

LOW ENERGY AVAILABILITY AND CHOLESTEROL METABOLISM IN ATHLETES

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Low energy availability and cholesterol metabolism in athletes

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Abstract

Background: Relative energy deficiency in sport (REDs) is a model describing the potential negative health and performance effects caused by problematic low energy availability (LEA). LEA can affect several physiological and psychological systems including hormonal balance, the reproductive system, bone health, mental well-being, growth and development as well as the cardiovascular system. Elevated low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) have been linked to LEA in different populations, but studies specifically on athletes are sparse. Additionally, some studies have reported beneficial changes in lipids after periods of LEA. Therefore, more research is needed to understand the interaction between LEA and cholesterol metabolism in athletes.

Aims: The aim of my thesis was to better understand the association between cholesterol metabolism and LEA in an athletic population. More specifically my aims were to determine: I) the prevalence of REDS and eating disorder symptoms in female athletes and their association with cholesterol values, II) REDs risk and cholesterol values during a training season in endurance athletes and to analyse if an association exists between these two in either a cross-sectional or longitudinal context, and III) the association between the serum metabolome and REDs risk in female and male athletes.

Methods: Data from two cohorts conducted on national- to international-level athletes at the University of Jyväskylä were used in this thesis; the cross-sectional Monitoring Illness and Injury in Athletes (MIIA) and the longitudinal Athletic Performance and Nutrition (NoRED-S). Participants self-reported physiological symptoms of LEA using the Low Energy Availability in Females Questionnaire (LEAF-Q) (Study I) and eating disorder symptoms using the Eating Disorder Examination Questionnaire Short (EDE-QS) (Studies I–III). REDs risk was assessed using the REDs Clinical Assessment Tool version 2 (REDs CAT 2) (Studies II & III). Serum cholesterol levels were determined from blood (Studies I & II) and the serum metabolome was analysed by nuclear magnetic resonance (NMR) (Study III). In Study I, the first measurements of female athletes from both cohorts, MIIA and NoRED-S, were used for a cross-sectional analysis to examine the relationship between EDE-QS, LEAF-Q and cholesterol values using Pearson's r and linear regression. I also separately studied participants representing weight-sensitive sports. In Study II, data of endurance athletes in the NoRED-S cohort were used. The participants were examined at the beginning (T1) and end (T2) of the training season, and I analysed the association and changes in REDs risk and cholesterol values between these timepoints using linear regression and restricted maximum likelihood. In Study III, all adult participants from the

NoRED-S cohort were included for analysis of the association between REDs risk and the serum metabolome using generalized estimating equation models. Sensitivity analyses were conducted in athletes representing weight-sensitive sports.

Results: The prevalence of REDs risk ranged from 36 to 84% (Studies I–III) and the prevalence of elevated LDL-C (≥3mmol/l) from 12 to 37% (Studies II&III). In Study I, higher EDE-QS scores were associated with higher LDL-C levels in the mixed-sport population, and both the LEAF-Q and EDE-QS were associated with higher LDL-C levels among athletes representing weight-sensitive sports. In Study II, the REDs risk was not associated with cholesterol levels in cross-sectional analyses, and no overall change in the REDs risk or the cholesterol levels was observed between T1 and T2. However, in female athletes, an increase in REDs risk status from low to medium/high between T1 and T2 was associated with a decrease in LDL-C and TC. In Study III, few associations between REDs risk and intermediate-density lipoprotein (IDL) and very-low-density lipoprotein (VLDL) profiles in female athletes were observed but not in male athletes and no changes in LDL-C or TC were found. Further, a lower body fat percentage was associated with a beneficial metabolic fingerprint, characterised by a larger-sized high-density lipoprotein (HDL) profile and lower levels of inflammatory markers.

Conclusions: Overall, I could observe a few associations between REDs risk and cholesterol levels or the serum metabolome in my studies, and the associations seem to be stronger in female athletes representing weight-sensitive sports. Regardless of REDs risk, up to one-third of the athletes had clinically elevated LDL-C, highlighting that the athletic population should not be overlooked in the primary prevention of cardiovascular disease. Eating disorder behaviour, which is also a significant risk factor for REDs, seems to be associated with higher LDL-C levels in female athletes, consistent with findings in patients with anorexia nervosa. However, it seems that even in healthy and fit athletes, lower body fat percentage is associated with a more beneficial metabolomic profile.

Tiivistelmä

Tausta: Urheilijoiden suhteellinen energiavaje (REDs) on malli, joka kuvastaa matalan energiansaatavuuden haitallisia vaikutuksia kehon ja mielen normaaliin toimintaan. Matala energiansaatavuus voi vaikuttaa mm. hormonitoimintaan, lisääntymisterveyteen, luuntiheyteen, psyykkiseen terveyteen, kasvuun ja kehitykseen sekä sydän- ja verisuonielimistön toimintaan. Tutkimuksissa on osoitettu, että kohonneet LDL-kolesteroli- ja kokonaiskolesteroliarvot ovat yhteydessä matalaan energiasaatavuuteen, mutta urheilijoita on tällä saralla tutkittu vasta vähän. Lisäksi osa tutkimuksista on havainnut matalan energiansaatavuuden olevan yhteydessä jopa myönteisiin muutoksiin kolesterolitasoissa.

Tavoitteet: Väitöskirjani tavoite oli ymmärtää paremmin urheilijoiden matalan energiansaatavuuden ja kolesteroliaineenvaihdunnan yhteyttä. Erityisesti tavoitteeni oli: I) tutkia urheilijoiden matalan energiasaatavuuden ja syömishäiriökäytöksen yhteyttä kolesteroliarvoihin, II) tutkia kestävyysurheilijoiden REDs-riskiä ja kolesteroliarvoja harjoituskauden eri vaiheissa sekä III) tutkia nais- ja miesurheilijoiden REDs-riskin ja seerumin metabolomin yhteyttä.

Menetelmät: Väitöskirjani pohjautuu kahteen Jyväskylän yliopistossa kerättyyn tutkimusaineistoon kansallisen ja kansainvälisen tason urheilijoilla: poikkileikkaustutkimus Monitoring Illness and Injury in Athletes (MIIA) sekä kolmivuotinen seurantatutkimus Urheiluravitsemus ja matala energiansaatavuus urheilijoilla (NoRED-S). Tutkittavat raportoivat kyselylomakkeilla matalan energiansaatavuuden oireita (Low Energy Availability in Females Questionnaire [LEAF-Q]) (tutkimus I) sekä syömishäiriöoireita (Eating Disorder Examination Questionnaire Short [EDE-QS]) (tutkimus I-III), ja REDs-riski määritettiin kliinisen arviointityökalun avulla (REDs CAT 2) (tutkimus II & III). Kolesteroliarvot määritettiin laskimoverinäytteistä (tutkimus I & II) ja metabolomi analysoitiin ydinmagneettisella resonanssispektroskopialla (tutkimus III). Tutkimuksessa I tutkin kaikkien naisurheilijoiden ensimmäisiä mittauskertoja MIIA- ja NoRED-S-tutkimuksissa poikkileikkausanalyysina. Tutkin EDE-QS- ja LEAF-Q-pisteiden yhteyttä kolesterolitasojen Pearsonin korrelaation sekä lineaarisen regression avulla. Tutkin myös erikseen painoherkkien lajien edustajilla. Tutkimuksessa II tutkin NoRED-S-tutkimukseen osallistuneita kestävyysurheilijoita. Urheilijoita oli tutkittu harjoituskauden alussa (T1) ja lopussa (T2) ja analysoin, tapahtuuko REDs-riskissä tai kolesteroliarvoissa muutosta näiden aikapisteiden välillä, sekä sitä, ovatko muuttujat tai muutokset keskenään yhteydessä. Käytin analyyseihin lineaarista regressiota sekä rajoitettua

suurimman uskottavuuden menetelmää. Tutkimuksessa III tutkin kaikkia aikuisurheilijoita NoRED-S-tutkimuksesta ja analysoin REDs-riskin ja metabolomin yhteyttä yleistetyllä estimointiyhtälöllä. Myös tässä tutkimuksessa tarkastelin erikseen painoherkkien lajien edustajia.

Tulokset: REDs-riskin yleisyys vaihteli eri tutkimuksissani 36 % ja 84 % välillä (tutkimukset I–III) ja kohonneen LDL-kolesterolin yleisyys 12 % ja 37 % välillä (tutkimukset II & III). Tutkimuksessa I korkeampi EDE-QS-tulos oli yhteydessä korkeampaan LDL-kolesterolitasoon kaikkien naisurheilijoiden keskuudessa ja painoherkkien lajien edustajilla sekä korkeampi EDE-QS- että LEAF-Q-tulos olivat yhteydessä korkeampaan LDL-kolesterolitasoon. Tutkimuksessa II havaitsin, ettei REDs riski ollut yhteydessä mihinkään tutkittuun kolesteroliarvoon, enkä havainnut muutosta REDs-riskissä tai kolesterolitasoissa mittauspisteiden välillä. Kuitenkin havaitsin, että naisurheilijoilla REDs-riskin nousu tutkimuksen aikana matalasta keskisuureen/suureen oli yhteydessä LDL-kolesterolin ja kokonaiskolesterolin laskuun. Tutkimuksessa III havaitsin REDs-riskin olevan yhteydessä yksittäisiin metaboliitteihin IDL- ja VLDL-profiileissa naisurheilijoilla, mutta ei miesurheilijoilla. Matalampi rasvaprosentti oli yhteydessä suotuisaan metabolomiin suurempikokoisen HDL-profiilin ja matalamman tulehdusmuuttujan suhteen.

Johtopäätökset: Yleisesti havaitsin väitöskirjassani vähäisiä yhteyksiä REDs-riskin ja kolesteroliarvojen tai metabolomin välillä, ja tämä yhteys vaikuttaa olevan vahvempi naisurheilijoilla, jotka edustavat painoherkkiä lajeja. Kuitenkin REDs-riskistä riippumatta lähes kolmasosalla urheilijoista oli kohonnut LDL-kolesteroli korostaen, ettei urheilijoiden sydän- ja verenkiertoelimistön terveyden edistämistä pidä ylenkatsoa. Syömishäiriökäytös, joka on myös REDs-riskitekijä, vaikuttaa olevan yhteydessä korkeampaan LDL-kolesteroliin naisurheilijoilla, mikä on linjassa aiempien syömishäiriöpotilailla tehtyjen tutkimusten kanssa. Kuitenkin myös terveillä ja hyväkuntoisilla urheilijoilla matalampi rasvaprosentti vaikuttaa olevan yhteydessä edullisempaan metabolomiin.

List of abbreviations

β	beta, statistical output for linear regression
Δ	delta for change
ABC	ATP-binding cassette
ANOVA	analysis of variance
Apo	apolipoprotein
AR	androgen receptor
ASCVD	atherosclerotic cardiovascular disease
BMD	bone mineral density
BMI	body mass index
BSI	bone stress injury
CE	cholesterol ester
CETP	cholesteryl ester transfer protein
CI	confidence interval
CIT	cold-induced thermogenesis
CoA	coenzyme A
COC	combined oral contraception
DE	disordered eating
DHEA	dehydroepiandrosterone
DXA	dual energy X-ray absorptiometry
DHA	docosahexaenoic acid
DIT	dietary-induced thermogenesis
E2	oestradiol
EA	energy availability
ED	eating disorder
EDE-Q	Eating Disorder Examination Questionnaire
EDE-QS	Eating Disorder Examination Questionnaire Short version
EEE	exercise energy expenditure
EHMC	exercise-hypogonadal male condition
EI	energy intake
eNOS	endothelial NO synthase
ER	oestrogen receptor
ESC	European Society of Cardiology
FFM	fat-free mass
FH	familial hypercholesterolaemia

FHA	functional hypothalamic amenorrhoea
FLMR	fat mass–to–lean mass ratio
FSH	follicle-stimulating hormone
GEE	generalised estimating equations
GH	growth hormone
GlycA	glycoprotein acetylation
GnRH	gonadotropin-releasing hormone
GPR30	G-protein-coupled ER
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HL	hepatic lipase
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPO	hypothalamic–pituitary–ovarian axis
hs-CRP	high-sensitivity C-reactive protein
IDL	intermediate-density lipoprotein
IGF-1	insulin-like growth factor 1
IOC	International Olympic Committee
IQR	interquartile range
kcal	kilocalorie
kg	kilogram
LCAT	lecithin–cholesterol acyltransferase
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	LDL receptor
LEA	low energy availability
LEAF-Q	Low Energy Availability in Female athletes Questionnaire
LEAM-Q	Low Energy Availability in Male athletes Questionnaire
LH	luteinising hormone
LPL	lipoprotein lipase
Lp(a)	lipoprotein(a)
LRP	LDLR-related protein
MHT	menopause hormone therapy
MIIA	Monitoring Illness and Injury in Athletes cohort
MUFA	monounsaturated fatty acids
n	number
NEAT	non-exercise activity thermogenesis
NMR	nuclear magnetic resonance
NO	nitric oxide
NoRED-S	Athletic Performance and Nutrition cohort
OC	oral contraception
OR	odds ratio
oxLDL	oxidised low-density lipoprotein

P4	progesterone
PCSK9	proprotein convertase subtilisin/kexin 9
PMOS	polyendocrine metabolic ovarian syndrome
PUFA	polyunsaturated fatty acids
PYY	peptide YY
r	Pearson's correlation coefficient
RCT	reverse cholesterol transport
REDs	relative energy deficiency in sport
REDs CAT 2	REDs Clinical Assessment Tool version 2
REE	resting energy expenditure
REML	restricted maximum likelihood
RMR	resting metabolic rate
SD	standard deviation
SR-B1	scavenger receptor class B type 1
T1	beginning of the training season
T2	end of the training season
T3	triiodothyronine
T4	thyroxine
TC	total cholesterol
TG	triglyceride
TRL	triglyceride-rich lipoproteins
TSH	thyroid-stimulating hormone
USA	United States of America
VLDL	very low-density lipoprotein
VO2max	maximal oxygen uptake (ml/kg/min)

List of original publications

This thesis is based on the following publications:

I **Silvennoinen JIK**, Ihalainen JK, Valtonen M, Mjøsund K, Sipilä PN. Association of LEAF-Q and EDE-QS scores with cholesterol levels in Finnish female athletes. BMJ Open Sport Exerc Med. 2024 Sep 13;10(3):e002050.

II **Silvennoinen JIK**, Sipilä PN, Valtonen M, Mjøsund K, Kinnula V, Hirvelä L, Mierlahti L, Ihalainen JK. Association between the risk of relative energy deficiency in sport and cholesterol levels in Finnish endurance athletes. BMJ Open Sport Exerc Med. 2025 Sep 1;11(3):e002644.

III **Voutilainen JIK***, Sarin H, Valtonen M, Mjøsund K, Koukku N, Ihalainen JK**, Sipilä PN**. Metabolome and REDs risk in Finnish athletes, manuscript

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**Designates joint last authorship

The publications are referred to in the text by their Roman numerals. They are also reprinted with the permission of their copyright holders

1 Introduction

Adequate energy intake is essential for athletes since it supports physiological health, training capacity, and recovery. A nutritionally adequate diet that provides sufficient energy, as well as essential macro- and micronutrients, forms the foundation for maintaining health, sustaining training load, and optimising athletic performance (Amawi et al. 2024; Holtzman and Ackerman 2021).

However, there are several factors that can lead to reduction in the energy available for the basic metabolism of the body to sustain good health along with exercise and training. Firstly, the excess energy need due to exercise can be so high that the compensation in the energy intake (EI) can be burdensome (Angelidi et al. 2024; Jagim et al. 2022). Secondly, athletes are prone to be affected by society's body ideals or their sport-specific requirements regarding body size, composition or appearance (Mancine et al. 2020). At worst, these expectations can disturb athletes' body image and eating behaviour, leading to disordered eating (DE), disordered exercise behaviour or even clinical eating disorders (ED)(Fatt et al. 2024). Ultimately these factors can lead to insufficient EI relative to the exercise energy expenditure (EEE) and basic physiological needs of the body, a phenomenon also called low energy availability (LEA)(Mountjoy et al. 2023).

Energy availability (EA) is defined as the energy available for basic physiological functions after the EEE has been subtracted from the total EI (Loucks et al. 2011). The spectrum between optimal EA and severe LEA includes a continuum of conditions, which can be grouped into adequate EA, adaptable LEA and problematic LEA (Mountjoy et al. 2023). Adaptable LEA refers to LEA that is short-termed and/or mild and can even have beneficial consequences on health and performance. Problematic LEA, however, is defined as LEA that is sufficiently severe or long-lasting to negatively affect the normal functioning of various body systems. Problematic LEA is at the core of the relative energy deficiency in sport (REDs) model, which is defined as impaired physiological and/or psychological functioning in athletes caused by problematic LEA (Mountjoy et al. 2023).

In the most recent 2023 International Olympic Committee (IOC) Consensus Statement, the REDs model includes impaired functioning of energy metabolism, reproductive function, musculoskeletal health, immunity, glycogen synthesis, haematological function and cardiovascular health in both female and male athletes (Mountjoy et al. 2023). Regarding the cardiovascular health and lipid metabolism,

elevated low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC), electrocardiogram abnormalities, impaired endothelial function, haemodynamic abnormalities and cardiac abnormalities are listed as potential REDs health outcomes.

Defining exposure to problematic LEA and REDs in the real-world is difficult (Heikura et al. 2018). The current gold standard method recommended by the IOC is the REDs Clinical Assessment Tool version 2 (REDS CAT 2 (Stellingwerff et al. 2023)), which relies on screening, risk stratification of potential REDs symptoms and clinical findings, and finally multi-disciplinary evaluation of at-risk individuals including exclusion of other potential causes or moderating factors. Elevated LDL-C and TC are among the secondary indicators of REDs in the risk stratification step.

The evidence linking LEA to elevated LDL-C and TC is derived from studies on patients with anorexia nervosa (severe form of LEA)(Hussain et al. 2019), females with disturbed menstrual cycles (potential surrogate marker of LEA)(Tegg et al. 2024), males going an through army ranger course (short-term multi-stress environment with profound LEA)(Friedl et al. 2000), and individual athletes going through a weight-loss protocol for weight-class sports (profound LEA and dehydration)(Kasper et al. 2019; Langan-Evans et al. 2021). However, contradicting findings have also been observed with no correlation between LEA and cholesterol levels (Ayres et al. 1998; D. L. Thompson et al. 1997) and even beneficial changes in cholesterol levels and the serum metabolome following short- to medium-term LEA exposure (Jouhki et al. 2024; Sarin et al. 2019; Nusser et al. 2025). Weight loss and decreased EI have been shown to have beneficial effects on the lipid profile in sedentary individuals (Most et al. 2018; Lefevre et al. 2009) but also in physique athletes (Jouhki et al. 2024; Sarin et al. 2019), and understanding the long-term effect of problematic LEA on athlete cardiovascular health remains inconclusive.

A causal link between LDL-C and risk of atherosclerotic cardiovascular disease (ASCVD) has been established (Ference et al. 2017). Therefore, understanding the interaction between LEA and cholesterol metabolism in athletes is important for not only improving athletes' long-term health, but also for the primary prevention of ASVCD and for public health, because LEA is not only a concern among high-level athletes, but recreational athletes are also prone to inadequate EI relative to their EEE (Karlsson et al. 2023).

2 Review of the literature

2.1 Low energy availability (LEA) and relative energy deficiency in sport (REDs)

2.1.1 Definitions of energy availability (EA), LEA and REDs

We as humans need energy to move our bodies (locomotion), to produce heat (thermogenesis), and to keep our vital organs running (physiological functions). Total energy expenditure can be divided into exercise energy expenditure (EEE), non-exercise activity thermogenesis (NEAT), dietary-induced thermogenesis (DIT), cold-induced thermogenesis (CIT), and resting energy expenditure (REE) (Müller and Bosy-Westphal 2013). Energy availability (EA) is defined as the amount of energy available for all physiological and other vital functions after the energy needs of exercise have been subtracted (Loucks et al. 2011). EA is calculated by subtracting the EEE from the total EI and correcting this value for the person's metabolically active mass (fat-free mass):

$$Energy\ Availability\ (EA) = \frac{Energy\ Intake\ (EI) - Exercise\ Energy\ Expenditure\ (EEE)}{Fat{-}Free\ Mass(FFM)}.$$

(Loucks et al. 2011)

LEA is a condition in which a person's EI does not match the EEE and the energy required to support physiological functions (Mountjoy et al. 2018, 2023). LEA is a continuum of diverse severities and durations and thus, is further divided into problematic and adaptable (Mountjoy et al. 2023). Adaptable LEA is characterised by a short-term, non-severe LEA that can have beneficial influence on health and even be used as a tool to enhance athletic performance in adults at the top-level with the supervision of an adequate team of professionals (Mountjoy et al. 2023). In contrast, problematic LEA is prolonged and/or severe and can have a negative impact on an athlete's performance and health (Mountjoy et al. 2023). Athletes are more susceptible to LEA due to the energy demands of exercise and training, and possible sport-specific requirements considering body weight and size.

Originally, the link between inadequate EI or DE, menstrual dysfunctions and low bone mineral density among female athletes was introduced in the 1990s as a condition called the female athlete triad (Yeager et al. 1993). In 2014, the IOC expanded the triad to relative energy deficiency in sport (REDs)(Mountjoy et al.

2014). REDs is by definition a syndrome of impaired physical and/or psychological health caused by problematic LEA (Mountjoy et al. 2023) and contrary to the female athlete triad, the REDs model acknowledges that the impact of LEA is not restricted to females (Mountjoy et al. 2014). In addition, the REDs model takes a wider view on the athlete's physiology and states that, in addition to disturbances in the menstrual cycle and bone metabolism, problematic LEA can impair the normal functioning of metabolic, cardiovascular, psychological, endocrine, immune, and gastrointestinal systems (Mountjoy et al. 2018) as well as performance and recovery (Melin et al. 2024; Mountjoy et al. 2023). The continuum from adequate EA to REDs is illustrated in Figure 1.

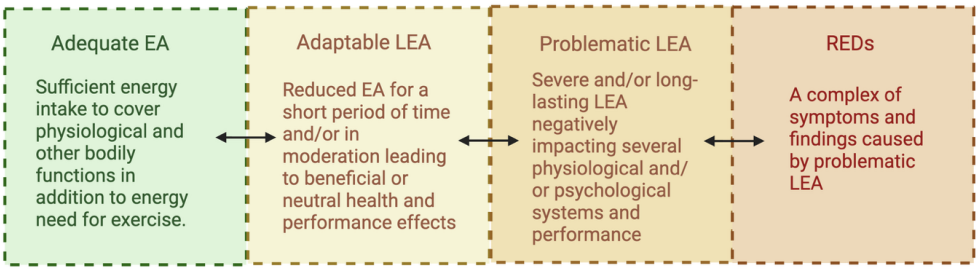


Figure 1 Illustration of the continuum from adequate energy availability (EA) to adaptable and problematic low energy availability (LEA) to relative energy deficiency in sport (REDs). Figure was created in the illustration website BioRender https://BioRender.com.

The threshold of calculated LEA for females is set to 30 kcal/day/kg (Loucks et al. 2011) since bone formation (Ihle and Loucks 2004), levels of triiodothyronine (T3)(Loucks and Heath 1994b) and reproductive functions (Loucks and Thuma 2003) are abruptly impaired below this threshold within five days after laboratory-induced LEA. Optimal EA for performance and health is thought to be achieved with 45 kcal/day/kg for sedentary females (Loucks and Thuma 2003) and 40 kcal/day/kg for recreationally active males (Koehler, Hoerner, Gibbs, Zinner, Braun, Souza, et al. 2016). Clear EA thresholds for elite female and male athletes have not been established (Melin et al. 2024). It is likely that moderating factors, e.g., sex, age and gynaecological age, genetics, type of sport, and macronutrient profile, may impact the individual LEA threshold (Loucks 2006; Heikura et al. 2022; Mountjoy et al. 2023).

2.1.2 Evaluation of EA and REDs

Individual EA can be calculated with the abovementioned formula using EI, EEE and FFM. The reliability of calculated EA in real-world settings is, however, questionable due to challenges in measuring the parameters. Large margins of error in the accuracy of self-reported measures of EI and EEE have led to considerable discrepancies between symptoms of LEA and EA calculations (Burke et al. 2018;

Capling et al. 2017; Hills et al. 2014) and many studies have found no correlation between clinical signs of LEA and calculated low EA values (Heikura et al. 2018; Koehler et al. 2013; Melin et al. 2014). Additionally, modes of measuring body composition yield varying results (Mathisen et al. 2023). Therefore, other tools, such as symptom screening questionnaires, have been suggested to be more reliable in detecting problematic LEA since these methods can provide a better representation of the athlete's long-term EA than a snapshot of calculated EA over a few days (Heikura et al. 2018). Also, possible DE patterns should be evaluated since they can be an underlying cause behind LEA and REDs (Logue et al. 2020; Fahrenholtz et al. 2022).

The current recommendation for assessing REDs risk is the REDs Clinical Assessment Tool version 2 (REDs CAT 2), developed by the IOC (Stellingwerff et al. 2023). The risk assessment is divided into three steps. The first step is to use REDs screening questionnaires to identify athletes potentially at risk of REDs. There are a variety of different screening questionnaires assessing possible symptoms and findings of REDs (Sim and Burns 2021), but so far, to the best of my knowledge, the only validated screening questionnaire is the Low Energy Availability in Female athletes Questionnaire (LEAF-Q), which has been validated in female endurance athletes (Melin et al. 2014). Thus, even if the questionnaires are inexpensive and easy to use, in most sports and athlete populations their validity is unknown, which challenges their reliability in detecting the athletes at risk. Clinical interviews can also be applied in screening athletes for risk of REDs.

The second phase in the risk assessment of REDs is to classify the risk of REDs using primary and secondary REDs indicators. The aim is to assess symptoms or clinical findings that could be caused by problematic LEA including hormonal function (T3, menstrual function for females and testosterone in males), bone health (bone mineral density [BMD], bone stress injuries [BSI]), growth in children and adolescents, ED symptoms, elevated cholesterol levels, and mental health problems. The more of these indicators an athlete presents with, the more probable it is that problematic LEA could be a common factor explaining them. A combination of different indicators yields a risk stratification ranging from green (none to very low), to yellow (mild), orange (moderate to high), and red (very high/extreme). The specific indicators are listed in Table 1, and the risk assessment is described in Table 2.

Table 1 Primary and secondary indicators of REDs according to the REDs CAT 2

Severe primary indicators (count as two primary indicators)	- primary amenorrhoea (no menstruation by the age of 15 years of within 5 years of breast development) or prolonged secondary amenorrhoea (absence of 12 or more consecutive menstrual cycles) due to FHA for females -clinically low free or total testosterone for males
Primary indicators	-secondary amenorrhoea (absence of 3–11 consecutive menstrual cycles) caused by FHA for females -sub-clinically low free or total testosterone for males -sub-clinically or clinically low (within or below the lowest 25% of reference range) total or free T3 -history of ≥1 high-risk (femoral neck, sacrum, pelvis) *or* ≥2 low-risk BSI (all other locations) within the previous 2 years *or* absence of ≥6 months from training due to BSI in the previous 2 years -pre-menopausal females and males <50 years old: BMD Z-score <-1 at the lumbar spine, total hip, or femoral neck or decrease in BMD Z-score from prior testing -children/adolescents: BMD Z-score <-1 at the lumbar spine or total body less head or decrease in BMD Z-score from prior testing -a negative deviation of a paediatric or adolescent athlete's previous growth trajectory (height and/or weight) -an elevated score for the EDE-Q global (>2.30 in females; >1.68 in males) and/or clinically diagnosed DSM-5-TR-defined eating disorder (*only 1 primary indicator for either or both outcomes*)
Secondary indicators	-oligomenorrhoea for females (>35 days between periods leading to <8 menstrual cycles per year) -history of 1 low-risk BSI within the previous 2 years *and* absence of <6 months from training due to BSI in the previous 2 years -elevated total or LDL cholesterol (above reference range) -clinically diagnosed depression and/or anxiety (*only 1 secondary indicator for either or both outcomes*)

REDs = relative energy deficiency in sport, REDs CAT 2 = REDs Clinical Assessment Tool version 2; FHA = functional hypothalamic amenorrhoea, T3 = triiodothyronine; BSI = bone stress injury; BMD = bone mineral density; EDE-Q = Eating Disorder Examination Questionnaire; DSM-5-TR = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; LDL = low-density lipoprotein

Table 2 Risk assessment of REDs according to the REDs CAT 2

red/extreme risk	3 primary & ≥2 secondary, or ≥4 primary indicators
orange/moderate to high risk	1 primary & ≥3 secondary, or 2 primary & ≥2 secondary, or 3 primary & ≤1 secondary indicators
yellow/mild risk	0 primary & ≥2 secondary, or 1 primary & ≤2 secondary, or 2 primary & ≤1 secondary indicators
green/very low risk	0 primary & ≤1 secondary indicators

REDs = relative energy deficiency in sport, REDs CAT 2 = REDs Clinical Assessment Tool version 2

The third and final step in the assessment of REDs risk is an individual evaluation led by an expert physician, preferably with a multidisciplinary team of professionals. Other possible conditions, diseases and origins behind the experienced symptoms and findings must be evaluated adequately before concluding LEA as a common cause. REDs is not, however, a clinical diagnosis and is not included in the most current 10th and 11th editions of the International Classification of Diseases (ICD-10 and ICD-11).

The REDs model has been criticised for being too calorie-centric and biased in assuming the symptoms are caused by LEA unless otherwise proven (Jeukendrup et al. 2024). Additionally, some of the causal relationship between LEA and health and performance outcomes have been stated to be based on insufficient scientific evidence (Jeukendrup et al. 2024; Williams et al. 2019). An alternative model, the Athlete Health and Readiness Checklist, has been suggested where, in addition to nutritional status, other potential factors affecting the hypothalamus–hormonal axes are evaluated. These factors include training, life and environment, mental health, DE behaviour or EDs, nutrition (including EI, carbohydrates, deficiencies and alcohol), sleep, infections and illness, as well as undiagnosed clinical conditions. In addition, the model proposes that moderating factors such as personal traits, genetics, development and experience should be evaluated (Jeukendrup et al. 2024).

2.1.3 Consequences of LEA

Problematic LEA has been associated with dysregulation of several physiological functions including alterations in the reproductive system, bone health, mental well-being, several endocrine systems, immune response, cardiovascular health, injury risk, and performance (Mountjoy et al. 2023). From an evolutionary perspective, it has been essential to regulate metabolism in periods of compromised EI to sustain life (Loucks and Thuma 2003). However, as described earlier, defining

and measuring LEA in the real-world is challenging, and current evidence is mostly based on short-term controlled LEA trials, or cross-sectional and observational studies with heterogeneous populations and surrogate markers of LEA. In this section, I will focus on the physiological and endocrine consequences of LEA. Figure 2 summarizes previous findings with a focus on the current REDs CAT 2 and potential endocrine and cardiovascular indicators.

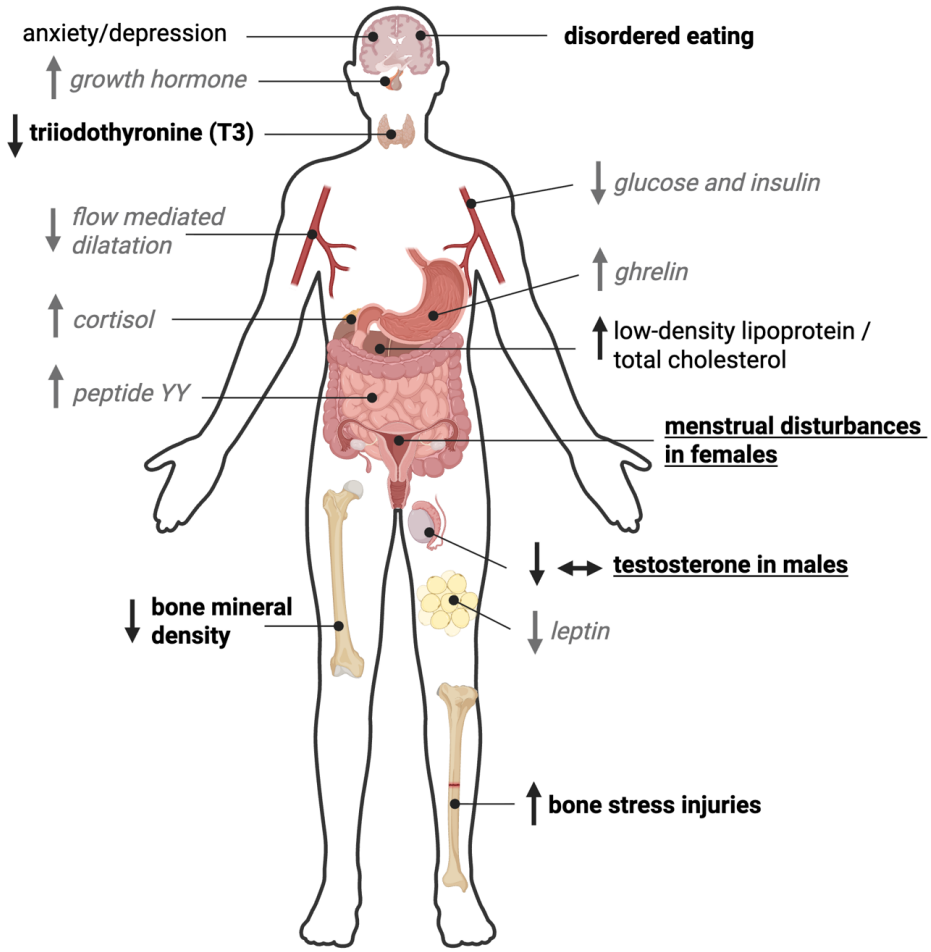


Figure 2 Causes and consequences of direct or surrogate measures of problematic low energy availability (LEA). Different fonts represent different indicators of relative energy deficiency in sport (REDs) in the current REDs Clinical Assessment Tool version 2: **severe primary indicators**, **primary indicators**, secondary indicators and potential indicators. Figure was created in the illustration website BioRender https://BioRender.com.

2.1.3.1 Reproductive system

In female athletes, menstrual dysfunction is one of the most studied consequences of problematic LEA. Menstrual dysfunction can range from anovulatory cycles to irregular periods (oligomenorrhoea, cycle length >35 days) and complete absence of menses for >3 months (amenorrhoea). Amenorrhoea caused by disturbances in the hypothalamic–pituitary–ovarian axis (HPO axis) is referred to as functional hypothalamic amenorrhoea (FHA) and can, in addition to LEA, result from physical or mental stress (Meczekalski et al. 2014; Saadedine et al. 2023; Kirsty J. Elliott-Sale et al. 2018). FHA is caused by insufficient release of gonadotropin-releasing hormone (GnRH) from the hypothalamus leading to downstream effects on blunted gonadotropin release (follicle stimulating hormone [FSH] and luteinising hormone [LH]) from the pituitary gland and steroid release (oestrogen) from the gonads (Roberts et al. 2020). In female athletes, the prevalence of menstrual disturbances has been reported to range from 0 to 61% across different disciplines with the highest prevalences in endurance sports and gymnastics (Gimunová et al. 2022).

In controlled short-term (4 days) studies of induced LEA, LEA has been shown to lead to disturbed LH pulse frequency and amplitude in sedentary females (Loucks and Thuma 2003; Loucks et al. 1998; A. B. Loucks and Heath 1994a). In two randomised controlled trials lasting for three consecutive menstrual cycles, a positive correlation between the magnitude of LEA and frequency of menstrual dysfunction was established, but not between the magnitude of LEA and the severity of menstrual dysfunction, nor could a specific EA threshold for menstrual disturbances be established (Williams et al. 2015; Lieberman et al. 2018). In a randomised controlled trial conducted on exercising females, the REFUEL study, an increase of ~330kcal in the daily EI, with no change in EEE, was associated with a 7 times greater odds for a recovery of menstrual abnormality (amenorrhoea and oligomenorrhoea) compared to the control group (De Souza et al. 2021).

Regarding oestrogen and short-term LEA (4 days), only a large reduction in EA to 10kcal/d/kg(FFM) has led to a reduction in 24h measured oestradiol (Loucks and Thuma 2003). However, FHA as a surrogate marker of prolonged LEA is associated with reduced levels of oestrogen (Allaway et al. 2016; Tornberg et al. 2017) although, naturally menstruating athletes have also been reported to have lower levels of oestrogen than sedentary controls (Laughlin and Yen 1996). Depending on the severity, menstrual dysfunction can impact fertility but is likely reversible if the root cause in treated (Ihalainen et al. 2024).

Regarding disturbances in sex hormones in male athletes exposed to LEA, studies have shown mixed results. Two short-term studies inducing LEA on exercising men and elite endurance athletes found no change in testosterone (Koehler, Hoerner, Gibbs, Zinner, Braun, De Souza, et al. 2016; McKay et al. 2022), but another study on endurance athletes found lower levels of testosterone to be associated with LEA (Kojima et al. 2020). However, athletes in general and

particularly athletes representing endurance or weight-sensitive sports, have been shown to have lower testosterone levels than sedentary healthy controls, a phenomenon also known as exercise-hypogonadal male condition (EHMC)(Kirsty J. Elliott-Sale et al. 2018; Hackney 2020). EHMC seems to be an adaptation to chronic exercise training with no other health defects, whereas reduced testosterone related to problematic LEA is accompanied by symptoms in other systems leading to compromised health and performance (Hackney 2020). Additionally, male patients with anorexia nervosa have been reported to have low levels of testosterone in acute disease phase with increasing levels (correlating with increasing leptin levels) after weight-restoration protocols (Tomova and Kumanov 1999; Wabitsch et al. 2001).

In females, studies have shown mixed results regarding testosterone. Reduced testosterone levels have been observed in female adolescents with amenorrhoea (Christo et al. 2008; Russell et al. 2009) and in female anorexia nervosa patients (Miller et al. 2007), but not in female adults with amenorrhoea (Miller et al. 2007; Rickenlund et al. 2004). Further, elevated levels of testosterone have been reported in females with oligomenorrhoea (Rickenlund et al. 2004). Taken together, the use of oligomenorrhoea or amenorrhoea as surrogate markers of problematic LEA without adequate aetiological investigations must be interpreted with caution, because there can also be other underlying causes for these menstrual disturbances, such as polyendocrine metabolic ovarian syndrome (PMOS; previously polycystic ovarian syndrome or PCOS), which usually presents with accompanying endocrine changes distinct from those in LEA (Teede et al. 2026).

2.1.3.2 Bone health

Bone metabolism and health are influenced by several endocrine pathways that may be compromised in a state of problematic LEA (Kirsty J. Elliott-Sale et al. 2018). In experimental studies, LEA has been shown to affect bone resorption and formation, particularly in females (Ihle and Loucks 2004; Papageorgiou et al. 2017; Papageorgiou, Martin, et al. 2018; C. Murphy and Koehler 2020). Female athletes with menstrual disturbances have been reported to have higher rates of bone stress injuries and decreased bone strength compared to eumenorrheic athletes or controls (Ackerman et al. 2015; Ackerman, Putman, et al. 2012; Heikura et al. 2018).

In experimental studies, males seem to be more resistant to adverse bone effects (Papageorgiou, Dolan, et al. 2018). However, in cross-sectional studies male athletes susceptible to LEA have also been reported to have compromised bone health (Tenforde et al. 2016).

2.1.3.3 Energy balance

A state of LEA induces changes in hormones regulating energy balance. In short-term studies (4–5 days), induced LEA led to reduced leptin levels (Koehler, Hoerner, Gibbs, Zinner, Braun, De Souza, et al. 2016), increased ghrelin and peptide YY (PYY), and suppressed insulin and glucose levels (Loucks and Thuma 2003; Koehler, Hoerner, Gibbs, Zinner, Braun, De Souza, et al. 2016; Loucks et al. 1998). Amenorrhoeic athletes have also been reported to have increased insulin sensitivity, decreased circulating insulin, and a reduced hypoglycaemic effect of insulin-like growth factor 1 (IGF-1)(Laughlin and Yen 1996).

Leptin is an adipose hormone that reflects the amount of body fat stores, as well as the current state of EA and carbohydrate availability.(Anne B. Loucks 2013) Leptin suppresses hunger and thus regulates EI in normal conditions (Stefanakis et al. 2024). In addition, leptin regulates several endocrine axes in the hypothalamus thus regulating the production of thyroid hormones, cortisol, IGF-1, and sex hormones, and impacts bone formation by regulating osteoblasts and osteoclasts (Stefanakis et al. 2024). Leptin has a permissive role in the function and development of reproduction since leptin acts on the hypothalamus via kisspeptin neurons, leading to activation of hypothalamic gonadotropin-releasing hormone (GnRH) neurons for the regulation of LH pulsatility (Castellano et al. 2010). In cross-sectional studies, lower levels of leptin have been measured in athletes with FHA or LEA (Ackerman, Slusarz, et al. 2012; Christo et al. 2008; Corr et al. 2011; Donoso et al. 2010; Hilton and Loucks 2000; Loucks and Thuma 2003), and the diurnal pulsatility of leptin has been disturbed in athletes with FHA (Laughlin and Yen 1997). Lower leptin and higher ghrelin levels have been associated with lower LH levels in amenorrhoeic athletes possibly contributing to the menstrual dysfunction.(Ackerman, Slusarz, et al. 2012) Leptin levels reflect body fat stores and thus not surprisingly were lower in Olympic male athletes representing weight-sensitive sports than those representing non-weight-sensitive sports (Hagmar et al. 2013). After a 23-week weight-loss programme, both female and male physique athletes had lower levels of fat mass and lower leptin levels (Isola et al. 2023).

Ghrelin is an orexigenic hormone secreted in the stomach in the fasted state and acts on the hypothalamus and pituitary gland, affecting other hormonal axes. Ghrelin levels have been reported to be elevated in amenorrhoeic athletes, in patients with anorexia nervosa and in women after weight loss (Christo et al. 2008; Ackerman, Slusarz, et al. 2012; Mary Jane De Souza et al. 2007; Scheid et al. 2011; Tolle et al. 2003). Female and male physique athletes had higher levels of ghrelin after a ~5-month weight-loss period with decreased fat mass (Isola et al. 2023). One study on male athletes showed no change in ghrelin after induction of LEA (Koehler, Hoerner, Gibbs, Zinner, Braun, Souza, et al. 2016), and also no change between male patients with anorexia nervosa and healthy controls was observed (Misra et al. 2008).

2.1.3.4 Energy metabolism

LEA can also interfere with other hormonal axes such as the hypothalamus–pituitary–thyroid axis. Studies have consistently reported decreased levels of T3, but variable levels of thyroxine (T4) and thyroid-stimulating hormone (TSH) in athletes or sedentary women with amenorrhoea (Berga et al. 1989; Mary Jane De Souza et al. 2007; Heikura et al. 2018; Harber et al. 1998; Tornberg et al. 2017) and in patients with anorexia nervosa (Estour et al. 2010). Two studies on sedentary women who underwent different protocols of LEA for 4 days showed significant reductions in both free T3 and total T3 due to the reduction of EA, but not from exercise alone if adequate EA was maintained (Loucks and Callister 1993; Loucks and Heath 1994b). In male athletes, lower (but not clinically low) T3 has been associated with lower levels of testosterone (within the lowest quartile of clinical range 9–38 nmol/L)(Heikura et al. 2018). Female and male physique athletes showed significantly reduced levels of T3 after a 23-week weight-loss programme for a fitness competition, but the changes were reversible after a recovery period and weight regain (Isola et al. 2023). In a case series of male patients with anorexia nervosa, low T3 and T4 have been reported with normal TSH levels (Skolnick et al. 2016).

Cortisol is a glucocorticoid steroid hormone secreted from the adrenal gland according to the circadian rhythm. Cortisol production is increased under stressful conditions which can be emotional, physical or biological (Habib et al. 2001). A U-shaped association has been observed between cortisol and body mass index (BMI) as well as fat mass; both extremes lead to activation of the hypothalamus–pituitary–adrenal axis and elevation of cortisol (Kirsty J. Elliott-Sale et al. 2018). Higher levels of cortisol have been reported among sedentary females and female athletes with FHA compared to eumenorrheic athletes and controls (Ackerman et al. 2013; Rickenlund et al. 2004; Tornberg et al. 2017; Melin et al. 2015; Biller et al. 1990; Berga et al. 1997), though not all studies have observed this (Schaal et al. 2011; Laughlin and Yen 1996; Villanueva et al. 1986). Additionally, higher cortisol levels have been observed among female athletes regardless of their menstrual status compared to non-athletes (Laughlin and Yen 1996; Villanueva et al. 1986). In males, to my knowledge, only one study has assessed cortisol levels in endurance athletes with reduced EA versus sedentary males with adequate EA, and no difference was observed (Hooper et al. 2017).

Growth hormone (GH) is a pituitary hormone that is important for muscle and bone anabolism and metabolism of carbohydrates, fats and proteins (Kirsty J. Elliott-Sale et al. 2018). The production of GH is affected by hormones such as ghrelin, and some of GH effects are strongly mediated by liver-produced IGF-1 (Kirsty J. Elliott-Sale et al. 2018). Studies on sedentary, eumenorrheic females reported elevated GH and reduced IGF-1 when EA was restricted from 45 to 20 or 10kcal/day/kg(FFM)(Loucks et al. 1998; Loucks and Thuma 2003). Decreased

levels of IGF-1 and increased levels of GH have been observed in patients with anorexia nervosa (Misra et al. 2004, 2003; Counts et al. 1992; Estour et al. 2010), in male wrestlers going through diet restriction (Roemmich and Sinning 1997), cyclists participating in an ultra-endurance cycling event (Geesmann et al. 2017), and in amenorrhoeic athletes (Rickenlund et al. 2004). In another study, amenorrhoeic athletes had similar 24h mean GH levels but significantly increased GH pulse frequency and elevated inter-pulse concentrations compared to athletes with natural cycles (Laughlin and Yen 1996; Rickenlund et al. 2004). GH resistance in the liver has been suggested to explain the elevated GH and decreased IGF-1 levels observed under LEA (Misra and Klibanski 2014). In a randomised crossover study on recreationally active females, sufficient intake of carbohydrates during periods of LEA was shown to attenuate the LEA-induced decline in IGF-1 (Nusser et al. 2026).

2.1.3.5 Cardiovascular health

It has been suggested that chronic LEA could disturb cholesterol metabolism, as well as hormonal and cardiovascular health in otherwise healthy athletes (Mountjoy et al. 2023). The hypothesis is that the insufficient EI in problematic LEA leads to the inhibition of the hypothalamic–pituitary–gonadal axis, which results in hormonal disturbances such as hypoestrogenism in females (Rickenlund et al. 2005) and low testosterone in males (Hooper et al. 2017; Angelidi et al. 2024). Impaired cardiovascular health, particularly endothelial function, was already suggested to be included into the female athlete triad already in 2013 and a model of female athlete tetrad was proposed (Temme and Hoch 2013).

Oestrogen has a particularly protective role in the cardiovascular system, which will be covered in more detail in section 2.2.8.1. The hypoestrogenism associated with problematic LEA could affect the cardiovascular health of young female athletes and predispose them to early pathologic changes in the cardiovascular system (Okoth et al. 2023). However, the findings are heterogeneous, with elevated LDL-C or TC among athletes at risk of LEA having been reported in some (Friday et al. 1993; Kaiserauer et al. 1989; Friedl et al. 2000; Tegg et al. 2024) but not all studies (Black et al. 2018; Jouhki et al. 2024; Ayres et al. 1998; Thompson et al. 1997). When using LEAF-Q as an indicator for high and low risk of LEA in athletes, no differences were found in LDL-C or TC levels between the groups (Black et al. 2018).

Female athletes with amenorrhoea have been shown to have reduced flow-mediated dilatation compared with naturally menstruating controls, reflecting compromised regulation of peripheric vasoconstriction (Rickenlund et al. 2005). However, these changes might be reversible since a study assessed endothelial and

vascular function in previously amenorrhoeic females and found no difference compared to constantly eumenorrheic participants.(Williford et al. 2025)

Patients with anorexia nervosa have been reported to present with several cardiovascular complications ranging from mild and more frequent symptoms such as bradycardia and hypotension (Sachs et al. 2016) to more severe and rare conditions including decreased left ventricular mass and systolic function, mitral valve prolapse, pericardial effusions, myocardial fibrosis, sinus node dysfunction, atrioventricular (AV) conduction delay, QT interval prolongation and increased QT dispersion, acrocyanosis, dysregulation of peripheral vasoconstriction, and even increased risk of sudden cardiac death (Friars et al. 2023).

2.1.3.6 Metabolome

Table 3 reports three metabolome studies on LEA that have so far been conducted in trained or athlete populations. Two observational studies on female and male physique athletes going through voluntary weight-loss programme for a fitness competition compared the serum metabolome before weight-loss, after weight-loss and after weight regain (Jouhki et al. 2024; Sarin et al. 2019). Jouhki et al. (2024) reported that a ~5month weight loss (~78% reduction in android fat mass and ~10.6kg reduction in body weight) led to a general shift towards a larger high-density lipoprotein (HDL) particle profile, decreased levels of inflammatory glycoprotein acetylation (GlycA) levels, decreased levels of triglycerides (TG) as well as into changes in the amount and composition of very-low-density lipoprotein (VLDL) particles. In addition, concentrations of several fatty acids were altered, along with increased ketone bodies and decreased glucose, lactate and acetate. The metabolomic changes were mostly attributed to reductions in android fat and EI. No change in LDL particle number or mean diameter was observed. Lipoprotein TG content increased rapidly back to baseline and beyond after one week of increased EA even without changes in weight or fat mass. After a 5-month weight-regain period, only particle number and composition changes of extra-extra-large VLDLs remained lower and HDL particle number higher than before the diet. As a novel change after weight-regain, particle number and cholesterol concentration in small HDL was higher than at baseline.

Similarly, Sarin et al. (2019) studied female physique athletes preparing for a fitness competition with a 21-week voluntary weight-loss programme. They reported that the weight loss (~73% reduction in visceral fat mass and ~8.1kg reduction in body weight) led to increased apolipoprotein A-1 (ApoA-1), HDL cholesterol and TG content, and a general shift towards a larger HDL profile, as well as a decrease in concentration of small HDL particles and TG content in VLDLs. Additionally, inflammatory markers high-sensitivity C-reactive protein (hs-CRP) and GlycA were reduced after weight loss. Similarly to what Jouhki et al. (2024)

reported, reduction in android fat mass was the best explanatory variable in the metabolomic changes. Interestingly and consistent with the anti-atherogenic alterations in the metabolome, aligning changes in enzymes, proteins, and expression of genes involved in the lipid and lipoprotein metabolism were also observed. However, after a 5-month weight-regain period, most of the metabolic and proteomic changes reversed back to baseline. Further, when comparing physique athletes at baseline to age- and BMI-matched female controls from the general population, physique athletes had more favourable lipid profiles and inflammation markers. Body composition explained differences in inflammatory markers but not in lipid profiles, suggesting other lifestyle factors affecting the lipid metabolism.

A randomised controlled single-blind study on 13 trained individuals was conducted by Nusser et al. (2025) looking into metabolomic changes after a short 3–5 day LEA with or without exercise. Short-term LEA of 15kcal/day/kg(FFM) led to weight-loss (-0.64 to -0.45) kg/day), increased ketone body production, decreased inflammation markers, TG, total fatty acids and VLDL particle number and size, and changed VLDL composition. They found that LEA led to similar metabolomic changes regardless of exercise. Beta-hydroxybutyrate was identified as the best individual metabolite for detecting short-term LEA independent of exercise. More specifically, the probability of LEA was ~100% with beta-hydroxybutyrate >0.09 mmol·L−1.

Table 3 Metabolic changes in short- and medium-term induced LEA studies

Article	N	Study design	Impact of LEA on metabolome
Nusser, V. et al. "Metabolic signature of short-term low energy availability." *Physiological Reports*, 2025	13	Randomised controlled trial on trained male (n=11) and female (n=2) individuals with a short term (3-5 days) exposure to LEA (EA of 15 kcal/kg(FFM)) with or without exercise	↑ beta-hydroxybutyrate, acetone ↓ triglycerides, total fatty acids, VLDL particle number and size, VLDL-TG/PL/FC/L, HDL-TG, GlycA, ala
Jouhki I. et al. "Effects of fat loss and low energy availability on the serum cardiometabolic profile of physique athletes" *Scan J Med Sci Sports*, 2024	23	Longitudinal observational study on female (n=10) and male (n=13) physique athletes going through a 20-week pre-competition diet (EA of 21 ± 6 kcal/kg(FFM)), followed by 1 week of increased energy availability and a 5-month weight regain period	↑ HDL-C/P/PL/L (general shift towards a larger HDL particle profile), ApoA-1, Omega-3(±%), DHA(%), LA, sphingomyelins, phosphatidyl-cholines, acetone, acetoacetate, 3-hydroxy-butyrate, creatinine, citrate, pyruvate, gln ↓ triglycerides, VLDL-TG/L and size, large to extra-extra-large VLDL-P/C/PL, GlycA, MUFA%, Omega-6/Omega-3, glucose, lactate, acetate, ala, his, phe, tyr
Sarin H. et al. "Substantial fat mass loss reduces low-grade inflammation and induces positive alteration in cardiometabolic factors in normal-weight individuals" *Scientific Reports*, 2019	25	Longitudinal observational study on female physique athletes going through a 21-week pre-competition diet, followed by an 18-week weight regain period	↑ HDL-C/TG, particle number and PL/C/CE content of L-HDL, Apo-A1 ↓ small HDL, VLDL-TG, GlycA, hs-CRP

LEA = low energy availability, EA = energy availability, FFM = fat free mass, HDL = high-density lipoprotein, VLDL = very-low-density lipoprotein, GlycA = glycoprotein acetylation, C = cholesterol, P = particle number, PL = phospholipids, FC = free cholesterol, L = total lipids, TG = triglycerides, ApoA-1 = apolipoprotein A-1, DHA = docosahexaenoic acid, LA = linoleic acid, MUFA = mono-unsaturated fatty acids, ala = alanine, his = histidine, phe = phenylalanine, tyr = tyrosine, gln = glutamine, hs-CRP = high-sensitivity C-reactive protein

2.1.4 Aetiology of LEA

LEA can result from either intentional restriction of EI—for example, due to DE patterns or weight-loss goals—or unintentional behaviours, such as failing to meet increased energy needs with higher training volumes (Melin et al. 2019). Different aetiologies behind LEA are illustrated in Figures 3 and 4.

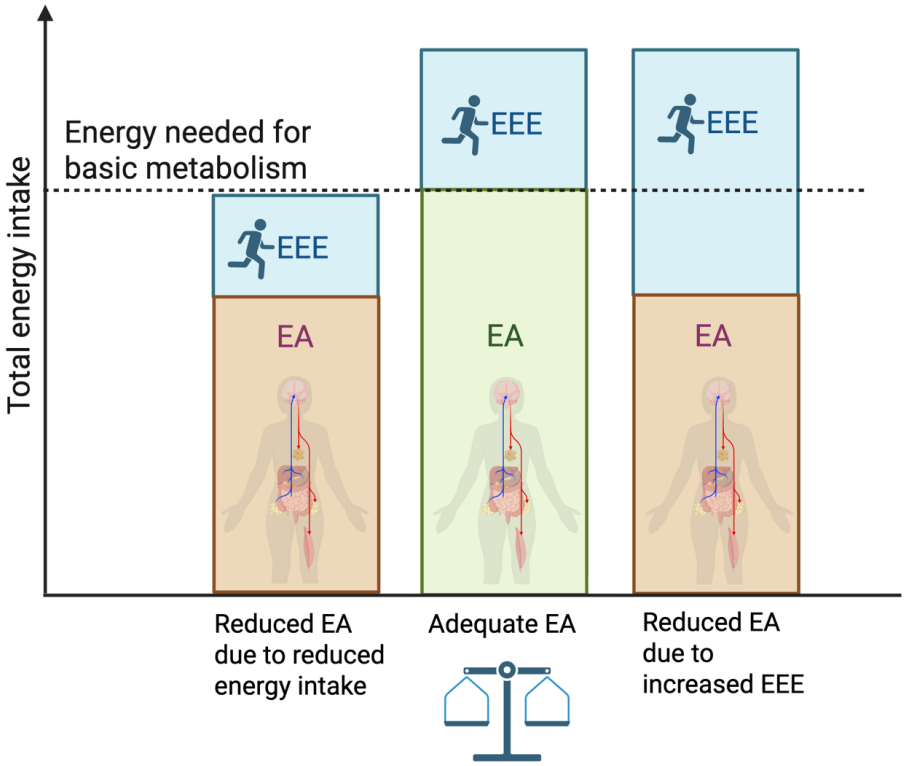


Figure 3 Illustration of potential aetiologies behind low energy availability (LEA). Y-axis represents energy intake and the heights of the bars describe the total energy intake in each scenario. The dashed line indicates the energy required to sustain basic metabolism. Blue bars represent exercise energy expenditure (EEE) which reduces the energy availability (EA) for basic metabolism. The bar to the left illustrates a situation where the energy intake is reduced leading to insufficient EA after the EEE is subtracted from the total energy intake. The bar in the middle represents a balanced situation where energy intake is sufficient to sustain both the EEE and basic metabolism. The bar to the right describes a situation where the EEE is so large that despite the high energy intake, the EA is reduced. Figure was created in the illustration website BioRender https://BioRender.com.

Large training volumes, abrupt increases in training load, lack of nutritional knowledge and lack of adequate hunger signalling can lead to LEA even without intentional food restriction or EDs (Angelidi et al. 2024; Caruso et al. 2023; Jagim et al. 2022; McCarthy et al. 2024). For example, in endurance sports, e.g., cross-

country skiing and triathlon, the daily energy expenditure can be so high that sufficient EI through regular food can be difficult (Wasserfurth et al. 2020). For adolescents, LEA is often unintentional because it can be difficult for children, adolescents and parents to understand the energy needs of a growing athlete (Armento et al. 2024). On the other hand, adolescents are more prone to restrictive eating behaviour than adults (Ward et al. 2019).

Athletes competing in weight classes go through extreme periods of rapid weight loss before competitions which lead to periods of severe LEA (Fogelholm et al. 1993; Mauricio et al. 2022). The most common reasons for intentional food restriction are, however, body dissatisfaction and the desire to modify body composition (Mancine et al. 2020). Reports indicate that female athletes face a higher risk of ED and body dissatisfaction compared to their male counterparts (J. Sundgot-Borgen and Torstveit 2004). Recent research suggests that the gender differences may be smaller than traditionally thought, as male athletes also often exhibit symptoms of atypical EDs (Lichtenstein et al. 2022; Riebl et al. 2007; McDonald et al. 2020; Vardardottir et al. 2023; J. Sundgot-Borgen et al. 2013).

EDs are more prevalent among athletes engaged in weight-sensitive sports (C. Murphy and Koehler 2020). In weight-sensitive disciplines, a lean physique is often considered beneficial, and managing nutrition might seem like an attractive way to enhance performance (J. Sundgot-Borgen et al. 2013). Unfortunately, this approach can negatively impact an athlete's relationship with food and body image, potentially leading to DE behaviour or even a clinical ED (J. Sundgot-Borgen et al. 2013). A recent meta-analysis of over 70,000 athletes world-wide concluded that the overall prevalence of self-reported ED was 19%, with a substantial heterogeneity between the studies (I^2 = 97.4%)(Ghazzawi et al. 2024). Prevalence rates differed considerably depending on geographics and the sports represented. For example among endurance athletes, prevalence rates of DE behaviour vary widely, with reports ranging from 18 to 70% (Riebl et al. 2007; J. Sundgot-Borgen and Torstveit 2004; Ravi et al. 2021; Moore et al. 2021; Viner et al. 2015; McCormack et al. 2019; Dervish et al. 2023; Karlsson et al. 2023; Fahrenholtz et al. 2022; Muia et al. 2016). No significant differences between elite athletes, trained athletes, and non-athletic control groups have been observed regarding DE behaviour (C. Sundgot-Borgen et al. 2025).

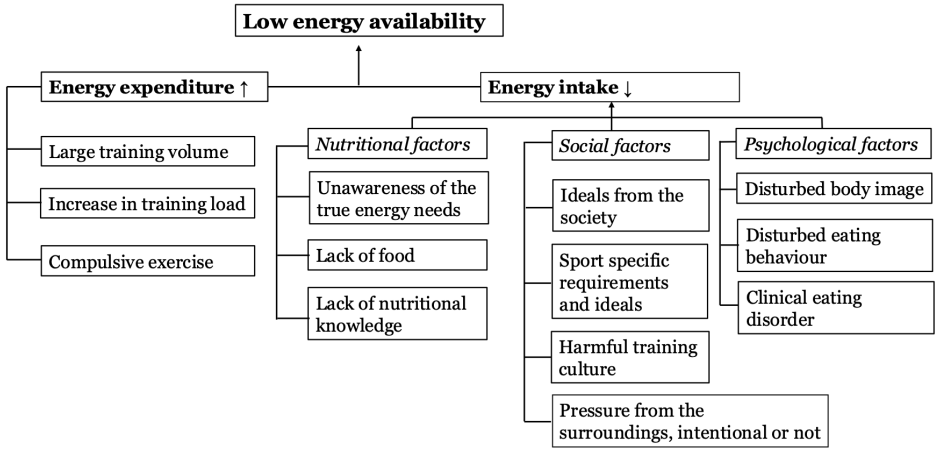


Figure 4 Different aetiologies behind low energy availability

2.1.5 Epidemiology of LEA and REDs

LEA is common in athletes and the prevalence of indicators of LEA among athletes has been estimated to range from 15 to 80%, depending on the study population, sex, and sport (Mountjoy et al. 2023). A recent meta-analysis reported that overall, 45% of athletes were at increased risk of LEA, more specifically 44% of female and 49% of male athletes (Gallant et al. 2024). However, the methods used to classify the risk of LEA and REDs vary significantly between studies, ranging from self-reported questionnaires and calculated EA based on food and training logs, to the reporting of a single symptom of REDs (Gallant et al. 2024). Many of these methods are prone to error and are only validated in specific athletic populations (Jeukendrup et al. 2024). Therefore, there is a considerable risk of overestimation of the prevalence since the heterogeneity in the meta-analysis was also large (I^2 = 91.38)(Gallant et al. 2024). However, similar risk prevalence rates have been obtained when using the golden standard REDs CAT 2 for assessing REDs risk. In a sample of more than 200 tier 3–5 athletes, the prevalence of REDs risk was reported to be 45% (more specifically 55% green, 36% yellow, 5% orange and 4% red, according to the REDs CAT 2)(Heikura et al. 2024).

Endurance athletes are particularly susceptible to problematic LEA and REDs due to their high training volumes, increased risk of DE, and the weight-sensitive nature of their sports (Gallant et al. 2024). Specifically, it has been reported that 18–80% of female endurance athletes (Melin et al. 2015; Kettunen et al. 2023; Muia et al. 2016; Fahrenholtz et al. 2022; Jesus et al. 2021; Karlsson et al. 2023; Dervish et al. 2023; Viner et al. 2015; McCormack et al. 2019) and 42–70% of male endurance athletes are considered at risk (Jesus et al. 2021; Viner et al. 2015; Lane et al. 2019; Moore et al. 2021; McCormack et al. 2019).

It is also important to remember that not only are professional athletes affected by REDs and LEA, but also recreational athletes and goal-oriented exercisers may also be at risk these conditions and their consequences on overall health (Karlsson et al. 2023; M. J. De Souza et al. 2010, 1998).

2.2 Cholesterol

2.2.1 Biological functions

Cholesterol is a biomolecule with many essential functions in the human body. Chemically, cholesterol is a 27-carbon molecule belonging to the family of sterols and consists of a steroid and alcohol groups. Cholesterol is an amphipathic molecule with unique properties since it is composed of both hydrophobic and hydrophilic sections (Sonal Sekhar et al. 2020). The chemical structure of cholesterol in shown in Figure 5.

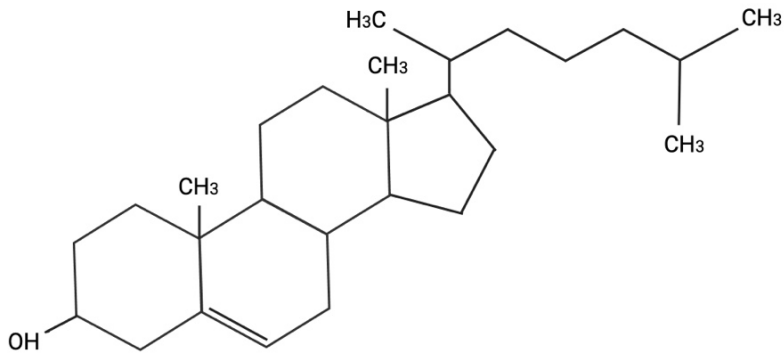


Figure 5 Chemical structure of cholesterol. Figure was created in the illustration website BioRender https://BioRender.com.

Cholesterol can be found in all cell membranes of the human body. Cholesterol increases the rigidity of the cell membrane and binds to the glycosphingolipids in the cell membrane making lipid rafts that are important in cell signalling (Sheng et al. 2012). Cholesterol also reduces the cell membrane's fluidity and thereby prevents phase transitions and increases permeability for certain ions such as sodium and hydrogen (Sonal Sekhar et al. 2020).

Oxidative cleavage of cholesterol side chains produces pregnenolone, which is the precursor of steroid hormones testosterone, progesterone, oestrogen,

glucocorticoids, and aldosterone (Guo et al. 2024). Cholesterol is also the precursor of vitamin D (Warren et al. 2021; Christakos et al. 2010). Cholesterol can be converted to bile salts (Hofmann and Hagey 2008), which together with cholesterol and phospholipids help emulsify lipids in the duodenum (Ikeda et al. 2017). Cholesterol is essential for the healthy functioning of the central nervous system, and many neurodegenerative diseases are characterised by disturbances in cholesterol turnover and balance (Sonal Sekhar et al. 2020; Guo et al. 2024). Interestingly, the brain is the most cholesterol-rich organ with a cholesterol metabolism distinct from rest of the body (Orth and Bellosta 2012). Finally, cholesterol is crucial in embryonic and foetal development and growth (Woollett and Shah 2000).

2.2.2 Lipoproteins

The major role of plasma lipoproteins is to transport water-insoluble lipids in the bloodstream to different tissues. Lipoproteins consist of a hydrophobic core of lipids (TG and cholesterol esters [CE]) and a hydrophilic membrane consisting of lipids (mainly phospholipids and free cholesterol) and apolipoproteins (Hevonoja et al. 2000; Feingold 2000). Chylomicron remnants, VLDLs, intermediate-density lipoproteins (IDL), LDLs, and lipoprotein-a (Lp(a)) are considered pro-atherogenic while HDLs are considered anti-atherogenic (Feingold 2000). Most lipoproteins originate from the liver except for chylomicrons, which are produced in the enterocytes (Feingold 2000). Lipoproteins differ in size, density, lipid composition, and apolipoprotein content, as shown in Table 4. These characteristics change dynamically through interaction with enzymes such as lipoprotein lipase (LPL), hepatic lipase (HL), lecithin–cholesterol acyltransferase (LCAT), and cholesteryl ester transfer protein (CETP), which will be covered in more detail in sections 2.2.4–2.2.6 (Hevonoja et al. 2000).

Table 4 Characteristics of major lipoproteins

	density (g/ml)	diameter (nm)	TG (%)	cholesterol (%)	CE (%)	PLs (%)	Apolipo-proteins
chylo-micron	<0.95	80–1000	90–95	1	2–4	2–6	ApoA-I, A-II, A-IV, A-V, **B-48**, C-II, C-III, E
VLDL	0.95–1.006	30–80	50–65	4–7	8–14	12–16	ApoA-I, A-V, **B-100**, C-II, C-III, E
IDL	1.006–1.019	25–30	25–40	7–11	20–35	16–24	**ApoB-100**, C-II, C-III, E
LDL	1.019–1.063	20–25	4–6	6–15	34–35	22–26	**ApoB-100**

HDL	1.063–1.210	8–30	7	5	10–20	55	**ApoA-I**, A-II, A-IV, C-II, C-III, E, M
Lp(a)	1.006–1.125	25–30	4–8	6–9	35–46	17–24	**apo(a),** B-100

Apo = apolipoprotein; CE = cholesterol ester, HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PLs = phospholipids; TG = triglyceride; VLDL = very low-density lipoprotein. Major apolipoproteins are bolded. Modified from (Sonal Sekhar et al. 2020; Mach, Baigent, Catapano, Koskinas, Casula, et al. 2020)

2.2.2.1 Chylomicrons

Chylomicrons are produced in the enterocytes, and their main function is to transport dietary TG and cholesterol to peripheral tissues and the liver (Sonal Sekhar et al. 2020). Chylomicrons are enriched in TG and comprise of multiple apolipoproteins, the most important of which is ApoB-48. As the name suggests, ApoB-48 is 48% of the size of ApoB-100 due to intestinal mRNA editing, leading to cessation of protein translation and formation of a shorter ApoB (Feingold 2000). Since chylomicron production is induced by ingestion of TGs, in healthy individuals chylomicrons are absent in a fasted state (>12h)(Julve et al. 2016; Sonal Sekhar et al. 2020). A diet rich in fat leads to the production of larger chylomicrons to account for the greater need for transportation of the ingested TG, while diets low in fat leads to smaller chylomicrons (Sonal Sekhar et al. 2020; Julve et al. 2016). In the circulation, the TG content in chylomicrons is hydrolysed for use in peripheral tissues and the chylomicrons diminish in size. These smaller and cholesterol-enriched chylomicron remnants are pro-atherogenic since they can migrate to arterial intima (Feingold 2000).

2.2.2.2 VLDL

VLDLs are rich in TG, and similar to chylomicrons. VLDLs are produced in the liver and they transport cholesterol from the liver to peripheral tissues (Guo et al. 2024). The main apolipoprotein of VLDL is ApoB-100. Like chylomicrons, the size of VLDLs can vary depending on the production rate of TG in the liver (Feingold 2000). Larger VLDL particles have been associated with the development of atherosclerosis, insulin resistance, liver fat and diabetes, whereas smaller VLDL particles are observed in metabolically healthy individuals (Lee et al. 2022; Adiels et al. 2006). In obesity, a larger TG content in VLDL has been observed (Magkos et al. 2007). As insulin resistance increases the synthesis of TG in the liver, the production of VLDL is also up-regulated in a state of insulin resistance (Smith et al. 2020). VLDLs and chylomicrons together form a group of TG-rich lipoproteins (TRL)(Chait et al. 2020).

2.2.2.3 IDL

IDLs are the product of VLDL metabolism in circulation. As the TG content of VLDLs is hydrolysed and released to muscles and adipose tissue, the lipoprotein becomes more enriched with cholesterol and diminishes in size becoming IDL, also called VLDL remnant (Feingold 2000). IDLs can contribute to the development of atherosclerotic plaque and have been associated with an increased risk of ASCVD events (Narang and Al-Horani 2026).

2.2.2.4 LDL

With the continued hydrolysis of the TG content in IDLs, the lipoprotein further enriches in cholesterol becoming LDL. LDL carries most of the cholesterol in the bloodstream. The major apolipoprotein of LDL is ApoB-100, which is a key factor in binding to the LDL receptor (LDLR)(Sonal Sekhar et al. 2020).

The causal link between LDL and ASCVD is well-established (Ference et al. 2017). However, LDL particles form a heterogenous group of lipoproteins with a spectrum of different sizes and densities. The smaller, more dense LDL particles are considered more pro-atherogenic due to several of their properties; they have a lower affinity for the LDLR, resulting in prolonged circulation time; they are more suspectable to migrating to arteria intima to bind to intra-arterial proteoglycans; and they are more prone to oxidation, which can result in increased production of foam cells (Berneis and Krauss 2002; Feingold 2000). Therefore, measurement of small dense LDL could predict the risk of ASCVD even better than traditional LDL-C measurement (Zubiran et al. 2025). In the healthy general population, LDL-C levels of ≥3mmol/l are considered abnormal and an independent risk factor for ASCVD (Mach, Baigent, Catapano, Koskinas, Casula, et al. 2020).

2.2.2.5 Lp(a)

Lp(a) is highly atherogenic with pro-inflammatory and pro-thrombotic properties and thus is a strong independent risk factor for ASCVD (Scipione et al. 2018) Lipoprotein a (Lp(a)) differs from LDL particles with an additional apo(a) connected to the ApoB-100 via a disulfide bridge (Maranhão et al. 2014). Unlike other lipoproteins that are impacted by diet and other lifestyle factors, the level of Lp(a) is mostly defined by genetics and a once-in-a-lifetime assessment is sufficient. At present, there are no pharmacological agents targeted specifically to Lp(a), but new pharmacological therapies are being widely investigated (De Los Reyes et al. 2025). In the future, the possibilities of lowering Lp(a) can have a substantial impact on cardiovascular disease prevention on the population level (Greco et al. 2025; De Los Reyes et al. 2025). Naturally, other cardiovascular risk factors in

individuals with high Lp(a) levels should be treated rigorously to minimise the total ASCVD risk (Greco et al. 2025).

2.2.2.6 HDL

HDL is the only anti-atherogenic group of lipoproteins. HDLs are responsible for reverse remnant transport and reverse cholesterol transport (RCT) from peripheral tissues back to the liver. Additionally, HDL particles have antioxidant, anti-inflammatory, anti-thrombotic, and anti-apoptotic properties, which may further contribute to their role in preventing the development of atherosclerosis. The major apolipoprotein in HDL is ApoA-1 (Feingold 2000). High-density lipoprotein cholesterol (HDL-C) levels <1.0mmol/l for males and <1.2mmol/l for females have been associated with increased cardiovascular risk (Catapano et al. 2016).

Even with the protective properties of HDL particles, higher levels are not necessarily better, and a U-shaped association between HDL-C and risk of ASCVD has been established. It has been shown that the risk of ASCVD plateaus at levels 1.6–2.1mmol/l, with no additional benefit above this range and even adverse effects above levels of ~2.3mmol/l (Mach, Baigent, Catapano, Koskinas, Casula, et al. 2020; Hussain and McNeil 2026). Recently, it has been proposed that not only the particle number but rather the size, composition and efflux capacity of HDL reflect the cardioprotective properties (Hussain and McNeil 2026). An inverse relationship between HDL size and cardiovascular disease has been established (Kontush 2015), and HDL size has been inversely associated with other cardiovascular risk factors such as BMI, waist:hip ratio and TG levels (Razavi et al. 2012). The larger HDL size reflects the lipolytic activity of TG by LPL since the smaller HDL3 acquires TRLs' surface material and increases in size, becoming larger HDL2 particles (Kontush 2020). The smaller HDL3s have been shown to have better cholesterol efflux capacity, which could explains their affinity to acquire remnant particles and become larger HDL2s (Wieczorek et al. 2021).

2.2.3 Cholesterol measurements

There are several methods to measure cholesterol levels in humans. The major categories are classical chemical methods based on the Abell–Kendall protocol, ultracentrifugation, fluorometric and colorimetric enzymatic assays and analytical instrumental approaches like gas and liquid chromatography or mass spectrometry (L.-H. Li et al. 2019; Nauck et al. 2002). The methods all require adequate sample preparation for analysis, including a saponification extraction step of total lipids and a multistage solvent extraction followed by purification and concentration. Traditionally, lipid measurements are recommended to be conducted in a fasted

state, but differences in fasting vs non-fasting lipid results seem small for most lipid parameters (Mach, Baigent, Catapano, Koskinas, Casula, et al. 2020).

The classical modified Abell–Kendall protocol is one of the two reference measurement procedures for blood cholesterol quantification by the National Institute of Standards and Technology (USA)(Abel et al. 1952; L.-H. Li et al. 2019). This multi-step classical chemical method involving saponification of CEs by hydroxide, extraction with hexane, and colour development with acetic anhydride–sulfuric acid (Abel et al. 1952) is no longer approved for routine tests due to the highly corrosive reagents used in the reaction (L.-H. Li et al. 2019).

Ultracentrifugation is used to separate lipoproteins with different densities. The plasma sample is first processed with salts such as NaBr and KBr and then centrifuged at density 1.006kg/L for at least 18 h at 105,000*g* to float VLDLs and chylomicrons. These TG-rich particles are tube-sliced or aspirated with a syringe or a pipette. Additional steps can be taken to further separate LDL-C, or LDL-C content can be mathematically calculated after measuring HDL-C with heparin-Mn^{2+}. This ultracentrifugation process is time-consuming and labile due to salt concentrations and centrifugal forces. In addition, the reproducibility of this procedure is highly dependent on the skills of the laboratory technician (Nauck et al. 2002).

Enzymatic assays for cholesterol measurements are currently widely used in automated analysers. First, CEs are esterified to free cholesterol using cholesterol esterase and then further oxidised to cholest-4-en-3-one by cholesterol oxidase. This reaction produces hydrogen peroxide which can be detected by colorimetric or fluorometric probes (Amundson and Zhou 1999; L.-H. Li et al. 2019).

Gas and liquid chromatography and mass spectrometry are more reliable, sensitive and accurate methods for measuring cholesterol levels. In addition, smaller volumes are required for the analysis. However, these methods require a more extensive sample preparation before analysis (L.-H. Li et al. 2019).

In addition to mass spectrometry, nuclear magnetic resonance (NMR) spectrometry not only detects clinical cholesterol levels but can be used for inspecting the whole serum metabolome including lipoproteins and their composition, lipids, fatty acid compositions, amino acids, and other low-molecular weight metabolites such as ketone bodies. NMR spectroscopy offers a robust, reproducible, unbiased, and quantitative method for metabolome profiling. NMR requires little sample preparation and reduced data processing. NMR is also suitable for measurements of large cohorts, multi-sites, longitudinal measures and clinical use (Letertre et al. 2021).

In addition, LDL-C can be, and often is, calculated using other components of the lipid panel to reduce the cost and turnaround time of the analysis (Islam et al. 2022). There are several calculation methods and the most commonly used formula is the Friedewald formula, which estimates LDL-C from measured TG, HDL-C and

TC: *LDL-C = TC − HDL-C − (TG/2.2) (in mmol/L)*(Islam et al. 2022). Even if the calculated LDL-C and measured LDL-C have a strong correlation on the population level, the Friedewald formula is prone to error at very low and high levels of TG and LDL-C, and this equation cannot be used if TG levels are >4.5mmol/l (Mach, Baigent, Catapano, Koskinas, Casula, et al. 2020).

The European Society of Cardiology (ESC) guidelines advise measuring LDL-C and TC levels for assessment of cardiovascular risk in clinical settings. In patients with diabetes, very high levels of TG, or with very low LDL-C, measurements of ApoB-containing particles and non-HDL-C are recommended to better reflect the true cardiovascular risk (Mach, Baigent, Catapano, Koskinas, Casula, et al. 2020).

2.2.4 Endogenous pathway

The endogenous cholesterol pathway describes *de novo* cholesterol production. Cholesterol can be synthesised in sufficient amounts in the body to meet its physiological needs. Most cells are capable of synthesising cholesterol, but the main site of production are hepatocytes (Afonso et al. 2018). Endogenous production of cholesterol is approximately 600–900mg/day, with a ratio between endogenous and exogenous pathways of 7:3 (L. Zhang et al. 2024).

Cholesterol is synthesised from acetyl coenzyme A (CoA) in a complicated and highly regulated process. The first step in the process is to form mevalonate from acetyl CoA by the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This is the rate-limiting step where cholesterol-lowering drugs, statins, also act by downregulating the enzymatic activity and thereby inhibiting the *de novo* production of cholesterol. Mevalonate is then converted into squalene and further transformed into lanosterol. The biosynthesis is then divided into two pathways: the Bloch and Kandutsch–Russell pathways, which both eventually produce cholesterol (Guo et al. 2024). The produced cholesterol is then either used by the cell or packed into lipoproteins for transportation into other tissues.

Cholesterol synthesis is a highly regulated process due to its energy-consuming nature (Guo et al. 2024). When intestinal cholesterol absorption is enhanced, cholesterol concentrations in the liver also increase. This leads to reduced cholesterol *de novo* synthesis, reduced absorption of cholesterol in the gut, increased hepatobiliary excretion of cholesterol into bile and reduced expression of LDLR on the cell membrane to prevent the accumulation of excess cholesterol in the cell (Sonal Sekhar et al. 2020; Antoni 2023). Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates the degradation of LDLR in the liver in response to the intracellular cholesterol concentrations and the inhibition of PCSK9 has been shown to be effective in the reduction of LDL-C levels (Page, and Watts 2016).

Both diet-derived and *de novo* synthesised cholesterol are carried from the liver to other tissues in VLDLs. As the VLDL exits the liver, a similar exchange of proteins with HDL occurs as with chylomicrons; the VLDL receives ApoE and ApoC-II. ApoC-II binds to the LPL and hydrolysis of TGs yields glycerol and free fatty acids for muscle and adipose tissue. As the TG content of the VLDL diminishes, ApoC-II is donated back to HDL and a VLDL remnant or IDL is formed (Chait et al. 2020).

The main protein components of IDL are ApoE and ApoB-100. ApoE can bind to LDLR and LRP in either the liver or in other tissues such as the adrenal cortex. In the adrenal cortex, cholesterol can be used for the synthesis of hormones aldosterone, cortisol or dehydroepiandrosterone (DHEA), or stored as CEs. IDL can undergo a lipolytic process in the sinusoidal surface of hepatocytes where the HL further hydrolyses the TG content (Feingold 2000). Due to the diminishing amount of TG content, the lipoprotein becomes progressively denser. Finally, the dense IDL donates ApoE back to HDL and becomes LDL. Approximately 25–75% of the formed IDLs are ultimately converted into LDLs (Chait et al. 2020), depending largely on the number of LDLR on the hepatocyte surface (Narang and Al-Horani 2026). The circulating LDL can either be taken into peripheral tissues, such as gonads and adrenal cortex for hormone production, or back to the liver via LDLRs for storage, use, or secretion (Sonal Sekhar et al. 2020).

2.2.5 Exogenous pathway

The exogenous cholesterol pathway describes the ingestion, absorption and transport of dietary cholesterol. In contrast to fatty acids that are mostly delivered by dietary intake, most of intestinal cholesterol is derived from bile (800–1200mg) rather than from diet (200–500mg)(Feingold 2000). Sources of dietary cholesterol are of animal origin since a plant-based diet contains plant-sterols that are poorly absorbed in the gut (Mu and Høy 2004; Feingold 2000). The current recommendation for dietary cholesterol is <300mg/day (Carson et al. 2020).

Ingested dietary lipids, including cholesterol, are absorbed into enterocytes in the duodenum with the help of bile and intestinal lipases (Okonkwo et al. 2026). In the enterocytes, the ingested hydrophobic lipids are coupled with a protein, ApoB-48, to enable transportation in the circulation (Mu and Høy 2004). This newly formed phospholipid-surrounded chylomicron consists of TG (majority), cholesterol and CEs. The chylomicron is taken into the lymphatic lacteal that will run to the thoracic duct and lead the lymph to the bloodstream (Mu and Høy 2004).

In the bloodstream, chylomicrons exchange proteins with HDL. A chylomicron receives ApoE and ApoC-II, the latter of which is crucial for activating the LPL on adipocytes and muscle cells for the hydrolysis of TGs into glycerol and free fatty acids. Free fatty acids are taken into muscle cells where they can be used for energy production. In adipocytes, free fatty acids are re-esterified with glycerol for energy

storage. After diminishing in TG content, the chylomicron returns ApoC-II back to HDL, which hinders further LPL-hydrolysis (Feingold 2000). Now, this so-called chylomicron remnant can bind to LDLR and LDLR-related protein (LRP) with ApoE and be taken into the liver (Mu and Høy 2004; Chait et al. 2020).

In the liver, the content of chylomicrons is used for different purposes. The proteins are broken down into amino acids, and the TGs can be stored. The cholesterol can be used for bile salts, incorporated into cell membranes or repacked with TGs into a VLDL (Sonal Sekhar et al. 2020).

2.2.6 Reverse cholesterol transport (RCT)

Since most cells are incapable of catabolising cholesterol, RCT is required to eliminate excess cholesterol. HDL is the main player in the RCT, where cholesterol is transported from other tissues back to the liver. RCT, endogenous and exogenous pathways are illustrated in Figure 6.

The main protein component of HDL, ApoA-1, is produced in the enterocytes and hepatocytes (Feingold 2000). Phospholipids and cholesterol from diminishing chylomicrons and VLDLs or from other cells by the ATP-binding cassette A1 (ABCA1) are attached to the ApoA-1 and pre-β HDL is formed (Alcover et al. 2025). LCAT is a critical enzyme in converting cholesterol on the surface of HDL to CEs stored in the core, allowing for more cholesterol to be taken into the HDL (Feingold 2000).

High cholesterol levels in the cell increase transcription of ABCD1 and ABCG1 receptors on the surface of cells, which enables the efflux of cholesterol from the cell into the HDL. As the pre-β HDL takes up cholesterol and increases in size, it first becomes HDL3 and then HDL2. This mature HDL2 can bind to the scavenger receptor class B type 1 (SR-B1) on other cells, by which cholesterol can be exchanged in a bidirectional way (Linton et al. 2000; Feingold 2000). The HDL molecule can take cholesterol back to the liver by SR-B1 (Feingold 2000).

HDLs can also exchange cholesterol to TGs with VLDLs, IDLs, and LDLs via the CETP, by which cholesterol can be taken up in the liver via LDLRs (Linton et al. 2000). Increased activation of CETP is associated with reduced levels of HDL (Sonal Sekhar et al. 2020) as well as production of small dense LDL particles (Narang and Al-Horani 2026; Vekic et al. 2022), and therefore might reflect increased ASCVD progression.

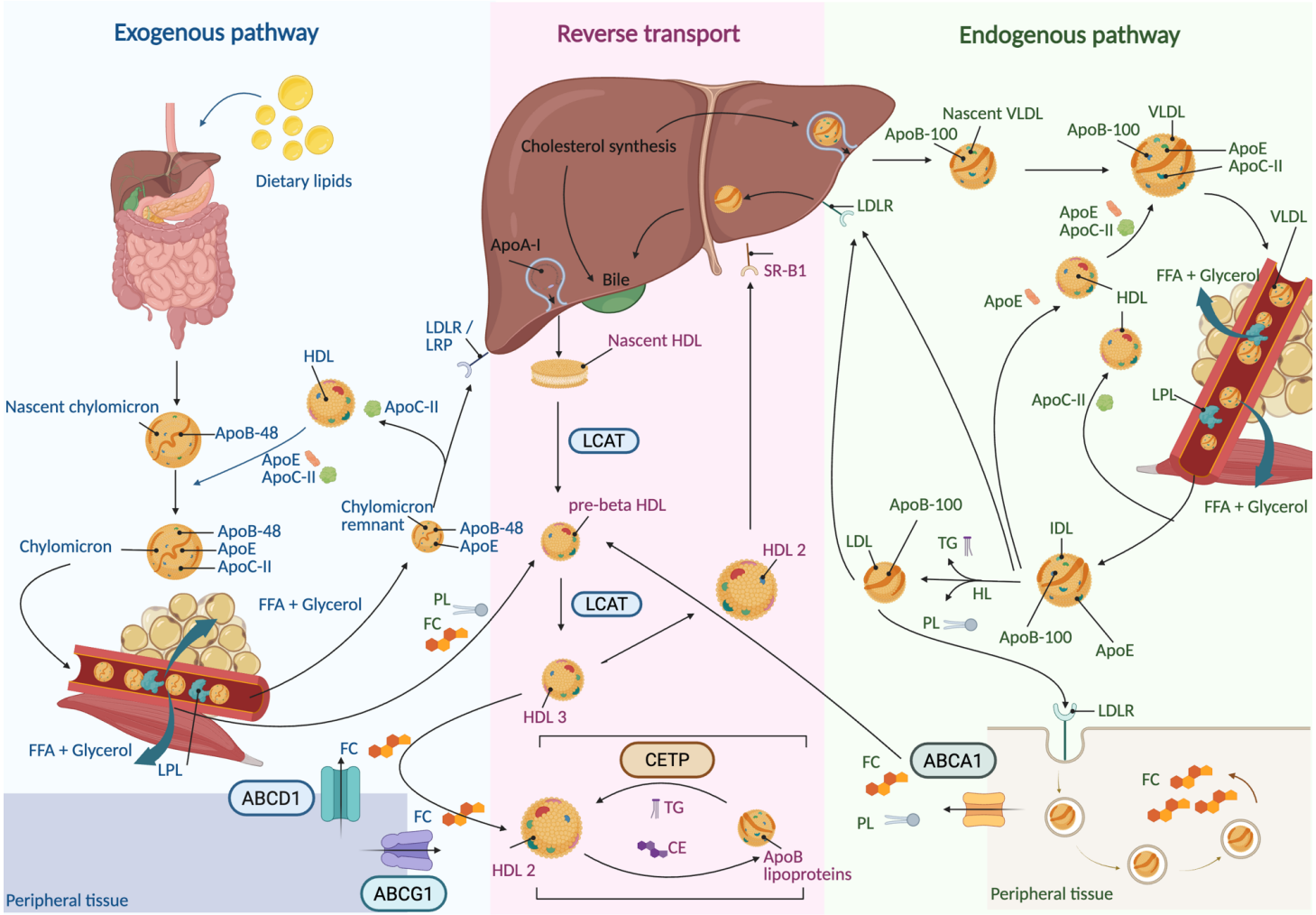

Exogenous pathway
Reverse transport
Endogenous pathway
Dietary lipids
Cholesterol synthesis
ApoA-I
Bile
SR-B1
LDLR
Nascent VLDL
ApoB-100
VLDL
ApoE
ApoC-II
LDLR / LRP
Nascent HDL
HDL
ApoC-II
Nascent chylomicron
ApoB-48
ApoE
ApoC-II
LCAT
pre-beta HDL
Chylomicron
ApoB-48
ApoE
ApoC-II
Chylomicron remnant
ApoB-48
ApoE
FFA + Glycerol
PL
FC
HDL 2
HDL 3
LCAT
CETP
TG
CE
ApoB lipoproteins
FFA + Glycerol
LPL
ABCD1
FC
ABCG1
Peripheral tissue
LDL
ApoB-100
TG
HL
IDL
PL
ApoB-100
ApoE
LDLR
FC
ABCA1
PL
FC
Peripheral tissue

Figure 6 Overview of the cholesterol metabolism. The exogenous pathway starts in the duodenum where the absorbed lipids and cholesterol are packed into TG-rich chylomicrons. In the circulation, chylomicrons receive ApoE and ApoC-II from HDL. ApoC-II is crucial for the activation of LPL, which results in the hydrolysis of TG into FFA and glycerol for energy production in muscle cells or storage in adipocytes. As chylomicron loses its ApoC-II back to HDL, hydrolysis is hindered and this smaller and cholesterol enriched chylomicron remnant is taken into the liver via LDLR or LRP with ApoE. In the liver the cholesterol from chylomicron remnants or *de novo* synthesis can be used, excreted to bile or repacked into VLDLs where the endogenous pathway begins. Like chylomicrons, VLDLs receive ApoE and ApoC-II from HDL, and LPL hydrolyses the TG content in VLDLs making it smaller and more enriched in cholesterol. As this smaller VLDL loses ApoC-II to HDL, it becomes IDL, which can either be taken up into the liver or further hydrolysed by HL to become LDL. Now, this ApoB-100-containing LDL particle can transport the cholesterol into peripheral tissues or back to the liver. The reverse cholesterol pathway describes the transport of cholesterol from peripheral tissues back to the liver. ApoA-1 is formed and released from the liver (or intestine) and as PL and cholesterol attach to it, it becomes a nascent HDL. LCAT facilitates the esterification of surface cholesterol into the core, making room for more cholesterol to bind. PL and FC from diminishing chylomicrons and VLDLs are also attached to the HDL, and it becomes pre-β HDL. Now, this HDL molecule can bind to ABCA1 receptors in peripheral tissues and receive both PL and FC. The HDL grows and becomes HDL3 and can further bind to ABCD1 and ABCG1 to receive more cholesterol from peripheral tissues, becoming larger HDL2. HDL2 can either be taken back to the liver via SR-B1 or it can exchange cholesterol to TG with ApoB-containing lipoproteins, which take the cholesterol back to the liver via LDLR or LRP. ABCA1 = ATP-binding cassette A1, ABCD1 = ATP-binding cassette D1, ABCG1 = ATP-binding cassette G1, ApoA1 = apolipoprotein A-1, ApoB-48 = apolipoprotein B-48, ApoB-100 = apolipoprotein B-100, ApoC-II = apolipoprotein C-II, ApoE = apolipoprotein E, CETP = cholesterol ester transfer protein, FC = free cholesterol, FFA = free fatty acids, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin-cholesterol acyltransferase, LDL = low-density lipoprotein, LDLR = LDL receptor, LPL = lipoprotein lipase, LRP = LDLR-related protein, PL = phospholipid, SR-B1 = scavenger receptor B1, VLDL = very-low-density lipoprotein. Figure is modified from (Alcover et al. 2025) and created in the illustration website BioRender https://BioRender.com.

2.2.7 Genetic pathways in cholesterol metabolism

Several genetic variations in cholesterol metabolism have been identified to explain genetic variation in cholesterol levels and turnover (Wong et al. 2022; Willer et al. 2013). Among most patients with dyslipidaemia, even with a pattern of inheritance, elevated cholesterol levels are not caused by one gene (monogenic) but rather a combination of different genes (polygenic) and lifestyle factors (Willer et al. 2013; Mach, Baigent, Catapano, Koskinas, Patel, et al. 2020).

Even though most interindividual variation of cholesterol metabolism is multifactorial, several monogenic cholesterol diseases have been identified (Mach, Baigent, Catapano, Koskinas, Patel, et al. 2020). The most common heritable dyslipidaemia is familial hypercholesterolaemia (FH) that is predominantly caused by autosomal dominant variants of *LDLR*, *APOB*, or *PCSK9* genes that interfere with normal LDL uptake (Leren and Bogsrud 2021). FH leads to elevated levels of LDL-C (4–12mmol/l in FH heterozygotes and >12mmol/l in FH homozygotes) and predisposes patients to premature ASCVD unless treated. The worldwide prevalence of heterozygotic FH has been estimated to be 1:300 in the general

population (Hu et al. 2020; Beheshti et al. 2020). Finland, however, has a very isolated population with 7 founder variants of the *LDLR* gene, accounting for up to 90% of FH cases (Vuorio et al. 2001). The prevalence of FH in Finland is 1:600 (Lahtinen et al. 2015) but the prevalence of LDLR mutations is up to 1:16 in patients with premature coronary artery disease (Jokiniitty et al. 2024).

2.2.8 Hormonal regulation of cholesterol metabolism

Since cholesterol is a vital molecule in the body with a highly regulated and complex metabolism, several endocrine axes affect it. In this section, I will describe the basics of the hormonal regulation of cholesterol metabolism, focusing on those hormones that are also stated to be affected in REDs.

2.2.8.1 Sex hormones

The incidence of coronary heart disease in females is delayed by 10 years compared to males, and the incidence of myocardial infarction and sudden death by 20 years (Hodis and Mack 2022). Substantial differences in lipid profiles exist between females and males, at least partly explaining the differences in risk and incidence of ASCVD between the sexes. Premenopausal females have higher HDL-C, and lower VLDL-C, LDL-C and TG than age-matched males (Magkos and Mittendorfer 2009; Cohn et al. 1988). However, the lipid profile drastically changes in menopause and postmenopausal females have been reported to have a more pro-atherogenic lipid profile than premenopausal females (Matthan et al. 2005). Oestrogen is thought to be at least partly responsible for these changes in lipid profiles and incidence of ASCVD between the sexes and throughout the female lifespan.

In addition to menopause, changes in cholesterol levels may occur during a single menstrual cycle. LDL-C was reported to be highest during the follicular phase and lowest during the luteal phase (a change of 5%) and HDL-C highest at ovulation (a change of 2%)(Mumford et al. 2010). However, in a study, no changes in TG or ApoB-100 kinetics in VLDL during the menstrual cycle were observed (Magkos et al. 2006). Combined (oestrogen + progesterone) oral contraception (COC) users have been reported to have significantly greater increases in levels of TC, TG, VLDL-C and HDL-C than non-hormonal-contraceptive users after a 3-year follow-up (Berenson et al. 2009; Dilshad et al. 2016). Progesterone-only injectable contraception seems to mainly affect HDL-C, but contradicting results have been observed (Berenson et al. 2009; Dilshad et al. 2016). In adolescents, oral contraception (OC) users with varying hormone combinations of oestrogen and progesterone had higher LDL-C, TC and TG levels than non-OC-users (Staudt et al. 2024).

Oestrogen is a cholesterol-derived steroid hormone and considered the main female reproductive hormone. The main form of oestrogen is oestradiol (E2), which is produced in the ovaries of fertile women, although smaller amounts of E2 are also produced in other tissues (Iorga et al. 2017). Oestrogen has many protective properties in the cardiovascular systems since it modulates vascular function, the inflammatory response, metabolism, insulin sensitivity, cardiac myocyte and stem cell survival, and the development of hypertrophy (Iorga et al. 2017).

Oestrogen protects the blood vessels from atherosclerotic lesion formation, and is associated with lower LDL-C and Lp(a) levels, and higher HDL-C and ApoA-1 levels (Meyer et al. 2006; Robinson et al. 2021). In vitro studies on human hepatoma cells and in vivo studies in rats have shown that oestrogen increases LDLR expression in the liver, leading to lower levels of circulating LDL-C (Palmisano et al. 2017). Oestrogen can increase nitric oxide (NO) signalling in target tissues by increasing the level of endothelial NO synthase (eNOS) and increase the activity of eNOS via phosphorylation, leading to vasodilation and reduced inflammation (E. Murphy 2011; Meyer et al. 2006). Oestrogen is important for maintaining and repairing the endothelium, and can lead to more favourable remodelling of the myocardium to reduce hypertrophy of the cardiac muscle (E. Murphy 2011). Finally, oestrogen contributes to fat accumulation in subcutaneous rather than visceral regions, contributing to enhanced TG metabolism and reduced risk of ASCVD (Canoy et al. 2007; Fried et al. 2015; Palmisano et al. 2018).

Oestrogen mediates the aforementioned effects on the cardiovascular system and other organs by activation of oestrogen receptors (ERα and ERβ), which can alter gene transcription in the nucleus or acutely activate kinase signalling in the cytosol (E. Murphy 2011). Oestrogen can also act via G-protein-coupled ER (GPER/GPR30)(Iorga et al. 2017). The liver is likely the main site of cholesterol metabolism to be impacted by oestrogen (Palmisano et al. 2018). Over 1000 human liver genes have been identified to display significant sex differences, with the most impacted pathways being lipid metabolism and genes related to ASCVD (Yijing Zhang et al. 2011). Oestrogen promotes the uptake capacity of cholesterol into the liver and promotes cholesterol secretion into bile via ERα in mice (Palmisano et al. 2017; H. H. Wang et al. 2004). It has also been suggested that oestrogen plays a key role in the efflux capacity of HDL in RCT, but studies on humans have not found consistent evidence to support this (Palmisano et al. 2018). Men also express these positive effects of oestrogen in their cardiovascular health when aromatase cleaves testosterone into oestrogen (Meyer et al. 2006).

Another female sex hormone is progesterone (P4), which is crucial for gestation and is also the precursor of all other endogenous steroid hormones (Jeong et al. 2024). In menopause hormone therapy (MHT) or contraceptive use, progesterone alone reduces TG levels and in combination with oestrogen counteracts oestrogen's rising effect on TG levels (Magkos and Mittendorfer 2009). In rats, progesterone

increases hepatic lipid content and lipid levels, primarily to ensure sufficient cholesterol supply to the foetus for development and growth (Jeong et al. 2024).

Testosterone is the major male sex hormone, dictating male sexual and physiological development and maintaining sexual function through life after puberty. Testosterone is also a cholesterol-derived steroid hormone that can alter cell metabolism through effects on gene transcription via the androgen receptor (AR) or through non-genomic signalling mechanisms similar to those of oestrogen (Palmisano et al. 2018). Although the mechanism is still unclear, AR signalling appears to influence insulin sensitivity, glucose metabolism, obesity and muscle mass, contributing to a favourable lipid profile and good cardiovascular health (Palmisano et al. 2018; Kelly and Jones 2013). In rats, the absence of testosterone upregulates PCSK9 in hepatocytes, which leads to the degradation of LDLR, resulting in an increase in LDL particles in the circulation (Yuefeng et al. 2022). However, in young cis-men and trans-men, testosterone has been associated with an increase in typically atherogenic VLDL subsets and the ApoB:ApoA1 ratio (Robinson et al. 2021). In females, hyperandrogenism (e.g., in PMOS) is associated with dyslipidaemia (Teede et al. 2026).

2.2.8.2 Thyroid hormones

Thyroid hormones (T4 and T3) play a key role in cholesterol metabolism, leading to decreased levels of ApoB-containing lipoproteins. Thyroid hormones affect the hepatic synthesis of cholesterol, decrease the expression of ApoB-100 and increase the expression of ApoA-1, decrease the export of cholesterol in VLDLs, increase RCT from peripheral tissues, increase reuptake into the liver via LDLR and LRP, and increase excretion into the intestine as bile acids (D. Zhang et al. 2022; Ness 1991).

2.2.8.3 Hormones related to energy metabolism

Insulin is produced in the fed state characterised by high levels of sugar and acetyl CoA. Insulin promotes cholesterol synthesis by e.g., increasing the activity of HMG-CoA-reductase (D. Zhang et al. 2022). Insulin also increases the activity of LPL, leading to the enhanced hydrolysis of TG in TRLs (Feingold 2000). Glucagon, on the other hand, is produced during fasting, when there is deprivation of sugar and acetyl CoA. As opposed to insulin, glucagon, similarly to cortisol, inhibits the activity of HMG-CoA-reductase, leading to a decreased rate of cholesterol production. Glucagon also reduces de novo fatty acid synthesis and thereby reduces VLDL release. Glucagon reduces a critical enzyme (acetyl CoA carboxylase) in the malonyl-CoA synthesis, which enhances free fatty acids release into the mitochondria for the beta-oxidation rather than into the blood in VLDLs (D. Zhang et al. 2022).

Leptin has been shown to increase LPL activity, and upregulate SR-B1 in mice (Lundåsen et al. 2003; Koh et al. 2008). An inverse relationship between leptin levels and HDL/ApoA-1 levels has been identified (Rainwater et al. 1997). In addition, leptin can increase the accumulation of CE in foam cells under hyperglycaemia, but under normoglycaemia, leptin can protect macrophages from excess cholesterol (Koh et al. 2008). However, it seems that leptin mostly influences the cholesterol levels by regulating food intake (Prieur et al. 2008).

GH stimulates hepatic LDLR and thereby reduces the circulating LDL-C (Lind et al. 2004). In aging individuals with decreasing GH levels, clearance of LDL-C is reduced and plasma levels of LDL-C are increased.(Lind et al. 2004) In patients with anorexia nervosa, elevated levels of GH have been suggested to have IGF-1-independent effects on lipolysis, leading to increased levels of LDL-C (Schorr and Miller 2017; Misra et al. 2006).

2.2.9 Cholesterol and pathophysiology of ASCVD

Although cholesterol is essential for human physiology, pathological accumulation of cholesterol in blood vessel walls is the leading cause of ASCVD. Atherosclerosis is characterised by the accumulation of lipids, fibrous elements, inflammatory cells, and calcification in the intima of arteries, a complex process influenced by blood flow, endothelial dysfunction, circulating levels of LDL, and inflammation (Jebari-Benslaiman et al. 2022). LDL can migrate into the subendothelial space of the arteries when LDL is circulating in the blood stream in excess and the endothelium of arteries is malfunctioning (Mundi et al. 2018). Prolonged circulation time, as well as small-dense size, increases the risk of endothelial migration (Zubiran et al. 2025). The accumulation of LDL in the intima increases the production of modified LDL through the oxidation process under the influence of reactive oxygen species which yields oxidised LDL (oxLDL). The oxidation process and accumulation of these modified LDL particles cause an inflammatory process in the subendothelial space that attracts monocytes that phagocytose oxLDL particles and turn into macrophages. As oxLDLs accumulate in the macrophage, the cell turns into a foam cell (Hermida and Balligand 2014). Foam cells can lead to smooth muscle cell migration and eventually to the formation of an atherosclerotic plaque (Linton et al. 2000).

2.3 Interplay between LEA and cholesterol metabolism

2.3.1 Hormonal disturbances and cholesterol metabolism

As described in the earlier sections, several hormonal axes can be influenced by problematic LEA and many of these hormones also influence cholesterol metabolism. Since disturbances in different hormonal systems could explain the altered lipid profiles, in this section, I will explain the current knowledge on the topic.

Menopause is characterised by a dramatic change in the hormonal milieu, leading to e.g., low levels of oestrogen, possibly contributing to changes in the serum lipid profile. Postmenopausal women have been reported to have higher levels of LDL-C, TC, TRL-C and TGs than premenopausal women (Matthews et al. 2009; Karvinen et al. 2019; Matthan et al. 2005; Hyvärinen et al. 2022) which was reported to be due to lower catabolic rates of ApoB-100- and ApoB-48-containing particles with no change in rate of production (Matthan et al. 2005). The role of the anti-atherogenic HDL-C during menopause is more controversial. Reports have suggested a decline (Jensen et al. 1990; Do et al. 2000), increase (El Khoudary, Chen, et al. 2021; Karvinen et al. 2019; Hyvärinen et al. 2022) and no change (Matthan et al. 2005; Matthews et al. 2009) in HDL-C, and the anti-atherogenic properties of HDL are also reported to be reduced (El Khoudary, Chen, et al. 2021). Studies on the serum metabolome in menopausal women have similarly reported pro-atherogenic changes in the lipoproteins and other metabolites (Q. Wang et al. 2018; Karppinen et al. 2022; Auro et al. 2014). Overall, 3–11% of the changes seen in the menopause-associated metabolites were explained by hormonal changes alone (Karppinen et al. 2022).

The timing of menopause has been suggested to influence the risk of ASCVD, but a bidirectional association between menopause and ASCVD has also been proposed. The Framingham Heart Study showed that higher TC and other cardiovascular risk factors before menopause were associated with earlier menopause (Kok et al. 2006). To support this, a pooled analysis of over 170,000 women from 9 studies showed that a first event of cardiovascular disease before the age of 35 years was associated with a doubling of the risk of an early menopause, whereas a first event occurring after the age of 35 was associated with a normal menopause at the age of 51 years (Zhu et al. 2019). It is thus possible that worse cardiovascular health before menopause could influence the onset of natural menopause.

The use of MHT seems like an attractive way to promote the cardiovascular health of postmenopausal women and has been a field of increasing interest in the past decades. Interestingly, contradicting findings have been observed in both lipid parameters and risk of future ASCVD. MHT constituting only oestrogen, has been

shown to lower LDL-C and elevate HDL-C levels, supporting the hormonal effect of lipid alteration during menopause instead of changes in body composition (Godsland 2001). However, the mode of administration plays a key role on the effects on lipids (Nie et al. 2022; Cho et al. 2023), and women with dyslipidaemia are advised to use transdermal MHT (Cho et al. 2023). Oral oestradiol alone has been shown to increase VLDL-TG levels compared to no effect with transdermal oestradiol (Walsh et al. 1991), and combining progesterone with MHT blunts this effect of increased TG levels (Magkos and Mittendorfer 2009). In addition to the mode of administration and combination of hormones, the timing of the MHT seems crucial since initiating MHT early after menopause seems to decrease the risk of ASCVD, whereas late onset of MHT has been shown to increase the risk (Manson et al. 2003; Hodis et al. 2016).

FHA is characterised by low levels of oestrogen, FSH, and LH (Roberts et al. 2020). A recent meta-analysis of 18 observational studies concluded that physically active females with secondary amenorrhoea had higher LDL-C, TC, HDL-C and TG compared to eumenorrheic females (Tegg et al. 2024). However, due to the nature of the studies, the certainty of the evidence was rated as very low. Similarly to the changes observed in menopause, higher levels of LDL-C and total TC have been reported among amenorrhoeic athletes compared to eumenorrheic athletes (Rickenlund et al. 2005). However, higher levels of HDL-C have also been observed among amenorrhoeic athletes compared to eumenorrheic athletes (O'Donnell and De Souza 2004), as well as in female endurance athletes compared to sedentary women regardless of the menstrual status (Kyte et al. 2022). In the Nurses' Health Study, a retrospective cohort study on over 700,000 women, premenopausal menstrual dysfunction was associated with a higher risk for future cardiovascular disease (Okoth et al. 2023). Additionally, the Women Ischemia Syndrome Evaluation (WISE) study showed that premenopausal women with hypoestrogenism of hypothalamic origin had an increased risk of coronary artery disease assessed by angiography (Bairey Merz et al. 2003). In young women, bilateral oophorectomy (removal of both ovaries) resulted in hypoestrogenism, increased levels of TC and LDL-C but no change in HDL-C (Suda et al. 1998), and increased the risk of several diseases, including coronary artery disease (Parker et al. 2009).

Hypoandrogenaemia (i.e. low levels of testosterone) in males is associated with low levels of HDL-C and elevated levels of LDL-C and TG (Wu and von Eckardstein 2003). However, the other extreme of the spectrum can also have deleterious effects on the lipid profile as the use of anabolic steroids (i.e. synthetic derivates of testosterone, often in doses several orders of magnitude higher than approved testosterone therapy prescribed in clinical settings) has been associated with low levels of HDL-C and elevated levels of LDL-C, as well as severe events of cardiac disease (Glazer 1991; Sullivan et al. 1998).

Several studies have shown decreased levels of T3 in LEA. In clinical thyroid disease, changes in cholesterol levels are also observed. In hypothyroidism, where both thyroid hormones T3 and T4 are clinically low (i.e., below the reference range), increased levels of LDL-C are observed, whereas in hyperthyroidism, with usually substantially elevated T3 and T4, decreased levels of LDL-C are seen (Duntas 2002). Hypothyroidism is associated with an increased risk of ASCVD (J. Li et al. 2024). Additionally, subclinical hypothyroidism, with normal levels of thyroid hormones and elevated levels of TSH, has been associated with elevated LDL-C and TC levels, with more pronounced effects with higher TSH (Ineck and Ng 2003). Overall, a positive relationship was found between LDL-C and TSH and a negative between LDL-C and thyroid hormones (Ineck and Ng 2003).

2.3.2 Disordered eating and cholesterol metabolism

Restrictive EDs, such as anorexia nervosa, are an extreme form of problematic LEA and even a form of starvation. As stated earlier, ED or DE can be an underlying cause for LEA.

ED and DE have been earlier associated with disturbances in cholesterol metabolism. Elevated non-HDL-C, HDL-C, and TC levels have been reported in adolescent girls suffering from amenorrhoea due to DE and weight loss (Swenne 2016). Additionally, EDs in the general population have been associated with higher LDL-C and TC levels (Tam et al. 2021; Hussain et al. 2019; Sachs et al. 2016). More specifically, a meta-analysis concluded that patients with anorexia nervosa have higher HDL-C, VLDL, LDL-C, TC, and TG compared to healthy controls, though most lipids were within the reference range (Hussain et al. 2019). In genome-wide association studies, a significant positive association was established between anorexia nervosa and total HDL-C, as well as the concentration of large HDL particles and their components (Duncan et al. 2017; Watson et al. 2019). A meta-analysis looking at the effect of refeeding treatment revealed no change in LDL-C or TC, but an increase in VLDL-C and a decrease in HDL-C after a weight-restoration treatment of ~86 days in duration and median BMI change from 14.85 to 19.07 kg/m^2 (Hussain et al. 2023).

Exact mechanisms behind lipid metabolism and anorexia nervosa have not been established. An increased intake of cholesterol or plant sterols from the diet seems improbable due to the low-fat nature of diets often followed in the disease (Allen et al. 2013). Several hormonal axes are affected by anorexia nervosa, as described earlier in LEA. Elevated GH, cortisol and glucagon, decreased oestrogen, insulin, IGF-1 and T3 have been reported, along with low glucose (Hussain et al. 2023). Additionally, CETP activity has been reported to be higher in patients with anorexia nervosa than in healthy controls, suggesting an accelerated cholesterol metabolism (Ohwada et al. 2006).

Patients with anorexia nervosa have one of the highest overall mortality and suicide rates among mental disorders (Chesney et al. 2014; Papadopoulos et al. 2009), and the incidence of major adverse cardiovascular events is significantly higher in patients with anorexia nervosa than the general population (Tseng et al. 2024). However, the long-term risk of some metabolic diseases (diabetes mellitus type 2, obesity) seems reduced in these patients compared to the normal population (Ji et al. 2016; Hudson et al. 2020). Additionally, due to the overall cardiovascular risk profile of anorexia nervosa patients, pharmacological treatment of dyslipidaemia is primarily not recommended and the treatment of the underlying cause should remain the focus (Hussain et al. 2019). To the best of my knowledge, the long-term risk of ASCVD has not been studied in recovered patients with anorexia nervosa.

2.3.3 Metabolic adaptations to LEA

When the EI does not supply enough energy for all essential physiological functions, metabolic adaptations occur. Physiological functions are preserved in a hierarchical order to guard the most vital functions. Evolutionarily, it has been essential to adapt to periods of low energy supply and prioritise locomotion, cell survival and thermogenesis (Rion and Kawecki 2007).

Long-lasting LEA and weight loss have been reported to be associated with a more pronounced reduction in resting metabolomic rate (RMR) than what would be predicted by the loss of lean mass. This is a phenomenon called adaptive thermogenesis, where several metabolic adaptations have been hypothesised to contribute to a reduced REE, including T3, leptin, ghrelin, and fat mass. Additionally, reduced inflammation has been observed during adaptive thermogenesis. Adaptive thermogenesis is often defined as the difference between expected and measured REE and has been observed in both obese and non-obese individuals (Müller et al. 2021; Martin et al. 2022; Heinitz et al. 2020) as well as highly trained physique athletes after weight loss and reduction in body fat percentage (Isola et al. 2023). The state seems to be reversible, but has also been associated with a higher risk of fat mass gain and redistribution of the gained fat mass (Dulloo 2025). RMR has been reported to be decreased in females with FHA or reduced EA (Mary Jane De Souza et al. 2007; Melin et al. 2015; Myerson et al. 1991) and in endurance males with low EI (Most et al. 2018; Lefevre et al. 2009).

Interestingly, a study conducted on sedentary females found that similar metabolic adaptations occurred with psychogenic FHA (not weight-loss- or exercise-induced) as in the LEA state. Females with psychogenic FHA had an altered GH pulse frequency and amplitude (with similar mean 24h GH levels), lower insulin and glucose response during eating, lower levels of LH and higher levels of cortisol and IGF-1, but similar levels of leptin (Laughlin et al. 1998). They

also found that females with psychogenic FHA had lower fat intake but similar total EI and BMI, and lower body fat percentage and higher lean body mass than healthy controls. However, these females also scored higher on questionnaires on EDs and depression, which may reflect that they might also have had underlying LEA predisposing to FHA.

Caloric restriction has also been associated with better cardiovascular health and reduced risk of ASCVD in non-obese healthy adults (Most et al. 2018; Lefevre et al. 2009; Magkos 2022). Caloric restriction has also been suggested to slow down and to some extent reverse age-related metabolomic changes (Green et al. 2022; Flanagan et al. 2020). Therefore, it seems that reduced EI can have beneficial or detrimental consequences on health, depending on how it is achieved.

2.4 Summary and open questions

Sport and exercise are beneficial for overall and cardiovascular health, but inadequate EI and problematic LEA may blunt and even reverse some of the positive outcomes. LEA and REDs have gained more attention in sports medicine research and clinics over the past decades, but many causal links are yet to be established. Given the methodological challenges in identifying and quantifying athletes with REDs or LEA, as well the ethical considerations in long-term exposure to LEA in randomised controlled trials, the research field is up against a real challenge.

Elevated LDL-C and TC are listed among potential symptoms of REDs based on studies conducted among female athletes with menstrual disturbances, patients with anorexia nervosa, male individuals going through army training and case studies of extreme weight loss in combat sports. However, not all studies have reported the same results. In addition, a few metabolomic studies have been conducted in physique athletes and active individuals where beneficial yet transient changes in the metabolome and lipid levels have been observed after short- to intermediate-term LEA. The conducted metabolomics studies have not identified changes in LDL-C and TC due to LEA.

The studies on cholesterol metabolism and LEA are still rare among athletes and more research is needed. Given the inconsistency in findings regarding REDs and cholesterol metabolism in athletes several questions remain to be answered. Also, even if patients with EDs have been shown to present with several changes in their lipidome, the impact of DE behaviour on particularly athletes' cholesterol metabolism has not yet been studied.

Cardiovascular diseases place a significant burden on our healthcare system, making primary prevention essential. It is also important to remember that not only professional athletes are affected by REDs and LEA, but recreational athletes and goal-oriented exercisers may also suffer from these conditions and their

consequences on overall health (Karlsson et al. 2023). Understanding the interplay between LEA and cholesterol is therefore of great importance for promoting cardiovascular health in athletes and in the general population.

3 Aims

My aim was to study the symptoms and risk of REDs, DE behaviour and cholesterol metabolism in Finnish athletes. I aimed to examine the associations between these factors, as well as potential sex- or sport-specific differences. More specifically, my aim was to answer the following questions:

I. Is there an association between symptoms of LEA or DE and cholesterol levels in Finnish female athletes? Are these results different when only examining athletes representing weight-sensitive sports?

II. Is there an association between REDs risk and cholesterol levels in Finnish endurance athletes? Do REDs risk or cholesterol levels vary over the course of an athletic year, and is there an association between the changes in the studied parameters?

III. Is there an association between REDs risk and the serum metabolome and what is the role of body fat percentage in this context? More specifically, can we identify metabolomic pathways that are more likely to be associated with REDs risk?

4 Methods

4.1 Study samples

4.1.1 Monitoring Illness and Injury in Athletes cohort (MIIA) (Study I)

Monitoring Illness and Injury in Athletes (MIIA) was a cross-sectional study examining the health of 167 Finnish female athletes. The study was conducted at the University of Jyväskylä. Participants were aged 16–35 years at the time of the data collection in 2019–2022 and represented ball sports, gymnastics, endurance sports, and track and field at national (tier 3) to world class (tier 5) levels (according to the Participant Classification Framework ranging from tier 0 [sedentary] to tier 5 [world class](McKay et al. 2021)). Acute injuries or previous severe medical conditions at baseline were criteria for exclusion. The participants were recruited from sport clubs, national federations and national teams.

4.1.2 Athletic Performance and Nutrition cohort (NoRED-S) (Studies I–III)

The Athletic Performance and Nutrition cohort (NoRED-S) was a 3-year follow-up study conducted at the University of Jyväskylä. The participants were examined at the beginning (T1) and end (T2) of their training season. At T1, the athletes had recently finished their off-season and were at the beginning of their general training phase. T2 took place at the end of their specific training phase before the start of the competition season. A total of 376 Finnish national (tier 3) to world class (tier 5) level female and male athletes (McKay et al. 2021), aged 16–35 years and without acute injuries or previous severe medical conditions at baseline, were included in the study, and were followed up from 2021 to 2024. The participants were recruited from clubs and national federations. The selection of study participants in each study is described in Figure 7.

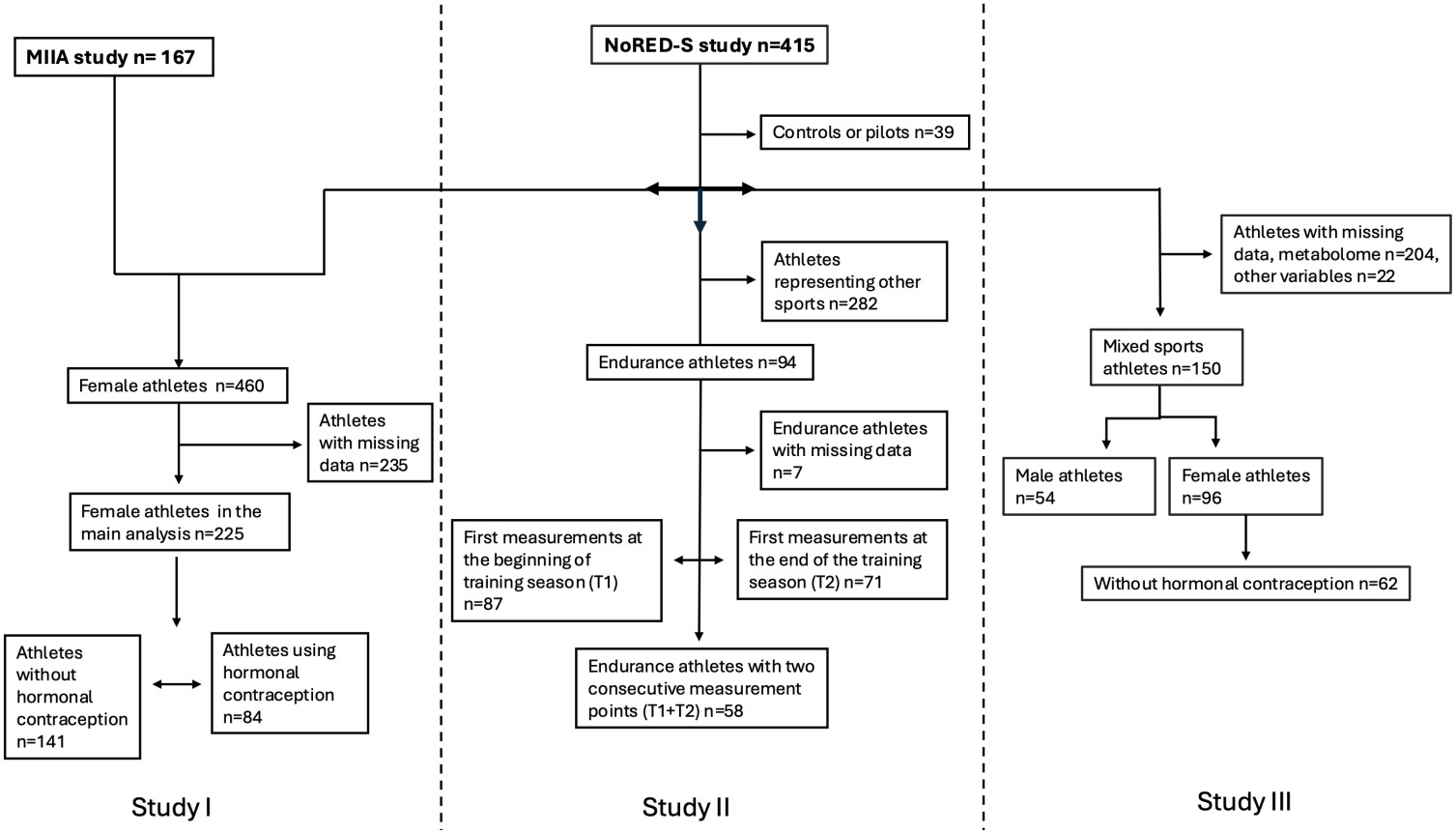


Figure 7 Flowchart describing study participants' selection in Studies I, II and III

4.1.3 Ethics declaration

Both the MIIA and NoRED-S studies followed the Declaration of Helsinki and were approved by the Ethics Committee of the Central Finland Health Care District (MIIA 5U/2019) and the Ethics Committee of the University of Jyväskylä (NoRED-S 514/13.00.04.00/2021). Participants provided written informed consent before enrolment in the study. All data were pseudonymised before analysis.

4.2 Measures

4.2.1 Questionnaires

4.2.1.1 Eating Disorder Examination Questionnaire Short (EDE-QS) (Studies I–III)

In both the MIIA and NoRED-S studies, athletes' eating disorder symptoms were assessed using the Eating Disorder Examination Questionnaire Short version (EDE-QS). The EDE-QS is a 12-item version of the original 28-item Eating Disorder Examination Questionnaire (EDE-Q)(Fairburn and Beglin 1994), assessing the severity, frequency, and range of ED symptoms during the past 7 days on a 4-point scale (Prnjak et al. 2020). This yields total scores ranging from 0 to 36, with higher scores indicating more unhealthy attitudes towards eating and body image. The EDE-Q has previously been validated on an athlete population of female long-distance runners (Lichtenstein et al. 2022). The EDE-QS has demonstrated high internal consistency (Cronbach's alpha=0.91) and convergent validity with the EDE-Q, both among those with (r=0.91) and without (r=0.82) an ED. High EDE-QS scores are a potential major risk factor for problematic LEA (Sim and Burns 2021; Wagner et al. 2016). I used the score of 15 as a cut-off to screen for individuals at risk for a clinical ED, as previously recommended (Prnjak et al. 2020).

4.2.1.2 Low Energy Availability in Female athletes Questionnaire (LEAF-Q) (Study I)

The Low Energy Availability in Female athletes Questionnaire (LEAF-Q) was used to assess physiological symptoms of LEA in female athletes in both MIIA and NoRED-S studies. The LEAF-Q is a screening tool to identify individuals potentially at risk for problematic LEA, comprising 25 questions about menstrual function, history of injuries, and gastrointestinal symptoms, with a total score ranging from 0 to 25 (Melin et al. 2014; Sim and Burns 2021). The questionnaire has been validated in athletes representing endurance sports; a score ≥8 indicates high risk

for LEA in female athletes, with a sensitivity of 78% and specificity of 90% (Melin et al. 2014). I excluded athletes that used any form of hormonal contraception from the LEAF-Q analysis because their menstrual function, which is a major component of the questionnaire, could not be interpreted.

4.2.2 REDs Clinical Assessment Tool version 2 (REDs CAT 2) (Studies II & III)

I used the REDs Clinical Assessment Tool version 2 (REDs CAT 2(Stellingwerff et al. 2023)) to identify athletes at risk of REDs. In Study II, athletes were initially categorised by the REDs CAT 2 into a traffic light system from green to yellow, orange, or red depending on the severity of the risk as presented in Tables 5 and 6. Since there was a low number of individuals categorised as orange or red, I analysed the athletes in two groups: low REDs risk, which included the athletes categorised as green, and medium-to-high REDs risk, which included athletes categorised as yellow, orange, or red. In Study III, I chose to analyse the risk of REDs as a continuous variable where the different REDs indicators yielded a total score of risk points (range of possible scores 0–6.5 for females and 0–6 for males), because this better reflects the continuum of risk and facilitates data analysis.

Due to the enrolment of our study prior to the publication of the REDs CAT 2, the indicators of the REDs risk in this study had some differences with the published tool (Stellingwerff et al. 2023). Information about the duration of amenorrhea was not collected and therefore, all forms of amenorrhoea were categorised as severe primary indicators, which in the published tool included any primary amenorrhoea and secondary amenorrhoea lasting for at least 12 months. I also lacked the data to assess anxiety and depression. I had a more concise version of the EDE-Q, the EDE-QS, for the measure of DE behaviour. Since all our studied participants were ≥18 years old, I excluded the criteria for adolescents and children. Finally, I excluded cholesterol levels from the risk assessment since my aim was to investigate the association between REDs risk and cholesterol levels.

Table 5 Primary and secondary indicators of REDs used in Studies II and III

Severe primary indicators = 2 points	-amenorrhoea (absence of menstrual cycle for >3 months) for females -clinically low total testosterone (<10nmol/l) for males
Primary indicators = 1 point	-sub-clinically low free or total testosterone (10–17nmol/l) for males -sub-clinically or clinically low total triiodothyronine (T3) (≤4.25pmol/l) -history of ≥1 high-risk (femoral neck, total hip, sacrum, pelvis) or ≥2 low-risk (all other locations) bone stress injuries (BSI) within the previous year

	-bone mineral density (BMD) Z-score <-1 at the lumbar spine (L1–L4) or femoral neck -Eating Disorder Examination Questionnaire Short (EDE-QS) score ≥15
Secondary indicators = 0.5 point	-oligomenorrhoea (>35 days between periods for a maximum of 8 periods/year) for females -history of 1 low-risk BSI

Indicators and reference levels are the same for female and male participants unless otherwise indicated. Points were used to calculate the total REDs risk score in Study III.

Table 6 Risk assessment of REDs used in Study II

red/severe risk	3 primary & ≥2 secondary, or ≥4 primary indicators
orange/high risk	1 primary & ≥3 secondary, or 2 primary & ≥2 secondary, or 3 primary & ≤1 secondary indicators
yellow/mild risk	0 primary & ≥2 secondary, or 1 primary & ≤2 secondary, or 2 primary & ≤1 secondary indicators
green/low risk	0 primary & ≤1 secondary indicators

In Study II, the data were analysed as low risk (green) vs medium-to-high risk (yellow, orange, or red) because very few athletes were categorised as orange or red.

4.2.3 Physical and clinical measurements

4.2.3.1 Anthropometrics and bone mineral density (Studies I–III)

In both MIIA and NoRED-S cohorts, anthropometric measurements were carried out between 7:00 and 10:00 AM after a fasting period of 10h; only small amounts of water (maximum 2 dl) were allowed to be consumed in the morning. Participants were advised to refrain from strenuous physical activity the preceding day and the morning of the measurement and to go to the toilet before the measurement. Dual energy X-ray absorptiometry (DXA; LUNAR Prodigy, GE Healthcare, Madison, WI, USA) was used to assess body composition and bone properties. BMD was evaluated using Z-scores. Fat mass–to–lean mass ratio (FLMR) was calculated by dividing the total fat mass by the total lean mass (Study II). The device manufacturer's standard procedures were followed, and the device was calibrated with a phantom each morning prior to the measurements for quality assurance. Participants were scanned in the supine position in the centre of the table using the default-scan mode automatically selected by the Prodigy software (Lunar Prodigy Advance Encore v. 14.10.022). In the NoRED-S cohort, athletes underwent whole-body DXA scans at both T1 and T2. However, due to ethical considerations, site-

specific BMD assessments of the lumbar spine and proximal femur were performed only once per athletic year. These values were used to represent both timepoints within the same annual cycle.

4.2.3.2 History of bone stress injuries (Studies II & III)

As part of the LEAF-Q for female athletes and Low Energy Availability in Male athletes Questionnaire (LEAM-Q) for male athletes, the participants were asked to verbally report their history of injuries during the past year in both MIAA and NoRED-S cohorts. Two researchers, who were licensed physicians (JIKS and PNS), independently classified the descriptions according to the REDs CAT 2 to identify high-risk BSIs and low-risk BSIs. Any differences in the classification were discussed, and the jointly agreed outcome was reported.

4.2.3.3 Menstrual function (Studies I–III)

As a part of the LEAF-Q, female participants reported their menstrual function as follows: amenorrhoea=no natural onset of menstrual cycle by the age of 15 or last menstrual bleeding ≥3 months ago; oligomenorrhoea=last menstrual bleeding 1–2 months ago; normal menstruation=last menstrual bleeding 1–4 weeks ago. Participants were also asked about use of hormonal contraception. In Study I, participants were grouped into two groups: normally menstruating athletes and athletes with menstrual disturbances (oligomenorrhoea + amenorrhoea). In Studies II and III, participants were categorised into three menstrual status groups: normal menstrual cycle, oligomenorrhoea and amenorrhoea. Participants who reported using hormonal contraception were excluded from the analysis of menstrual function.

4.2.3.4 Blood measurements (cholesterol and hormone levels) (Studies I–III)

Fasting venous blood samples were drawn from the antecubital vein in a supine position between 7:00 and 10:00 AM. For serum separation, whole blood was left to clot for 30 minutes at room temperature and centrifuged at 2.200g before aliquoting and storing the sera at −80°C until analysis. T3 and testosterone concentrations were determined using IMMULITE 2000 XPi (Siemens Healthcare Diagnostics, UK). Serum HDL-C, LDL-C, and TC were measured using a KONELAB 20 XTi or Indiko analyser (Thermo Fisher Scientific, Finland) according to the manufacturer's instructions. All blood sample preparation and processing were performed by professional laboratory personnel.

4.2.3.5 Nuclear magnetic resonance (NMR) serum metabolome (Study III)

As part of the NoRED-S cohort, NMR was used to quantify 250 metabolites from the serum sample in a commercial laboratory (Nightingale Health Plc, Helsinki, Finland). The serum samples were measured by using a Bruker AVANCE III HD NMR 500MHz spectrometer equipped with a cryogenically cooled TCI CryoProbe Prodigy. The whole process of sample preparation and quantification has been described in detail earlier (Würtz et al. 2017; Soininen et al. 2015). The analysed metabolites included measures of cholesterol and TGs, lipoprotein subclasses and their lipid composition, apolipoproteins, fatty acids, amino acids, ketone bodies, glycolysis-related metabolites, and metabolites related to fluid balance and inflammation, and are listed in Table 7 (Soininen et al. 2015).

Table 7 Metabolite measures obtained from nuclear magnetic resonance spectroscopy in Study III

cholesterol (C) (mmol/l)	VLDL-C, LDL-C, HDL-C, total C, free C, esterified C, remnant C
lipoprotein particle size (nm)	mean diameter of VLDL, LDL and HDL
lipid measures for each lipoprotein (mmol and % of total lipids)	esterified cholesterol, free cholesterol, TG, phospholipids, total cholesterol (mmol/l), total lipids (µmol/l)
apolipoproteins (g/l)	ApoA1, ApoB, ApoB/ApoA1
ketone bodies (mmol/l)	beta-hydroxybutyrate, acetate, acetone, acetoacetate
glycolysis-related metabolites (mmol/l)	glucose, lactate, pyruvate, citrate, glycerol
inflammation (mmol/l)	glycoprotein acetyls (GlycA)
fatty acids (FA) (mmol/l)	total FA, estimated FA chain length, estimated degree of saturation, omega-3 FA, omega-6 FA, polyunsaturated FA, monounsaturated FA (16:1, 18:1), saturated FA, docosahexaenoic acid (22:6), linoleic acid (18:2), conjugated linoleic acid
amino acids (mmol/l)	alanine, glutamine, glycine, histidine, isoleucine, valine, leucine, phenylalanine, tyrosine
fluid balance	creatinine (µmol/l), albumin (g/l)
glycerides and phospholipids (mmol/l)	VLDL-TG, LDL-TG, HDL-TG, TG, phosphatidylcholines, total cholines, sphingomyelins

VLDL = very-low-density lipoprotein, LDL = low-density lipoprotein, HDL = high-density lipoprotein, ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, TG = triglyceride

4.3 Statistical analysis

All data analyses were conducted in R (version 2023. R 4.3.0 GUI 1.79 or higher). Descriptive results are reported as means ± standard deviation (SD) (normally distributed data), or median and interquartile range (IQR) (non-normally distributed data). All confidence intervals (CI) are reported at the 95% confidence level. The significance level (α) was set to 0.05.

4.3.1 Data quality control

The normality of parameters was assessed by performing a Shapiro–Wilk test (Study I) and by inspecting data using dot plots and histograms (Studies I–III). Nonparametric tests were used to analyse non-normally distributed data. Data were inspected using dot plots and histograms to evaluate skewness and outliers to ensure data quality and reproducibility of the results.

4.3.2 Between-group differences (Studies I–III)

Differences in descriptive statistics between different groups were assessed using Student's *t*-test for continuous variables and Pearson's chi-squared test for categorical variables (Studies I & II). In Study III with three or more groups being compared, continuous variables were analysed using one-way analysis of variance (ANOVA) and Tukey's honestly significant difference test. Due to a highly skewed distribution, group differences in REDs scores were analysed using non-parametric methods (Kruskal–Wallis with Dunn's post hoc test)(Study III). When analysing group differences between menstrual status and testosterone groups in Study III, non-parametric methods were used given the small sample sizes in some groups.

4.3.3 Cross-sectional associations (Studies I & II)

Cross-sectional relationships between variables were assessed using Pearson's correlation coefficients and linear regression models for continuous variables and logistic regression for binary categorical variables. In Study I, I used Pearson's correlation and linear regression models to study the associations of the LEAF-Q, EDE-QS, and menstrual disturbances with cholesterol levels among female athletes. In Study II, I used Pearson's correlation and linear regression models to study association between REDs risk and cholesterol levels, as well as the association between the differences in these parameters from training to competition season. HDL-C, LDL-C, and TC were the outcome variables and EDE-QS, LEAF-Q, menstrual status, or REDs risk were the explanatory variables in my analyses. All linear regression models were adjusted for age, and in Study I also for

sport. In addition, in Study II, I conducted a sensitivity analysis with further adjustment of the model for FLMR, body fat percentage, and season of the year. Logistic regression was used in Study I to calculate the odds ratio for having elevated LDL-C in case of elevated LEAF-Q score, EDE-QS score or menstrual disturbances. Logistic regression was adjusted for age and sport.

Correlation analyses were used to assess if an association existed between two variables. Pearson product-moment correlation yields a correlation coefficient (r) that can have a value between 0 and 1. There are no universally established descriptions of correlation strength but a value below 0.2 is typically considered weak, a value between 0.2 and 0.7 is considered fair or moderate and a value greater than 0.7 is considered strong (Overholser and Sowinski 2008). For non-normally distributed data, I used Spearman's rank correlation coefficient, which is a non-parametric version of the Pearson's product-moment correlation. Both tests assume a linear relationship between the studied variables (Overholser and Sowinski 2008).

Linear regression analysis was used in studies I and II to explore associations between cholesterol values and REDs risk or its indicators. Linear regression model yields a statistical output beta (β) that describes the change in the dependent or response variable (HDL-C, LDL-C, TC) when the independent variable (LEAF-Q, EDE-QS, REDs risk, menstrual status) increases by one unit. This also indicates the mean difference in the dependent variable when the independent variables had a difference of one unit.(Overholser and Sowinski 2008) Regression models can be adjusted for confounding factors. We examined the assumptions of linear regression, including linearity of associations, using residuals.

I used logistic regression in Study I to analyse associations between binomial variables. Logistic regression is a form of regression analysis where the response variable is binomial and the model yields an output variable odds ratio (OR)(Sperandei 2014). The OR describes the odds for observing the event of interest under a certain exposure compared to the odds of observing the event of interest without the exposure (Sperandei 2014). In Study I, I analysed the OR for having elevated LDL-C (≥3mmol/l) if the participant scored high or low in the LEAF-Q or EDE-QS or had menstrual disturbances.

4.3.4 Restricted maximum likelihood (REML) (Study II)

In Study II, to investigate changes over time points of the training season in the study parameters, I fit a separate linear mixed model for each parameter with fixed effects for the timepoint, as well as age for adjustment (Brown 2021). Random intercepts for each participant were also specified to account for individual variability. The model was estimated using restricted maximum likelihood

(REML)(Bates et al. 2015). REML was used to obtain unbiased estimates of the random effects variance.

4.3.5 Generalised estimation equation (GEE) (Study III)

In Study III, I used a repeated measures dataset and analysed associations between metabolites and REDs risk or body fat percentage using generalised population-averaged estimating equations (GEE) with Gaussian family, linear link function, and exchangeable correlation structure. Participant ID was used as the clustering variable. GEEs are an extension for generalised linear models and allow for the analysis of correlated non-normally distributed variables (Ziegler and Vens 2010). REDs risk, body fat percentage, and testosterone were continuous explanatory variables and metabolites were response variables. Analyses on menstrual status were restricted to females with a natural menstrual cycle. Menstrual cycle status was modelled as a categorical variable with three levels: normal cycle, oligomenorrhoea, and amenorrhoea. The overall association between menstrual cycle status and metabolite concentrations was evaluated using omnibus Wald tests.

All models were adjusted for age and time of the season (T1 vs T2) and REDs models further for binary sport category (weight-sensitive vs non-weight-sensitive) or in additional analysis, body fat percentage. I adjusted all p-values for multiple testing using principal component analysis (PCA)(Jolliffe and Cadima 2016) and Bonferroni correction (Armstrong 2014). For females, in the PCA analysis I identified 14 components explaining >95% of the variance and for males 8 components. These values were used in Bonferroni correction for multiple testing (threshold 0.00357 for females and 0.00625 for males).

Heatmaps and bar plots are used to visually represent the nominal and significant results from the GEE analysis. For this, continuous explanatory variables had to be categorised. REDs risk was divided into three categories (0–0.5, 1–1.5 and 2–4) due to the maximum score of 4 in our study population. For body fat percentage, females were categorised into low <17%, medium 17–30%, and high >30% (Jeukendrup and Gleeson 2009; Redman and Loucks 2005; Salmón-Gómez et al. 2023) and males into low <7%, medium 7–20%, and high >20%(Jeukendrup and Gleeson 2009; Salmón-Gómez et al. 2023; Friedl et al. 1994). For heatmaps and bar plots, only the first measurements of each participant were used.

5 Results

5.1 Association of LEA and ED symptoms with cholesterol levels in female athletes (Study I)

5.1.1 Participant characteristics

For Study I, the first measurements of adult (≥18 years old) female athletes from both cohorts, MIIA and NoREDS, were used for a cross-sectional design (n=460). Participants with missing data on key variables (cholesterol values, LEAF-Q, EDE-QS, BMI, body fat percentage, and use of hormonal contraception) were excluded (n=166). Thus, the final study sample consisted of 294 female athletes (Figure 7). In total, 176 participants were not using hormonal contraception and could be included in the analyses of LEAF-Q scores and menstrual function. The most common sports were ice hockey, track and field, volleyball, football, and cross-country skiing (Figure 8). I also separately analysed weight-sensitive sports (n=80), i.e., endurance, aesthetic, and weight-dependent sports, which emphasise leanness (long-distance running, triathlon, race walking, cross-country skiing, orienteering, team gymnastics, aesthetic group gymnastics, cheerleading, and ski jumping).

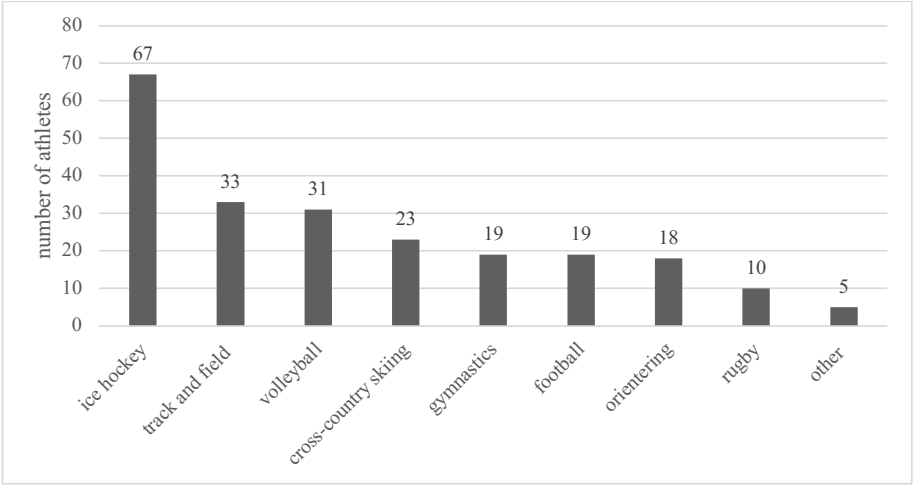


Figure 8 Distribution of participants within different sports in Study I. "Other" includes sports represented by very few participants (triathlon and ski jumping)

In the EDE-QS, 21 (7%) of the 294 participants scored ≥15 points, which indicates a high risk for EDs. In total, 176 participants were not using hormonal contraception and could be included in the analyses of LEAF-Q scores and menstrual function. A potential state of problematic LEA was identified in 72 (41%) of the 176 participants who scored ≥8 points in the LEAF-Q. Menstrual disturbances were reported by 44 (25%) of the 176 participants. LDL-C was elevated (≥3mmol/l) among 57 (19%) of the 294 participants. Further characteristics of the participants are described in Table 8.

Table 8 Characteristics of study participants in Study I

	By LEA symptoms (LEAF-Q score)					By eating disorder symptoms (EDE-QS score)					Total	
	Low LEAF-Q score (<8)		High LEAF-Q score (≥8)			Low EDE-QS score (<15)		High EDE-QS score (≥15)				
Characteristic	**N**	**mean (SD) / n (%)**	**N**	**mean (SD) / n (%)**	**p**	**N**	**mean (SD) / n (%)**	**N**	**mean (SD) / n (%)**	**p**	**N**	**mean (SD) / n (%)**
Age	104	21.6 (5.0)	72	21.2 (4.3)	0.61	273	22.0 (4.7)	21	22.2 (4.5)	0.87	294	22.0 (4.7)
BMI	104	23.3 (3.4)	72	22.4 (2.7)	0.072	273	23.0 (2.7)	21	25.8 (4.7)	**<0.001**	294	23.1 (3.0)
Body fat %	104	25.0 (8.0)	72	22.6 (8.0)	0.051	273	24.3 (7.5)	21	28.1 (10.2)	**0.031**	294	24.5 (7.8)
LEAF-Q	104	4.1 (1.8)	72	11.0 (2.8)	**<0.001**	164	6.9 (4.0)	12	7.1 (6.0)	0.90	176	6.9 (4.1)
EDE-QS	104	4.8 (5.1)	72	6.0 (4.7)	0.10	273	4.4 (3.5)	21	18.7 (2.7)	**<0.001**	294	5.4 (5.0)
HDL-C	104	1.6 (0.5)	72	1.7 (0.5)	0.33	273	1.8 (0.7)	21	1.6 (0.6)	0.37	294	2.0 (0.7)
LDL-C	104	2.4 (0.8)	72	2.6 (0.5)	**0.024**	273	2.5 (0.8)	21	2.7 (1.0)	0.13	294	2.5 (1.0)
TC	104	4.2 (1.0)	72	4.6 (0.7)	**0.020**	273	4.4 (1.0)	21	4.7 (1.0)	0.16	294	4.4 (1.0)
Menstrual disturbances	104	11 (11%)	72	33 (45%)	**<0.001**	164	38 (23%)	12	6 (50%)	0.084	176	44 (25%)
Use of hormonal contraception	-	-	-	-	-	273	109 (40%)	21	9 (42%)	0.90	294	118 (40%)

	Low LDL-C (<3mmol/l)		High LDL-C (≥3mmol/l)			Normal menstrual cycle		Disturbed menstrual cycle		
Characteristic	**N**	**mean (SD) / n (%)**	**N**	**mean (SD) / n (%)**	**p**	**N**	**mean (SD)**	**N**	**mean (SD)**	**p**
Age	237	21.8 (4.6)	57	22.9 (5.0)	0.20	132	21.7 (5.0)	44	20.5 (3.9)	0.16
BMI	237	23.0 (2.8)	57	23.9 (3.6)	**0.022**	132	23.3 (3.3)	44	21.7 (2.4)	**0.0052**
Body fat %	237	24.3 (7.4)	57	25.7 (9.1)	0.21	132	25.0 (8.2)	44	21.0 (6.7)	**0.0036**
LEAF-Q	148	6.8 (3.9)	28	7.9 (5.0)	0.19	132	6.0 (3.5)	44	9.8 (4.4)	**<0.001**
EDE-QS	237	5.0 (4.6)	57	7.1 (6.2)	**0.004**	132	4.9 (4.7)	44	6.5 (5.6)	0.055
HDL-C	237	1.7 (0.7)	57	1.8 (0.4)	0.91	132	1.6 (0.4)	44	1.7 (0.5)	0.86
LDL-C	237	2.2 (0.5)	57	3.6 (0.9)	**<0.001**	132	2.4 (0.7)	44	2.5 (0.7)	0.38
TC	237	4.1 (0.7)	57	5.7 (0.9)	**<0.001**	132	4.3 (0.9)	44	4.5 (1.0)	0.40
Menstrual disturbances	148	34 (23%)	28	10 (36%)	0.23	-	-	-	-	-
Use of hormonal contraception	237	89 (38%)	57	29 (51%)	0.16	-	-	-	-	-

p values are for difference between low vs. high LEAF-Q and EDE-QS scores and LDL-C levels and menstrual status groups respectively. Bolded results are statistically significant <0.05. BMI = body mass index (kg/m2); LEAF-Q = Low Energy Availability in Female athletes Questionnaire; EDE-QS = Eating Disorder Examination Questionnaire Short version; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l); SD = standard deviation

5.1.2 LEA symptoms and cholesterol

There was no significant correlation between LEAF-Q score and LDL-C (Table 9). Of those scoring below the cutoff (<8 points) in LEAF-Q, 15% had LDL-C over the clinical reference value of ≥3mmol/l and of those scoring above the cutoff (≥8 points) in LEAF-Q, 17% had elevated LDL-C (adjusted OR 1.17, 95% CI 0.64–2.15, p 0.62, Table 10). Menstrual disturbances were not associated with HDL-C, LDL-C, or TC (Table 9).

5.1.3 ED symptoms and cholesterol

EDE-QS scores were positively associated with LDL-C, and TC levels (Table 9). The association between EDE-QS and LDL-C was strengthened after further adjusting the model for LEAF-Q score in addition to age and sport (β 0.049 95% CI 0.030–0.069, p <0.001). Of those scoring below the cutoff (<15 points) in EDE-QS, 18% had LDL-C over the clinical reference value of ≥3mmol/l and of those scoring above the cutoff (≥15 points), 38% had elevated LDL-C (adjusted OR 2.82, 95% CI 1.06–7.05, p 0.030, Table 10).

5.1.4 Analysis restricted to weight-sensitive sports

In total 80 athletes represented wight-sensitive sports in the analysis of EDE-QS and 60 in analysis of LEAF-Q. Among them, 7 (9%) of 80 athletes scored ≥15 points in the EDE-QS, 28 (47%) of 60 athletes scored ≥8 points in the LEAF-Q, and 23 (38%) of 60 athletes had menstrual dysfunction. The point estimates for associations between the LEAF-Q and EDE-QS with LDL-C were higher than in the whole sample (Table 11).

Table 9 Associations and correlations of LEAF-Q, EDE-QS, and menstrual disturbances with cholesterol levels

Outcome	β	95% CI	p	r	95% CI	p
HDL cholesterol						
EDE-QS	-0.0077	-0.024–0.0085	0.35	-0.006	-0.13–0.12	0.93
LEAF-Q	0.0087	-0.0069–0.024	0.27	0.11	-0.04–0.25	0.15
Menstrual disturbances	-0.040	-0.19–0.11	0.60	0.01	-0.13–0.16	0.86
LDL cholesterol						
EDE-QS	0.028	0.0098–0.046	**0.0029**	0.15	0.04–0.26	**0.010**
LEAF-Q	0.024	-0.0011–0.049	0.061	0.13	0.10–0.28	0.076
Menstrual disturbances	0.028	-0.22–0.27	0.82	0.07	-0.08–0.21	0.38
Total cholesterol						
EDE-QS	0.036	0.013–0.058	**0.0023**	0.17	0.05–0.28	**0.0041**
LEAF-Q	0.023	-0.0089–0.056	0.15	0.12	-0.03–0.27	0.10
Menstrual disturbances	0.0097	-0.31–0.33	0.95	-0.06	-0.08–0.21	0.40

Betas (β) are reported per unit change in exposure variable and adjusted for age and sport. Bolded results are statistically significant <0.05. CI = confidence interval; p = p value; r = Pearson's correlation coefficient; HDL = high-density lipoprotein; LEAF-Q = Low Energy Availability in Female athletes Questionnaire; EDE-QS = Eating Disorder Examination Questionnaire Short; LDL = low-density lipoprotein

Table 10 Associations between elevated LEAF-Q and EDE-QS scores and menstrual disturbances with elevated LDL-C

		LDL-C		
		<3 mmol/l n (%)	**≥3 mmol/l n (%)**	**OR [95% CI] (p value)**
LEAF-Q score	<8	88 (85%)	16 (15%)	1.17 [0.64–2.15] (0.62)
	≥8	60 (83%)	12 (17%)	
EDE-QS score	<15	224 (82%)	49 (18%)	2.94 [1.06–7.78] **(0.031)**
	≥15	13 (62%)	8 (38%)	
Menstrual function	normal	114 (86%)	18 (14%)	1.57 [0.59–4.07] (0.36)
	disturbed	34 (77%)	10 (23%)	

ORs were adjusted for age and sport. Bolded results are statistically significant <0.05. LEAF-Q = Low Energy Availability in Female athletes Questionnaire; EDE-QS = Eating Disorder Examination Questionnaire Short; LDL-C = low-density lipoprotein cholesterol; OR = odds ratio, CI = confidence interval

Table 11 Associations and correlations of LEAF-Q, EDE-QS, and menstrual disturbances with cholesterol levels among athletes representing weight-sensitive sports

Outcome	β	95% CI	p	r	95% CI	p
HDL cholesterol						
EDE-QS	-0.0039	-0.027–0.019	0.74	-0.11	-0.32–0.11	0.32
LEAF-Q	0.012	-0.017–0.042	0.41	0.11	-0.14–0.36	0.39
Menstrual disturbances	-0.076	-0.36–0.21	0.59	0.023	-0.23–0.27	0.86
LDL cholesterol						
EDE-QS	0.036	0.0041–0.068	**0.028**	0.17	-0.05–0.38	0.13
LEAF-Q	0.043	0.0041–0.08	**0.031**	0.23	-0.03–0.46	0.079
Menstrual disturbances	0.074	-0.30–0.45	0.70	0.12	-0.14–0.36	0.36
Total cholesterol						
EDE-QS	0.036	-0.0066–0.079	0.096	0.10	-0.12–0.31	0.37
LEAF-Q	0.035	-0.017–0.086	0.19	0.16	-0.099–0.40	0.23
menstrual disturbances	0.014	-0.48–0.51	0.96	0.076	-0.18–0.32	0.56

Betas (β) are reported per unit change in exposure variable and adjusted for age and sport. Bolded results are statistically significant <0.05. CI = confidence interval, p=p-value; r = Pearson's correlation coefficient; HD L= high-density lipoprotein; LEAF-Q = Low Energy Availability in Female athletes Questionnaire; EDE-QS = Eating Disorder Examination Questionnaire Short; LDL = low-density lipoprotein cholesterol

5.2 Association between REDs risk and cholesterol levels in endurance athletes (Study II)

5.2.1 Participant characteristics

For Study II, I included adult (≥18 years) female and male athletes from endurance sports (long-distance running, cross-country skiing, Nordic combined, biathlon, triathlon, orienteering, and race walking) from the NoRED-S cohort. For the first part of the study, I included the first measurements of all athletes from T1 and T2 for two separate cross-sectional analyses. For the second part of this study, I included participants who had completed two consecutive measurements within one athletic season (T1+T2). Participants with missing data on key variables

(cholesterol values, BMD, T3, testosterone, ED symptoms, and BMI) were excluded (n=7). Thus, the final sample comprised 87 (T1), 71 (T2), and 58 (T1+T2) athletes (Figure 7). Athletes in the longitudinal analysis represented the same sports as the athletes in the cross-sectional analysis.

Our analytic sample comprised 44 female and 43 male athletes at the beginning (T1), and 36 female and 35 male athletes at the end (T2), of the training season. In total, 27 female and 31 male athletes had completed measurements at both timepoints (T1 + T2) and were included in the longitudinal analysis with a mean time difference of 4.4 months (SD 1.3) between T1 and T2. VO2max increased among females (p 0.002), and body fat percentage (p 0.013) and FLMR (p 0.019) increased among males from T1 to T2 (Table 12). Further characteristics of the participants are described in Table 12.

Table 12 Characteristics of study participants who had participated on measurements at the beginning (T1) and end (T2) of the training season

	Female athletes					Male athletes				
	n	T1	n	T2	p value	n	T1	n	T2	p value
Age	27	23.8 ±3.7	27	24.2 ±3.7	**<0.001**	31	24.9 ±3.5	31	25.2 ±3.5	**<0.001**
BMI	27	20.6 ±1.7	27	20.6 ±1.7	0.87	31	22.7 ±1.7	31	22.8 ±1.5	0.24
fat %	27	16.5 [12.0–20.2]	27	16.3 [12.7–20.1]	0.41	31	8.3 [6.8–10.8]	31	8.9 [7.1–11.4]	**0.013**
FLMR	27	0.20 ±0.08	26	0.21 ±0.08	0.98	31	0.10 ±0.03	31	0.11 ±0.04	**0.019**
Medium- to-high REDs risk	27	21 (78%)	27	19 (70%)	0.75	31	21 (68%)	31	26 (84%)	0.18
EDE-QS	27	5.0 [2.0–7.0]	27	4.0 [2.0–7.5]	0.46	31	2.0 [0–6.0]	31	2.0 [1.0–5.5]	0.52
EDE-QS ≥15	27	<5 (<19%)	27	0	NA	31	0	31	<5 (<16%)	NA
BMD Z-score	27	-0.1 ±1.0	27	-0.1 ±1.0	0.79	31	-0.2 ±0.8	31	-0.2 ±0.8	0.26
BMD ≤-1	27	<5 (<19%)	27	<5 (<19%)	NA	31	6 (19%)	31	6 (19%)	NA
BSI ≥1	27	7 (26%)	27	<5 (<19%)	0.25	31	<5 (<16%)	31	<5 (<16%)	1
Amen/ oligo	22	8 (36%)	19	<5 (<26%)	-	-	-	-	-	-
Testosterone	-	-	-	-	-	31	17.0 ±3.7	31	16.1 ±5.2	0.43
Low testosterone	-	-	-	-	-	31	15 (48%)	31	20 (65%)	0.23
T3	27	4.3 ±1.6	27	3.9 ±0.8	0.27	31	4.6 ±1.1	31	4.8 ±1.4	0.44
T3 ≤4.25	27	17 (63%)	27	17 (63%)	1	31	13 (42%)	31	12 (39%)	1
HDL-C	27	1.6 [1.4–2.0]	27	1.7 [1.6–2.0]	0.48	31	1.5 [1.3–1.8]	31	1.5 [1.3–1.8]	0.53
LDL-C	27	2.4 ±0.7	27	2.4 ±0.7	0.75	31	2.3 ±0.6	31	2.5 ±0.6	0.062

TC	27	4.4 ±0.9	27	4.5 ±1.0	0.35	31	4.1 ±0.7	31	4.3 ±0.8	0.092
VO2max	22	59.8 ±5.0	23	61.4 ±4.6	**0.002**	30	70.0 ±5.8	27	70.6 ±6.0	0.80

Data are mean ±standard deviation, median [interquartile range], or n (%). Bolded results are statistically significant <0.05. T1 = beginning of the training season; T2 = end of the training season; BMI = body mass index (kg/m^2); FMLR = fat mass–to–lean mass ratio; REDs = relative energy deficiency in sport; EDE-QS = Eating Disorder Examination Questionnaire Short version; BMD = bone mineral density; BSI = bone stress injury; amen = amenorrhoea; oligo = oligomenorrhoea; T3 = triiodothyronine; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l); VO2max = maximal oxygen uptake (ml/kg/min). Low testosterone indicates clinically low values ≤17nmol/l.

5.2.2 REDs risk

Over two-thirds of both female and male athletes were at medium-to-high REDs risk both at the beginning (T1) and at the end (T2) of the training season (Table 12). No significant change in REDs risks was observed between T1 and T2 (p 0.75 for females and p 0.18 for males).

5.2.3 Clinically elevated cholesterol levels

At T1, 7 (16%) of the 44 female athletes and 5 (12%) of the 43 male athletes had a clinically elevated LDL-C (≥3mmol/l). At T2, 11 (31%) of the 36 female athletes and 7 (20%) of the 35 male athletes had a clinically elevated LDL-C. At T1, 13 (30%) of the 44 female athletes and 5 (12%) of the 43 male athletes had a clinically elevated TC (≥5mmol/l). At T2, 13 (36%) of the 36 female athletes and 7 (20%) of the male athletes had clinically elevated TC.

5.2.4 REDs risk and cholesterol levels

As presented in Table 13, no association between REDs risk and HDL-C, LDL-C, or TC was observed at either T1 or T2. I also investigated individual REDs indicators, and a negative association between HDL-C and T3 was observed in males at both T1 and T2 (Table 14). No association was found between LDL-C or TC and individual REDs indicators (Tables 15–16).

Table 13 Association of HDL-C, LDL-C, and TC with REDs risk in female and male athletes in a cross-sectional analysis at the beginning (T1) and end (T2) of the training season

	n	β adjusted for age	95% CI	p value
Females T1				
HDL-C	44	0.19	-0.097–0.47	0.19
LDL-C	44	-0.027	-0.53–0.48	0.92
TC	44	0.045	-0.65–0.096	0.90
Females T2				
HDL-C	36	0.074	-0.28–0.43	0.68
LDL-C	36	-0.28	-0.90–0.35	0.38
TC	36	-0.32	-1.13–0.50	0.43
Males T1				
HDL-C	43	0.064	-0.22–0.35	0.66
LDL-C	43	-0.049	-0.48–0.38	0.82

TC	43	-0.15	-0.70–0.40	0.58
Males T2				
HDL-C	35	0.091	-0.21–0.39	0.54
LDL-C	35	0.14	-0.41–0.69	0.60
TC	35	0.20	-0.53–0.94	0.57

β = beta; CI = confidence interval; REDs = relative energy deficiency in sport; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l)

Table 14 Association of HDL-C with REDs indicators in female and male athletes in a cross-sectional linear regression model at the beginning (T1) and end (T2) of the training season

T1 females	**n**	**β adjusted for age**	**95%CI**	**p value**
Menstrual status	33	0.003	-0.21–0.22	0.98
BMD	44	-0.10	-0.22–0.0005	0.051
EDE-QS	44	-0.00060	-0.028–0.026	0.96
T3	44	-0.034	-0.12–0.052	0.43
T1 males				
Testosterone	43	-0.026	-0.057–0.0054	0.10
BMD	43	0.13	-0.002–0.27	0.054
EDE-QS	43	0.00012	-0.037–0.038	0.99
T3	43	-0.12	-0.23– (-0.0084)	**0.035**
T2 females				
Menstrual status	28	-0.06	-0.47–0.35	0.77
BMD	36	-0.11	-0.27–0.032	0.12
EDE-QS	36	0.0024	-0.037–0.042	0.90
T3	36	-0.072	-0.27–0.13	0.47
T2 males				
Testosterone	35	0.00025	-0.014–0.014	0.97
BMD	35	0.066	-0.036–0.17	0.20
EDE-QS	35	0.0080	-0.021–0.037	0.57
T3	35	-0.075	-0.14–(-0.0070)	**0.031**

Bolded results are statistically significant <0.05. β = beta; CI = confidence interval; REDs = relative energy deficiency in sport; BMD = bone mineral density; EDE-QS = eating disorder examination questionnaire short version; T3 = triiodothyronine; Menstrual status = eumenorrhea/oligomenorrhoea/amenorrhoea, use of hormonal contraception excluded

Table 15 Association of LDL-C with REDs indicators in female and male athletes in a cross-sectional linear regression model at the beginning (T1) and end (T2) of the training season

T1 females	n	β adjusted for age	95%CI	p value
Menstrual status	33	0.17	-0.18–0.52	0.33
BMD	44	-0.03	-0.23–0.17	0.76
EDE-QS	44	0.034	-0.013–0.080	0.15
T3	44	0.14	-0.006–0.29	0.060
T1 males				
Testosterone	43	0.025	-0.023–0.073	0.30
BMD	43	-0.028	-0.24–0.19	0.80
EDE-QS	43	-0.0036	-0.090–0.018	0.18
T3	43	0.067	-0.11–0.24	0.44
T2 females				
Menstrual status	28	-0.22	-1.16–0.71	0.62
BMD	36	-0.06	-0.32–0.20	0.66
EDE-QS	36	-0.0043	-0.074–0.065	0.90
T3	36	0.066	-0.30–0.42	0.75
T2 males				
Testosterone	35	-0.0023	-0.027–0.023	0.85
BMD	35	0.16	-0.021–0.34	0.082
EDE-QS	35	0.023	-0.028–0.075	0.36
T3	35	0.052	-0.080–0.18	0.43

β = beta; CI = confidence interval; REDs = relative energy deficiency in sport; BMD = bone mineral density; EDE-QS = eating disorder examination questionnaire short version; T3 = triiodothyronine; Menstrual status = eumenorrhea/oligomenorrhoea/amenorrhoea, use of hormonal contraception excluded

Table 16 Association of TC with REDs indicators in female and male athletes in a cross-sectional linear regression model at the beginning (T1) and at the end (T2) of the training season

T1 females	n	β adjusted for age	95%CI	p value
Menstrual status	33	0.15	-0.34–0.64	0.55
BMD	44	-0.17	-0.44–0.10	0.21
EDE-QS	44	0.03	-0.038–0.092	0.41
T3	44	0.14	-0.068–0.35	0.18
T1 males				
Testosterone	43	0.02	-0.043–0.08	0.55
BMD	43	0.07	-0.20–0.34	0.59

EDE-QS	43	-0.05	-0.12–0.022	0.18
T3	43	0.003	-0.22–0.22	0.98
T2 females				
Menstrual status	28	-0.26	-1.45–0.92	0.65
BMD	36	-0.26	-0.59–0.085	0.14
EDE-QS	36	-0.0001	-0.091–0091	0.997
T3	36	0.05	-0.42–0.51	0.84
T2 males				
Testosterone	35	-0.004	-0.038–0.029	0.79
BMD	35	0.31	0.071–0.53	0.012
EDE-QS	35	0.04	-0.034–0.10	0.31
T3	35	-0.02	-0.20–0.16	0.84

β = beta; CI = confidence interval; BMD = bone mineral density; EDE-QS = eating disorder examination questionnaire short version; T3 = triiodothyronine; Menstrual status = eumenorrhea/oligomenorrhoea/amenorrhoea, use of hormonal contraception excluded

5.2.5 Change in cholesterol levels between T1 and T2

No significant change was observed in HDL-C, LDL-C, or TC between T1 and T2 (Tables 12 and 17). The associations between changes (Δ) in REDs risk and cholesterol levels between T1 and T2 are shown in Table 18. In female athletes I observed a negative association between the Δ REDs risk with the Δ LDL-C (adjusted β -0.62, 95% CI -0.94– (-0.30)) and the Δ TC (-0.85, 95% CI -1.42– (-0.28)).

Table 17 Multilevel model for the differences in cholesterol values between the beginning (T1) and end (T2) of the training season

Females	**n**	**β adjusted for age**	**95%CI**	**p value**
LDL-C	27	0.022	-0.21–0.25	0.85
HDL-C	27	0.076	-0.078–0.23	0.33
TC	27	0.18	-0.20–0.57	0.35
Males				
LDL-C	31	0.19	-0.017–0.39	0.079
HDL-C	31	-0.025	-0.13–0.077	0.63
TC	31	0.23	-0.054–0.52	0.12

β = beta; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l)

Table 18 Association of the change (Δ) in REDs risk between the beginning (T1) to the end (T2) of the training season with the change in cholesterol values

Δ REDs risk	n	β unadjusted	95%CI	p value	β adjusted for age	95%CI	p value
Females							
Δ HDL-C	27	-0.13	-0.38–0.12	0.30	-0.15	-0.029–0.061	0.25
Δ LDL-C	27	-0.60	-0.91– (-0.28)	**<0.001**	-0.62	-0.94– (-0.30)	**<0.001**
Δ TC	27	-0.79	-1.35– (-0.22)	**0.0082**	-0.85	-1.42– (-0.28)	**0.0050**
Males							
Δ HDL-C	31	-0.10	-0.31–0.10	0.31	-0.11	-0.34–0.12	0.35
Δ LDL-C	31	0.22	-0.19–0.62	0.28	0.21	-0.25–0.66	0.36
Δ TC	31	0.031	-0.55–0.61	0.92	0.063	-0.59–0.11	0.85

Bolded results are statistically significant <0.05. β = beta; CI = confidence interval; REDs = relative energy deficiency in sport; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l)

5.2.6 Sensitivity analysis

Hormonal contraception was used by 11 female athletes (25%) at T1 and 8 (22%) at T2. Female athletes not using hormonal contraception (n=19) were included in the longitudinal sensitivity analysis (T1+T2). The results were similar with the main analysis. We observed no association between the REDs risk and HDL-C, LDL-C, or TC at either T1 or T2 (Table 19), and Δ REDs risk had a negative association with Δ LDL-C and Δ TC (Table 20).

Table 19 Association of HDL-C, LDL-C, and TC with REDs risk in female athletes not using hormonal contraception in a cross-sectional linear regression model at the beginning (T1) and end (T2) of the training season

	n	β adjusted for age	95% CI	p value
T1				
HDL-C	33	0.06	-0.33–0.44	0.77
LDL-C	33	-0.15	-0.82–0.50	0.64
TC	33	-0.29	-1.19–0.09	0.52
T2				
HDL-C	28	0.04	-0.35–0.42	0.85
LDL-C	28	-0.01	-0.82–0.79	0.97
TC	28	-0.06	-1.09–0.98	0.91

β = beta; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l)

Table 20 Association of the change (Δ) in REDs risk from the beginning (T1) to the end (T2) of the training season with the change in cholesterol values in female athletes not using hormonal contraception

Δ REDs risk	**n**	**β unadjusted**	**95%CI**	**p value**	**β adjusted for age**	**95%CI**	**p value**
Δ HDL-C	19	-0.16	-0.47–0.14	0.28	-0.24	-0.55–0.064	0.11
Δ LDL-C	19	-0.57	-0.96– (-0.19)	**0.0061**	-0.62	-1.04– (-0.10)	**0.0054**
Δ TC	19	-0.79	-1.51– (-0.08)	**0.032**	-0.95	-1.69– (-0.21)	**0.015**

Bolded results are statistically significant <0.05. β = beta; CI = confidence interval; REDs = relative energy deficiency in sport; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l)

I also conducted sensitivity analyses to account for the potential effects of body composition or season of the year (winter, spring, summer, fall). The main findings reported in Table 18 remained similar after additional adjustment for changes in

body fat percentage or FLMR (Table 21). Additionally, the associations of change in REDs risk with change in LDL-C and TC were significant among females in both the main models (Table 18) and after further adjustment for the season of the year (ΔLDL-C β -0.55, 95% CI -0.88– (-0.22), p 0.0020; ΔTC β -0.79, 95% CI -1.39– (-0.19), p 0.012).

Table 21 Association of the change in REDs risk from the beginning (T1) to the end (T2) of the training season with the change in cholesterol values with adjustment for body fat percentage and FLMR

Δ REDs risk	n	β adjusted for Δ fat%	95%CI	p value	β adjusted for Δ FLMR	95%CI	p value
Females							
Δ HDL-C	27	-0.18	-0.44–0.079	0.17	-0.18	-0.44–0.079	0.16
Δ LDL-C	27	-0.60	-0.91– (-0.28)	**<0.001**	-0.56	-0.89– (-0.23)	**0.0020**
Δ TC	27	-0.79	-1.36– (-0.21)	**0.0090**	-0.80	-1.39– (-0.19)	**0.012**
Males							
Δ HDL-C	31	-0.09	-0.29–0.11	0.36	-0.09	-0.29–0.11	0.37
Δ LDL-C	31	0.20	-0.21–0.60	0.32	0.20	-0.21–0.60	0.33
Δ TC	31	0.020	-0.57–0.61	0.95	0.018	-0.57–0.61	0.95

Bolded results are statistically significant <0.05. β = beta; CI = confidence interval; REDs = relative energy deficiency in sport; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l); FMLR = fat mass–to–lean mass ratio

5.3 Association between REDs risk and the metabolome (Study III)

5.3.1 Participant characteristics

Our final study sample included 150 participants and 329 measurements (1–6 measurements per individual) (Figure 7). Of the 150 participants, 96 (64%) were female and 54 (36%) were male. Participants represented endurance sports (long-distance running, cross-country skiing, Nordic combined, biathlon, triathlon, orienteering, and race walking, n=67, 45%), other weight-sensitive sports (track and field and ski jumping, n=21, 14%) and non-weight-sensitive sports (javelin throw, rugby, and ice hockey, n=62, 41%). Details of participant characteristics are shown in Table 22. During the first measurements, 25 (26%) of the 96 female athletes and 20 (37%) of the 54 male athletes had elevated LDL-C (≥3mmol/l). Among females, athletes representing non-weight-sensitive sports had significantly

higher BMI and body fat percentage than endurance athletes and athletes representing other weight-sensitive sports ($p < 0.001$ for all comparisons). Additionally, athletes representing non-weight-sensitive sports had significantly lower HDL-C than endurance athletes (p 0.026) and lower REDs scores than both endurance athletes (p 0.033) and athletes representing other weight-sensitive sports (p 0.045).

Among males, athletes representing other weight-sensitive sports had significantly lower BMIs than athletes representing non-weight-sensitive ($p < 0.001$) or endurance sports ($p < 0.001$), and endurance athletes also had lower BMIs than athletes representing non-weight-sensitive sports ($p < 0.001$). Athletes representing non-weight-sensitive sports had a significantly higher body fat percentage than athletes representing other weight-sensitive ($p < 0.001$) or endurance sports ($p < 0.001$). Athletes representing non-weight-sensitive sports also had higher LDL-C than athletes representing other weight-sensitive (p 0.008) or endurance sports (p 0.030).

Table 22 Characteristics of study participants in their first measurement separated by sport categories

	Females				Males			
	Endurance	**Other weight-sensitive**	**Non-weight-sensitive**	**p(Female)**	**Endurance**	**Other weight-sensitive**	**Non-weight-sensitive**	**p(Male)**
n	34	10	52		33	11	10	
Age	24.7 ± 4.1	23.7 ± 4.2	24.3 ± 4.9	0.702	25.1 ± 3.6	22.3 ± 3.2	23.3 ± 3.0	0.058
BMI	20.7 ± 1.4	20.8 ± 1.5	24.7 ± 2.6	**<0.001**	22.4 ± 1.7	19.6 ± 0.9	27.8 ± 1.8	**<0.001**
Body fat %	16.7 ± 4.3	18.9 ± 6.1	28.2 ± 6.2	**<0.001**	9.4 ± 3.9	6.6 ± 1.6	18.8 ± 7.0	**<0.001**
REDs score	0 [0–1]	0.5 [0–1.9]	0 [0–0]	**0.008**	1 [0–1]	1 [0.5–1]	1 [0.2–1]	0.897
HDL-C	1.7 ± 0.4	1.6 ± 0.4	1.5 ± 0.3	**0.01**	1.5 ± 0.3	1.4 ± 0.3	1.3 ± 0.2	**0.033**
LDL-C	2.7 ± 0.7	2.6 ± 0.4	2.6 ± 0.6	0.366	2.7 ± 0.7	2.6 ± 0.6	3.3 ± 0.6	**0.033**
TC	5.1 ± 1.0	4.9 ± 0.8	4.7 ± 0.8	**0.037**	4.7 ± 0.8	4.4 ± 0.6	5.2 ± 0.5	0.22
TG	0.8 ± 0.2	0.8 ± 0.5	0.8 ± 0.4	0.747	0.8 ± 0.3	0.7 ± 0.1	1.0 ± 0.5	0.229

Results reported as mean ± standard deviation or median [interquartile range], p values represent analysis of variance (ANOVA)/Kruskal–Wallis between-group differences, bolded text represents statistically significant results (<0.05). BMI = body mass index (kg/m^2); HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein (mmol/l); TC = total cholesterol (mmol/l); TG = triglycerides (mmol/l); REDs = relative energy deficiency in sport

5.3.2 REDs risk

Of the female participants' first measurements, 26 of 96 (27%) were classified as being at risk of REDs (>0.5 points). In total 36 of 52 (69%) males scored over 0.5 points in their first measurements and were categorised as being at REDs risk. In all measurements of female athletes (n=218), in 55 cases (25%) the athlete was classified as being at risk of REDs and among male athletes (n=111), there were 69 cases (62%) of REDs risk. In total, 59 (86%) of these REDS risk cases in males were solely due to sub-clinically low testosterone.

5.3.3 REDs risk and the metabolome

I analysed the association between the metabolome and REDs risk with GEE analysis adjusted for season, age and binary sport class. All nominally significant results are presented in a heatmap (Figure 9A and 9B). Metabolites that remained significant after correction for multiple testing are shown in the bar plot (Figure 9C).

Among female athletes, IDL particle concentration and phospholipid content in extra-small VLDL particles had a statistically significant positive association with REDs risk in the GEE analysis after correction for multiple testing (Figure 9). I also conducted a sensitivity analysis for females not using hormonal contraception (n=137), where only albumin was found to have a statistically significant positive association with REDs risk after correction for multiple testing.

Among male athletes, no statistically significant association was observed between the metabolome and REDs risk after correction for multiple testing.

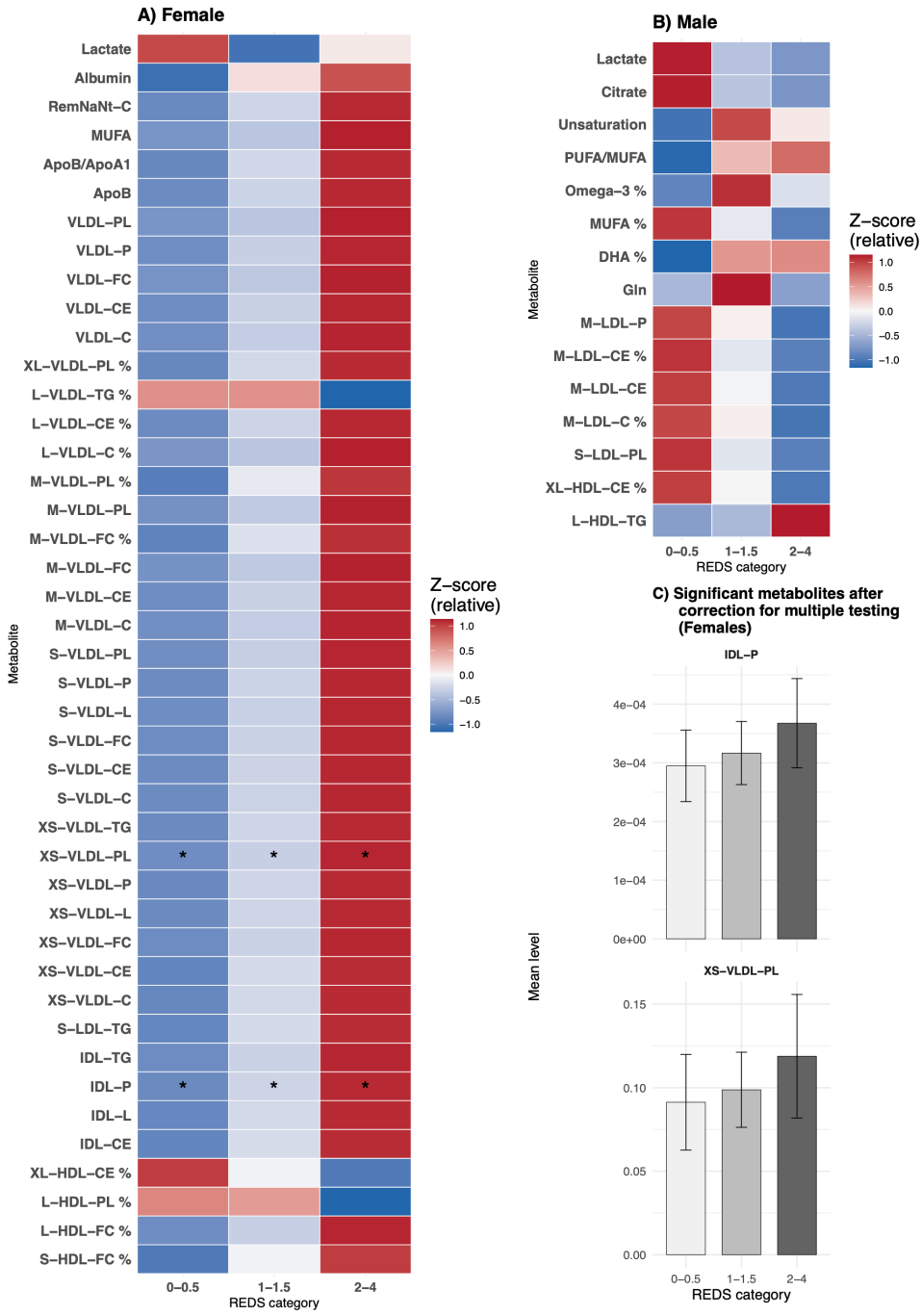

A) Female
Lactate
Albumin
RemNaNt–C
MUFA
ApoB/ApoA1
ApoB
VLDL–PL
VLDL–P
VLDL–FC
VLDL–CE
VLDL–C
XL–VLDL–PL %
L–VLDL–TG %
L–VLDL–CE %
L–VLDL–C %
M–VLDL–PL %
M–VLDL–PL
M–VLDL–FC %
M–VLDL–FC
M–VLDL–CE
M–VLDL–C
S–VLDL–PL
S–VLDL–P
S–VLDL–L
S–VLDL–FC
S–VLDL–CE
S–VLDL–C
XS–VLDL–TG
XS–VLDL–PL
XS–VLDL–P
XS–VLDL–L
XS–VLDL–FC
XS–VLDL–CE
XS–VLDL–C
S–LDL–TG
IDL–TG
IDL–P
IDL–L
IDL–CE
XL–HDL–CE %
L–HDL–PL %
L–HDL–FC %
S–HDL–FC %
Metabolite
0–0.5
1–1.5
2–4
REDS category
Z–score (relative)
1.0
0.5
0.0
–0.5
–1.0
B) Male
Lactate
Citrate
Unsaturation
PUFA/MUFA
Omega–3 %
MUFA %
DHA %
Gln
M–LDL–P
M–LDL–CE %
M–LDL–CE
M–LDL–C %
S–LDL–PL
XL–HDL–CE %
L–HDL–TG
Metabolite
0–0.5
1–1.5
2–4
REDS category
Z–score (relative)
1.0
0.5
0.0
–0.5
–1.0
C) Significant metabolites after correction for multiple testing (Females)
IDL–P
4e–04
3e–04
2e–04
1e–04
0e+00
XS–VLDL–PL
0.15
0.10
0.05
0.00
Mean level
0–0.5
1–1.5
2–4
REDS category

Figure 9 Heatmap representing associations between the metabolome and REDs score in females and males and bar plot of significant metabolites after correction for multiple testing. In panels A and B, all metabolites with association trend (nominally statistically significant) with REDs scores are presented. Associations that remained statistically significant after correction for multiple testing are marked with an asterisk (*). A) Metabolites associated with REDs score in females. B) Metabolites associated with REDs score in males. C) Bar plots represent mean ± standard deviation of metabolites that remained significant after correction for multiple testing in females. Continuously modelled associations are shown in REDs score categories for illustration. There were no associations that remained significant after correction for multiple testing among males. All analyses were adjusted for season, age and sport. Metabolite colours are represented as standard deviation (SD) change from reference Z-score. Reference Z-score level was set from the pooled sex-specific metabolite mean. Results from the first measurement point are used for the heatmaps and bar plots. For visualisation, REDs scores were divided into three categories: 0–0,5; 1–1.5, 2–4. REDs = relative energy deficiency in sport; S/M/L/XL = small/medium/large/extra-large; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; C = cholesterol; CE = cholesterol esters; L = total lipids; P = particles concentration; PL = phospholipids; FC = free cholesterol; BCAA = branch-chained amino acids; MUFA = mono-unsaturated fatty acids; DHA = docosahexaenoic acid; PUFA = poly-unsaturated fatty acid

5.3.1 Sensitivity analysis on menstrual status and testosterone

As a sensitivity analysis, I examined associations of menstrual status and testosterone with the metabolome in more detail since amenorrhoea in female athletes and low testosterone in male athletes are considered severe primary indicators of REDs (Stellingwerff et al. 2023). Characteristics of participants in each group are presented in Table 23. Among females, LDL-C was higher among athletes with amenorrhoea when compared with athletes with oligomenorrhoea (p 0.045). Among males, there were no between-group differences, apart from REDs risk score.

GEE analyses between menstrual status or testosterone and the metabolome were adjusted for season, age and binary sport class. Lipid ratios of large and extra-large VLDL particles, as well as glucose level, had a significant association with menstrual status after correction for multiple testing (Figure 10A). For testosterone, after correction for multiple testing, a positive association was found with free-cholesterol content in small HDL particles, composition of medium LDL particles and content and proportion of mono-unsaturated fatty acids (MUFA), and a negative association with poly-unsaturated fatty acids (PUFA), PUFA:MUFA ratio and degree of unsaturation in fatty acids (Figure 10B).

Table 23 Characteristics of female participants in each menstrual status group and of male participants in each testosterone group

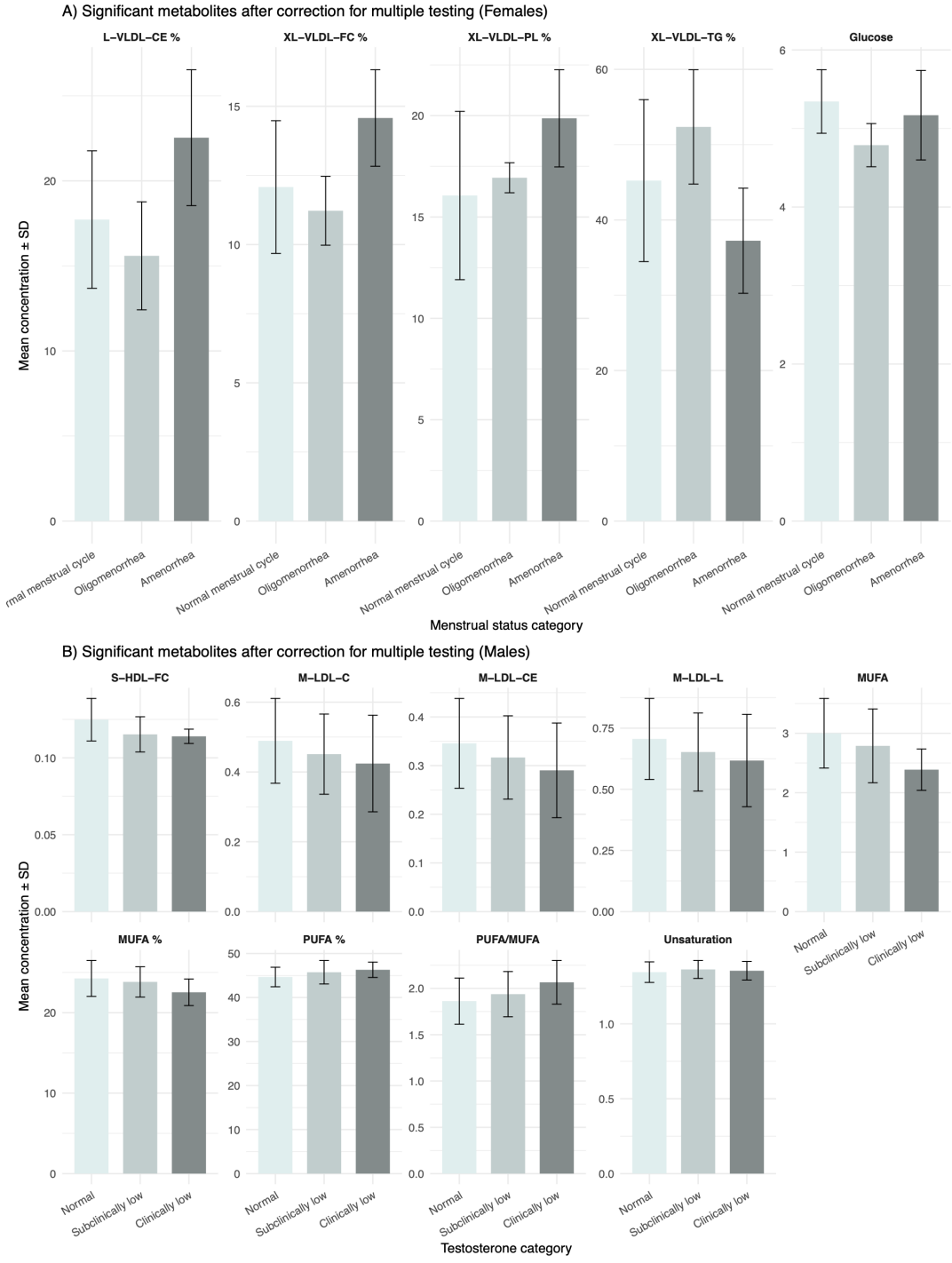
	Hormonal contraception	Normal menstrual cycle	Oligomenorrhoea	Amenorrhoea
n	37	48	4	7

Age	24.2 ± 4.8	24.9 ± 4.4	25.2 ± 6.6	21.6 ± 2.2
BMI	23.0 ± 3.0	23.3 ± 2.9	20.7 ± 2.7	20.9 ± 0.8
Body fat %	24.6 ± 7.5	23.3 ± 8.2	18.5 ± 6.2	17.3 ± 4.5
REDs score	0 [0–0.5]	0 [0–0]	0.5 [0.5–0.8]	2 [2–3.5]
HDL-C	1.6 ± 0.4	1.6 ± 0.4	1.4 ± 0.2	1.6 ± 0.3
LDL-C	2.5 ± 0.5	2.6 ± 0.6	2.1 ± 0.5	3.2 ± 0.7
TC	4.8 ± 0.8	4.8 ± 0.8	4.1 ± 0.4	5.6 ± 1.0
TG	0.9 ± 0.4	0.7 ± 0.2	0.6 ± 0.2	0.8 ± 0.3

	Normal testosterone	**Subclinically low testosterone**	**Clinically low testosterone**
n	22	29	3
Age	24.3 ± 3.5	24.4 ± 3.8	22.3 ± 0.7
BMI	22.7 ± 2.5	23.3 ± 3.5	20.7 ± 2.8
Body fat %	9.5 ± 3.1	11.9 ± 7.4	5.9 ± 1.1
REDs score	0 [0–0]	1 [1–1]	2 [2–2]
HDL-C	1.5 ± 0.3	1.3 ± 0.3	1.5 ± 0.2
LDL-C	2.9 ± 0.7	2.7 ± 0.7	2.6 ± 0.9
TC	5.0 ± 0.7	4.6 ± 0.8	4.6 ± 1.0
TG	0.9 ± 0.3	0.9 ± 0.4	0.7 ± 0.2

Results reported as mean ± standard deviation or median [interquartile range]. BMI = body mass index; % = percentage; REDs = relative energy deficiency in sport; HDL-C = high-density lipoprotein cholesterol (mmol/l); LDL-C = low-density lipoprotein cholesterol (mmol/l); TC = total cholesterol (mmol/l); TG = triglycerides (mmol/l)

Figure 10 Associations between the metabolome and menstrual status in females and testosterone in males. Bar plots represent mean ± standard deviation (SD) of metabolites that remained significant after correction for multiple testing. For testosterone, continuously modelled associations are shown in categories for illustration. A) Association between the metabolome and menstrual status in females, model adjusted for age, season and sport. B) Association between metabolome and testosterone in males, adjusted for age, season and sport. S/M/L = small/medium/large; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; C = cholesterol; CE = cholesterol esters; TG = triglycerides; L = total lipids; PL = phospholipids; FC = free cholesterol; MUFA = mono-unsaturated fatty acids; PUFA = poly-unsaturated fatty acid


A) Significant metabolites after correction for multiple testing (Females)
L−VLDL−CE %
XL−VLDL−FC %
XL−VLDL−PL %
XL−VLDL−TG %
Glucose
Mean concentration ± SD
Normal menstrual cycle
Oligomenorrhea
Amenorrhea
Menstrual status category
B) Significant metabolites after correction for multiple testing (Males)
S−HDL−FC
M−LDL−C
M−LDL−CE
M−LDL−L
MUFA
MUFA %
PUFA %
PUFA/MUFA
Unsaturation
Normal
Subclinically low
Clinically low
Testosterone category

5.3.2 Sensitivity analysis in athletes representing weight-sensitive sports

As another sensitivity analysis, we examined the associations between REDs risk and the metabolome among athletes representing weight-sensitive sports. Among female athletes representing weight-sensitive sports, after correction for multiple testing, a significant association between REDs risk and particle count and TG content of IDL and lipid measures, predominantly in extra-small VLDL particles, was observed. In addition, a negative association with lactate was observed. These findings remained robust when considering only those athletes not using hormonal contraception, except for lactate. After adjusting the main analysis to body fat percentage, both large and small VLDL pathways were strengthened, and a positive association between REDs risk and TG content in LDL particles was observed.

Among male athletes representing weight-sensitive sports, only creatine was associated with REDs risk. However, when inspecting the bar plots, a U-shaped association is seen (mean ± SD 88.0 ±11, 83.8±9.2, and 89.2±9 μmol/l for REDs categories 0–0.5, 1–1.5 and 2–4, respectively).

We also specifically looked into endurance athletes due to their particular training modalities that could predispose them to specific metabolic pathways. Among female endurance athletes, in the main analysis, no statistically significant associations were identified after correction for multiple testing. However, similar to what was observed in weight-sensitive female athletes, the associations were strengthened after adjustment for body fat percentage. In these analyses, REDs risk was significantly associated with lipids ratios of large VLDLs and omega-6 % after correction for multiple testing.

Among male endurance athletes, adjustment for body fat percentage did not affect the results. After correction for multiple testing, a significant positive association with TG content in large HDL and a negative association with creatinine was observed both before and after adjustment for body fat percentage.

5.3.3 Body fat percentage and the metabolome

We analysed the association between the metabolome and body fat percentage using GEE analysis adjusted for season and age. All nominally significant results are presented in a heatmap (Figure 11). Among both female and male athletes, body fat percentage had the strongest associations with HDL metabolites. Specifically in females, after correction for multiple testing increasing body fat percentage was associated with a decrease in HDL size; a decrease in the concentration of large HDL particles and their content of cholesterol, CEs, and free cholesterol; a decrease in the concentration of extra-large HDL particles, as well as their content of lipids and phospholipids; and an increase in small HDL particles and their content of

cholesterol, CEs and lipids; and a decrease of free cholesterol proportion in small, medium and large HDLs, but an increase in extra-large HDL particles. We observed a positive association between body fat percentage and glucose and the inflammatory marker GlycA after correction for multiple testing. Of the amino acids, phenylalanine and leucine showed a positive association with body fat percentage in females after correction for multiple testing.

Among male athletes, several associations between body fat percentage and the metabolome were observed after multiple testing. We found a positive association between body fat percentage and the proportion of free cholesterol in extra-large HDL particles and a negative association with cholesterol, CEs, free cholesterol, lipids, and phospholipids in large HDLs, as well as with extra-large HDL particle concentration and their content of lipids and phospholipids. A negative association between body fat percentage and ketone bodies acetone and beta-hydroxybutyrate was observed. There was a positive association between body fat percentage and docosahexaenoic acid (DHA), glucose and GlycA. A positive association was observed between body fat percentage and tyrosine in males.

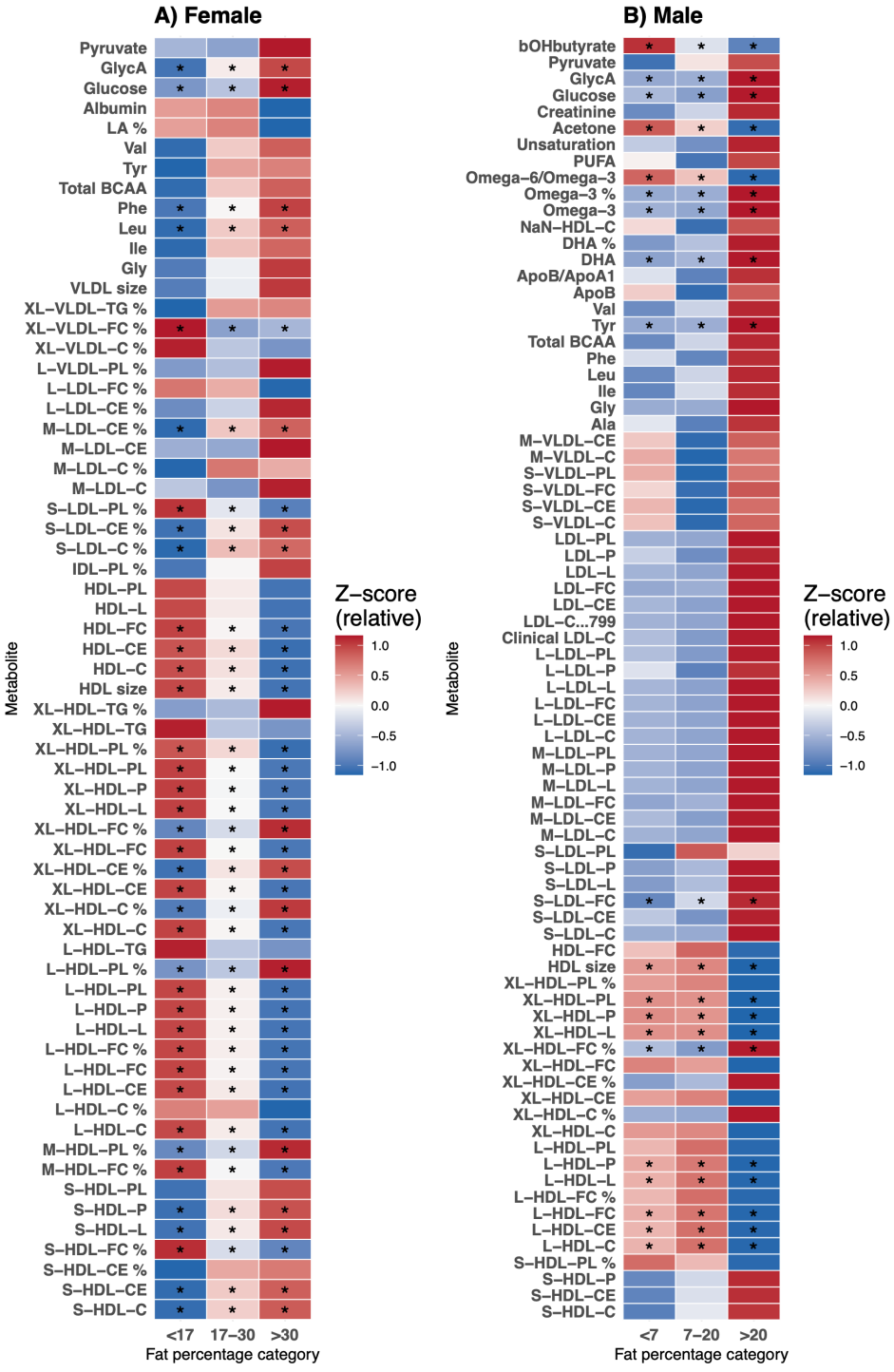

A) Female
Pyruvate
GlycA
Glucose
Albumin
LA %
Val
Tyr
Total BCAA
Phe
Leu
Ile
Gly
VLDL size
XL–VLDL–TG %
XL–VLDL–FC %
XL–VLDL–C %
L–VLDL–PL %
L–LDL–FC %
L–LDL–CE %
M–LDL–CE %
M–LDL–CE
M–LDL–C %
M–LDL–C
S–LDL–PL %
S–LDL–CE %
S–LDL–C %
IDL–PL %
HDL–PL
HDL–L
HDL–FC
HDL–CE
HDL–C
HDL size
XL–HDL–TG %
XL–HDL–TG
XL–HDL–PL %
XL–HDL–PL
XL–HDL–P
XL–HDL–L
XL–HDL–FC %
XL–HDL–FC
XL–HDL–CE %
XL–HDL–CE
XL–HDL–C %
XL–HDL–C
L–HDL–TG
L–HDL–PL %
L–HDL–PL
L–HDL–P
L–HDL–L
L–HDL–FC %
L–HDL–FC
L–HDL–CE
L–HDL–C %
L–HDL–C
M–HDL–PL %
M–HDL–FC %
S–HDL–PL
S–HDL–P
S–HDL–L
S–HDL–FC %
S–HDL–CE %
S–HDL–CE
S–HDL–C
Metabolite
<17
17–30
>30
Fat percentage category
Z–score (relative)
1.0
0.5
0.0
−0.5
−1.0
B) Male
bOHbutyrate
Pyruvate
GlycA
Glucose
Creatinine
Acetone
Unsaturation
PUFA
Omega–6/Omega–3
Omega–3 %
Omega–3
NaN–HDL–C
DHA %
DHA
ApoB/ApoA1
ApoB
Val
Tyr
Total BCAA
Phe
Leu
Ile
Gly
Ala
M–VLDL–CE
M–VLDL–C
S–VLDL–PL
S–VLDL–FC
S–VLDL–CE
S–VLDL–C
LDL–PL
LDL–P
LDL–L
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L–HDL–L
L–HDL–FC %
L–HDL–FC
L–HDL–CE
L–HDL–C
S–HDL–PL %
S–HDL–P
S–HDL–CE
S–HDL–C
Metabolite
<7
7–20
>20
Fat percentage category
Z–score (relative)
1.0
0.5
0.0
−0.5
−1.0

Figure 11 Heatmap representing associations between the metabolome and body fat percentage in females and males. In panels A and B, all metabolites with association trend (nominally statistically significant) with body fat percentage are presented. Associations that remained statistically significant after correction for multiple testing are marked with an asterisk (*). A) Metabolites associated with body fat percentage in females. B) Metabolites associated with body fat percentage in males. Continuously modelled associations are shown in fat percentage categories for illustration. All analyses were adjusted for season, age and sport. Metabolite colours are represented as standard deviation (SD) change from reference Z-score. Reference Z-score level was set from pooled sex-specific metabolite mean. Results from the first measurement point are used for the heatmaps and bar plots. For visualisation, body fat percentages were divided into three categories: <17%, 17–30%, and >30% for females and >7%, 7<-20%, and >20% for males. S/M/L/XL = small/medium/large/extra-large; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; C = cholesterol; CE = cholesterol esters; L = total lipids; P = particles concentration; PL = phospholipids; FC = free cholesterol; TG = triglycerides, BCAA = branch-chained amino acids; Ala = alanine; Ile = isoleucine; Val = valine; Tyr = tyrosine; Gly = glycine; Leu =leucine; Phe = phenylalanine; DHA = docosahexaenoic acid; PUFA = poly-unsaturated fatty acid; GlycA = glycoprotein acetylation; LA = linoleic acid; bOHbutyrate = beta-hydroxybutyrate; NaN-HDL-C = total cholesterol minus HDL-C; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B

6 Discussion

6.1 Summary of main findings

In Study I, I investigated the association between cholesterol levels and symptoms of LEA and EDs in a cross-sectional design of Finnish female athletes representing a mixed-sport sample. Symptoms of LEA were assessed with the LEAF-Q and ED symptoms with the EDE-QS. In the entire study sample, I found a positive association between EDE-QS score and LDL-C and TC, and the OR for having elevated LDL-C in the high-scoring EDE-QS group (≥15 points) was 2.94. In a sensitivity analysis restricted to athletes representing weight-sensitive sports, a positive association of both the LEAF-Q and EDE-QS with LDL-C was identified. Surprisingly, I did not observe any association between menstrual disturbances and cholesterol levels.

In Study II, I investigated the association between REDs risk and cholesterol levels in Finnish endurance athletes at two timepoints (T1 and T2) of their training season. In the cross-sectional analysis, I found no association between any of the studied cholesterol levels and REDs risk, nor did I see any significant change in the studied parameters from T1 to T2. Interestingly, among female athletes an inverse relationship between change of REDs risk and change in LDL-C between T1 and T2 was identified. Additionally, up to 30% of the athletes had elevated LDL-C levels (≥3mmol/l), regardless of their REDs risk.

In Study III, I analysed the serum metabolome in a mixed-sports sample consisting of both female and male athletes. Among females, REDs risk was associated with a few changes in VLDL and IDL pathways, and but not among males. In female athletes representing weigh-sensitive sports these associations were further strengthened. Interestingly, body fat percentage had very distinct patterns of association with the metabolome than REDs risk, and in both females and males lower body fat percentage was strongly associated with a larger HDL profile and reduced inflammation, indicating a more beneficial metabolic fingerprint.

6.2 Prevalence of REDs risk in the Finnish athletic population

As stated previously, identifying REDs in the real-world is difficult. Current recommendations for identifying athletes at risk of REDs advise to search for symptoms and clinical findings possibly caused by problematic LEA (Stellingwerff et al. 2023). After identifying athletes at risk, a fundamental clinical evaluation should be carried out individually to identify other possible reasons and conditions behind the findings. Therefore, questionnaires and even symptoms and clinical findings alone cannot be used to diagnose REDs but rather identify at-risk individuals.

In Study I, I used the LEAF-Q to identify female athletes at risk of REDs. The LEAF-Q score was elevated (≥8 points) in 44% of athletes in the mixed-sport sample. When looking more specifically into menstrual dysfunction – one of the primary indicators of REDs in females – 25% of the participants had either oligomenorrhoea or amenorrhoea. Of athletes representing weight-sensitive sports, 47% scored above the 8-point threshold in the LEAF-Q and 38% had menstrual dysfunction.

In Studies II and III, I used the modified REDs CAT 2 to identify athletes at risk of REDs. In Study II, over two-thirds of both female and male endurance athletes were categorised as being at risk of REDs, and up to 36% of the females had menstrual dysfunction. In Study III, 25% of female athletes and 62% of male athletes were categorised as being at risk of REDs and 23% of females had some type of menstrual dysfunction.

Our results reflect the current state of varying REDs prevalences. Our REDs risk prevalences align with previous results, where the prevalence of indicators of problematic LEA among athletes has been estimated to range from 15 to 80%, depending on the study population, sex, and sport (Mountjoy et al. 2023). A recent meta-analysis reported that, overall, 45% of athletes were at increased risk of LEA, and 61.1% were classified as having REDs (Gallant et al. 2024). The heterogeneity in the meta-analysis was large (I^2 = 72.4–91.38), which can be due to the inconsistent methods used to classify the risk of LEA and REDs between studies, ranging from self-reported questionnaires and calculated EA based on food and training logs, to the reporting of a single symptom of REDs (Gallant et al. 2024). Many of the used classification methods are prone to error, and have only been validated in specific athletic populations (Jeukendrup et al. 2024). Additionally, terms and classifications of REDs and LEA were used interchangeably between studies. However, similar REDs risk prevalence rates were obtained in a study using the REDs CAT 2. In a sample of more than 200 tier 3–5 athletes, the prevalence of REDs risk was 45% (more specifically 55% were classified as green, 36% as yellow, 5% as orange and 4% as red, according to the REDs CAT 2 [for more details see

Table 2])(Heikura et al. 2024). It is important to distinguish that the risk of REDs and LEA describe athletes who may potentially be impacted by these conditions and cannot be interpreted as REDs or LEA prevalences. Therefore, there is a considerable risk of overestimation of the prevalence of REDs in the previously conducted studies, and these results should be interpreted as prevalences of risk and not as confirmed cases.

Others have also reported elevated prevalence rates of REDs and LEA in endurance athletes compared to other athlete populations. Endurance athletes are particularly susceptible to problematic LEA and REDs due to their high training volumes, increased risk of DE, and the weight-sensitive nature of their sports (Gallant et al. 2024). Specifically, it has been reported that 18–80% of female endurance athletes (Melin et al. 2015; Kettunen et al. 2023; Muia et al. 2016; Fahrenholtz et al. 2022; Jesus et al. 2021; Karlsson et al. 2023; Dervish et al. 2023; Viner et al. 2015; McCormack et al. 2019) and 42–70% of male endurance athletes are considered at risk of REDs or LEA (Jesus et al. 2021; Viner et al. 2015; Lane et al. 2019; Moore et al. 2021; McCormack et al. 2019). The observed high prevalence rates of REDs risk in my studies align with previous results.

In both Studies II and III, a substantial proportion of male athletes had sub-clinically or clinically low testosterone levels. In Study II, 48–60% of male endurance athletes fell below the threshold of sub-clinically low testosterone and in Study III, 53% of males representing a mixed-sports sample had at least sub-clinically low testosterone. All these athletes were classified as at-risk athletes according to the REDs CAT 2, but it is also possible that many of them could have decreased levels of testosterone due to exercise, as has been described as EHMC (Hackney 2020). In particular, those athletes who scored for sub-clinically low testosterone in the REDs CAT 2 (86% of at-risk cases in Study III) could indeed represent EHMC rather than problematic LEA.

Taken together, it is important to highlight that the prevalence estimates in my studies indicate the *risk* of REDs, and a thorough individual evaluation could not be conducted. A further clinical and laboratory examination by an expert physician, preferably in a multi-professional team, would have been required to obtain information about the individual situation, to rule out other potential causes, and to strengthen the evaluation of REDs (Stellingwerff et al. 2023). Given the burdensome path for confirming a state of REDs in the healthcare system, these resources are rarely available for athletes, which poses a potential major threat for athletes' health and well-being.

6.3 Cholesterol and REDs risk

Elevated LDL-C and TC are listed among potential indicators of REDs in the REDs IOC Consensus Statement 2023 and REDs CAT 2 (Mountjoy et al. 2023;

Stellingwerff et al. 2023). The studies supporting this association are from patients with anorexia nervosa (a prolonged extreme form of LEA), military service (8-week extreme LEA) and case studies of athletes with extreme weight-loss strategies (5-day extreme LEA and dehydration)(Hussain et al. 2019; Friedl et al. 2000; Langan-Evans et al. 2021). In addition, a recent meta-analysis of 18 observational studies concluded that physically active females with secondary amenorrhoea (a potential indicator of LEA) had elevated LDL-C, TC, HDL-C and TG compared to females with normal menstrual cycles (Tegg et al. 2024), but due to the nature of the studies, the certainty of the evidence was rated very low. Further, some studies did not find any association between menstrual disturbances and levels of LDL-C or TC (Ayres et al. 1998; D. L. Thompson et al. 1997). Female athletes with FHA and patients with anorexia nervosa can have similar disturbances in different hormonal axes, contributing to the observed alterations in cholesterol metabolism (Kirsty J. Elliott-Sale et al. 2018; Hussain et al. 2019, 2023). Particularly low levels of oestrogen, as observed post menopause and linked with changes in cholesterol (Matthan et al. 2005), have been proposed to affect the development of pro-atherogenic lipid profiles in amenorrhoeic athletes (Rickenlund et al. 2005).

In Study I, I could only identify a positive association between LEAF-Q score and LDL-C in weight-sensitive athletes, but not among a mixed-sports sample. Since the LEAF-Q has only been validated in female endurance athletes, its reliability in other athlete populations is uncertain and could therefore explain the discrepancy in the results. However, in neither Study II nor III, did I find any association between REDs risk, assessed with the REDs CAT 2, and HDL-C, LDL-C or TC in cross-sectional analysis of either mixed-sports sample or endurance athletes. Therefore, I did not find consistent results to support the current REDs model, where elevated LDL-C and TC are listed as secondary indicators.

One explanation for the lack of association in my studies could be the severity of REDs risk. In Studies II and III, only a few athletes were at high REDs risk, and most were rated as mild to moderate risk. As previous studies have shown, moderate- or short-term energy deprivation tends to have beneficial effects on the lipid profile (Most et al. 2018; Lefevre et al. 2009; Magkos 2022; Karimi et al. 2021), whereas severe and prologued starvation can lead to the opposite effects (Hussain et al. 2019; Friedl et al. 2000; Langan-Evans et al. 2021). Moderate energy reduction or weight loss may induce positive changes in the fat and overall composition of the diet and in the body composition without drastic changes in the endocrine milieu, whereas extreme or prolonged LEA can lead to a chronic hypometabolic state altering several hormonal axes, and even altered lipid metabolism.

Interestingly, in Study II, I could identify an inverse relationship between change in REDs risk and change in LDL-C and TC from T1 to T2 (with a time difference of 4.4 months) among female endurance athletes. Although I could not

see a group level change in REDs risk or cholesterol levels between the timepoints, my results indicate that those females whose REDs risk increased during the athletic year tended to show reductions in their LDL-C and TC levels. This could be due to the acute positive effect that LEA can have on cholesterol levels and health (Most et al. 2018; Lefevre et al. 2009; Magkos 2022; Jouhki et al. 2024; Sarin et al. 2019; Nusser et al. 2025). With reduced EA, these individuals could have reduced the intake of saturated fat and cholesterol. On the other hand, those with increased EA and therefore reduced REDs risk status might have increased their intake of saturated fat and cholesterol, leading to a short-term elevation in LDL-C and TC. However, due to their unreliability (Burke et al. 2018; Capling et al. 2017), food diaries were not analysed in my studies and thus, these reasonings remain hypothetical.

Since amenorrhoea is considered a severe primary indicator of REDs in females, I also specifically investigated the association between menstrual status and cholesterol levels. Surprisingly, in Studies I and II, I could not identify any association between menstrual dysfunction (athletes with amenorrhoea or oligomenorrhoea vs normally menstruating athletes) and cholesterol levels in any of our study populations.

In Study III, I compared athletes in three groups: those with amenorrhoea, those with oligomenorrhoea and those with a normal menstrual cycle. I observed that LDL-C was higher among athletes with amenorrhoea when compared with athletes with oligomenorrhoea (3.2mmol/l vs 2.1 mmol/l for amenorrhoea and oligomenorrhoea respectively, p 0.045). This phenomenon of the most beneficial cholesterol levels being observed in athletes with oligomenorrhoea has been reported previously (Rickenlund et al. 2005), and distinct endocrine pathways have been suggested for amenorrhoea and oligomenorrhoea (Rickenlund et al. 2004). In my study, athletes with oligomenorrhoea had similar BMIs (20.7) and body fat percentages (18.5%) to females with amenorrhoea (20.9, and 17.3%, respectively), which suggests that anthropometrics alone cannot be used to distinguish menstrual dysfunction associated with further endocrine disturbances. Females with amenorrhoea also seemed to have higher LDL-C (3.2 vs 2.6mmol/l) and TC (5.6 vs 4.8mmol/l), but similar HDL-C (1.6 vs 1.6mmol/l), than naturally menstruating females, but no statistically significant differences could be observed. Females with amenorrhoea also seemed to have lower body fat percentage (17.3 vs 23.3%) and BMI (20.9 vs 23.3) than naturally menstruating females, but these differences were not statistically significant.

These results suggest that the categorisation of both those with amenorrhoea and those with oligomenorrhoea into the same group of menstrual disturbances in Studies I and II might have affected the results and our findings of between-group differences. Additionally, the classification of menstrual status was solely based on self-reported questionnaire responses. No hormonal investigation was performed

to distinguish FHA from other potential causes of menstrual dysfunction, which may have affected our findings. Due to the low number of participants, these results remain exploratory and need further replication. Future studies should analyse amenorrhoea and oligomenorrhoea distinctly in relation to cholesterol levels.

6.4 Cholesterol and ED behaviour

In Study I, ED behaviour (assessed with EDE-QS score) was associated with both LDL-C and TC in females representing mixed-sport as well in females representing weight-sensitive sports. DE behaviour and clinical EDs are risk factors for REDs (Mountjoy et al. 2023), and screening for DE behaviour is part of the recommended REDs screening (Stellingwerff et al. 2023). The EDE-QS might have captured athletes at risk of problematic LEA but, interestingly, adjusting the model to LEA symptoms (LEAF-Q) further strengthened the association between the EDE-QS and LDL-C and TC. This suggests that ED behaviour might have an independent association with these cholesterol levels.

Our findings are in line with previous studies on patients with EDs. Anorexia nervosa is an extreme form of LEA and patients with anorexia nervosa have in many ways compromised health due to the severe starvation (Papadopoulos et al. 2009; Schorr and Miller 2017; Sachs et al. 2016). Elevated LDL-C and TC levels have been reported in patients with anorexia nervosa before and after weight-restoration treatment (Hussain et al. 2023). Since the hyperlipidaemia persists even after weight restoration, it has been proposed that this phenomenon could be unrelated to LEA, but rather associated with the anorexia nervosa phenotype per se (Hussain et al. 2023). However, this might be a precipitous conclusion since the lipid levels had been re-evaluated after only ~3 months of weight-restoration treatment. Even if the patients had normalised their BMI, this might not be sufficient for normalisation of all physiological and endocrine functioning.

Additionally, in less severe forms of DE, elevated LDL-C and TC have been observed. Adolescent girls with DE behaviour leading to weight loss and amenorrhoea were reported to have elevated LDL-C and TC levels (Swenne 2016). Females with lower gynaecological age have been reported to be at greater risk of developing endocrine disturbances due to problematic LEA (Loucks 2006). To my knowledge, previous studies have not studies the cholesterol levels of athletes with DE behaviour or clinical EDs. Therefore, our analysis on the association between EDE-QS and LDL-C and TC was novel.

In Studies II and III, the EDE-QS was included in the REDs risk assessment, contributing to the identification of athletes at risk of REDs, but no specific analyses examining the association between ED behaviour and cholesterol or the metabolome were conducted.

6.5 Elevated LDL-C levels in the Finnish athletic population

In Study II, I reported that up to 30% of athletes had elevated LDL-C levels (≥3mmol/l) and in Study III, 26% of female athletes and 37% of male athletes had elevated LDL-C. These prevalences correspond to those in the general population of young adults (Zheutlin et al. 2024; Yiyi Zhang et al. 2022), suggesting that athletes are not protected from dyslipidaemia but rather are at a similar risk to age-matched peers. Similar results have also been previously reported in Italian Olympic athletes, where 26% of athletes had elevated LDL-C (>3mmol/l)(Gioia et al. 2024). However, the exercise modality or body composition may influence LDL-C levels since in Study III, athletes representing non-weight-sensitive sports had significantly higher LDL-C than athletes representing other weight-sensitive or endurance sports. Mean HDL-C levels ranged from 1.6 to 2.0 in females in Studies I, II and III and 1.3–1.5 in males in Studies II and III, which are considered protective for cardiovascular health (Mach, Baigent, Catapano, Koskinas, Casula, et al. 2020). However, given the causal role of LDL-C in the development of ASCVD (Ference et al. 2017), my results suggest that measurements of traditional cholesterol levels in athletes should not be overlooked in promoting their cardiovascular health and risk profile.

6.6 Metabolome and REDs risk

To our knowledge, we are the first group to investigate the association between the serum metabolome and real-life REDs risk in a mixed-sport sample of high-level athletes (Study III). Since identifying REDs in the real-world is difficult and currently based on symptoms and clinical findings possibly caused by problematic LEA, I also examined the severe primary REDs indicators (amenorrhoea for females and clinically low testosterone for males) and body fat percentage to better understand the underlying mechanisms.

Overall, a few significant associations between the REDs risk and metabolome were observed in my study after correcting for multiple testing. In females, increasing REDs risk had a positive association with IDL particle number and phospholipid content in extra-small VLDL particles, which were robust to sensitivity analysis restricted to athletes representing weight-sensitive sports. In males, no association between REDs risk and the metabolome was found and in sensitivity analysis on athletes representing weight-sensitive sports only creatinine had a negative association with increasing REDs risk. As for testosterone as a surrogate marker of REDs in males, scattered associations were observed mainly in HDL and VLDL profiles.

Aligning with previous metabolome research (Jouhki et al. 2024; Sarin et al. 2019; Nusser et al. 2025), my analysis showed that lower body fat percentage is associated with more beneficial metabolomic pathways regarding HDL and inflammation. In the next sections, I will walk you through my findings regarding each metabolome pathway.

6.6.1 HDL profile

No association between REDs risk and the HDL metabolome was found at any of our athlete populations. Previous studies investigating the association between hormonal disturbances or LEA and the HDL-C axis have yielded contradictory results. Higher HDL-C in athletes and adolescent girls with amenorrhoea have been reported compared to normally menstruating counterparts (Rickenlund et al. 2005; Swenne 2016), and patients with anorexia nervosa have been reported to have higher levels of HDL-C (Hussain et al. 2019) that decrease after weight restoration treatment (Hussain et al. 2023). In genome-wide association studies, a significant positive association between anorexia nervosa and total HDL-C, as well as HDL size, has been established (Duncan et al. 2017; Watson et al. 2019). Oophorectomy-induced hypoestrogenism in young women resulted in no change in HDL-C (Suda et al. 1998), and hypoestrogenism after menopause has been associated with q decline (Jensen et al. 1990; Do et al. 2000), increase (El Khoudary, Chen, et al. 2021; Karvinen et al. 2019; Hyvärinen et al. 2022) and no change (Matthan et al. 2005; Matthews et al. 2009) in HDL-C.

Contrary to the REDs risk analysis but in line with previous metabolome research (Jouhki et al. 2024; Sarin et al. 2019; Nusser et al. 2025), lower body fat percentage was associated with several beneficial metabolomic pathways regarding HDL in my study. In both sexes, a negative association was observed between body fat percentage and HDL size and particle number and lipid composition of large and extra-large HDLs, indicating that lower body fat percentage was associated with a tendency of having a larger-sized HDL profile. It has been proposed that the size, composition and efflux capacity of HDLs better reflect the cardioprotective properties than particle number per se (Hussain and McNeil 2026). A larger-sized HDL profile has been associated with a more beneficial cardiovascular health and risk factor profile (Kontush 2015; Razavi et al. 2012), probably due to increased lipolysis, as well as smaller HDL3 acquiring surface material from TG-rich lipoproteins (chylomicrons and VLDLs), resulting in larger HDL2 particles (Wieczorek et al. 2021). However, pharmacological interventions increasing HDL-C have not led to anticipated improvements in cardiovascular health and it has been suggested that the composition and functionality of HDL particles might be more crucial in their role in promoting cardiovascular health (Hussain and McNeil 2026). To further highlight the complexity of HDL's role in cardiovascular health, there is

a U-shaped association between HDL-C and risk of ASCVD. The risk of ASCVD plateaus at HDL-C levels 1.6–2.1mmol/l, with no additional decrease above this range and even adverse associations above levels of ~2.3mmol/l (Mach, Baigent, Catapano, Koskinas, Casula, et al. 2020; Hussain and McNeil 2026).

Interestingly in Study II, I observed a negative association between HDL-C and T3, indicating higher levels of HDL-C with lower levels of T3. Lower T3 has been associated with lower body fat percentage, weight loss and LEA (Isola et al. 2023; Mountjoy et al. 2023; Loucks and Heath 1994b). T3 is also involved in increasing the expression of ApoA-1, the main apolipoprotein of HDL, and in increasing RCT from peripheral tissues. It is thus possible that T3 could be mediating the increase in HDL-C in lower body fat percentage (D. Zhang et al. 2022; Ness 1991). Another hormone closely connected to fat mass is leptin. Leptin has an inverse relationship with HDL-C, possibly by increasing the expression of SR-B1 in the liver to facilitate the transport of HDL from the bloodstream (Koh et al. 2008). Thus, lower levels of leptin observed in individuals with less fat mass could contribute to the increased levels and larger sizes of HDL observed in Study III. Unfortunately, we didn't have the required data to investigate this hypothesis in our cohort.

6.6.2 IDL profile

IDL particle count was associated with REDs risk in females, both in the whole study sample and among weight-sensitive athletes. This association was robust to hormonal contraception use in weight-sensitive sports, but not in the whole female population. IDL, also known as VLDL remnant, is the precursor of LDL (Feingold 2000). IDL has been associated with elevated risk of an ASCVD event and disease progression, and of all ApoB-containing particles, IDLs have the highest reactivity for proteoglycans in the arterial intima, promoting development of atherosclerotic plaque (Anber et al. 1997). Previous studies have identified metabolic syndrome, diabetes, sedentary lifestyle, red meat consumption, and high intake of saturated fats as factors associated with elevated IDL levels (Narang and Al-Horani 2026). Interestingly, previous metabolome studies on athletes have not identified similar changes in IDL after short- to medium-term LEA (Jouhki et al. 2024; Sarin et al. 2019; Nusser et al. 2025). Although elevated IDL has been linked to cardiometabolic risk in the general population, it remains uncertain whether the alterations I observed in athletes with increased REDs risk represent adverse long-term consequences or reversible adaptations to prolonged LEA and high training load.

6.6.3 LDL profile

In line with previous LEA–metabolome studies (Jouhki et al. 2024; Sarin et al. 2019; Nusser et al. 2025) but contrary to the REDs CAT 2 model, few associations with the LDL profile were identified in my analysis. Across all analyses except one, no significant associations were identified between REDs risk and LDL particle profiles. Among males, few lipid measures in medium-sized LDL particles were associated with testosterone, but no association with overall LDL-C or LDL size could be detected. Body fat percentage was associated with few lipid measures in small and medium LDL particles. Overall, based on our results REDs risk, surrogate markers of REDs and body fat percentage did not have strong associations with LDL-C or LDL size, which have been most strongly associated with risk of ASCVD (Ference et al. 2017; Zubiran et al. 2025).

6.6.4 VLDL profile

In females, REDs risk and its surrogate marker menstrual status were associated with lipid measures in small and large VLDL particles. In females, regardless of sport, REDs risk was associated with changes in lipid measures in extra-small VLDL particles. Further adjustment for body fat percentage in weight-sensitive and endurance athletes strengthened the VLDL pathway, suggesting that REDs risk, regardless of body fat percentage, is associated with a more pronounced small-sized VLDL profile in athletes representing weight-sensitive or endurance sports. When looking into menstrual status as a surrogate marker of REDs, differences in large and extra-large VLDL lipid ratios were observed. I did not, however, observe any overall change in size of the VLDLs. Smaller VLDL particles have been linked to better cardiovascular health (Lee et al. 2022; Adiels et al. 2006), and decreasing size in VLDL particles has previously been observed after short- and medium-term LEA exposure (Jouhki et al. 2024; Nusser et al. 2025), indicating a beneficial effect of weight-loss on the VLDL lipidome corresponding to some of our findings. Jouhki et al. (2024) hypothesised that their observed decrease in VLDL size after weight loss could be due to the enhanced exchange of TG between HDL and VLDL and/or increased lipolysis of VLDL particles. Surprisingly, unlike the previous metabolomic research (Jouhki et al. 2024; Nusser et al. 2025), we did not find any association between body fat percentage and VLDL profile.

6.6.5 Other metabolites

An inverse relationship between body fat percentage and the inflammatory marker GlycA could be observed in both males and females, aligning with what has been observed previously after short- and medium-term LEA leading to reduced fat mass

and body weight (Sarin et al. 2019; Nusser et al. 2025; Jouhki et al. 2024). GlycA is a biomarker quantifying both acute-phase protein concentrations and their glycosylation state (Mehta et al. 2020) and is indicative of a proinflammatory state and adipose tissue dysfunction (Dullaart et al. 2015). GlycA has a positive association with BMI, hs-CRP, leptin and leptin/adiponectin ratio (Dullaart et al. 2015), and increased GlycA levels have been associated with several autoimmune diseases (Mehta et al. 2020), increased risk of ASCVD and type 2 diabetes mellitus in women (Akinkuolie et al. 2015, 2014). Although reduced GlycA levels are associated with better cardiovascular health independent of other inflammatory markers (Benson et al. 2018), no universal reference levels have been established (Ballout and Remaley 2020). In post-menopausal women, elevated GlycA levels have been observed in some (Q. Wang et al. 2018) but not all studies (Karppinen et al. 2022). Finally, regular exercise has been shown to reduce GlycA levels in a habitually sedentary population independent of confounding factors such as BMI (Barber et al. 2018). Our findings suggest that also in athletes reduced body fat percentage is associated with reduced inflammation, possibly contributing to better cardiovascular health.

Earlier, the ketone body beta-hydroxybutyrate was identified as the best metabolomic predictor of short-term LEA with a threshold of >0.09nmol/l (Nusser et al. 2025). In our cohort 10% of males and 7% of females had levels above 0.09nmol/l indicating LEA, but I could not identify any association between beta-hydroxybutyrate and REDs risk or its surrogate indicators in my study. However, in males, an inverse relationship between body fat percentage and beta-hydroxybutyrate was found. Acetone, another ketone body, also had a negative association with body fat percentage among males, similar to what has been observed after short- to medium-term LEA (Jouhki et al. 2024; Nusser et al. 2025).

Among male athletes representing weight-sensitive sports, a negative association between REDs risk and creatinine was observed. However, the clinical significance of this finding is questionable because the observed differences were small and within reference range (Hosten 1990). Among females representing weight-sensitive sports, a negative relationship between REDs risk and lactate was observed. Lactate has been reported to be higher in people with obesity (Jansson et al. 1994; Crawford et al. 2008) and with type 2 diabetes (Crawford et al. 2010), and it has been proposed to serve as a biomarker for glucose-related insulin resistance in obese individuals (Chondronikola et al. 2018). The relevance of this finding in our athlete population is, however, unclear.

In our study, body fat percentage was associated with multiple fatty acids. Among males, an overall positive association between body fat percentage and omega-3, omega-3 % and DHA was observed, and a negative association between body fat percentage and omega-6:omega-3 ratio. These results indicate a more beneficial fatty acid composition among those with higher body fat percentage.

Omega-3 and omega-6 fatty acids are essential for the human body, since they cannot be produced in the body and must be received from the diet. An optimal ratio of omega-6 to omega-3 is considered to be 1:1, but with the modern western diet being excessive in omega-6 but lacking in omega-3, the ratio is reaching 20:1 (Simopoulos 2016). A higher ratio of omega-6 to omega-3 fatty acids is associated with an increased risk of obesity (Simopoulos 2016) and inflammatory states and diseases (DiNicolantonio and O'Keefe 2021). In our sample, the omega-6 to omega-3 ratios were on average 9.8 (SD 3.1) among females and 11.7 (SD 3.6) among males, which is above the recommendation but in line with what has previously been reported in athletes (Ramadoss et al. 2021). Contrary to my findings, in physique athletes the concentration of omega-3 increased and omega-6:omega-3 ratio reduced after the 5-month weight-loss period (Jouhki et al. 2024).

6.7 Strengths

My study has some important strengths. One of the principal strengths is the sample size, which is large compared to many previous studies in the field. The participants were national- to world-class-level athletes, enabling the assessment of REDs risk and cholesterol levels in a highly trained athlete population. In addition to studying mixed-sport athletes, I investigated athletes representing weight-sensitive and endurance sports in more detail. This allowed for the examination of possible differences between susceptibility to problematic LEA in different athletic populations.

Standard protocols in the measurement of body composition, BMD, and blood samples were used. For assessing the REDs risk, I used the LEAF-Q questionnaire, which has been validated in female endurance athletes (Melin et al. 2014), and the IOC-recommended REDs CAT2, which is the current golden standard for assessing REDs risk and has been validated by a process of expert validation (Mountjoy et al. 2023; Stellingwerff et al. 2023). All of these methods were invented to identify long-term consequences of LEA. To my knowledge, REDs risk and cholesterol levels have not previously been assessed using specifically the REDs CAT 2. For analysing the metabolome, we used the NMR, which is highly reproducible and commonly used (Soininen et al. 2015).

6.8 Limitations

My study also has some important limitations. Causality cannot be inferred because the studies were observational in nature. In addition, although I used validated measures for screening REDs risk and ED symptoms, no clinical evaluation for REDs or EDs was done. The EDE-QS has not been validated in an athlete population, but the original EDE-Q has shown a sensitivity of 90% and specificity

of 100% among athletes (Lichtenstein et al. 2022). Additionally, the LEAF-Q has, to the best of my knowledge, only been validated in female endurance athletes, but in Study I, it was used in a sample representing mixed sports.

There are also some limitations in my assessment of REDs risk. First, because data collection began prior to the publication of the REDs CAT 2, I did not have all the required information, such as psychiatric assessment for anxiety and depression, or the duration of amenorrhoea. I used the short version of the EDE-Q (EDE-QS) and a common 15-point cutoff for both female and male athletes, as there are no specific cutoffs for males (Prnjak et al. 2020). The common cutoff might underestimate DE behaviour among men. DXA for BMD assessment was conducted only once during the athletic year, and the result was used to represent both timepoints within the same annual cycle. However, because changes in BMD usually occur slowly, I believe that significant changes in BMD between the two timepoints are rare (Kendler et al. 2019). Females reported their own menstrual cycle and no verification via urine or blood tests was conducted. The gold standard for classification of menstrual status includes self-reported menstrual bleeding, LH-surge test via urinary sample and serum hormone sampling with blood tests (Kirsty Jayne Elliott-Sale et al. 2025). As in REDs CAT 2, we assessed the thyrois function using T3, but a clinical evaluation of thyroid function would include T4 and TSH. Finally, the accuracy of the REDs CAT 2 in screening athletes with REDs requires further study (Jeukendrup et al. 2024), and the model remains to be investigated and further developed (Stellingwerff et al. 2023; Jeukendrup et al. 2024). Taken together, these limitations may have led to an over- or underestimation of the REDs risk.

Even if I handled REDs risk as a continuous variable, the score does not indicate a linear risk, let alone severity, of REDs. It reflects the number of possible REDs symptoms or findings, with an increasing probability of REDs syndrome with a higher number of symptoms or findings. Therefore, most likely at lower scores, these athletes represent a heterogeneous group with some possibly having metabolic adaptations due to LEA (problematic or adaptable) and some having completely other reasons explaining the findings.

We cannot exclude the possibility of unknown confounding factors affecting our findings. We were unable to collect specific training information, which limits the interpretation of the potential effect of training on cholesterol levels. Future studies could also assess whether there are systematic differences in athletes' diet within the training season. Genetic factors, potentially influencing cholesterol metabolism, could not be assessed, but no extremely high LDL-C levels (≥4.9mmol/l) were observed, which would raise concern of familial hypercholesterolaemia (Bouhairie and Goldberg 2015). Although mean cholesterol levels in Finland are similar when compared to other European countries (Timmis et al. 2022), further studies are

needed to assess the generalisability of our findings to athletes from other sports, and cultural and ethnic backgrounds.

7 Conclusions and future directions

The current field of research regarding REDs and LEA is active and there is a growing amount of evidence to improve our understanding on how LEA and its different forms affect athlete physiology and health. As summarised in the literature review, the link between LEA and cholesterol metabolism is still inconclusive, which was the driving force of my thesis.

Based on the literature review, I identified several aims and now, I will conclude the main findings of my research:

I) ED behaviour (measured with EDE-QS) has a weak positive association with LDL-C and TC among female athletes, both those representing mixed sports and those representing weight-sensitive sports. Among female athletes representing weight-sensitive sports, LEA symptoms (assessed with the LEAF-Q) have a weak positive association with LDL-C and TC.

II) REDs risk (assessed using the REDs CAT 2) is not associated with cholesterol values in female or male endurance athletes. However, among female endurance athletes, a change in REDs risk during a training season has an adverse association with a change in LDL-C and TC.

III) REDs risk has a positive association with IDL and VLDL, but not LDL, metabolome pathways in female athletes, particularly those representing weight-sensitive sports. Interestingly, also in athletic population lower body fat percentage is also associated with a beneficial metabolomic fingerprint characterised by larger-sized HDL particles and lower inflammation, highlighting the role of adipose tissue in lipid metabolism.

IV) Finally, a substantial proportion of the studied athlete population had elevated LDL-C levels. These results suggest that cholesterol measurements in athletes should not be overlooked in promoting their cardiovascular health and risk profile.

Based on my findings, I state that even among athletes, body fat percentage is a strong indicator of metabolic health. However, ED behaviour and problematic LEA with hormonal disturbances may adverse these benefits, particularly in females representing weight-sensitive sports. Future studies should aim to quantify problematic LEA and REDs for a robust understanding of the interplay between problematic LEA and cholesterol levels, as well as the metabolome.

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References

Abel, L. L., B. B. Levy, B. B. Brodie, and F. E. Kendall. 1952. 'A Simplified Method for the Estimation of Total Cholesterol in Serum and Demonstration of Its Specificity'. *The Journal of Biological Chemistry* 195 (1): 357–66.

Ackerman, Kathryn E., Natalia Cano Sokoloff, Giovana DE Nardo Maffazioli, Hannah M. Clarke, Hang Lee, and Madhusmita Misra. 2015. 'Fractures in Relation to Menstrual Status and Bone Parameters in Young Athletes'. *Medicine and Science in Sports and Exercise* 47 (8): 1577–86. https://doi.org/10.1249/MSS.0000000000000574.

Ackerman, Kathryn E., Kamal T. Patel, Gabriela Guereca, Lisa Pierce, David B. Herzog, and Madhusmita Misra. 2013. 'Cortisol Secretory Parameters in Young Exercisers in Relation to LH Secretion and Bone Parameters'. *Clinical Endocrinology* 78 (1): 114–19. https://doi.org/10.1111/j.1365-2265.2012.04458.x.

Ackerman, Kathryn E., Melissa Putman, Gabriela Guereca, et al. 2012. 'Cortical Microstructure and Estimated Bone Strength in Young Amenorrheic Athletes, Eumenorrheic Athletes and Non-Athletes'. *Bone* 51 (4): 680–87. https://doi.org/10.1016/j.bone.2012.07.019.

Ackerman, Kathryn E., Katherine Slusarz, Gabriela Guereca, et al. 2012. 'Higher Ghrelin and Lower Leptin Secretion Are Associated with Lower LH Secretion in Young Amenorrheic Athletes Compared with Eumenorrheic Athletes and Controls'. *American Journal of Physiology-Endocrinology and Metabolism* 302 (7): E800–806. https://doi.org/10.1152/ajpendo.00598.2011.

Adiels, M., M. R. Taskinen, C. Packard, et al. 2006. 'Overproduction of Large VLDL Particles Is Driven by Increased Liver Fat Content in Man'. *Diabetologia* 49 (4): 755–65. https://doi.org/10.1007/s00125-005-0125-z.

Afonso, Milessa Silva, Roberta Marcondes Machado, Maria Silvia Lavrador, Eder Carlos Rocha Quintao, Kathryn J. Moore, and Ana Maria Lottenberg. 2018. 'Molecular Pathways Underlying Cholesterol Homeostasis'. *Nutrients* 10 (6): 760. https://doi.org/10.3390/nu10060760.

Akinkuolie, Akintunde O., Julie E. Buring, Paul M. Ridker, and Samia Mora. 2014. 'A Novel Protein Glycan Biomarker and Future Cardiovascular Disease Events'. *Journal of the American Heart Association* 3 (5): e001221. https://doi.org/10.1161/JAHA.114.001221.

Akinkuolie, Akintunde O., Aruna D. Pradhan, Julie E. Buring, Paul M. Ridker, and Samia Mora. 2015. 'Novel Protein Glycan Side-Chain Biomarker and Risk of Incident Type 2 Diabetes Mellitus'. *Arteriosclerosis, Thrombosis, and Vascular Biology* 35 (6): 1544–50. https://doi.org/10.1161/ATVBAHA.115.305635.

Alcover, Sebastià, Lisaidy Ramos-Regalado, Gabriela Girón, Natàlia Muñoz-García, and Gemma Vilahur. 2025. 'HDL-Cholesterol and Triglycerides Dynamics: Essential Players in Metabolic Syndrome'. *Antioxidants* 14 (4): 434. https://doi.org/10.3390/antiox14040434.

Allaway, Heather C. M., Emily A. Southmayd, and Mary Jane De Souza. 2016. 'The Physiology of Functional Hypothalamic Amenorrhea Associated with Energy Deficiency in Exercising Women and in Women with Anorexia Nervosa'. *Hormone Molecular Biology and Clinical Investigation* 25 (2): 91–119. https://doi.org/10.1515/hmbci-2015-0053.

Allen, K. L., T. A. Mori, L. Beilin, S. M. Byrne, S. Hickling, and W. H. Oddy. 2013. 'Dietary Intake in Population-Based Adolescents: Support for a Relationship between Eating Disorder Symptoms, Low Fatty Acid Intake and Depressive Symptoms'. *Journal of Human Nutrition and Dietetics: The Official Journal of the British Dietetic Association* 26 (5): 459–69. https://doi.org/10.1111/jhn.12024.

Amawi, Adam, Walaa AlKasasbeh, Manar Jaradat, et al. 2024. 'Athletes' Nutritional Demands: A Narrative Review of Nutritional Requirements'. *Frontiers in Nutrition* 10 (January): 1331854. https://doi.org/10.3389/fnut.2023.1331854.

Amundson, Drake M., and Mingjie Zhou. 1999. 'Fluorometric Method for the Enzymatic Determination of Cholesterol'. *Journal of Biochemical and Biophysical Methods* 38 (1): 43–52. https://doi.org/10.1016/S0165-022X(98)00036-0.

Anber, V., J. S. Millar, M. McConnell, J. Shepherd, and C. J. Packard. 1997. 'Interaction of Very-Low-Density, Intermediate-Density, and Low-Density Lipoproteins with Human Arterial Wall Proteoglycans'. *Arteriosclerosis, Thrombosis, and Vascular Biology* 17 (11): 2507–14. https://doi.org/10.1161/01.atv.17.11.2507.

Angelidi, Angeliki M., Konstantinos Stefanakis, Sharon H. Chou, et al. 2024. 'Relative Energy Deficiency in Sport (REDs): Endocrine Manifestations, Pathophysiology and Treatments'. *Endocrine Reviews* 45 (5): 676–708. https://doi.org/10.1210/endrev/bnae011.

Antoni, Rona. 2023. 'Dietary Saturated Fat and Cholesterol: Cracking the Myths around Eggs and Cardiovascular Disease'. *Journal of Nutritional Science* 12 (September): e97. https://doi.org/10.1017/jns.2023.82.

Armento, Aubrey M., Madison Brna, Corrine Seehusen, Amanda McCarthy, Karin D. VanBaak, and David R. Howell. 2024. 'Examination of Sex Differences in Energy Availability, Disordered Eating, and Compulsive Exercise Among Male and Female Adolescent Athletes'. *Clinical Journal of Sport Medicine: Official Journal of the Canadian Academy of Sport Medicine*, ahead of print, November 21. https://doi.org/10.1097/JSM.0000000000001307.

Armstrong, Richard A. 2014. 'When to Use the Bonferroni Correction'. *Ophthalmic & Physiological Optics: The Journal of the British College of Ophthalmic Opticians* (Optometrists) 34 (5): 502–8. https://doi.org/10.1111/opo.12131.

Auro, Kirsi, Anni Joensuu, Krista Fischer, et al. 2014. 'A Metabolic View on Menopause and Ageing'. *Nature Communications* 5 (August): 4708. https://doi.org/10.1038/ncomms5708.

Ayres, Stacey, Janine Baer, and M. T. Ravi Subbiah. 1998. 'Exercised-Induced Increase in Lipid Peroxidation Parameters in Amenorrhelc Female Athletes'. *Fertility and Sterility* 69 (1): 73–77. https://doi.org/10.1016/S0015-0282(97)00428-7.

Bairey Merz, C. Noel, B. Delia Johnson, Barry L. Sharaf, et al. 2003. 'Hypoestrogenemia of Hypothalamic Origin and Coronary Artery Disease in Premenopausal Women: A Report from the NHLBI-Sponsored WISE Study'. *Journal of the American College of Cardiology* 41 (3): 413–19. https://doi.org/10.1016/s0735-1097(02)02763-8.

Ballout, Rami A., and Alan T. Remaley. 2020. 'GlycA: A New Biomarker for Systemic Inflammation and Cardiovascular Disease (CVD) Risk Assessment'. *Journal of Laboratory and Precision Medicine* 5 (April): 17. https://doi.org/10.21037/jlpm.2020.03.03.

Barber, Jacob L., William E. Kraus, Timothy S. Church, et al. 2018. 'Effects of Regular Endurance Exercise on GlycA: Combined Analysis of 14 Exercise Interventions'. *Atherosclerosis* 277 (October): 1–6. https://doi.org/10.1016/j.atherosclerosis.2018.07.029.

Bates, Douglas, Martin Mächler, Ben Bolker, and Steve Walker. 2015. 'Fitting Linear Mixed-Effects Models Using Lme4'. *Journal of Statistical Software* 67 (October): 1–48. https://doi.org/10.18637/jss.v067.i01.

Beheshti, Sabina O., Christian M. Madsen, Anette Varbo, and Børge G. Nordestgaard. 2020. 'Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects'. *Journal of the American College of Cardiology* 75 (20): 2553–66. https://doi.org/10.1016/j.jacc.2020.03.057.

Benson, Eve-Marie A., Martin Tibuakuu, Di Zhao, et al. 2018. 'Associations of Ideal Cardiovascular Health with GlycA, a Novel Inflammatory Marker: The Multi-Ethnic Study of Atherosclerosis'. *Clinical Cardiology* 41 (11): 1439–45. https://doi.org/10.1002/clc.23069.

Berenson, Abbey B., Mahbubur Rahman, and Gregg Wilkinson. 2009. 'Effect of Injectable and Oral Contraceptives on Serum Lipids'. *Obstetrics and Gynecology* 114 (4): 786–94. https://doi.org/10.1097/AOG.0b013e3181b76bea.

Berga, S. L., T. L. Daniels, and D. E. Giles. 1997. 'Women with Functional Hypothalamic Amenorrhea but Not Other Forms of Anovulation Display Amplified Cortisol Concentrations'. *Fertility and Sterility* 67 (6): 1024–30. https://doi.org/10.1016/s0015-0282(97)81434-3.

Berga, S. L., J. F. Mortola, L. Girton, et al. 1989. 'Neuroendocrine Aberrations in Women with Functional Hypothalamic Amenorrhea'. *The Journal of Clinical Endocrinology and Metabolism* 68 (2): 301–8. https://doi.org/10.1210/jcem-68-2-301.

Berneis, Kaspar K., and Ronald M. Krauss. 2002. 'Metabolic Origins and Clinical Significance of LDL Heterogeneity'. *Journal of Lipid Research* 43 (9): 1363–79. https://doi.org/10.1194/jlr.R200004-JLR200.

Biller, B. M., H. J. Federoff, J. I. Koenig, and A. Klibanski. 1990. 'Abnormal Cortisol Secretion and Responses to Corticotropin-Releasing Hormone in Women with Hypothalamic Amenorrhea'. *The Journal of Clinical Endocrinology and Metabolism* 70 (2): 311–17. https://doi.org/10.1210/jcem-70-2-311.

Black, Katherine, Joanne Slater, Rachel C. Brown, and Rebecca Cooke. 2018. 'Low Energy Availability, Plasma Lipids, and Hormonal Profiles of Recreational Athletes'. *The Journal of Strength & Conditioning Research* 32 (10): 2816. https://doi.org/10.1519/JSC.0000000000002540.

Bouhairie, Victoria Enchia, and Anne Carol Goldberg. 2015. 'Familial Hypercholesterolemia'. *Cardiology Clinics* 33 (2): 169–79. https://doi.org/10.1016/j.ccl.2015.01.001.

Brown, Violet A. 2021. 'An Introduction to Linear Mixed-Effects Modeling in R'. *Advances in Methods and Practices in Psychological Science* 4 (1): 2515245920960351. https://doi.org/10.1177/2515245920960351.

Burke, Louise M., Bronwen Lundy, Ida L. Fahrenholtz, and Anna K. Melin. 2018. 'Pitfalls of Conducting and Interpreting Estimates of Energy Availability in Free-Living Athletes'. International Journal of Sport Nutrition and Exercise Metabolism. *International Journal of Sport Nutrition and Exercise Metabolism* 28 (4): 350–63. https://doi.org/10.1123/ijsnem.2018-0142.

Canoy, Dexter, S. Matthijs Boekholdt, Nicholas Wareham, et al. 2007. 'Body Fat Distribution and Risk of Coronary Heart Disease in Men and Women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk Cohort: A Population-Based Prospective Study'. *Circulation* 116 (25): 2933–43. https://doi.org/10.1161/CIRCULATIONAHA.106.673756.

Capling, Louise, Kathryn L. Beck, Janelle A. Gifford, Gary Slater, Victoria M. Flood, and Helen O'Connor. 2017. 'Validity of Dietary Assessment in Athletes: A Systematic Review'. *Nutrients* 9 (12): 1313. https://doi.org/10.3390/nu9121313.

Carson, Jo Ann S., Alice H. Lichtenstein, Cheryl A. M. Anderson, et al. 2020. 'Dietary Cholesterol and Cardiovascular Risk: A Science Advisory From the American Heart Association'. *Circulation* 141 (3): e39–53. https://doi.org/10.1161/CIR.0000000000000743.

Caruso, Lorenzo, Enrico Zauli, and Mauro Vaccarezza. 2023. 'Physical Exercise and Appetite Regulation: New Insights'. *Biomolecules* 13 (8): 1170. https://doi.org/10.3390/biom13081170.

Castellano, Juan M., Agnete H. Bentsen, Jens D. Mikkelsen, and Manuel Tena-Sempere. 2010. 'Kisspeptins: Bridging Energy Homeostasis and Reproduction'. *Brain Research* 1364 (December): 129–38. https://doi.org/10.1016/j.brainres.2010.08.057.

Catapano, Alberico L., Ian Graham, Guy De Backer, et al. 2016. '2016 ESC/EAS Guidelines for the Management of Dyslipidaemias'. *European Heart Journal* 37 (39): 2999–3058. https://doi.org/10.1093/eurheartj/ehw272.

Chait, Alan, Henry N. Ginsberg, Tomas Vaisar, Jay W. Heinecke, Ira J. Goldberg, and Karin E. Bornfeldt. 2020. 'Remnants of the Triglyceride-Rich Lipoproteins, Diabetes, and Cardiovascular Disease'. *Diabetes* 69 (4): 508–16. https://doi.org/10.2337/dbi19-0007.

Chesney, Edward, Guy M. Goodwin, and Seena Fazel. 2014. 'Risks of All-Cause and Suicide Mortality in Mental Disorders: A Meta-Review'. *World Psychiatry: Official Journal of the World Psychiatric Association* (WPA) 13 (2): 153–60. https://doi.org/10.1002/wps.20128.

Cho, Leslie, Andrew M. Kaunitz, Stephanie S. Faubion, et al. 2023. 'Rethinking Menopausal Hormone Therapy: For Whom, What, When, and How Long?' *Circulation* 147 (7): 597–610. https://doi.org/10.1161/CIRCULATIONAHA.122.061559.

Chondronikola, Maria, Faidon Magkos, Jun Yoshino, et al. 2018. 'Effect of Progressive Weight Loss on Lactate Metabolism: A Randomized Controlled Trial'. *Obesity (Silver Spring, Md.)* 26 (4): 683–88. https://doi.org/10.1002/oby.22129.

Christakos, Sylvia, Dare V. Ajibade, Puneet Dhawan, Adam J. Fechner, and Leila J. Mady. 2010. 'Vitamin D: Metabolism'. *Endocrinology and Metabolism Clinics of North America* 39 (2): 243–53. https://doi.org/10.1016/j.ecl.2010.02.002.

Christo, Karla, Jennalee Cord, Nara Mendes, et al. 2008. 'Acylated Ghrelin and Leptin in Adolescent Athletes with Amenorrhea, Eumenorrheic Athletes and Controls: A Cross-Sectional Study'. *Clinical Endocrinology* 69 (4): 628–33. https://doi.org/10.1111/j.1365-2265.2008.03237.x.

Cohn, J. S., J. R. McNamara, S. D. Cohn, J. M. Ordovas, and E. J. Schaefer. 1988. 'Postprandial Plasma Lipoprotein Changes in Human Subjects of Different Ages.' *Journal of Lipid Research* 29 (4): 469–79. https://doi.org/10.1016/S0022-2275(20)38520-5.

Corr, M., M. J. De Souza, R. J. Toombs, and N. I. Williams. 2011. 'Circulating Leptin Concentrations Do Not Distinguish Menstrual Status in Exercising Women'. *Human Reproduction* 26 (3): 685–94. https://doi.org/10.1093/humrep/deq375.

Counts, D. R., H. Gwirtsman, L. M. Carlsson, M. Lesem, and G. B. Cutler Jr. 1992. 'The Effect of Anorexia Nervosa and Refeeding on Growth Hormone-Binding Protein, the Insulin-like Growth Factors (IGFs), and the IGF-Binding Proteins'. *The Journal of Clinical Endocrinology & Metabolism* 75 (3): 762–67. https://doi.org/10.1210/jcem.75.3.1381372.

Crawford, Stephen O., Marietta S. Ambrose, Ron C. Hoogeveen, Frederick L. Brancati, Christie M. Ballantyne, and J. Hunter Young. 2008. 'Association of Lactate with Blood Pressure before and after Rapid Weight Loss'. *American Journal of Hypertension* 21 (12): 1337–42. https://doi.org/10.1038/ajh.2008.282.

Crawford, Stephen O., Ron C. Hoogeveen, Frederick L. Brancati, et al. 2010. 'Association of Blood Lactate with Type 2 Diabetes: The Atherosclerosis Risk in Communities Carotid MRI Study'. *International Journal of Epidemiology* 39 (6): 1647–55. https://doi.org/10.1093/ije/dyq126.

De Los Reyes, Chris, Rishi Raj Rikhi, Sean Doherty, et al. 2025. 'Current Clinical Trials for Treating Elevated Lipoprotein(a)'. *Current Cardiovascular Risk Reports* 19 (1): 7. https://doi.org/10.1007/s12170-025-00759-8.

De Souza, M. J., B. E. Miller, A. B. Loucks, et al. 1998. 'High Frequency of Luteal Phase Deficiency and Anovulation in Recreational Women Runners: Blunted Elevation in Follicle-Stimulating Hormone Observed during Luteal-Follicular Transition'. *The Journal of Clinical Endocrinology and Metabolism* 83 (12): 4220–32. https://doi.org/10.1210/jcem.83.12.5334.

De Souza, M. J., R. J. Toombs, J. L. Scheid, E. O'Donnell, S. L. West, and N. I. Williams. 2010. 'High Prevalence of Subtle and Severe Menstrual Disturbances in Exercising Women: Confirmation Using Daily Hormone Measures'. *Human Reproduction* (Oxford, England) 25 (2): 491–503. https://doi.org/10.1093/humrep/dep411.

De Souza, Rebecca J. Mallinson, Nicole C. A. Strock, et al. 2021. 'Randomised Controlled Trial of the Effects of Increased Energy Intake on Menstrual Recovery in Exercising Women with Menstrual Disturbances: The "REFUEL" Study'. *Human Reproduction* (Oxford, England) 36 (8): 2285–97. https://doi.org/10.1093/humrep/deab149.

De Souza, Mary Jane, Daniel K. Lee, Jaci L. VanHeest, Jennifer L. Scheid, Sarah L. West, and Nancy I. Williams. 2007. 'Severity of Energy-Related Menstrual Disturbances Increases in Proportion to Indices of Energy Conservation in Exercising Women'. *Fertility and Sterility* 88 (4): 971–75. https://doi.org/10.1016/j.fertnstert.2006.11.171.

Dervish, R. A., L. J. Wilson, and C. Curtis. 2023. 'Investigating the Prevalence of Low Energy Availability, Disordered Eating and Eating Disorders in Competitive and Recreational Female Endurance Runners'. *European Journal of Sport Science* 23 (5): 869–76. https://doi.org/10.1080/17461391.2022.2079423.

Dilshad, Huma, Rabia Ismail, Safila Naveed, Khan Usmanghani, M. Tanweer Alam, and Ghulam Sarwar. 2016. 'Effect of Hormonal Contraceptives on Serum Lipids: A Prospective Study'. *Pakistan Journal of Pharmaceutical Sciences* 29 (4 Suppl): 1379–82.

DiNicolantonio, James J., and James O'Keefe. 2021. 'The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Autoimmune Diseases, Asthma, and Allergies'. *Missouri Medicine* 118 (5): 453–59.

Do, K. A., A. Green, J. R. Guthrie, E. C. Dudley, H. G. Burger, and L. Dennerstein. 2000. 'Longitudinal Study of Risk Factors for Coronary Heart Disease across the Menopausal Transition'. *American Journal of Epidemiology* 151 (6): 584–93. https://doi.org/10.1093/oxfordjournals.aje.a010246.

Donoso, M. A., M. T. Muñoz-Calvo, V. Barrios, G. Garrido, F. Hawkins, and J. Argente. 2010. 'Increased Circulating Adiponectin Levels and Decreased Leptin/Soluble Leptin Receptor Ratio throughout Puberty in Female Ballet Dancers: Association with Body Composition and the Delay in Puberty'. *European Journal of Endocrinology* 162 (5): 905–11. https://doi.org/10.1530/EJE-09-0874.

Dullaart, Robin P. F., Eke G. Gruppen, Margery A. Connelly, James D. Otvos, and Joop D. Lefrandt. 2015. 'GlycA, a Biomarker of Inflammatory Glycoproteins, Is More Closely Related to the Leptin/Adiponectin Ratio than to Glucose Tolerance Status'. *Clinical Biochemistry* 48 (12): 811–14. https://doi.org/10.1016/j.clinbiochem.2015.05.001.

Dulloo, Abdul G. 2025. 'Adaptive Thermogenesis Driving Catch-up Fat during Weight Regain: A Role for Skeletal Muscle Hypothyroidism and a Risk for Sarcopenic Obesity'. *Reviews in Endocrine & Metabolic Disorders* 26 (5): 871–88. https://doi.org/10.1007/s11154-025-09970-9.

Duncan, Laramie, Zeynep Yilmaz, Helena Gaspar, et al. 2017. 'Significant Locus and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of Anorexia Nervosa'.

American Journal of Psychiatry 174 (September): 850–58. https://doi.org/10.1176/appi.ajp.2017.16121402.

Duntas, Leonidas H. 2002. 'Thyroid Disease and Lipids'. *Thyroid: Official Journal of the American Thyroid Association* 12 (4): 287–93. https://doi.org/10.1089/10507250252949405.

El Khoudary, Samar R., Xirun Chen, Alexis Nasr, et al. 2021. 'HDL (High-Density Lipoprotein) Subclasses, Lipid Content, and Function Trajectories Across the Menopause Transition: SWAN-HDL Study'. *Arteriosclerosis, Thrombosis, and Vascular Biology* 41 (2): 951–61. https://doi.org/10.1161/ATVBAHA.120.315355.

El Khoudary, Samar R., Xirun Chen, Alexis Nasr, et al. 2021. 'HDL Subclasses, Lipid Content, and Function Trajectories across the Menopause Transition: SWAN-HDL Study'. *Arteriosclerosis, Thrombosis, and Vascular Biology* 41 (2): 951–61. https://doi.org/10.1161/ATVBAHA.120.315355.

Elliott-Sale, Kirsty J., Adam S. Tenforde, Allyson L. Parziale, Bryan Holtzman, and Kathryn E. Ackerman. 2018. 'Endocrine Effects of Relative Energy Deficiency in Sport'. International Journal of Sport Nutrition and Exercise Metabolism. *International Journal of Sport Nutrition and Exercise Metabolism* 28 (4): 335–49. https://doi.org/10.1123/ijsnem.2018-0127.

Elliott-Sale, Kirsty Jayne, Marco Altini, Patricia Doyle-Baker, et al. 2025. 'Why We Must Stop Assuming and Estimating Menstrual Cycle Phases in Laboratory and Field-Based Sport Related Research'. *Sports Medicine (Auckland, N.z.)* 55 (6): 1339–51. https://doi.org/10.1007/s40279-025-02189-3.

Estour, Bruno, Natacha Germain, Eric Diconne, et al. 2010. 'Hormonal Profile Heterogeneity and Short-Term Physical Risk in Restrictive Anorexia Nervosa'. *The Journal of Clinical Endocrinology & Metabolism* 95 (5): 2203–10. https://doi.org/10.1210/jc.2009-2608.

Fahrenholtz, Ida Lysdahl, Anna Katarina Melin, Paulina Wasserfurth, et al. 2022. 'Risk of Low Energy Availability, Disordered Eating, Exercise Addiction, and Food Intolerances in Female Endurance Athletes'. *Frontiers in Sports and Active Living* 4 (May): 869594. https://doi.org/10.3389/fspor.2022.869594.

Fairburn, Christopher G., and Sarah J. Beglin. 1994. 'Assessment of Eating Disorders: Interview or Self-Report Questionnaire?' *International Journal of Eating Disorders* 16 (4): 363–70. https://doi.org/10.1002/1098-108X(199412)16:4%3C363::AID-EAT2260160405%3E3.0.CO;2-%23.

Fatt, Scott J., Emma George, Phillipa Hay, Nikki Jeacocke, Emily Gotkiewicz, and Deborah Mitchison. 2024. 'An Umbrella Review of Body Image Concerns, Disordered Eating, and Eating Disorders in Elite Athletes'. *Journal of Clinical Medicine* 13 (14): 14. https://doi.org/10.3390/jcm13144171.

Feingold, Kenneth R. 2000. 'Introduction to Lipids and Lipoproteins'. In *Endotext*, edited by Kenneth R. Feingold, Robert A. Adler, S. Faisal Ahmed, et al. MDText.com, Inc. http://www.ncbi.nlm.nih.gov/books/NBK305896/.

Ference, Brian A., Henry N. Ginsberg, Ian Graham, et al. 2017. 'Low-Density Lipoproteins Cause Atherosclerotic Cardiovascular Disease. 1. Evidence from Genetic, Epidemiologic, and

Clinical Studies. A Consensus Statement from the European Atherosclerosis Society Consensus Panel'. *European Heart Journal* 38 (32): 2459–72. https://doi.org/10.1093/eurheartj/ehx144.

Flanagan, Emily W., Jasper Most, Jacob T. Mey, and Leanne M. Redman. 2020. 'Calorie Restriction and Aging in Humans'. *Annual Review of Nutrition* 40 (September): 105–33. https://doi.org/10.1146/annurev-nutr-122319-034601.

Fogelholm, G. Mikael, Risto Koskinen, Juha Laakso, Tuomo Rankinen, and Inkeri Ruokonen. 1993. 'Gradual and Rapid Weight Loss: Effects on Nutrition and Performance in Male Athletes'. *Medicine & Science in Sports & Exercise* 25 (3): 371.

Friars, Dara, Orla Walsh, and Fiona McNicholas. 2023. 'Assessment and Management of Cardiovascular Complications in Eating Disorders'. *Journal of Eating Disorders* 11 (1): 13. https://doi.org/10.1186/s40337-022-00724-5.

Friday, K. E., B. L. Drinkwater, B. Bruemmer, C. Chesnut 3rd, and A. Chait. 1993. 'Elevated Plasma Low-Density Lipoprotein and High-Density Lipoprotein Cholesterol Levels in Amenorrheic Athletes: Effects of Endogenous Hormone Status and Nutrient Intake'. *The Journal of Clinical Endocrinology & Metabolism* 77 (6): 1605–9. https://doi.org/10.1210/jcem.77.6.8263148.

Fried, Susan K., Mi-Jeong Lee, and Kalypso Karastergiou. 2015. 'Shaping Fat Distribution: New Insights into the Molecular Determinants of Depot- and Sex-Dependent Adipose Biology'. *Obesity* (Silver Spring, Md.) 23 (7): 1345–52. https://doi.org/10.1002/oby.21133.

Friedl, K. E., R. J. Moore, R. W. Hoyt, L. J. Marchitelli, L. E. Martinez-Lopez, and E. W. Askew. 2000. 'Endocrine Markers of Semistarvation in Healthy Lean Men in a Multistressor Environment'. *Journal of Applied Physiology (Bethesda, Md.: 1985)* 88 (5): 1820–30. https://doi.org/10.1152/jappl.2000.88.5.1820.

Friedl, K. E., R. J. Moore, L. E. Martinez-Lopez, et al. 1994. 'Lower Limit of Body Fat in Healthy Active Men'. *Journal of Applied Physiology* (Bethesda, Md. : 1985) 77 (2): 933–40. https://doi.org/10.1152/jappl.1994.77.2.933.

Gallant, Tara L., Lauren F. Ong, Laura Wong, et al. 2024. 'Low Energy Availability and Relative Energy Deficiency in Sport: A Systematic Review and Meta-Analysis'. *Sports Medicine*, ahead of print, November 1. https://doi.org/10.1007/s40279-024-02130-0.

Geesmann, Bjoern, Jenna C. Gibbs, Joachim Mester, and Karsten Koehler. 2017. 'Association Between Energy Balance and Metabolic Hormone Suppression During Ultraendurance Exercise'. *International Journal of Sports Physiology and Performance* 12 (7): 984–89. https://doi.org/10.1123/ijspp.2016-0061.

Ghazzawi, Hadeel A., Lana S. Nimer, Areen Jamal Haddad, et al. 2024. 'A Systematic Review, Meta-Analysis, and Meta-Regression of the Prevalence of Self-Reported Disordered Eating and Associated Factors among Athletes Worldwide'. *Journal of Eating Disorders* 12 (1): 24. https://doi.org/10.1186/s40337-024-00982-5.

Gimunová, Marta, Alexandra Paulínyová, Martina Bernaciková, and Ana Carolina Paludo. 2022. 'The Prevalence of Menstrual Cycle Disorders in Female Athletes from Different Sports

Disciplines: A Rapid Review'. *International Journal of Environmental Research and Public Health* 19 (21): 14243. https://doi.org/10.3390/ijerph192114243.

Gioia, Giuseppe Di, Lorenzo Buzzelli, Viviana Maestrini, et al. 2024. 'Long-Term Evaluation of Lipid Profile Changes in Olympic Athletes'. International Journal of Sport Nutrition and Exercise Metabolism. *International Journal of Sport Nutrition and Exercise Metabolism* 34 (5): 267–74. https://doi.org/10.1123/ijsnem.2023-0266.

Glazer, G. 1991. 'Atherogenic Effects of Anabolic Steroids on Serum Lipid Levels. A Literature Review'. *Archives of Internal Medicine* 151 (10): 1925–33.

Godsland, I. F. 2001. 'Effects of Postmenopausal Hormone Replacement Therapy on Lipid, Lipoprotein, and Apolipoprotein (a) Concentrations: Analysis of Studies Published from 1974-2000'. *Fertility and Sterility* 75 (5): 898–915. https://doi.org/10.1016/s0015-0282(01)01699-5.

Greco, Antonio, Simone Finocchiaro, Marco Spagnolo, et al. 2025. 'Lipoprotein(a) as a Pharmacological Target: Premises, Promises, and Prospects'. *Circulation* 151 (6): 400–415. https://doi.org/10.1161/CIRCULATIONAHA.124.069210.

Green, Cara L., Dudley W. Lamming, and Luigi Fontana. 2022. 'Molecular Mechanisms of Dietary Restriction Promoting Health and Longevity'. *Nature Reviews. Molecular Cell Biology* 23 (1): 56–73. https://doi.org/10.1038/s41580-021-00411-4.

Guo, Jiarui, Silong Chen, Ying Zhang, et al. 2024. 'Cholesterol Metabolism: Physiological Regulation and Diseases'. *MedComm* 5 (2): e476. https://doi.org/10.1002/mco2.476.

Habib, K. E., P. W. Gold, and G. P. Chrousos. 2001. 'Neuroendocrinology of Stress'. *Endocrinology and Metabolism Clinics of North America* 30 (3): 695–728; vii–viii. https://doi.org/10.1016/s0889-8529(05)70208-5.

Hackney, Anthony C. 2020. 'Hypogonadism in Exercising Males: Dysfunction or Adaptive-Regulatory Adjustment?' *Frontiers in Endocrinology* 11 (January). https://doi.org/10.3389/fendo.2020.00011.

Hagmar, Magnus, Bo Berglund, Kerstin Brismar, and Angelica Lindén Hirschberg. 2013. 'Body Composition and Endocrine Profile of Male Olympic Athletes Striving for Leanness'. *Clinical Journal of Sport Medicine* 23 (3): 197. https://doi.org/10.1097/JSM.0b013e31827a8809.

Harber, V. J., S. R. Petersen, and P. D. Chilibeck. 1998. 'Thyroid Hormone Concentrations and Muscle Metabolism in Amenorrheic and Eumenorrheic Athletes'. *Canadian Journal of Applied Physiology = Revue Canadienne De Physiologie Appliquee* 23 (3): 293–306. https://doi.org/10.1139/h98-017.

Heikura, Ida A., Walter T. P. McCluskey, Ming-Chang Tsai, et al. 2024. 'Application of the IOC Relative Energy Deficiency in Sport (REDs) Clinical Assessment Tool Version 2 (CAT2) across 200+ Elite Athletes'. Original Research. *British Journal of Sports Medicine*, ahead of print, August 20. https://doi.org/10.1136/bjsports-2024-108121.

Heikura, Ida A., Trent Stellingwerff, and Jose L. Areta. 2022. 'Low Energy Availability in Female Athletes: From the Lab to the Field'. *European Journal of Sport Science* 22 (5): 709–19. https://doi.org/10.1080/17461391.2021.1915391.

Heikura, Ida A., Arja L. T. Uusitalo, Trent Stellingwerff, Dan Bergland, Antti A. Mero, and Louise M. Burke. 2018. '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* 28 (4): 403–11. https://doi.org/10.1123/ijsnem.2017-0313.

Heinitz, Sascha, Tim Hollstein, Takafumi Ando, et al. 2020. 'Early Adaptive Thermogenesis Is a Determinant of Weight Loss after Six Weeks of Caloric Restriction in Overweight Subjects'. *Metabolism: Clinical and Experimental* 110 (September): 154303. https://doi.org/10.1016/j.metabol.2020.154303.

Hermida, Nerea, and Jean-Luc Balligand. 2014. 'Low-Density Lipoprotein-Cholesterol-Induced Endothelial Dysfunction and Oxidative Stress: The Role of Statins'. *Antioxidants & Redox Signaling* 20 (8): 1216–37. https://doi.org/10.1089/ars.2013.5537.

Hevonoja, Tiia, Markku O. Pentikäinen, Marja T. Hyvönen, Petri T. Kovanen, and Mika Ala-Korpela. 2000. 'Structure of Low Density Lipoprotein (LDL) Particles: Basis for Understanding Molecular Changes in Modified LDL'. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1488 (3): 189–210. https://doi.org/10.1016/S1388-1981(00)00123-2.

Hills, Andrew P., Najat Mokhtar, and Nuala M. Byrne. 2014. 'Assessment of Physical Activity and Energy Expenditure: An Overview of Objective Measures'. *Frontiers in Nutrition* 1: 5. https://doi.org/10.3389/fnut.2014.00005.

Hilton, L. K., and A. B. Loucks. 2000. 'Low Energy Availability, Not Exercise Stress, Suppresses the Diurnal Rhythm of Leptin in Healthy Young Women'. *American Journal of Physiology-Endocrinology and Metabolism* 278 (1): E43–49. https://doi.org/10.1152/ajpendo.2000.278.1.E43.

Hodis, Howard N., and Wendy J. Mack. 2022. 'Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease: It's About Time and Timing'. *Cancer Journal (Sudbury, Mass.)* 28 (3): 208–23. https://doi.org/10.1097/PPO.0000000000000591.

Hodis, Howard N., Wendy J. Mack, Victor W. Henderson, et al. 2016. 'Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol'. *The New England Journal of Medicine* 374 (13): 1221–31. https://doi.org/10.1056/NEJMoa1505241.

Hofmann, A. F., and L. R. Hagey. 2008. 'Bile Acids: Chemistry, Pathochemistry, Biology, Pathobiology, and Therapeutics'. *Cellular and Molecular Life Sciences* 65 (16): 2461–83. https://doi.org/10.1007/s00018-008-7568-6.

Holtzman, Bryan, and Kathryn E. Ackerman. 2021. 'Recommendations and Nutritional Considerations for Female Athletes: Health and Performance'. *Sports Medicine (Auckland, N.z.)* 51 (Suppl 1): 43–57. https://doi.org/10.1007/s40279-021-01508-8.

Hooper, David R., William J. Kraemer, Catherine Saenz, et al. 2017. 'The Presence of Symptoms of Testosterone Deficiency in the Exercise-Hypogonadal Male Condition and the Role of Nutrition'. *European Journal of Applied Physiology* 117 (7): 1349–57. https://doi.org/10.1007/s00421-017-3623-z.

Hosten, Adrian O. 1990. 'BUN and Creatinine'. In *Clinical Methods: The History, Physical, and Laboratory Examinations*, 3rd edn, edited by H. Kenneth Walker, W. Dallas Hall, and J. Willis Hurst. Butterworths. http://www.ncbi.nlm.nih.gov/books/NBK305/.

Hu, Pengwei, Kanika I. Dharmayat, Christophe A. T. Stevens, et al. 2020. 'Prevalence of Familial Hypercholesterolemia Among the General Population and Patients With Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analysis'. *Circulation* 141 (22): 1742–59. https://doi.org/10.1161/CIRCULATIONAHA.119.044795.

Hudson, James I., Kristin N. Javaras, and Harrison G. Pope. 2020. 'THE CHALLENGES OF METABOLIC SYNDROME IN EATING DISORDERS'. *Psychiatric Annals* 50 (8): 346–50. https://doi.org/10.3928/00485713-20200713-02.

Hussain, Mesut Bilgin, Jessica Carlsson, et al. 2023. 'Elevated Lipid Class Concentrations in Females with Anorexia Nervosa before and after Intensive Weight Restoration Treatment-A Lipidomics Study'. *The International Journal of Eating Disorders*, ahead of print, September 15. https://doi.org/10.1002/eat.24063.

Hussain, Christopher Hübel, Mathias Hindborg, et al. 2019. 'Increased Lipid and Lipoprotein Concentrations in Anorexia Nervosa: A Systematic Review and Meta-Analysis'. *The International Journal of Eating Disorders* 52 (6): 611–29. https://doi.org/10.1002/eat.23051.

Hussain, Sultana Monira, and John J. McNeil. 2026. 'An HDL Cholesterol Paradox'. *Cardiovascular Drugs and Therapy* 40 (1): 1–5. https://doi.org/10.1007/s10557-025-07703-3.

Hyvärinen, Matti, Hanna-Kaarina Juppi, Sara Taskinen, et al. 2022. 'Metabolic Health, Menopause, and Physical Activity—a 4-Year Follow-up Study'. *International Journal of Obesity* 46 (3): 544–54. https://doi.org/10.1038/s41366-021-01022-x.

Ihalainen, Johanna K., Ritva S. Mikkonen, Kathryn E. Ackerman, et al. 2024. 'Beyond Menstrual Dysfunction: Does Altered Endocrine Function Caused by Problematic Low Energy Availability Impair Health and Sports Performance in Female Athletes?' *Sports Medicine*, ahead of print, July 12. https://doi.org/10.1007/s40279-024-02065-6.

Ihle, Rayan, and Anne B. Loucks. 2004. 'Dose-Response Relationships Between Energy Availability and Bone Turnover in Young Exercising Women'. *Journal of Bone and Mineral Research* 19 (8): 1231–40. https://doi.org/10.1359/JBMR.040410.

Ikeda, Yoshito, Shin-ya Morita, and Tomohiro Terada. 2017. 'Cholesterol Attenuates Cytoprotective Effects of Phosphatidylcholine against Bile Salts'. *Scientific Reports* 7 (1): 306. https://doi.org/10.1038/s41598-017-00476-2.

Ineck, Beata A., and Tien M. H. Ng. 2003. 'Effects of Subclinical Hypothyroidism and Its Treatment on Serum Lipids'. *The Annals of Pharmacotherapy* 37 (5): 725–30. https://doi.org/10.1345/aph.1C376.

Iorga, Andrea, Christine M. Cunningham, Shayan Moazeni, Gregoire Ruffenach, Soban Umar, and Mansoureh Eghbali. 2017. 'The Protective Role of Estrogen and Estrogen Receptors in Cardiovascular Disease and the Controversial Use of Estrogen Therapy'. *Biology of Sex Differences* 8 (1): 33. https://doi.org/10.1186/s13293-017-0152-8.

Islam, S. M. Touhidul, Bremansu Osa-Andrews, Patricia Mary Jones, Alagar R. Muthukumar, Ibrahim Hashim, and Jing Cao. 2022. 'Methods of Low-Density Lipoprotein-Cholesterol Measurement: Analytical and Clinical Applications'. *EJIFCC* 33 (4): 282–94.

Isola, Ville, Juha J. Hulmi, Pirita Petäjä, Eric R. Helms, Jari E. Karppinen, and Juha P. Ahtiainen. 2023. 'Weight Loss Induces Changes in Adaptive Thermogenesis in Female and Male Physique Athletes'. *Applied Physiology, Nutrition, and Metabolism* 48 (4): 307–20. https://doi.org/10.1139/apnm-2022-0372.

Jagim, Andrew R., Jennifer Fields, Meghan K. Magee, Chad M. Kerksick, and Margaret T. Jones. 2022. 'Contributing Factors to Low Energy Availability in Female Athletes: A Narrative Review of Energy Availability, Training Demands, Nutrition Barriers, Body Image, and Disordered Eating'. *Nutrients* 14 (5): 986. https://doi.org/10.3390/nu14050986.

Jansson, P. A., A. Larsson, U. Smith, and P. Lönnroth. 1994. 'Lactate Release from the Subcutaneous Tissue in Lean and Obese Men'. *The Journal of Clinical Investigation* 93 (1): 240–46. https://doi.org/10.1172/JCI116951.

Jebari-Benslaiman, Shifa, Unai Galicia-García, Asier Larrea-Sebal, et al. 2022. 'Pathophysiology of Atherosclerosis'. *International Journal of Molecular Sciences* 23 (6): 3346. https://doi.org/10.3390/ijms23063346.

Jensen, J., L. Nilas, and C. Christiansen. 1990. 'Influence of Menopause on Serum Lipids and Lipoproteins'. *Maturitas* 12 (4): 321–31. https://doi.org/10.1016/0378-5122(90)90012-u.

Jeong, Kang Ju, Moeka Mukae, Sang R. Lee, et al. 2024. 'Progesterone Increases Hepatic Lipid Content and Plasma Lipid Levels through PR- B-Mediated Lipogenesis'. *Biomedicine & Pharmacotherapy* 172 (March): 116281. https://doi.org/10.1016/j.biopha.2024.116281.

Jesus, Filipe, Inês Castela, Analiza M. Silva, Pedro A. Branco, and Mónica Sousa. 2021. 'Risk of Low Energy Availability among Female and Male Elite Runners Competing at the 26th European Cross-Country Championships'. *Nutrients* 13 (3): 873. https://doi.org/10.3390/nu13030873.

Jeukendrup, A. E., and Michael Gleeson. 2009. 'Normal Ranges of Body Weight and Body Fat'. In *Sport Nutrition-Human Kinetics*, 2nd Edition, vol. 2009. https://us.humankinetics.com/blogs/excerpt/normal-ranges-of-body-weight-and-body-fat.

Jeukendrup, Jose L. Areta, Lara Van Genechten, et al. 2024. 'Does Relative Energy Deficiency in Sport (REDs) Syndrome Exist?' *Sports Medicine (Auckland, N.z.)* 54 (11): 2793–816. https://doi.org/10.1007/s40279-024-02108-y.

Ji, Jianguang, Jan Sundquist, and Kristina Sundquist. 2016. 'Association between Anorexia Nervosa and Type 2 Diabetes in Sweden: Etiological Clue for the Primary Prevention of Type 2 Diabetes'. *Endocrine Research* 41 (4): 310–16. https://doi.org/10.3109/07435800.2016.1141948.

Jokiniitty, Antti, Markku Eskola, Saara Metso, Martin Bogsrud, Heini Huhtala, and Tanja Saarela. 2024. 'Genetic Testing for Familial Hypercholesterolemia in a Finnish Cohort of Patients with Premature Coronary Artery Disease and Elevated LDL-C Levels'. *Frontiers in Cardiovascular Medicine* 11 (July): 1433042. https://doi.org/10.3389/fcvm.2024.1433042.

Jolliffe, Ian T., and Jorge Cadima. 2016. 'Principal Component Analysis: A Review and Recent Developments'. *Philosophical Transactions. Series A, Mathematical, Physical, and Engineering Sciences* 374 (2065): 20150202. https://doi.org/10.1098/rsta.2015.0202.

Jouhki, I., H. V. Sarin, M. Jauhiainen, et al. 2024. 'Effects of Fat Loss and Low Energy Availability on the Serum Cardiometabolic Profile of Physique Athletes'. *Scandinavian Journal of Medicine & Science in Sports* 34 (1): e14553. https://doi.org/10.1111/sms.14553.

Julve, Josep, Jesús M. Martín-Campos, Joan Carles Escolà-Gil, and Francisco Blanco-Vaca. 2016. 'Chylomicrons: Advances in Biology, Pathology, Laboratory Testing, and Therapeutics'. *Clinica Chimica Acta* 455 (April): 134–48. https://doi.org/10.1016/j.cca.2016.02.004.

Kaiserauer, Susanne, Ann C. Snyder, Mark Sleeper, and Juleen Zierath. 1989. 'Nutritional, Physiological, and Menstrual Status of Distance Runners'. *Medicine & Science in Sports & Exercise* 21 (2): 120.

Karimi, Reza, Anita Cleven, Fawzy Elbarbry, and Huy Hoang. 2021. 'The Impact of Fasting on Major Metabolic Pathways of Macronutrients and Pharmacokinetics Steps of Drugs'. *European Journal of Drug Metabolism and Pharmacokinetics* 46 (1): 25–39. https://doi.org/10.1007/s13318-020-00656-y.

Karlsson, Elin, Marie Alricsson, and Anna Melin. 2023. 'Symptoms of Eating Disorders and Low Energy Availability in Recreational Active Female Runners'. Original Research. *BMJ Open Sport & Exercise Medicine* 9 (3): e001623. https://doi.org/10.1136/bmjsem-2023-001623.

Karppinen, Jari E., Timo Törmäkangas, Urho M. Kujala, et al. 2022. 'Menopause Modulates the Circulating Metabolome: Evidence from a Prospective Cohort Study'. *European Journal of Preventive Cardiology* 29 (10): 1448–59. https://doi.org/10.1093/eurjpc/zwac060.

Karvinen, Sira, Matthew J. Jergenson, Matti Hyvärinen, et al. 2019. 'Menopausal Status and Physical Activity Are Independently Associated With Cardiovascular Risk Factors of Healthy Middle-Aged Women: Cross-Sectional and Longitudinal Evidence'. *Frontiers in Endocrinology* 10 (August). https://doi.org/10.3389/fendo.2019.00589.

Kasper, Andreas M., Ben Crighton, Carl Langan-Evans, et al. 2019. *Case Study: Extreme Weight Making Causes Relative Energy Deficiency, Dehydration, and Acute Kidney Injury in a Male Mixed Martial Arts Athlete*. International Journal of Sport Nutrition and Exercise Metabolism. May 1. https://doi.org/10.1123/ijsnem.2018-0029.

Kelly, Daniel M., and T. Hugh Jones. 2013. *Testosterone: A Metabolic Hormone in Health and Disease*. Journal of Endocrinology. June 1. https://doi.org/10.1530/JOE-12-0455.

Kendler, David L., Juliet Compston, John J. Carey, Chih-Hsing Wu, Ammar Ibrahim, and E. Michael Lewiecki. 2019. 'Repeating Measurement of Bone Mineral Density When Monitoring with Dual-Energy X-Ray Absorptiometry: 2019 ISCD Official Position'. *Journal of Clinical Densitometry* 22 (4): 489–500. https://doi.org/10.1016/j.jocd.2019.07.010.

Kettunen, Oona, Ritva Mikkonen, Vesa Linnamo, Jaakko Mursu, Heikki Kyröläinen, and Johanna K. Ihalainen. 2023. 'Nutritional Intake and Anthropometric Characteristics Are Associated with Endurance Performance and Markers of Low Energy Availability in Young Female Cross-Country Skiers'. *Journal of the International Society of Sports Nutrition* 20 (1): 2226639. https://doi.org/10.1080/15502783.2023.2226639.

Koehler, Karsten, Silvia Achtzehn, Hans Braun, Joachim Mester, and Wilhelm Schaenzer. 2013. 'Comparison of Self-Reported Energy Availability and Metabolic Hormones to Assess Adequacy of Dietary Energy Intake in Young Elite Athletes'. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme* 38 (7): 725–33. https://doi.org/10.1139/apnm-2012-0373.

Koehler, Karsten, Neele Hoerner, Jenna Gibbs, Christoph Zinner, Hans Braun, Mary De Souza, et al. 2016. 'Low Energy Availability in Exercising Men Is Associated with Reduced Leptin and Insulin but Not with Changes in Other Metabolic Hormones'. *Nutrition and Health Sciences -- Faculty Publications*, January 1. https://digitalcommons.unl.edu/nutritionfacpub/85.

Koehler, Karsten, Neele R. Hoerner, Jenna C. Gibbs, Christoph Zinner, Hans Braun, Mary Jane De Souza, et al. 2016. 'Low Energy Availability in Exercising Men Is Associated with Reduced Leptin and Insulin but Not with Changes in Other Metabolic Hormones'. *Journal of Sports Sciences* 34 (20): 1921–29. https://doi.org/10.1080/02640414.2016.1142109.

Koh, Kwang Kon, Sang Min Park, and Michael J. Quon. 2008. 'Leptin and Cardiovascular Disease'. *Circulation* 117 (25): 3238–49. https://doi.org/10.1161/CIRCULATIONAHA.107.741645.

Kojima, Chihiro, Aya Ishibashi, Yoko Tanabe, et al. 2020. 'Muscle Glycogen Content during Endurance Training under Low Energy Availability'. *Medicine & Science in Sports & Exercise* 52 (1): 187. https://doi.org/10.1249/MSS.0000000000002098.

Kok, Helen S., Kristel M. van Asselt, Yvonne T. van der Schouw, et al. 2006. 'Heart Disease Risk Determines Menopausal Age Rather than the Reverse'. *Journal of the American College of Cardiology* 47 (10): 1976–83. https://doi.org/10.1016/j.jacc.2005.12.066.

Kontush, Anatol. 2015. 'HDL Particle Number and Size as Predictors of Cardiovascular Disease'. *Frontiers in Pharmacology* 6 (October): 218. https://doi.org/10.3389/fphar.2015.00218.

Kontush, Anatol. 2020. 'HDL and Reverse Remnant-Cholesterol Transport (RRT): Relevance to Cardiovascular Disease'. *Trends in Molecular Medicine* 26 (12): 1086–100. https://doi.org/10.1016/j.molmed.2020.07.005.

Kyte, Karoline Holsen, Trine Stensrud, Tore Julsrud Berg, Ingebjørg Seljeflot, and Jonny Hisdal. 2022. 'Vascular Function in Norwegian Female Elite Runners: A Cross-Sectional, Controlled Study'. *Sports* 10 (3): 3. https://doi.org/10.3390/sports10030037.

Lahtinen, Annukka M., Aki S. Havulinna, Antti Jula, Veikko Salomaa, and Kimmo Kontula. 2015. 'Prevalence and Clinical Correlates of Familial Hypercholesterolemia Founder Mutations in the General Population'. *Atherosclerosis* 238 (1): 64–69. https://doi.org/10.1016/j.atherosclerosis.2014.11.015.

Lane, Amy R., Anthony C. Hackney, Abbie Smith-Ryan, Kristen Kucera, Johna Registar-Mihalik, and Kristin Ondrak. 2019. 'Prevalence of Low Energy Availability in Competitively Trained

Male Endurance Athletes'. *Medicina (Kaunas, Lithuania)* 55 (10): 665. https://doi.org/10.3390/medicina55100665.

Langan-Evans, Carl, Mark Germaine, Mario Artukovic, et al. 2021. 'The Psychological and Physiological Consequences of Low Energy Availability in a Male Combat Sport Athlete'. *Medicine and Science in Sports and Exercise* 53 (4): 673–83. https://doi.org/10.1249/MSS.0000000000002519.

Laughlin, G. A., C. E. Dominguez, and S. S. C. Yen. 1998. 'Nutritional and Endocrine-Metabolic Aberrations in Women with Functional Hypothalamic Amenorrhea1'. *The Journal of Clinical Endocrinology & Metabolism* 83 (1): 25–32. https://doi.org/10.1210/jcem.83.1.4502.

Laughlin, G. A., and S. S. Yen. 1996. 'Nutritional and Endocrine-Metabolic Aberrations in Amenorrheic Athletes'. *The Journal of Clinical Endocrinology and Metabolism* 81 (12): 4301–9. https://doi.org/10.1210/jcem.81.12.8954031.

Laughlin, G. A., and S. S. Yen. 1997. 'Hypoleptinemia in Women Athletes: Absence of a Diurnal Rhythm with Amenorrhea'. *The Journal of Clinical Endocrinology and Metabolism* 82 (1): 318–21. https://doi.org/10.1210/jcem.82.1.3840.

Lee, Hsiang-Chun, Alexander Akhmedov, and Chu-Huang Chen. 2022. 'Spotlight on Very-Low-Density Lipoprotein as a Driver of Cardiometabolic Disorders: Implications for Disease Progression and Mechanistic Insights'. *Frontiers in Cardiovascular Medicine* 9 (October): 993633. https://doi.org/10.3389/fcvm.2022.993633.

Lefevre, Michael, Leanne M. Redman, Leonie K. Heilbronn, et al. 2009. 'Caloric Restriction Alone and with Exercise Improves CVD Risk in Healthy Non-Obese Individuals'. *Atherosclerosis* 203 (1): 206–13. https://doi.org/10.1016/j.atherosclerosis.2008.05.036.

Leren, Trond P., and Martin Prøven Bogsrud. 2021. 'The Importance of Cascade Genetic Screening for Diagnosing Autosomal Dominant Hypercholesterolemia: Results from Twenty Years of a National Screening Program in Norway'. *Journal of Clinical Lipidology* 15 (5): 674–81. https://doi.org/10.1016/j.jacl.2021.08.007.

Letertre, Marine P. M., Patrick Giraudeau, and Pascal de Tullio. 2021. 'Nuclear Magnetic Resonance Spectroscopy in Clinical Metabolomics and Personalized Medicine: Current Challenges and Perspectives'. *Frontiers in Molecular Biosciences* 8 (September). https://doi.org/10.3389/fmolb.2021.698337.

Li, Jiarui, Yihan Wang, Xiaoting Luo, et al. 2024. 'Causal Relationship between Hypothyroidism and Coronary Atherosclerotic Cardiovascular Disease: A Bidirectional Two-Sample Mendelian Randomization'. *Frontiers in Cardiovascular Medicine* 11: 1402359. https://doi.org/10.3389/fcvm.2024.1402359.

Li, Li-Hua, Ewelina P. Dutkiewicz, Ying-Chen Huang, Hsin-Bai Zhou, and Cheng-Chih Hsu. 2019. 'Analytical Methods for Cholesterol Quantification'. *Journal of Food and Drug Analysis* 27 (2): 375–86. https://doi.org/10.1016/j.jfda.2018.09.001.

Lichtenstein, Mia Beck, Karen Krogh Johansen, Eik Runge, Marina Bohn Hansen, Trine Theresa Holmberg, and Kristine Tarp. 2022. 'Behind the Athletic Body: A Clinical Interview Study

of Identification of Eating Disorder Symptoms and Diagnoses in Elite Athletes'. *BMJ Open Sport & Exercise Medicine* 8 (2): e001265. https://doi.org/10.1136/bmjsem-2021-001265.

Lieberman, Jay L., Mary Jane DE Souza, David A. Wagstaff, and Nancy I. Williams. 2018. 'Menstrual Disruption with Exercise Is Not Linked to an Energy Availability Threshold'. *Medicine and Science in Sports and Exercise* 50 (3): 551–61. https://doi.org/10.1249/MSS.0000000000001451.

Lind, Suzanne, Mats Rudling, Sverker Ericsson, et al. 2004. 'Growth Hormone Induces Low-Density Lipoprotein Clearance but Not Bile Acid Synthesis in Humans'. *Arteriosclerosis, Thrombosis, and Vascular Biology* 24 (2): 349–56. https://doi.org/10.1161/01.ATV.0000110657.67317.90.

Linton, MacRae F., Patricia G. Yancey, Sean S. Davies, et al. 2000. 'The Role of Lipids and Lipoproteins in Atherosclerosis'. In *Endotext*, edited by Kenneth R. Feingold, Robert A. Adler, S. Faisal Ahmed, et al. MDText.com, Inc. http://www.ncbi.nlm.nih.gov/books/NBK343489/.

Logue, Danielle M., Sharon M. Madigan, Anna Melin, et al. 2020. 'Low Energy Availability in Athletes 2020: An Updated Narrative Review of Prevalence, Risk, Within-Day Energy Balance, Knowledge, and Impact on Sports Performance'. *Nutrients* 12 (3): 835. https://doi.org/10.3390/nu12030835.

Loucks. 2006. 'The Response of Luteinizing Hormone Pulsatility to 5 Days of Low Energy Availability Disappears by 14 Years of Gynecological Age'. *The Journal of Clinical Endocrinology and Metabolism* 91 (8): 3158–64. https://doi.org/10.1210/jc.2006-0570.

Loucks, A. B., and E. M. Heath. 1994a. 'Dietary Restriction Reduces Luteinizing Hormone (LH) Pulse Frequency during Waking Hours and Increases LH Pulse Amplitude during Sleep in Young Menstruating Women'. *The Journal of Clinical Endocrinology and Metabolism* 78 (4): 910–15. https://doi.org/10.1210/jcem.78.4.8157720.

Loucks, Anne B. 2013. 'Exercise Training in the Normal Female: Effects of Low Energy Availability on Reproductive Function'. In *Endocrinology of Physical Activity and Sport: Second Edition*, edited by Naama Constantini and Anthony C. Hackney. Humana Press. https://doi.org/10.1007/978-1-62703-314-5_11.

Loucks, and R. Callister. 1993. 'Induction and Prevention of Low-T3 Syndrome in Exercising Women'. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 264 (5): R924–30. https://doi.org/10.1152/ajpregu.1993.264.5.R924.

Loucks, and E. M. Heath. 1994b. 'Induction of Low-T3 Syndrome in Exercising Women Occurs at a Threshold of Energy Availability'. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 266 (3): R817–23. https://doi.org/10.1152/ajpregu.1994.266.3.R817.

Loucks, Bente Kiens, and Hattie H. Wright. 2011. 'Energy Availability in Athletes'. *Journal of Sports Sciences* 29 (sup1): S7–15. https://doi.org/10.1080/02640414.2011.588958.

Loucks, and Jean R. Thuma. 2003. 'Luteinizing Hormone Pulsatility Is Disrupted at a Threshold of Energy Availability in Regularly Menstruating Women'. *The Journal of Clinical Endocrinology & Metabolism* 88 (1): 297–311. https://doi.org/10.1210/jc.2002-020369.

Loucks, M. Verdun, and E. M. Heath. 1998. 'Low Energy Availability, Not Stress of Exercise, Alters LH Pulsatility in Exercising Women'. *Journal of Applied Physiology* 84 (1): 37–46. https://doi.org/10.1152/jappl.1998.84.1.37.

Lundåsen, Thomas, Wei Liao, Bo Angelin, and Mats Rudling. 2003. 'Leptin Induces the Hepatic High Density Lipoprotein Receptor Scavenger Receptor B Type I (SR-BI) but Not Cholesterol 7alpha-Hydroxylase (Cyp7a1) in Leptin-Deficient (Ob/Ob) Mice'. *The Journal of Biological Chemistry* 278 (44): 43224–28. https://doi.org/10.1074/jbc.M302645200.

Mach, François, Colin Baigent, Alberico L. Catapano, Konstantinos C. Koskinas, Manuela Casula, et al. 2020. '2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: *Lipid Modification to Reduce Cardiovascular Risk*'. *European Heart Journal* 41 (1): 111–88. https://doi.org/10.1093/eurheartj/ehz455.

Mach, François, Colin Baigent, Alberico L. Catapano, Konstantinos C. Koskinas, Manuela Casula, et al. 2020. '2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)'. *European Heart Journal* 41 (1): 111–88. https://doi.org/10.1093/eurheartj/ehz455.

Magkos, Faidon. 2022. 'Is Calorie Restriction Beneficial for Normal-Weight Individuals? A Narrative Review of the Effects of Weight Loss in the Presence and Absence of Obesity'. *Nutrition Reviews* 80 (7): 1811–25. https://doi.org/10.1093/nutrit/nuac006.

Magkos, Faidon, and Bettina Mittendorfer. 2009. 'Gender Differences in Lipid Metabolism and the Effect of Obesity'. *Obstetrics and Gynecology Clinics of North America* 36 (2): 245–65, vii. https://doi.org/10.1016/j.ogc.2009.03.001.

Magkos, Faidon, Bruce W. Patterson, and Bettina Mittendorfer. 2006. 'No Effect of Menstrual Cycle Phase on Basal Very-Low-Density Lipoprotein Triglyceride and Apolipoprotein B-100 Kinetics'. *American Journal of Physiology. Endocrinology and Metabolism* 291 (6): E1243-1249. https://doi.org/10.1152/ajpendo.00246.2006.

Magkos, Faidon, Bruce W. Patterson, B. Selma Mohammed, Samuel Klein, and Bettina Mittendorfer. 2007. 'Women Produce Fewer but Triglyceride-Richer Very Low-Density Lipoproteins than Men'. *The Journal of Clinical Endocrinology and Metabolism* 92 (4): 1311–18. https://doi.org/10.1210/jc.2006-2215.

Mancine, Ryley P., Donald W. Gusfa, Ali Moshrefi, and Samantha F. Kennedy. 2020. 'Prevalence of Disordered Eating in Athletes Categorized by Emphasis on Leanness and Activity Type – a Systematic Review'. *Journal of Eating Disorders* 8 (September): 47. https://doi.org/10.1186/s40337-020-00323-2.

Manson, JoAnn E., Judith Hsia, Karen C. Johnson, et al. 2003. 'Estrogen plus Progestin and the Risk of Coronary Heart Disease'. *The New England Journal of Medicine* 349 (6): 523–34. https://doi.org/10.1056/NEJMoa030808.

Maranhão, Raul Cavalcante, Priscila Oliveira Carvalho, Celia Cassaro Strunz, and Fulvio Pileggi. 2014. 'Lipoprotein (a): Structure, Pathophysiology and Clinical Implications'. *Arquivos Brasileiros De Cardiologia* 103 (1): 76–84. https://doi.org/10.5935/abc.20140101.

Martin, Alexandra, Darius Fox, Chaise A. Murphy, Hande Hofmann, and Karsten Koehler. 2022. 'Tissue Losses and Metabolic Adaptations Both Contribute to the Reduction in Resting Metabolic Rate Following Weight Loss'. *International Journal of Obesity* 46 (6): 1168–75. https://doi.org/10.1038/s41366-022-01090-7.

Mathisen, Therese Fostervold, Timothy Ackland, Louise M. Burke, et al. 2023. 'Best Practice Recommendations for Body Composition Considerations in Sport to Reduce Health and Performance Risks: A Critical Review, Original Survey and Expert Opinion by a Subgroup of the IOC Consensus on Relative Energy Deficiency in Sport (REDs)'. *British Journal of Sports Medicine* 57 (17): 1148–58. https://doi.org/10.1136/bjsports-2023-106812.

Matthan, Nirupa R., Susan M. Jalbert, Stefania Lamon-Fava, et al. 2005. 'TRL, IDL, and LDL Apolipoprotein B-100 and HDL Apolipoprotein A-I Kinetics as a Function of Age and Menopausal Status'. *Arteriosclerosis, Thrombosis, and Vascular Biology* 25 (8): 1691–96. https://doi.org/10.1161/01.ATV.0000172629.12846.b8.

Matthews, Karen A., Sybil L. Crawford, Claudia U. Chae, et al. 2009. 'Are Changes in Cardiovascular Disease Risk Factors in Midlife Women Due to Chronological Aging or to the Menopausal Transition?' *Journal of the American College of Cardiology* 54 (25): 2366–73. https://doi.org/10.1016/j.jacc.2009.10.009.

Mauricio, Clóvis De Albuquerque, Pablo Merino, Rodrigo Merlo, et al. 2022. 'Rapid Weight Loss of Up to Five Percent of the Body Mass in Less Than 7 Days Does Not Affect Physical Performance in Official Olympic Combat Athletes With Weight Classes: A Systematic Review With Meta-Analysis'. *Frontiers in Physiology* 13 (April). https://doi.org/10.3389/fphys.2022.830229.

McCarthy, Seth F., Jessica A. L. Tucker, and Tom J. Hazell. 2024. 'Exercise-Induced Appetite Suppression: An Update on Potential Mechanisms'. *Physiological Reports* 12 (16): e70022. https://doi.org/10.14814/phy2.70022.

McCormack, William P., Todd C. Shoepe, Joseph LaBrie, and Hawley C. Almstedt. 2019. 'Bone Mineral Density, Energy Availability, and Dietary Restraint in Collegiate Cross-Country Runners and Non-Running Controls'. *European Journal of Applied Physiology* 119 (8): 1747–56. https://doi.org/10.1007/s00421-019-04164-z.

McDonald, Anna Holdiman, Mary Pritchard, and Mary Kate McGuire. 2020. 'Self-Reported Eating Disorder Risk in Lean and Non-Lean NCAA Collegiate Athletes'. *Eating and Weight Disorders: EWD* 25 (3): 745–50. https://doi.org/10.1007/s40519-019-00681-0.

McKay, Alannah K. A., Peter Peeling, David B. Pyne, et al. 2022. 'Six Days of Low Carbohydrate, Not Energy Availability, Alters the Iron and Immune Response to Exercise in Elite Athletes'. *Medicine and Science in Sports and Exercise* 54 (3): 377–87. https://doi.org/10.1249/MSS.0000000000002819.

McKay, Alannah K. A., Trent Stellingwerff, Ella S. Smith, et al. 2021. *Defining Training and Performance Caliber: A Participant Classification Framework*. International Journal of Sports Physiology and Performance. December 29. https://doi.org/10.1123/ijspp.2021-0451.

Meczekalski, B., K. Katulski, A. Czyzyk, A. Podfigurna-Stopa, and M. Maciejewska-Jeske. 2014. 'Functional Hypothalamic Amenorrhea and Its Influence on Women's Health'. *Journal of Endocrinological Investigation* 37 (11): 1049–56. https://doi.org/10.1007/s40618-014-0169-3.

Mehta, Nehal N., Amit K. Dey, Reethika Maddineni, William E. Kraus, and Kim M. Huffman. 2020. 'GlycA Measured by NMR Spectroscopy Is Associated with Disease Activity and Cardiovascular Disease Risk in Chronic Inflammatory Diseases'. *American Journal of Preventive Cardiology* 4 (November): 100120. https://doi.org/10.1016/j.ajpc.2020.100120.

Melin, Anna K., Ida A. Heikura, Adam Tenforde, and Margo Mountjoy. 2019. 'Energy Availability in Athletics: Health, Performance, and Physique'. *International Journal of Sport Nutrition and Exercise Metabolism* 29 (2): 152–64. https://doi.org/10.1123/ijsnem.2018-0201.

Melin, José L. Areta, Ida A. Heikura, Trent Stellingwerff, Monica Klungland Torstveit, and Anthony C. Hackney. 2024. 'Direct and Indirect Impact of Low Energy Availability on Sports Performance'. *Scandinavian Journal of Medicine & Science in Sports* 34 (1): e14327. https://doi.org/10.1111/sms.14327.

Melin, Å. B. Tornberg, S. Skouby, et al. 2015. 'Energy Availability and the Female Athlete Triad in Elite Endurance Athletes'. *Scandinavian Journal of Medicine & Science in Sports* 25 (5): 610–22. https://doi.org/10.1111/sms.12261.

Melin, Åsa B. Tornberg, Sven Skouby, et al. 2014. 'The LEAF Questionnaire: A Screening Tool for the Identification of Female Athletes at Risk for the Female Athlete Triad'. Original Article. *British Journal of Sports Medicine* 48 (7): 540–45. https://doi.org/10.1136/bjsports-2013-093240.

Meyer, Matthias R., Elvira Haas, and Matthias Barton. 2006. 'Gender Differences of Cardiovascular Disease'. *Hypertension* 47 (6): 1019–26. https://doi.org/10.1161/01.HYP.0000223064.62762.0b.

Miller, K. K., E. A. Lawson, V. Mathur, et al. 2007. 'Androgens in Women with Anorexia Nervosa and Normal-Weight Women with Hypothalamic Amenorrhea'. *The Journal of Clinical Endocrinology and Metabolism* 92 (4): 1334–39. https://doi.org/10.1210/jc.2006-2501.

Misra, Madhusmita, Debra K. Katzman, Jennalee Cord, et al. 2008. 'Bone Metabolism in Adolescent Boys with Anorexia Nervosa'. *The Journal of Clinical Endocrinology and Metabolism* 93 (8): 3029–36. https://doi.org/10.1210/jc.2008-0170.

Misra, Madhusmita, and Anne Klibanski. 2014. 'Endocrine Consequences of Anorexia Nervosa'. *The Lancet. Diabetes & Endocrinology* 2 (7): 581–92. https://doi.org/10.1016/S2213-8587(13)70180-3.

Misra, Madhusmita, Karen K. Miller, Jennifer Bjornson, et al. 2003. 'Alterations in Growth Hormone Secretory Dynamics in Adolescent Girls with Anorexia Nervosa and Effects on Bone Metabolism'. *The Journal of Clinical Endocrinology and Metabolism* 88 (12): 5615–23. https://doi.org/10.1210/jc.2003-030532.

Misra, Madhusmita, Karen K. Miller, David B. Herzog, et al. 2004. 'Growth Hormone and Ghrelin Responses to an Oral Glucose Load in Adolescent Girls with Anorexia Nervosa and

Controls'. *The Journal of Clinical Endocrinology and Metabolism* 89 (4): 1605–12. https://doi.org/10.1210/jc.2003-031861.

Misra, Madhusmita, Karen K. Miller, Patrika Tsai, et al. 2006. 'Uncoupling of Cardiovascular Risk Markers in Adolescent Girls with Anorexia Nervosa'. *The Journal of Pediatrics* 149 (6): 763-769.e1. https://doi.org/10.1016/j.jpeds.2006.08.043.

Moore, Erin M., Clemens Drenowatz, David F. Stodden, et al. 2021. 'Examination of Athlete Triad Symptoms Among Endurance-Trained Male Athletes: A Field Study'. *Frontiers in Nutrition* 8: 737777. https://doi.org/10.3389/fnut.2021.737777.

Most, Jasper, L. Anne Gilmore, Steven R. Smith, Hongmei Han, Eric Ravussin, and Leanne M. Redman. 2018. 'Significant Improvement in Cardiometabolic Health in Healthy Nonobese Individuals during Caloric Restriction-Induced Weight Loss and Weight Loss Maintenance'. *American Journal of Physiology. Endocrinology and Metabolism* 314 (4): E396–405. https://doi.org/10.1152/ajpendo.00261.2017.

Mountjoy, Margo, Kathryn E. Ackerman, David M. Bailey, et al. 2023. '2023 International Olympic Committee's (IOC) Consensus Statement on Relative Energy Deficiency in Sport (REDs)'. Consensus Statement. *British Journal of Sports Medicine* 57 (17): 1073–97. https://doi.org/10.1136/bjsports-2023-106994.

Mountjoy, Margo, Jorunn Sundgot-Borgen, Louise Burke, et al. 2014. 'The IOC Consensus Statement: Beyond the Female Athlete Triad—Relative Energy Deficiency in Sport (RED-S)'. Consensus Statement. *British Journal of Sports Medicine* 48 (7): 491–97. https://doi.org/10.1136/bjsports-2014-093502.

Mountjoy, Margo, Jorunn Kaiander Sundgot-Borgen, Louise M. Burke, et al. 2018. 'IOC Consensus Statement on Relative Energy Deficiency in Sport (RED-S): 2018 Update'. Consensus Statement. *British Journal of Sports Medicine* 52 (11): 687–97. https://doi.org/10.1136/bjsports-2018-099193.

Mu, Huiling, and Carl-Erik Høy. 2004. 'The Digestion of Dietary Triacylglycerols'. *Progress in Lipid Research* 43 (2): 105–33. https://doi.org/10.1016/S0163-7827(03)00050-X.

Muia, Esther N., Hattie H. Wright, Vincent O. Onywera, and Elizabeth N. Kuria. 2016. 'Adolescent Elite Kenyan Runners Are at Risk for Energy Deficiency, Menstrual Dysfunction and Disordered Eating'. *Journal of Sports Sciences* 34 (7): 598–606. https://doi.org/10.1080/02640414.2015.1065340.

Müller, and A. Bosy-Westphal. 2013. 'Adaptive Thermogenesis with Weight Loss in Humans'. *Obesity* 21 (2): 218–28. https://doi.org/10.1002/oby.20027.

Müller, Manfred J., Steven B. Heymsfield, and Anja Bosy-Westphal. 2021. 'Are Metabolic Adaptations to Weight Changes an Artefact?' *The American Journal of Clinical Nutrition* 114 (4): 1386–95. https://doi.org/10.1093/ajcn/nqab184.

Mumford, Sunni L., Enrique F. Schisterman, Anna Maria Siega-Riz, et al. 2010. 'A Longitudinal Study of Serum Lipoproteins in Relation to Endogenous Reproductive Hormones during the Menstrual Cycle: Findings from the BioCycle Study'. *The Journal of Clinical Endocrinology & Metabolism* 95 (9): E80–85. https://doi.org/10.1210/jc.2010-0109.

Mundi, Santa, Marika Massaro, Egeria Scoditti, et al. 2018. 'Endothelial Permeability, LDL Deposition, and Cardiovascular Risk Factors—a Review'. *Cardiovascular Research* 114 (1): 35–52. https://doi.org/10.1093/cvr/cvx226.

Murphy, Chaise, and Karsten Koehler. 2020. 'Caloric Restriction Induces Anabolic Resistance to Resistance Exercise'. *European Journal of Applied Physiology* 120 (5): 1155–64. https://doi.org/10.1007/s00421-020-04354-0.

Murphy, Elizabeth. 2011. 'Estrogen Signaling and Cardiovascular Disease'. *Circulation Research* 109 (6): 687–96. https://doi.org/10.1161/CIRCRESAHA.110.236687.

Myerson, M., B. Gutin, M. P. Warren, et al. 1991. 'Resting Metabolic Rate and Energy Balance in Amenorrheic and Eumenorrheic Runners'. *Medicine and Science in Sports and Exercise* 23 (1): 15–22.

Narang, Deepanshu, and Rami A. Al-Horani. 2026. 'Biochemistry, Intermediate Density Lipoprotein'. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK613290/.

Nauck, Matthias, G. Russell Warnick, and Nader Rifai. 2002. 'Methods for Measurement of LDL-Cholesterol: A Critical Assessment of Direct Measurement by Homogeneous Assays versus Calculation'. *Clinical Chemistry* 48 (2): 236–54. https://doi.org/10.1093/clinchem/48.2.236.

Ness, G. C. 1991. 'Thyroid Hormone. Basis for Its Hypocholesterolemic Effect'. *The Journal of the Florida Medical Association* 78 (6): 383–85.

Nie, Guangning, Xiaofei Yang, Yangyang Wang, et al. 2022. 'The Effects of Menopause Hormone Therapy on Lipid Profile in Postmenopausal Women: A Systematic Review and Meta-Analysis'. *Frontiers in Pharmacology* 13 (April). https://doi.org/10.3389/fphar.2022.850815.

Nusser, Valentin, Chaise Murphy, Sieglinde Hechenbichler Figueroa, et al. 2025. 'Metabolic Signature of Short-Term Low Energy Availability'. *Physiological Reports* 13 (19): e70582. https://doi.org/10.14814/phy2.70582.

Nusser, Valentin, Jan Teubner, Simon A. Buerger, et al. 2026. 'Increased Carbohydrate Availability Partially Attenuates Endocrine Suppression in Response to Low Energy Availability'. *Journal of Applied Physiology* (Bethesda, Md. : 1985), ahead of print, July 16. https://doi.org/10.1152/japplphysiol.00207.2026.

O'Donnell, Emma, and Mary Jane De Souza. 2004. 'The Cardiovascular Effects of Chronic Hypoestrogenism in Amenorrhoeic Athletes'. *Sports Medicine* 34 (9): 601–27. https://doi.org/10.2165/00007256-200434090-00004.

Ohwada, Rina, Mari Hotta, Shinichi Oikawa, and Kazue Takano. 2006. 'Etiology of Hypercholesterolemia in Patients with Anorexia Nervosa'. *The International Journal of Eating Disorders* 39 (7): 598–601. https://doi.org/10.1002/eat.20298.

Okonkwo, Oluchukwu, David Zezoff, and Adebayo Adeyinka. 2026. 'Biochemistry, Cholecystokinin'. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK534204/.

Okoth, Kelvin, William Parry Smith, G. Neil Thomas, Krishnarajah Nirantharakumar, and Nicola J. Adderley. 2023. 'The Association between Menstrual Cycle Characteristics and Cardiometabolic Outcomes in Later Life: A Retrospective Matched Cohort Study of 704,743 Women from the UK'. *BMC Medicine* 21 (1): 104. https://doi.org/10.1186/s12916-023-02794-x.

Orth, Matthias, and Stefano Bellosta. 2012. 'Cholesterol: Its Regulation and Role in Central Nervous System Disorders'. *Cholesterol* 2012: 292598. https://doi.org/10.1155/2012/292598.

Overholser, Brian R., and Kevin M. Sowinski. 2008. 'Biostatistics Primer: Part 2'. *Nutrition in Clinical Practice* 23 (1): 76–84. https://doi.org/10.1177/011542650802300176.

Page, Michael M., and Gerald F. Watts. 2016. 'PCSK9 Inhibitors – Mechanisms of Action'. *Australian Prescriber* 39 (5): 164–67. https://doi.org/10.18773/austprescr.2016.060.

Palazzo, Roberto, Tommaso Parisi, Sara Rosa, Marco Corsi, Edoardo Falconi, and Laura Stefani. 2024. 'Energy Availability and Body Composition in Professional Athletes: Two Sides of the Same Coin'. *Nutrients* 16 (20): 3507. https://doi.org/10.3390/nu16203507.

Palmisano, Brian T., Lin Zhu, Robert H. Eckel, and John M. Stafford. 2018. 'Sex Differences in Lipid and Lipoprotein Metabolism'. *Molecular Metabolism* 15 (May): 45–55. https://doi.org/10.1016/j.molmet.2018.05.008.

Palmisano, Brian T., Lin Zhu, and John M. Stafford. 2017. 'Estrogens in the Regulation of Liver Lipid Metabolism'. *Advances in Experimental Medicine and Biology* 1043: 227–56. https://doi.org/10.1007/978-3-319-70178-3_12.

Papadopoulos, Fotios C., Anders Ekbom, Lena Brandt, and Lisa Ekselius. 2009. 'Excess Mortality, Causes of Death and Prognostic Factors in Anorexia Nervosa'. *The British Journal of Psychiatry* 194 (1): 10–17. https://doi.org/10.1192/bjp.bp.108.054742.

Papageorgiou, Maria, Eimear Dolan, Kirsty J. Elliott-Sale, and Craig Sale. 2018. 'Reduced Energy Availability: Implications for Bone Health in Physically Active Populations'. *European Journal of Nutrition* 57 (3): 847–59. https://doi.org/10.1007/s00394-017-1498-8.

Papageorgiou, Maria, Kirsty J. Elliott-Sale, Alan Parsons, et al. 2017. 'Effects of Reduced Energy Availability on Bone Metabolism in Women and Men'. *Bone* 105 (December): 191–99. https://doi.org/10.1016/j.bone.2017.08.019.

Papageorgiou, Maria, Daniel Martin, Hannah Colgan, et al. 2018. 'Bone Metabolic Responses to Low Energy Availability Achieved by Diet or Exercise in Active Eumenorrheic Women'. *Bone* 114 (September): 181–88. https://doi.org/10.1016/j.bone.2018.06.016.

Parker, William H., Vanessa Jacoby, Donna Shoupe, and Walter Rocca. 2009. 'Effect of Bilateral Oophorectomy on Women's Long-Term Health'. *Women's Health* (London, England) 5 (5): 565–76. https://doi.org/10.2217/whe.09.42.

Prieur, Xavier, Y. C. Loraine Tung, Julian L. Griffin, I. Sadaf Farooqi, Stephen O'Rahilly, and Anthony P. Coll. 2008. 'Leptin Regulates Peripheral Lipid Metabolism Primarily through Central Effects on Food Intake'. *Endocrinology* 149 (11): 5432–39. https://doi.org/10.1210/en.2008-0498.

Prnjak, Katarina, Deborah Mitchison, Scott Griffiths, et al. 2020. 'Further Development of the 12-Item EDE-QS: Identifying a Cut-off for Screening Purposes'. *BMC Psychiatry* 20 (1): 146. https://doi.org/10.1186/s12888-020-02565-5.

Rainwater, D. L., A. G. Comuzzie, J. L. VandeBerg, M. C. Mahaney, and J. Blangero. 1997. 'Serum Leptin Levels Are Independently Correlated with Two Measures of HDL'. *Atherosclerosis* 132 (2): 237–43. https://doi.org/10.1016/s0021-9150(97)00104-4.

Ramadoss, Rohit, Quentin Nichols, and Stella Volpe. 2021. 'Dietary Intake Patterns of Omega Fatty Acid Profiles in Athletes'. *Current Developments in Nutrition* 5 (June): 1297. https://doi.org/10.1093/cdn/nzab058_010.

Ravi, Suvi, Johanna K. Ihalainen, Ritva S. Taipale-Mikkonen, et al. 2021. 'Self-Reported Restrictive Eating, Eating Disorders, Menstrual Dysfunction, and Injuries in Athletes Competing at Different Levels and Sports'. *Nutrients* 13 (9): 3275. https://doi.org/10.3390/nu13093275.

Razavi, Amirnader Emami, Mohsen Ani, Morteza Pourfarzam, and Gholam Ali Naderi. 2012. 'Associations between High Density Lipoprotein Mean Particle Size and Serum Paraoxonase-1 Activity'. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences* 17 (11): 1020–26.

Redman, Leanne M., and Anne B. Loucks. 2005. 'Menstrual Disorders in Athletes'. *Sports Medicine* (Auckland, N.Z.) 35 (9): 747–55. https://doi.org/10.2165/00007256-200535090-00002.

Rickenlund, Anette, Maria J. Eriksson, Karin Schenck-Gustafsson, and Angelica Lindén Hirschberg. 2005. 'Amenorrhea in Female Athletes Is Associated with Endothelial Dysfunction and Unfavorable Lipid Profile'. *The Journal of Clinical Endocrinology and Metabolism* 90 (3): 1354–59. https://doi.org/10.1210/jc.2004-1286.

Rickenlund, Anette, Marja Thorén, Kjell Carlström, Bo von Schoultz, and Angelica Lindén Hirschberg. 2004. 'Diurnal Profiles of Testosterone and Pituitary Hormones Suggest Different Mechanisms for Menstrual Disturbances in Endurance Athletes'. *The Journal of Clinical Endocrinology & Metabolism* 89 (2): 702–7. https://doi.org/10.1210/jc.2003-030306.

Riebl, Shaun K., Andrew W. Subudhi, Jeffery P. Broker, Kim Schenck, and Jacqueline R. Berning. 2007. 'The Prevalence of Subclinical Eating Disorders among Male Cyclists'. *Journal of the American Dietetic Association* 107 (7): 1214–17. https://doi.org/10.1016/j.jada.2007.04.017.

Rion, S., and T. J. Kawecki. 2007. 'Evolutionary Biology of Starvation Resistance: What We Have Learned from Drosophila'. *Journal of Evolutionary Biology* 20 (5): 1655–64. https://doi.org/10.1111/j.1420-9101.2007.01405.x.

Roberts, Rachel E., Linda Farahani, Lisa Webber, and Channa Jayasena. 2020. 'Current Understanding of Hypothalamic Amenorrhoea'. *Therapeutic Advances in Endocrinology and Metabolism* 11 (July): 2042018820945854. https://doi.org/10.1177/2042018820945854.

Robinson, George A., Junjie Peng, Hannah Peckham, et al. 2021. 'Sex Hormones Drive Changes in Lipoprotein Metabolism'. *iScience* 24 (11): 103257. https://doi.org/10.1016/j.isci.2021.103257.

Roemmich, James N., and Wayne E. Sinning. 1997. 'Weight Loss and Wrestling Training: Effects on Growth-Related Hormones'. *Journal of Applied Physiology* 82 (6): 1760–64. https://doi.org/10.1152/jappl.1997.82.6.1760.

Russell, Melissa, Jenna Stark, Shriddha Nayak, et al. 2009. 'Peptide YY in Adolescent Athletes with Amenorrhea, Eumenorrheic Athletes and Non-Athletic Controls'. *Bone* 45 (1): 104–9. https://doi.org/10.1016/j.bone.2009.03.668.

Saadedine, Mariam, Ekta Kapoor, and Chrisandra Shufelt. 2023. 'Functional Hypothalamic Amenorrhea: Recognition and Management of a Challenging Diagnosis'. *Mayo Clinic Proceedings* 98 (9): 1376–85. https://doi.org/10.1016/j.mayocp.2023.05.027.

Sachs, Katherine V., Ben Harnke, Philip S. Mehler, and Mori J. Krantz. 2016. 'Cardiovascular complications of anorexia nervosa: A systematic review'. *International Journal of Eating Disorders* 49 (3): 238–48. https://doi.org/10.1002/eat.22481.

Salmón-Gómez, Laura, Victoria Catalán, Gema Frühbeck, and Javier Gómez-Ambrosi. 2023. 'Relevance of Body Composition in Phenotyping the Obesities'. *Reviews in Endocrine & Metabolic Disorders* 24 (5): 809–23. https://doi.org/10.1007/s11154-023-09796-3.

Sarin, H. V., J. H. Lee, M. Jauhiainen, et al. 2019. 'Substantial Fat Mass Loss Reduces Low-Grade Inflammation and Induces Positive Alteration in Cardiometabolic Factors in Normal-Weight Individuals'. *Scientific Reports* 9 (1): 3450. https://doi.org/10.1038/s41598-019-40107-6.

Schaal, Karine, Marta D. Van Loan, and Gretchen A. Casazza. 2011. 'Reduced Catecholamine Response to Exercise in Amenorrheic Athletes'. *Medicine and Science in Sports and Exercise* 43 (1): 34–43. https://doi.org/10.1249/MSS.0b013e3181e91ece.

Scheid, Jennifer L., Mary Jane De Souza, Heather J. Leidy, and Nancy I. Williams. 2011. 'Ghrelin but Not Peptide YY Is Related to Change in Body Weight and Energy Availability'. *Medicine and Science in Sports and Exercise* 43 (11): 2063–71. https://doi.org/10.1249/MSS.0b013e31821e52ab.

Schorr, Melanie, and Karen K. Miller. 2017. 'The Endocrine Manifestations of Anorexia Nervosa: Mechanisms and Management'. *Nature Reviews. Endocrinology* 13 (3): 174–86. https://doi.org/10.1038/nrendo.2016.175.

Scipione, Corey A., Marlys L. Koschinsky, and Michael B. Boffa. 2018. 'Lipoprotein(a) in Clinical Practice: New Perspectives from Basic and Translational Science'. *Critical Reviews in Clinical Laboratory Sciences* 55 (1): 33–54. https://doi.org/10.1080/10408363.2017.1415866.

Sheng, Ren, Yong Chen, Heon Yung Gee, et al. 2012. 'Cholesterol Modulates Cell Signaling and Protein Networking by Specifically Interacting with PDZ Domain-Containing Scaffold Proteins'. *Nature Communications* 3: 1249. https://doi.org/10.1038/ncomms2221.

Sim, Alexiaa, and Stephen F. Burns. 2021. 'Review: Questionnaires as Measures for Low Energy Availability (LEA) and Relative Energy Deficiency in Sport (RED-S) in Athletes'. *Journal of Eating Disorders* 9 (March): 41. https://doi.org/10.1186/s40337-021-00396-7.

Simopoulos, Artemis P. 2016. 'An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity'. *Nutrients* 8 (3): 128. https://doi.org/10.3390/nu8030128.

Skolnick, Aren, Rifka C. Schulman, Rodolfo J. Galindo, and Jeffrey I. Mechanick. 2016. 'The Endocrinopathies of Male Anorexia Nervosa: Case Series'. *AACE Clinical Case Reports* 2 (4): e351–57. https://doi.org/10.4158/EP15945.CR.

Smith, Gordon I., Mahalakshmi Shankaran, Mihoko Yoshino, et al. 2020. 'Insulin Resistance Drives Hepatic de Novo Lipogenesis in Nonalcoholic Fatty Liver Disease'. *The Journal of Clinical Investigation* 130 (3): 1453–60. https://doi.org/10.1172/JCI134165.

Soininen, Pasi, Antti J. Kangas, Peter Würtz, Teemu Suna, and Mika Ala-Korpela. 2015. 'Quantitative Serum Nuclear Magnetic Resonance Metabolomics in Cardiovascular Epidemiology and Genetics'. *Circulation: Cardiovascular Genetics* 8 (1): 192–206. https://doi.org/10.1161/CIRCGENETICS.114.000216.

Sonal Sekhar, M., Srujitha Marupuru, B. Shrikar Reddy, Shilia Jacob Kurian, and Mahadev Rao. 2020. 'Chapter 21 - Physiological Role of Cholesterol in Human Body'. In *Dietary Sugar, Salt and Fat in Human Health*, edited by Harry G. Preuss and Debasis Bagchi. Academic Press. https://doi.org/10.1016/B978-0-12-816918-6.00021-4.

Sperandei, Sandro. 2014. 'Understanding Logistic Regression Analysis'. *Biochemia Medica* 24 (1): 12–18. https://doi.org/10.11613/BM.2014.003.

Staudt, Anna, Sophia J. Kiechl, Nina Gande, et al. 2024. 'Influence of Oral Contraceptives on Lipid Profile and Trajectories in Healthy Adolescents—Data From the EVA-Tyrol Study'. *Journal of Adolescent Health* 75 (3): 479–86. https://doi.org/10.1016/j.jadohealth.2024.04.017.

Stefanakis, Konstantinos, Jagriti Upadhyay, Arantxa Ramirez-Cisneros, Nihar Patel, Akshat Sahai, and Christos S. Mantzoros. 2024. 'Leptin Physiology and Pathophysiology in Energy Homeostasis, Immune Function, Neuroendocrine Regulation and Bone Health'. *Metabolism* 161 (December): 156056. https://doi.org/10.1016/j.metabol.2024.156056.

Stellingwerff, Trent, Margo Mountjoy, Walter TP McCluskey, Kathryn E. Ackerman, Evert Verhagen, and Ida A. Heikura. 2023. 'Review of the Scientific Rationale, Development and Validation of the International Olympic Committee Relative Energy Deficiency in Sport Clinical Assessment Tool: V.2 (IOC REDs CAT2)—by a Subgroup of the IOC Consensus on REDs'. Review. *British Journal of Sports Medicine* 57 (17): 1109–21. https://doi.org/10.1136/bjsports-2023-106914.

Suda, Y., H. Ohta, K. Makita, K. Takamatsu, F. Horiguchi, and S. Nozawa. 1998. 'Influence of Bilateral Oophorectomy upon Lipid Metabolism'. *Maturitas* 29 (2): 147–54. https://doi.org/10.1016/s0378-5122(97)00089-3.

Sullivan, Mack Lee, Charles M. Martinez, Paul Gennis, and E. John Gallagher. 1998. 'The Cardiac Toxicity of Anabolic Steroids'. *Progress in Cardiovascular Diseases*, Special Articles, vol. 41 (1): 1–15. https://doi.org/10.1016/S0033-0620(98)80019-4.

Sundgot-Borgen, Christine, Jorunn Sundgot-Borgen, Nina Sølvberg, Monica Klungland Torstveit, Margo Mountjoy, and Therese Fostervold Mathisen. 2025. 'Factors Predicting Disordered Eating and the Prevalence of Eating Disorders in Adolescent Elite Athletes, Trained Athletes and a Reference Group: A Prospective Controlled Two-Step Study'. Original Research. *British Journal of Sports Medicine* 59 (15): 1043–54. https://doi.org/10.1136/bjsports-2024-108808.

Sundgot-Borgen, Jorunn, Nanna L. Meyer, Timothy G. Lohman, et al. 2013. 'How to Minimise the Health Risks to Athletes Who Compete in Weight-Sensitive Sports Review and Position Statement on Behalf of the Ad Hoc Research Working Group on Body Composition, Health and Performance, under the Auspices of the IOC Medical Commission'. Consensus Statement. *British Journal of Sports Medicine* 47 (16): 1012–22. https://doi.org/10.1136/bjsports-2013-092966.

Sundgot-Borgen, Jorunn, and Monica Klungland Torstveit. 2004. 'Prevalence of Eating Disorders in Elite Athletes Is Higher Than in the General Population'. *Clinical Journal of Sport Medicine* 14 (1): 25.

Swenne, Ingemar. 2016. 'Plasma Cholesterol Is Related to Menstrual Status in Adolescent Girls with Eating Disorders and Weight Loss'. *Acta Paediatrica (Oslo, Norway: 1992)* 105 (3): 317–23. https://doi.org/10.1111/apa.13258.

Tam, Friederike I., Mathias J. Gerl, Christian Klose, et al. 2021. 'Adverse Effects of Refeeding on the Plasma Lipidome in Young Individuals With Anorexia Nervosa?' *Journal of the American Academy of Child and Adolescent Psychiatry* 60 (12): 1479–90. https://doi.org/10.1016/j.jaac.2021.02.014.

Teede, Helena J., Mahnaz Bahri Khomami, Rachel Morman, et al. 2026. 'Polyendocrine Metabolic Ovarian Syndrome, the New Name for Polycystic Ovary Syndrome: A Multistep Global Consensus Process'. *The Lancet* 407 (10545): 2329–39. https://doi.org/10.1016/S0140-6736(26)00717-8.

Tegg, Nicole L., Caitlynd Myburgh, Emma O'Donnell, Megan Kennedy, and Colleen M. Norris. 2024. 'Impact of Secondary Amenorrhea on Cardiovascular Disease Risk in Physically Active Women: A Systematic Review and Meta-Analysis'. *Journal of the American Heart Association* 13 (6): e033154. https://doi.org/10.1161/JAHA.123.033154.

Temme, Kate E., and Anne Z. Hoch. 2013. 'Recognition and Rehabilitation of the Female Athlete Triad/Tetrad: A Multidisciplinary Approach'. *Current Sports Medicine Reports* 12 (3): 190. https://doi.org/10.1249/JSR.0b013e318296190b.

Tenforde, Adam S., Michelle T. Barrack, Aurelia Nattiv, and Michael Fredericson. 2016. 'Parallels with the Female Athlete Triad in Male Athletes'. *Sports Medicine* 46 (2): 171–82. https://doi.org/10.1007/s40279-015-0411-y.

Thompson, D. L., D. B. Snead, R. L. Seip, J. Y. Weltman, A. D. Rogol, and A. Weltman. 1997. 'Serum Lipid Levels and Steroidal Hormones in Women Runners with Irregular Menses'. *Canadian Journal of Applied Physiology = Revue Canadienne De Physiologie Appliquee* 22 (1): 66–77. https://doi.org/10.1139/h97-007.

Timmis, Adam, Panos Vardas, Nick Townsend, et al. 2022. 'European Society of Cardiology: Cardiovascular Disease Statistics 2021'. *European Heart Journal* 43 (8): 716–99. https://doi.org/10.1093/eurheartj/ehab892.

Tolle, Virginie, Myriam Kadem, Marie-Therese Bluet-Pajot, et al. 2003. 'Balance in Ghrelin and Leptin Plasma Levels in Anorexia Nervosa Patients and Constitutionally Thin Women'. *The Journal of Clinical Endocrinology and Metabolism* 88 (1): 109–16. https://doi.org/10.1210/jc.2002-020645.

Tomova, A., and P. Kumanov. 1999. 'Sex Differences and Similarities of Hormonal Alterations in Patients with Anorexia Nervosa'. *Andrologia* 31 (3): 143–47. https://doi.org/10.1046/j.1439-0272.1999.00262.x.

Tornberg, Åsa B., Anna Melin, Fiona Manderson Koivula, et al. 2017. 'Reduced Neuromuscular Performance in Amenorrheic Elite Endurance Athletes'. *Medicine and Science in Sports and Exercise* 49 (12): 2478–85. https://doi.org/10.1249/MSS.0000000000001383.

Tseng, Mei-Chih Meg, Kuan-Rau Chiou, Joni Yu-Hsuan Shao, and Hung-Yi Liu. 2024. 'Incidence and Risk of Cardiovascular Outcomes in Patients With Anorexia Nervosa'. *JAMA Network Open* 7 (12): e2451094. https://doi.org/10.1001/jamanetworkopen.2024.51094.

Vardardottir, Birna, Anna Sigridur Olafsdottir, and Sigridur Lara Gudmundsdottir. 2023. 'Body Dissatisfaction, Disordered Eating and Exercise Behaviours: Associations with Symptoms of REDs in Male and Female Athletes'. *BMJ Open Sport & Exercise Medicine* 9 (4): e001731. https://doi.org/10.1136/bmjsem-2023-001731.

Vekic, Jelena, Aleksandra Zeljkovic, Arrigo F. G. Cicero, et al. 2022. 'Atherosclerosis Development and Progression: The Role of Atherogenic Small, Dense LDL'. *Medicina* 58 (2). https://doi.org/10.3390/medicina58020299.

Villanueva, A. L., C. Schlosser, B. Hopper, J. H. Liu, D. I. Hoffman, and R. W. Rebar. 1986. 'Increased Cortisol Production in Women Runners'. *The Journal of Clinical Endocrinology and Metabolism* 63 (1): 133–36. https://doi.org/10.1210/jcem-63-1-133.

Viner, Rebecca T., Margaret Harris, Jackie R. Berning, and Nanna L. Meyer. 2015. '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* 25 (6): 594–602. https://doi.org/10.1123/ijsnem.2015-0073.

Vuorio, Alpo F., Katriina Aalto-Setälä, Ulla-Maija Koivisto, et al. 2001. 'Familial Hypercholesterolaemia in Finland: Common, Rare and Mild Mutations of the LDL Receptor and Their Clinical Consequences'. *Annals of Medicine* 33 (6): 410–21. https://doi.org/10.3109/07853890108995954.

Wabitsch, M., A. Ballauff, R. Holl, et al. 2001. 'Serum Leptin, Gonadotropin, and Testosterone Concentrations in Male Patients with Anorexia Nervosa during Weight Gain'. *The Journal of Clinical Endocrinology and Metabolism* 86 (7): 2982–88. https://doi.org/10.1210/jcem.86.7.7685.

Wagner, Alyssa J., Casey D. Erickson, Dayna K. Tierney, Megan N. Houston, and Cailee E. Welch Bacon. 2016. 'The Diagnostic Accuracy of Screening Tools to Detect Eating Disorders in

Female Athletes'. *Journal of Sport Rehabilitation* 25 (4): 395–98. https://doi.org/10.1123/jsr.2014-0337.

Walsh, B. W., I. Schiff, B. Rosner, L. Greenberg, V. Ravnikar, and F. M. Sacks. 1991. 'Effects of Postmenopausal Estrogen Replacement on the Concentrations and Metabolism of Plasma Lipoproteins'. *The New England Journal of Medicine* 325 (17): 1196–204. https://doi.org/10.1056/NEJM199110243251702.

Wang, Helen H., Nezam H. Afdhal, and David Q. H. Wang. 2004. 'Estrogen Receptor Alpha, but Not Beta, Plays a Major Role in 17beta-Estradiol-Induced Murine Cholesterol Gallstones'. *Gastroenterology* 127 (1): 239–49. https://doi.org/10.1053/j.gastro.2004.03.059.

Wang, Qin, Diana L. Santos Ferreira, Scott M. Nelson, Naveed Sattar, Mika Ala-Korpela, and Debbie A. Lawlor. 2018. 'Metabolic Characterization of Menopause: Cross-Sectional and Longitudinal Evidence'. *BMC Medicine* 16 (1): 17. https://doi.org/10.1186/s12916-018-1008-8.

Ward, Zachary J., Patricia Rodriguez, Davene R. Wright, S. Bryn Austin, and Michael W. Long. 2019. 'Estimation of Eating Disorders Prevalence by Age and Associations With Mortality in a Simulated Nationally Representative US Cohort'. *JAMA Network Open* 2 (10): e1912925. https://doi.org/10.1001/jamanetworkopen.2019.12925.

Warren, Tara, Roisin McAllister, Amy Morgan, et al. 2021. 'The Interdependency and Co-Regulation of the Vitamin D and Cholesterol Metabolism'. *Cells* 10 (8): 2007. https://doi.org/10.3390/cells10082007.

Wasserfurth, Paulina, Jana Palmowski, Andreas Hahn, and Karsten Krüger. 2020. 'Reasons for and Consequences of Low Energy Availability in Female and Male Athletes: Social Environment, Adaptations, and Prevention'. *Sports Medicine - Open* 6 (September): 44. https://doi.org/10.1186/s40798-020-00275-6.

Watson, Hunna J., Zeynep Yilmaz, Laura M. Thornton, et al. 2019. 'Genome-Wide Association Study Identifies Eight Risk Loci and Implicates Metabo-Psychiatric Origins for Anorexia Nervosa'. *Nature Genetics* 51 (8): 1207–14. https://doi.org/10.1038/s41588-019-0439-2.

Wieczorek, Ewa, Agnieszka Ćwiklińska, Agnieszka Kuchta, Barbara Kortas-Stempak, Anna Gliwińska, and Maciej Jankowski. 2021. 'The Differential Effects of HDL Subpopulations on Lipoprotein Lipase (LPL)-Mediated VLDL Catabolism'. *Biomedicines* 9 (12): 1839. https://doi.org/10.3390/biomedicines9121839.

Willer, Cristen J., Ellen M. Schmidt, Sebanti Sengupta, et al. 2013. 'Discovery and Refinement of Loci Associated with Lipid Levels'. *Nature Genetics* 45 (11): 1274–83. https://doi.org/10.1038/ng.2797.

Williams, Nancy I., Kristen J. Koltun, Nicole C. A. Strock, and Mary Jane De Souza. 2019. 'Female Athlete Triad and Relative Energy Deficiency in Sport: A Focus on Scientific Rigor'. *Exercise and Sport Sciences Reviews* 47 (4): 197–205. https://doi.org/10.1249/JES.0000000000000200.

Williams, Nancy I., Heather J. Leidy, Brenna R. Hill, Jay L. Lieberman, Richard S. Legro, and Mary Jane De Souza. 2015. 'Magnitude of Daily Energy Deficit Predicts Frequency but Not Severity of Menstrual Disturbances Associated with Exercise and Caloric Restriction'.

American Journal of Physiology. Endocrinology and Metabolism 308 (1): E29-39. https://doi.org/10.1152/ajpendo.00386.2013.

Williford, Katherine T., Emma V. Frye, and Rebecca M. Kappus. 2025. 'The Effects of Previous Amenorrhea on Endothelial and Vascular Function'. *International Journal of Endocrinology* 2025 (1): 6305659. https://doi.org/10.1155/ije/6305659.

Wong, Sok Kuan, Fitri Fareez Ramli, Adli Ali, and Nurul 'Izzah Ibrahim. 2022. 'Genetics of Cholesterol-Related Genes in Metabolic Syndrome: A Review of Current Evidence'. *Biomedicines* 10 (12): 3239. https://doi.org/10.3390/biomedicines10123239.

Woollett, Laura A., and Amy S. Shah. 2000. 'Fetal and Neonatal Sterol Metabolism'. In *Endotext*, edited by Kenneth R. Feingold, S. Faisal Ahmed, Bradley Anawalt, et al. MDText.com, Inc. http://www.ncbi.nlm.nih.gov/books/NBK395580/.

Wu, Fredrick C. W., and Arnold von Eckardstein. 2003. 'Androgens and Coronary Artery Disease'. *Endocrine Reviews* 24 (2): 183–217. https://doi.org/10.1210/er.2001-0025.

Würtz, Peter, Antti J. Kangas, Pasi Soininen, Debbie A. Lawlor, George Davey Smith, and Mika Ala-Korpela. 2017. 'Quantitative Serum Nuclear Magnetic Resonance Metabolomics in Large-Scale Epidemiology: A Primer on -Omic Technologies'. *American Journal of Epidemiology* 186 (9): 1084–96. https://doi.org/10.1093/aje/kwx016.

Yeager, K. K., R. Agostini, A. Nattiv, and B. Drinkwater. 1993. 'The Female Athlete Triad: Disordered Eating, Amenorrhea, Osteoporosis'. *Medicine and Science in Sports and Exercise* 25 (7): 775–77. https://doi.org/10.1249/00005768-199307000-00003.

Yuefeng, Yu, Lin Zhiqi, Chen Yi, et al. 2022. 'Testosterone Deficiency Promotes Hypercholesteremia and Attenuates Cholesterol Liver Uptake via AR/PCSK9/LDLR Pathways'. *International Journal of Endocrinology* 2022: 7989751. https://doi.org/10.1155/2022/7989751.

Zhang, Dengke, Yanghui Wei, Qingnan Huang, et al. 2022. 'Important Hormones Regulating Lipid Metabolism'. *Molecules* 27 (20): 7052. https://doi.org/10.3390/molecules27207052.

Zhang, Linqiang, Yongqiong Shi, Bin Liang, and Xi Li. 2024. 'An Overview of the Cholesterol Metabolism and Its Proinflammatory Role in the Development of MASLD'. *Hepatology Communications* 8 (5): e0434. https://doi.org/10.1097/HC9.0000000000000434.

Zhang, Yijing, Kathrin Klein, Aarathi Sugathan, et al. 2011. 'Transcriptional Profiling of Human Liver Identifies Sex-Biased Genes Associated with Polygenic Dyslipidemia and Coronary Artery Disease'. *PloS One* 6 (8): e23506. https://doi.org/10.1371/journal.pone.0023506.

Zhang, Yiyi, Jaejin An, Kristi Reynolds, Monika M. Safford, Paul Muntner, and Andrew E. Moran. 2022. 'Trends of Elevated Low-Density Lipoprotein Cholesterol, Awareness, and Screening Among Young Adults in the US, 2003-2020'. *JAMA Cardiology* 7 (10): 1079–80. https://doi.org/10.1001/jamacardio.2022.2641.

Zheutlin, Alexander R., Samuel Luebbe, Alexander Chaitoff, Eric L. Stulberg, and John T. Wilkins. 2024. 'Low-Density Lipoprotein Cholesterol, Cardiovascular Risk Factors, and Predicted Risk in Young Adults'. *Clinical Cardiology* 47 (9): e70009. https://doi.org/10.1002/clc.70009.

Zhu, Dongshan, Hsin-Fang Chung, Nirmala Pandeya, et al. 2019. 'Premenopausal Cardiovascular Disease and Age at Natural Menopause: A Pooled Analysis of over 170,000 Women'. *European Journal of Epidemiology* 34 (3): 235–46. https://doi.org/10.1007/s10654-019-00490-w.

Ziegler, A., and M. Vens. 2010. 'Generalized Estimating Equations. Notes on the Choice of the Working Correlation Matrix'. *Methods of Information in Medicine* 49 (5): 421–25; discussion 426-432. https://doi.org/10.3414/ME10-01-0026.

Zubiran, Rafael, Maureen Sampson, Anna Wolska, and Alan T. Remaley. 2025. 'Estimated Small, Dense LDL Cholesterol and Atherosclerotic Cardiovascular Risk in the UK Biobank'. *Arteriosclerosis, Thrombosis, and Vascular Biology* 45 (10): e512–22. https://doi.org/10.1161/ATVBAHA.125.323157.

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