.3–30.0). 17 Norwegian healthy controls, mean age 26.0 years (24.0–27.5).  PA Level: Elite runners trained ≥8 hours per week in endurance training. Controls were inactive women from the University of Oslo, engaging in ≤2 hours of training per week. | Among the elite long-distance runners, 44% were at LEA risk. No significant differences were found between runners (N =16) and the control group (N =17) in SP (110 mmHg for both groups, *P* = 0.789), DP (70 mmHg in both groups, *P* = 0.542), or TC (4.4 mmol/L for runners vs. 4.0 mmol/L for controls, *P* = 0.101). However, runners had significantly higher HDL-C levels compared to controls (1.9 mmol/L vs. 1.5 mmol/L, *P* = 0.017). Moreover, no significant differences were found between runners and control in LDL-C (2.0 vs. 2.1 mmol/L; *P* = 0.624), the TC/HDL ratio (2.4 vs. 2.7, *P* = 0.198), or TC levels (0.8 mmol/L in both groups; in *P* = 0.732). Apolipoprotein A levels were higher in Norwegian female elite long-distance runners compared to inactive females (1.82 vs. 1.49, *P* = 0.027), while apolipoprotein B levels showed no significant difference (*P* = 0.193). Additionally, no significant differences between the groups in FMD (*P* = 0.719), CIMT (*P* = 0.486), CAR % (*P* = 0.816), or PWV (*P* = 0.512).  Diet type not reported. | Runners showed significantly higher HDL-C (*P* = 0.017), and greater insulin sensitivity compared to the control group (Insulin: *P* = 0.022; HOMA-IR, *P* = 0.025). Moreover, runners had as good vascular function and morphology as inactive women of the same age. |
| Melin *et* *al*. (2014) | To examine the associations between EA, MD and energy metabolism, and the prevalence of triad-associated conditions in Swedish and Danish elite endurance athletes. | Cross-sectional. | Data collection took place over two consecutive days. On day one, participants underwent DEXA scans, BP and reproductive function assessments. The second day involved evaluations of energy metabolism through a seven-day record, assessments of aerobic capacity, and an examination of ED using the EDE-16 and EDI-3 surveys. | *n*: 40 females Age: 26.2 ± 5.5 years  PA Level: Elite endurance athletes (national team or regional club level) from Denmark and Sweden, training ≥5 times per week. | Athletes with LEA had significantly lower RMR compared to those with optimal EA (*P* < 0.01). Athletes with MD had lower RMR than eumenorrheic athletes (*P* < 0.05). A negative association was found between EA and daily exercise duration (*P* = 0.019), with longer exercise reducing EA. Additionally, a negative association was observed between exercise hours per week and BMD in both the whole body and lumbar spine (*P* = 0.035, *P* = 0.037).  Resting HR (46.3 ± 8.0 beats/min, SBP ( 113.1 ± 11.2 mmHg, DBP (67.5 ± 9.5 mmHg), TC (4.5 mmol/L, IQRs:3.9 – 5.3), LDL-C (2.3 mmol/L, IQRs:1.9 – 3.0), HDL-C (1.8 mmol/L, IQRs:0 – 3), LDL-C/HDL-C ratio (1.3 mmol/L, IQRs:1.1-1.8), and TC (0.66 mmol/L, IQRs :0.56 -0.83).  Diet type not reported. | A quarter (25%) of the sample had hypercholesterolemia, though their LDL-C/HDL-C ratios remained normal due to elevated HDL-C levels. Additionally, 38% had TC levels of ≥ 5mmol/L. Among the elite endurance athletes with elevated TC, 73% had low or reduced EA and/or DE/ED, despite 33% remaining eumenorrheic. One of the seven participants with hypotension was diagnosed with anorexia nervosa. Hypotension was more common in participants with LEA, and those with MD and low or reduced EA had lower supine BP compared to those with MD and optimal EA. However, most participants with hypotension maintained a BMI within the normal range (≥18.5). |
| Sygo *et* *al*. (2018) | To examine the prevalence of signs and symptoms of LEA in elite female sprinters at the start (PRE) and end of a 5-month indoor training period (POST). | Experimental. | Data collection took place in November-December 2016 ("PRE"), post-Olympic break, and included demographics, blood work, blood pressure, DEXA scans, anthropometry, RMR, and questionnaires. The sample of elite female sprinters was reevaluated in late April-May 2017 ("POST"), during the transition from indoor to outdoor training, with all baseline measurements repeated. | *n:* 13 females  Age: 21 ± 3 years  PA Level: Elite track and field sprinters from two national training centres in Canada. | At the start of the training season, 31% of athletes presented with at least one primary (e.g., amenorrhea, low BMD, low sex hormones, RMR ≤29 kcal/kg FFM, LEAF-Q ≥8) and one secondary indicator of LEA (e.g., low fasting glucose, low free T3, low ferritin). By the end of the 5-month training period, this increased to 54%, with three athletes showing consistent LEA across both time points  At baseline (PRE), the lipid and blood pressure values were as follows: TC, 4.05 ± 0.68 mmol/L; LDL-C, 1.94 ± 0.44 mmol/L; HDL-C, 1.78 ± 0.45 mmol/L; SBP, 105 ± 9 mmHg; DBP, 63 ± 6 mmHg.    After five months of indoor training (POST), the values shifted to: TC, 4.33 ± 0.6 mmol/L; LDL-C, 2.12 ± 0.42 mmol/L; HLD-C, 1.88 ± 0.44 mmol/L; SBP, 110 ± 7 mmHg; DBP, 73 ± 10 mmHg.  Diet type not reported. | Signs and symptoms of LEA increased over the 5-month period. At the start of the season (PRE), 31% of athletes exhibited at least one primary and one secondary indicator of LEA, which increased to 54% by the end of the training period (POST).  In addition, TC, LDL-C, and HDL-C levels were reported within normal ranges at both PRE and POST periods. |
| Varga *et* *al*. (2020) | To assess whether blood lipid metabolites and their changes are linked with various cardiometabolic,  endocrine, bone and energy-related comorbidities of RED-S in female elite endurance athletes. | Observational. | Underwent a day-long exercise protocol. Blood samples were collected in a fasting state and at four additional times: before and after two intensive exercise tests (designed to obtain VO2peak values) that athletes undertook during the day. Clinical biomarkers were assessed in the fasting state. Untargeted lipidomics were performed on all blood samples. | *n:* 38 females  Age: 26.5 years (IQR: 21.3–29.0).  PA Level: Swedish and Danish elite endurance athletes (national or regional level), training ≥5 per week. | Lipid profiles: HDL-C (1.8 mmol/l, IQRs:1.6-2.07), LDL-C (2.3 mmol/l, IQRs: 2.12-2.9), TC (4.55 mmol/l, IQRs: 4.1-5.1), and TG (0.67 mmol/L, IQRs: 0.61-0.87).  Lipidomic associations: HDL-C SM(d38:1) (β = 0.233, SE = 0.041, *P* = 1.56E-06, PFDR = 0.009), HLD-C SM(d32:1) (β = 0.200, SE = 0.045, *P* = 9.29E-05, PFDR = 0.041), and HDL-C PC(O-36:2) (β = 0.200, SE = 0.045, *P* = 9.38E-05, PFDR = 0.041), TC SM(d33:1) (β = 0.488, SE = 0.111, *P* = 9.41E-05, PFDR = 0.041), TC SM(d18:2/18:1) (β = 0.482, SE = 0.112, *P* = 1.18E-04, PFDR = 0.047), and TC CE(18:2) + Unknown CE (667.6219) (β = 0.474, SE = 0.113, *P* = 1.62E-04, PFDR = 0.048).  Blood samples reflecting CVD biomarkers were collected immediately following exercise  Diet type not reported. | In total, 20 associations between lipidomic features and clinical biomarkers had PFDR < 0.050 were detected. Mean lipid trajectories were generated for 201 named features for the cohort and subsequently stratified by participants’ EA and MD status. |
|  | Abbreviations: EA, energy availability; RED-S, Relative energy deficiency in sport; BED-Q, Brief Eating Disorder in Athletes Questionnaire; ESP, the Eating disorder Screen for Primary care; LEA, low energy availability; LEAF-Q, low energy availability in females questionnaire; PA, physical activity; OR, odds ratio; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TGs, triglycerides; CVD, cardiovascular disease; MD, menstrual dysfunction; NCAA, National Collegiate Athletic Association; EAT-26, Eating Attitudes Test; SD, Standard deviation; RMR, resting metabolic rate; Vo2, volume of oxygen; EI, energy intake; EE, energy expenditure; SC/EU, Subclinical/Eumenorrheic; EA, energy availability; EEEmpva, exercise energy expenditure from moderate and vigorous physical activity; EEETPA, exercise energy expenditure from total physical activity; HRV, heart rate variability; EB, eating behaviour; RMSSD, root-mean-square of successive differences; IQR, interquartile range; Pnn50%, percentage of successive normal R-R intervals above 50 ms; LF, low-frequency power; HF, high-frequency power; DE, disordered eating; BMD, bone mineral density; FMD, flow-mediated dilation; FM, fat mass; FFM, fat free mass; EDE-Q, Eating Disorder Examination Questionnaire; DEXA, dual X-ray absorptiometry; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; CAR%, carotid artery reactivity; cIMT; carotid intima media thickness; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; ED, eating disorders; BP, blood pressure; EDE-16, Eating Disorder Examination; EDE-3, Eating Disorders Inventory-3; CS, cholesterol synthesis; CE, cholesteryl esters; FDR, false discovery rate; PFDR, false discovery rate-adjusted p-value. | | | | | |

**Subjectively assessing cardiovascular risk**

One study subjectively assessed the CVD risks associated with LEA using an online questionnaire with 1,000 physically active females. The study employed an adapted version of the heart health questions from the Preparticipation Examination—Fourth Edition (American Academy of Family Physicians, American College of Sports Medicine and American Medical Society for Sports Medicine, 2010) and found a significant association between LEA and CVD risk, finding athletes with LEA estimated to be more than 2.5 times more likely to experience CVD issues (odds ratio = 2.53, 95% confidence interval [1.49, 4.32], *p* = .001; Ackerman et al., 2019).

**Discussion**

This systematic review is the first to critically evaluate the current scientific evidence on CVD risk indicators linked with LEA in physically active females. The findings from the nine included studies highlight that LEA may be linked to CVD disease risk factors and/or direct measures of vascular structure and function.

Consistent with previous research supporting the link between LEA and dyslipidemia (Mountjoy et al., 2014), one study (Melin et al., 2014) included in this review identified abnormal lipid levels. It found that 73% of elite endurance athletes with elevated TC had current LEA and/or DE/ED (73%), with 33% being amenorrheic (Melin et al., 2014). While this could suggest that changes in cholesterol synthesis may be caused by energy deficiency, despite normal weight and amenorrhea (Melin et al., 2014), a direct causal relationship has not been established. Further research is required to investigate the mechanisms by which energy deficiency influences lipid metabolism, independent of weight status and menstrual function. Elevated TC levels are also frequently observed in individuals with anorexia nervosa (Meczekalski et al., 2013) and tend to decrease with weight gain (Ohwada et al., 2006). The adverse lipid profiles associated with LEA may result from disturbances in lipid metabolism, including increased TG concentrations in HDL and very low-density lipoprotein (VLDL) subclasses due to accelerated VLDL particle lipolysis and lipid transfer to HDL particles (Jouhki et al., 2024). Additionally, LEA has also been associated with visceral fat accumulation, which has been shown to disrupt lipid and glucose metabolism, and induce low-grade inflammation, thereby increasing cardiovascular risk (Jouhki et al., 2024). Despite this, further research is needed to fully elucidate the association and underlying mechanisms.

Although LEA’s negative effects on health can lead to endothelial and lipid dysfunction (Rickenlund et al., 2005), specific research on LEA’s impact on plasma lipids and increased CVD risk is minimal, with most studies focusing on amenorrhea female participants (Black et al., 2018). This review highlights that only five studies investigated using blood lipid profiles to assess the CVD risk of LEA (Black et al., 2018; Clark et al., 2018; Kyte et al., 2022; Melin et al., 2014; Sygo et al., 2018), which yielded mixed findings. Most studies found no significant effect of LEA on lipid profile levels (i.e., TC, LDL-C, HDL-C; Black et al., 2018; Kyte et al., 2022; Sygo et al., 2018), consistent with previous research finding no impact on cholesterol concentrations (Baer, 1999). Genetic factors likely contribute to the variation in lipid levels among individuals with LEA, as genetic variability plays a significant role in interindividual differences in lipid levels (Matey-Hernandez et al., 2018). Although genetic factors may influence lipid levels in individuals with LEA, the specific genes and mechanisms involved remain unclear. Future studies should investigate genetic variants linked to lipid dysregulation in LEA and their interaction with environmental factors, as this could inform targeted intervention strategies.

Existing research links unhealthy lipid profiles with comorbidities of LEA and RED-S, such as the increased prevalence of MD (Rickenlund et al., 2005) and decreases in BMD (Soleimany et al., 2012) in female athletes. However, research on LEA in physically active females, beyond its impact on blood lipid profiles, remains limited. Only one study has explored lipidomics to provide a detailed resolution of lipid profiles and associations with RED-S comorbidities including lipid, hormonal, anthropometric, and energy-related clinical biomarkers in elite endurance female athletes (Varga et al., 2020). This study was the first of its kind to show that elite female endurance athletes with RED-S exhibited blunted metabolomic responses in their lipid profiles, likely due to overtraining and inadequate nutrition (Varga et al., 2020). These findings suggest that overtraining may impair the adaptive metabolic response to exercise interventions (Jaguri et al., 2023).

Cortisol levels were positively associated with several lipidomic features, including lysophosphatidylcholine and phosphatidylcholine, which may serve as biomarkers for metabolic disruptions caused by RED-S (Varga et al., 2020). The overrepresentation of significant associations between cortisol and lipidomic features suggests that elevated cortisol levels could contribute to the dysregulation of lipid metabolism in these individuals (Varga et al., 2020). This aligns with previous research showing chronically mildly elevated cortisol levels in elite endurance athletes and a link between FHA status and higher fasting serum cortisol levels (Melin et al., 2019). Although elevated levels of stress biomarkers, such as salivary alpha-amylase and cortisol, have been detected before and during sports competitions (Mehrsafar et al., 2021), short-term LEA has also been shown to significantly increase systemic cortisol levels, with a 22.3% rise reported after 14 days of LEA (*p* < .001; Jeppesen et al., 2024). However, this influence seems to be reversible, as cortisol levels returned to baseline following 3 days of refueling (*p* = 1.000; Jeppesen et al., 2024). These findings suggest that LEA, rather than external stressors such as competition, is the primary factor driving this hormonal response.

Athletes with LEA or MD exhibit abnormal TG responses to exercise, whereas those with normal menstrual cycles maintain typical patterns (Varga et al., 2020). While natural estrogen fluctuations influence fat oxidation during exercise (Frandsen et al., 2020), impaired metabolism in LEA may stem from reduced estrogen levels (Oosthuyse and Bosch, 2010), which are linked to decreased glycogen sparing and fat oxidation capacity (Hackney, 1999). Varga et al. (2020) categorised participants by menstrual function, whereas others have used EA. For example, TG, particularly VLDL-TG, decreased during LEA but rebounded post energy restoration, suggesting LEA alone may not cause lasting metabolic disruptions (Jouhki et al., 2024). However, MD might indicate a more persistent metabolic disturbance. This raises the question of whether hormonal disruptions (e.g., low estrogen, high cortisol) impact lipid metabolism independently of energy restriction, potentially increasing CVD risk in athletes with LEA.

LEA impacts multiple endocrine pathways beyond the hypothalamic-pituitary-ovarian (HPO) axis, affecting the hypothalamic-pituitary-adrenal (HPA) axis (elevating cortisol), the hypothalamic-pituitary-thyroid (HPT) axis (lowering T3 and metabolic rate), and growth hormone (GH)-IGF-1 (reducing IGF-1, impairing muscle and bone health) axes (Ihalainen et al., 2024). It also disrupts insulin regulation, alters leptin and ghrelin (affecting appetite and energy balance), and influences androgen levels based on metabolic conditions (Ihalainen et al., 2024). These widespread hormonal effects make it difficult to isolate LEA from MD alone. While menstrual irregularities are common in LEA, other stressors, including psychological and physical stress, can also suppress the HPO axis (Elliott-Sale et al., 2018; Hakimi and Cameron, 2017). Thus, MD is not always a definitive marker of LEA (Ihalainen et al., 2024) but often signals significant hormonal disruption. Tracking ovulation markers, such as the LH surge and peak luteal-phase progesterone, can help differentiate LEA-induced changes from other causes (Ihalainen et al., 2024). Additionally, LEA affects metabolic, thyroid, and adrenal function, lowering T3, IGF-1, and leptin while increasing cortisol (Dipla et al., 2021; Elliott-Sale et al., 2018; Loucks and Thuma, 2003). A comprehensive assessment, including menstrual tracking, hormonal profiling (T3, IGF-1, leptin, cortisol), and an evaluating of psychological and physiological stressors, is essential for accurate diagnosis (Ihalainen et al., 2024).

Blood samples reflecting CVD biomarkers were collected immediately following exercise in one study in this review (Varga et al., 2020), which may mediate or independently influenced their reported observations. Acute exercise has been observed to temporarily reduce TG levels and increase HDL-C by enhancing fat metabolism and cholesterol transport (Sui et al., 2017; Swift et al., 2013). This process involves the transfer of plasma apoC2 apolipoprotein moiety to TG-rich lipoproteins, initiating a cascade that activates lipoprotein lipases on endothelial surfaces. This activation hydrolyses TG components in TG-rich lipoproteins, which are then exchanged for cholesterol esters from HDL-C molecules (Sulague et al., 2022). Circulating HDL-C subsequently serves as a reservoir for apoC2 after lipoprotein remnant separation (Wolska et al., 2017). As a result, lipid profiles assessed immediately after exercise may appear artificially improved compared to true resting baselines. Although the objective of these studies was to examine the effects of exercise, it is crucial to interpret the findings of Gifford et al. (2020) and Varga et al. (2020) with the limitation of any potential residual effects of acute exercise in mind.

Two studies in this review assessed vascular function and morphology, yielding mixed results. No significant difference was found in FMD values regarding the brachial artery between elite long-distance runners and inactive control groups (Kyte et al., 2022). This finding aligns with previous research showing similar FMD between amenorrheic athletes and sedentary females (Rickenlund et al., 2005). Additionally, high-intensity running did not adversely affect athletes’ endothelial function (Kyte et al., 2022). Despite an observed inverse relationship between peak shear rate and the baseline diameter of the brachial artery during a reactive hyperemia test (Pyke et al., 2004), no significant difference in baseline diameter was found between elite long-distance runners and inactive control groups, suggesting that variations in diameter or shear rate are unlikely to have influenced FMD results (Kyte et al., 2022).

Vascular function and morphology were assessed in elite dancers, and amenorrhea and oligomenorrheic dancers were found to have reduced FMD (Hoch et al., 2011). This result is consistent with findings in collegiate runners with amenorrhea (Hoch et al., 2003) and Swedish endurance athletes (Rickenlund et al., 2005). The key factor contributing to the decreased FMD appears to be low estrogen levels, as all amenorrhea and oligomenorrheic elite dancers, including those using hormonal contraception showed impaired FMD (Hoch et al., 2011). Lower estrogen levels may play a significant role in cardiovascular dysfunction among women experiencing LEA. Reduced estrogen levels may be a key factor contributing to cardiovascular dysfunction in women with LEA. Estrogen supports vascular health by stimulating nitric oxide production for vasodilation (Murphy, 2011) and protecting the endothelium, cardiac muscle, and metabolic function (Reckelhoff, 2005). It also prevents the oxidation and accumulation of LDL particles (Cid et al., 2002). Conversely, hypoestrogenism disrupts nitric oxide activity, causes endothelial dysfunction, and negatively affects lipid profiles, leading to higher levels of cholesterol, TG, and LDL-C (Ouyang et al., 2006; Schunkert et al., 1997). Premenopausal women on calorie-restricted diets and amenorrheic athletes show elevated LDL-C levels (Friday et al., 1993), and those with hypothalamic amenorrhea exhibit impaired brachial artery dilation, a precursor to coronary artery dysfunction (Gordon et al., 2017).

Moreover, 71% of the elite dancers with LEA had reduced FMD (Hoch et al., 2011), suggesting that endothelial dysfunction, as reflected by impaired FMD, may be influenced by multiple factors including menstrual status, aerobic fitness, and EA, rather than estrogen levels alone (Hoch et al., 2011). However, no correlation between FMD and EA was found (Hoch et al., 2011). This lack of correlation could be attributed to the severity or duration of LEA, as FMD has been shown not to change following 2 days of very low EI (500 calories for women, 600 calories for men; Headland et al., 2018). However, the severity or duration of LEA in Hoch et al. (2011) sample was not specified.

Extremes in exercise can become detrimental potentially due to an inverted-U shape dose–response curve for exercise-related benefits on arterial stiffness (Vlachopoulos et al., 2010). For instance, marathon runners exhibit impaired endothelial function postrace (Dawson et al., 2008), though endothelial progenitor cells seem to be unaffected (Adams et al., 2008). A persistent sympathetic adrenergic vasoconstriction driven by high levels of circulating catecholamine levels might also contribute to increased aortic stiffness (Iellamo et al., 2002). The only study in this review that assessed arterial stiffness using PWV found no significant difference between elite long-distance runners and inactive control groups (Kyte et al., 2022). This result aligns with previous research showing no difference in PWV between triathletes and controls (Ianê-Siva et al., 2023), as well as between runners, sedentary controls, and normally active controls (Bjarnegård et al., 2018). However, no relationship between arterial stiffness and aerobic capacity in healthy young adults has also been reported (Namgoong et al., 2018), with an inverse relationship between VO2max and augmentation index (a surrogate marker of arterial stiffness) being proposed (Denham et al., 2016).

Limited studies have explored vascular stiffness as a marker for the consequences of LEA, and the findings remain inconsistent. For example, one study found no significant changes in arterial stiffness between the control condition (45 kcal·kg FFM−1·day−1 EA) and the LEA condition (15 kcal·kg·FFM−1·day−1) after 3 days of LEA (*p* = .952; Hutson et al., 2024). Similarly, in line with the only study is this review that assessed PWV and LEA, that reported no significant difference in PWV between elite long-distance runners and inactive females (*p* = .342; Kyte et al., 2022). However, another study observed a trend toward higher PWV values in elite New Zealand female rugby seven players at risk of LEA (6.55 ± 1.54 m/s) compared to those not at risk of LEA (5.69 ± 1.11 m/s), with a mean difference of 0.86 m/s (95% confidence interval: [−0.68, 2.40]), suggesting a possible link between LEA and increased arterial stiffness (Christensen, 2019). Given the potential cardiovascular risks associated with LEA, which resemble those seen in anorexia nervosa (Kyte et al., 2022) and the similarities between anorexia nervosa and LEA (Wells et al., 2020), research in anorexia nervosa concerning vascular stiffness may be relevant to LEA. For example, prior research has found significant increases in vascular stiffness, indicated by PWV, in anorexia nervosa patients compared to healthy controls (Jenkins et al., 2021), suggesting a higher risk of CVD in this population (Kyte et al., 2022). Despite their similarities, LEA and anorexia nervosa are distinct. Anorexia nervosa involves severe calorie restriction due to psychological factors, while LEA includes both restricted calorie intake and increased energy expenditure from high training loads (Roche, 2023). For instance, individuals with LEA may eat normally but still face energy deficits due to extreme physical activity. Therefore, findings related to one may not always be applicable to the other.

One study investigated the impact of LEA on the autonomic nervous system activity through HRV. While no significant association was observed between higher EA and HRV (P > 0.10) in female officer cadets (Gifford et al., 2020), there were increases in para-sympathetic (RMSSD, pnn50, PNS index) and decreases in sympathetic activity in time domain measures (SNS index), which were marginally below the means for athletes (Shaffer and Ginsberg, 2017). Considering HRV typically decreases following negative psychological stress (i.e., reduction of HF band, linked with parasympathetic vagal activity) (Kim et al., 2018) and increases with enhanced aerobic capacity (Task Force, 1996). Despite experiencing psychological stress throughout the 11-month basic military training course, female officer cadets showed autonomic benefits (i.e., RMSSD) that were not directly linked to improvements in cardiovascular fitness or EA, aligning with previous research (Gifford et al., 2018). This suggests that positive adaptations from exercise can occur even with significant energy deficits during strenuous activities (Gifford et al., 2019). Overall, limited direct evidence concerning cardiovascular health and HRV in relation to LEA among athletes exists, necessitating a need for further research to determine these associations (Williams et al., 2019). Understanding these relationships is critical, as it could provide insights into how LEA impacts the cardiovascular system and autonomic regulation, contributing to improved health management and performance optimisation for athletes.

One study assessed CVD risks associated with LEA using self-reported questions adapted from the heart health section of the Preparticipation Examination—Fourth Edition (American Academy of Family Physicians, American College of Sports Medicine and American Medical Society for Sports Medicine, 2010). Physically active females were classified at risk if they claimed to have three or more positive responses to questions. The study showed a significant association (odds ratio = 2.53, 95% confidence interval [1.49, 4.32], *p* = .001), indicating physically active females with LEA were more than 2.5 times more likely to experience CVD symptoms (Ackerman et al., 2019), supporting the link between CVD and LEA in the RED-S model (Mountjoy et al., 2014). While this highlights the potential prevalence and severity of the CVD risks linked with LEA, the questionnaire only predicts CVD risks and does not directly or objectively measure cardiovascular health (National Institute for Health and Care Excellence, 2023). Future research should investigate the CVD risk indicators linked with LEA using comprehensive testing such as blood lipid profiles, ECGs, PWV, and FMD, in conjunction with other measures to offer greater insights onto the underlying mechanisms.

Other factors may have played a role in mediating or indirectly influencing the findings of the reviewed studies. For instance, diet plays a fundamental role in preventing cardiovascular disease (Verschuren, Boer and Temme, 2022). Dietary habits impact CVD risk factors by regulating blood pressure, lipid profiles, obesity, inflammation, and endothelial function (Mozaffarian, 2016). Vegetarian and vegan diets have been associated with lower CVD and all-cause mortality rates; however, the precise mechanisms underlying this relationship remain uncertain (Salehin et al., 2023). Reduced systemic inflammation associated with plant-based diets may lower the risk of plaque formation and coronary artery disease (Salehin et al., 2023), whereas meat-rich diets have been linked to increased pro-inflammatory cytokine production, potentially contributing to endothelial dysfunction and accelerating atherosclerosis (Davignon and Ganz, 2004). Additionally, plant-based diets may help mitigate key risk factors such as hypertension, diabetes mellitus, and hyperlipidemia, ultimately improving cardiovascular health outcomes (Salehin et al., 2023). Moreover, these diets can support the growth of beneficial gut microbiota, reducing intestinal inflammation and enhancing nutrient absorption (Sakkas et al., 2020). While numerous studies highlight the advantages of plant-based diets, the overall body of evidence remains inconclusive, with some research failing to establish a definitive link between animal product consumption and adverse cardiovascular health effects (Giosuè et al., 2022; Budhathoki et al., 2019). Therefore, further investigation is required to compare different dietary patterns and their impact on CVD development (Salehin et al., 2023). Regarding the studies included in this review, the specific effects of dietary patterns (e.g., plant-based vs. meat-based diets) on CVD risk factors associated with LEA were not examined. This highlights a key limitation of previous research, as dietary preferences may influence these outcomes. Given the potential impact of diet on LEA and cardiovascular health, future studies should report participants’ dietary patterns to better understand this relationship.

Age is a significant factor in the decline of cardiovascular function, increasing the risk of CVD in older adults (Curtis et al., 2018). The incidence of CVD rises with age, encompassing conditions such as atherosclerosis, stroke, and myocardial infarction (Yazdanyar and Newman, 2009). The pathophysiology of CVD in aged adults involves functional and structural cardiac changes driven by oxidative stress, inflammation, and mitochondrial dysfunction. Aging hearts exhibit diastolic and systolic dysfunction, arrhythmias, and increased production of reactive oxygen species, which contribute to chronic inflammation, apoptosis, and myocardial deterioration (Curtis et al., 2018; North and Sinclair, 2012; Steenman and Lande, 2017). Elevated inflammatory markers (interleukin-6, tumor necrosis factor-alpha, C-reactive protein) and extracellular matrix remodeling, resulting from dysregulated matrix metalloproteinases and their inhibitors (Tissue Inhibitors of Metalloproteinases (TIMPs)), lead to fibrosis, hypertrophy, and atrial fibrillation (Burstein and Nattel, 2008; Meschiari et al., 2017). Mitochondrial damage impairs adenosine triphosphate (ATP) production and calcium signaling, exacerbates lipid oxidation, and promotes atherosclerosis (Carew, 1989; Martín-Fernández and Gredilla, 2016; Nakou et al., 2016; Xie et al., 2015). While age could serve as a mediator or independently affect the reported outcomes, it is unlikely to have significantly influenced CVD-related findings, as the studies in this review included young females aged 15.6–31.7 years (see Table 1 for the ages of all participants).

This review’s primary strength is being the first to systematically examine and critically evaluate the current scientific evidence on the CVD risk indicators linked with LEA in physically active females. However, the review only included a small number of studies and focused on a narrow range of physically active female groups, along with the risk of selection bias (Karlsson et al., 2023), which limits statistical power and generalisability (Faber and Fonseca, 2014).

**Conclusion**

Restricted EI and/or high EE may put physically active females at a higher risk of LEA, which can negatively impact health and performance, including CVD risk. Our findings highlighted that LEA was associated with various CVD risk markers, including abnormal lipid profiles and endothelial dysfunction, though these effects were inconsistent across studies. The evidence linking LEA to increased CVD risk is therefore limited and inconclusive, requiring more robust longitudinal research with larger sample sizes. Future work should focus on direct measures of vascular function (e.g., FMD, CAR%, cIMT, PWV) and more comprehensive lipidomic analyses to clarify these associations across diverse physically active female populations.

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**Supplementary materials**

**Supplementary materials 1. PRISMA flowchart showing the process of study selection.**

Additional records identified through other sources (*n* = 26)

Manual searches via Google Scholar (*n* = 26)

Total (*n* = 26)

Records identified from: One Science (*n* = 14) PubMed (*n* = 252) Scopus (*n* = 25) SPORTDiscus (*n* = 68) Total (*n* = 359)

**Identification**

Records removed before screening: Duplicates records removed (*n* = 8)

**Screening**

Records excluded (*n* = 361)

Records screened by title and abstract (*n* = 377)

Full-text articles excluded, with reasons (*n* = 7)

* Ineligible study design (*n* = 5)
* Ineligible participants characteristics (*n* = 2)

Full-text articles assessed for eligibility (*n* = 16)

**Eligibility**

**Inclusion**

Studies included in this systematic review (*n* = 9)

**Supplementary materials 2. Quality assessment for all studies included studies using The National Institutes of Health (NIH) Quality Assessment Criteria**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Criteria** | **Ackerman *et* *al*. (2019)** | **Black *et* *al*. (2018)** | **Clark *et* *al*. (2018)** | **Gifford *et* *al*. (2020)** | **Hoch *et* *al*. (2011)** | **Kyte *et* *al*. (2022)** | **Melin *et* *al*. (2014)** | **Sygo *et* *al*. (2018)** | **Varga *et* *al*. (2020)** |
| Study objectives stated | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Study population defined | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Eligible participation rate at least 50% | No | No | No | No | No | No | No | No | No |
| Participant selection and inclusion/exclusion criteria uniformity | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Sample size sufficient and/or described | Yes | No | No | No | No | No | No | No | No |
| Exposure measures prior to outcome | No | No | No | No | No | No | No | No | No |
| Sufficient time frame for association between exposure and outcome | No | No | No | Yes | No | No | No | No | Yes |
| Inclusion exposure level | N.A. | N.A. | N.A. | N.A. | N.A. | N.A. | N.A. | N.A. | N.A. |
| Exposure measure valid and reliable | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Multiple exposure measurements | No | No | No | Yes | No | No | No | Yes | Yes |
| Outcome measures valid and reliable | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Outcome assessor(s) blinded | C.D. | C.D. | C.D. | C.D. | C.D. | C.D. | C.D. | C.D. | C.D |
| Loss to follow up post-baseline 20% or less | N.A. | N.A. | N.A. | Yes | N.A. | N.A. | N.A. | Yes | N.A. |
| Confounders measured and adjusted statistically between exposure and outcome | Yes | No | No | Yes | No | No | Yes | No | Yes |
| **Risk of Bias** | Fair | Fair | Fair | Good | Fair | Fair | Fair | Fair | Fair |
| Abbreviations: CD, cannot determine; NA, not applicable. | | | | | | | | | |