Relative Energy Deficiency in Sport (RED-S) among Norwegian male athletes

Energy availability, health, and performance among male athletes at different age and performance levels

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This dissertation is dedicated to my dad, who was diagnosed with cancer in 2017 and died shortly after. His legacy will forever follow me wherever I am.

"Why do we fall Bruce? So that we can learn to pick ourselves up…"
Linus Roache as Thomas Wayne, in Batman Begins (2005)

Preface

This thesis represent research conducted by the author at the University of Agder (UIA), at the Norwegian Olympic and Paralympic Committee and Confederation of Sports and the Norwegian School of Sport Sciences between October 2016 and August 2021.

Firstly, I must pay a tribute to my two supervisors, Professor **Monica Klungland Torstveit** and Dr. **Anna Katarina Melin**. Without both of you, this dissertation would not have been possible to write. Your dedication to the field of RED-S is truly incredible and has affected me in many ways. **Monica**, being under your wings has taught me a lot. Your dedication is overwhelmingly inspiring, with widespread effects on everyone around you. I have rarely met anyone as problem oriented as you, who never says no, and who was always positive in front of me. **Anna**, thank you for all the invaluable help you have provided me with, even in times when things weren't quite alright. Your professionalism and dedication are truly inspiring. Despite your busy schedule, you have always had time for a conversation, something I truly appreciate. Your dedication to the field, your vast network, and connections to other great researchers around the world, in conjunction with your clinical experience has been invaluable for me as a student and for the three projects presented in this paper.

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med og fått ansvar for undervisning på «Outdoor Education». Denne tilliten har betydd svært mye for meg, både på det personlige og faglige plan. Du er en fornøyelse å være sammen med, og det er svært interessant og lærerikt å både se og observere dine pedagogiske og faglige ferdigheter – dette er noe jeg har lært utrolig mye av og noe som kommer til å ha en signifikant betydning for meg resten av livet.

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Men, å skrive en PhD er ikke lett og kommer med en høy pris. Prisen betalt av familie og venner må ikke undervurderes.

Kære **mor** og **far**, tak for alt den hjælp i har givet mig både før og undervejs i min doktorgrad. Jeres støtte har altid vejet stort hos mig, noget jeg er glad for. **Far**, i en alt for tidlig alder rev kræften dig væk fra os hårdt og brutalt i september 2017, og det gør mig oprigtig ondt at du ikke nåede at opleve dine børnebørn i levende live, samt at du aldrig kommer til at opleve at se mig aflevere min afhandling og senere disputere. Sorgen har været vanskelig at bearbejde og dit savn er enormt. Derfor vil jeg gerne dedikere min afhandling til dig! **Mor**, tusind tak for at du fortsat er her, tak for de dejlige samtaler vi har, og tusind tak for at du altid har lyst til at rejse fra Odense og komme op til os i Norge. Dine børnebørn og vi sætter stor pris på dig. Tak til jer begge for at lære mig om livets op og nedturer, noget sitatet i denne afhandling minder os om. Kjære **svigerfamilie**, sammen har vi opplevd mye vanskelig, som for alltid knytter oss ekstra tett, spesielt i januar 2013, september 2017 og i mai 2020. Takk for al hjelpen dere har bistått oss med i den vanskelige tiden som jeg vi fikk oppleve etter pappas bortgang. Takk for all den hjelp dere har gitt oss når jeg har vært stresset med datainnsamling eller vært bortreist og undervist. Dette har betydd veldig mye for vår familie, og jeg er imponert over alt det dere har ofret i vanskelige tider for å hjelpe oss.

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Takk.

Fevik, august 2021
Thomas Birkedal Stenqvist

List of papers

Paper I: Stenqvist, T. B., Torstveit, M. K., Faber, J., & Melin, A. K. (2020). Impact of a 4-Week Intensified Endurance Training Intervention on Markers of Relative Energy Deficiency in Sport (RED-S) and Performance Among Well-trained Male Cyclists. *Frontiers in Endocrinology*, *11:512365*.

Paper II: Stenqvist, T. B., Melin, A. K., Garthe, I., Slater, G. S., Paulsen, G., Iraki, J., Areta, J., & Torstveit, M. K. (2021). Prevalence of surrogate markers of relative energy deficiency in male Norwegian Olympic-level athletes. *Accepted in International Journal of Sport Nutrition and Exercise Metabolism*

Paper III: Stenqvist, T. B., Melin, A. K., & Torstveit, M. K. Prevalence of Relative Energy Deficiency in Sport in male adolescent endurance athletes: A 3-year longitudinal study. *Submitted to Scandinavian Journal of Medicine & Science in Sports*

Summary

Background: Relative Energy Deficiency in Sport (RED-S) is a syndrome where low energy availability (LEA) has a negative impact on health [e.g., endocrine and metabolic alterations, reproductive dysfunction, impaired bone mineral density (BMD)] and performance. In females, the development and prevalence of RED-S have been well-investigated. However, research on males of all ages and performance levels is lacking.

Purpose: The overall aim of this dissertation was therefore to investigate RED-S among Norwegian male athletes at different age and performance levels. Three independent studies have been performed, and three original papers are included in this dissertation. The aims of **Studies I** and **II** were to investigate RED-S in well-trained and Olympic-level adult athletes, whereas **Study III** investigated RED-S among adolescent athletes attending elite sport high schools. **Study I** investigated how a four-week intensified endurance training period specifically designed to increase aerobic performance would affect markers of RED-S, including resting metabolic rate (RMR), body composition and bone health, energy intake (EI), and metabolic and endocrine markers in well-trained cyclists. **Study II** investigated the prevalence of surrogate RED-S markers in a cohort of Norwegian Olympic-level athletes using similar markers as in **Study I**, including RMR, body composition, bone health, and altered metabolic and endocrine markers. **Study III** investigated RED-S in adolescent endurance athletes attending Norwegian elite sport high schools over a three-year period, with special attention to bone health, energy availability (EA), RMR, as well as aerobic performance and muscular strength.

Methods: A total of 80 healthy athletes participated in the studies, but three were excluded from the analysis. Low RMR was defined as an $RMR_{ratio} < 0.90$ (measured RMR divided by predicted RMR) in all three studies. Z-score < –1.0 was defined as low BMD among adults, and "at risk" of low bone mass among adolescents. In **Study I**, 20 cyclists (33.3 ± 6.7 years [mean ± SD]) completed four weeks of intensified endurance training, consisting of three supervised high-intensity interval sessions per week. Testing was performed during the week before and after the training intervention. Protocols included assessment of RMR using a ventilated hood, body composition, and bone health using dual-energy X-ray

absorptiometry (DXA), blood samples [total and free testosterone, cortisol, testosterone:cortisol ratio, triiodothyronine (T_3), insulin and insulin-like growth factor 1 (IGF-1) levels)], EI, aerobic performance [peak oxygen uptake (VO_{2peak}) and functional threshold power (FTP)]. Poor recovery was investigated using a subgroup analysis of the five participants with the largest decrease in testosterone:cortisol ratio compared with five participants with better recovery (increase in testosterone:cortisol ratio). In **Study II**, 44 Olympic-level athletes (24.7 ± 3.8 years) were investigated, and protocols included assessment of RMR, body composition, and bone health using DXA and metabolic and endocrine markers [total and free testosterone, free T_3 (fT_3), cortisol, and low-density lipoprotein (LDL)]. In **Study III**, 13 endurance athletes (16.3 ± 0.4 years at baseline) were monitored for RED-S variables during a three-year period, while attending elite sport high schools in Norway. Testing was performed every six months, yielding a total of five sampling points (the last testing was canceled due to the COVID-19 pandemic). Protocols included assessment of body composition and bone health using DXA, RMR assessment, EA, self-reported disordered eating (DE) behavior, drive for leanness, and exercise addiction behavior, as well as performance variables such VO_{2peak}, and muscle strength in both legs using a pneumatic leg extension machine.

Results: In **Study I**, the intensified training period increased athletes' VO_{2peak} (2.4%, $p = 0.005$) and FTP (6.5%, $p < 0.001$). No changes were observed in body weight, body composition, or EI. Changes were observed in endocrine markers, including an increase in total testosterone (8.1%, $p = 0.011$), cortisol (12.9%, $p = 0.021$), as well as a decrease in T_3 (4.8%, $p = 0.008$). Decreases in absolute RMR (3.0%, $p = 0.010$), relative RMR (2.6%, $p = 0.013$), and RMR_{ratio} (3.3%, $p = 0.011$) were observed. A subgroup analysis of five participants with better recovery revealed a greater improvement in FTP (9.5% vs 2.5%, $p = 0.037$), and higher relative RMR (0.6% vs –4.2% $p = 0.039$) compared with the athletes with poor recovery. In **Study II**, seven athletes (16%) categorized with low RMR (RMR_{ratio} 0.81 ± 0.07) had lower testosterone levels (12.9 ± 5.3 vs 19.0 ± 5.3 $nmol.L^{-1}$, $p = 0.020$) compared with the normal RMR (1.04 ± 0.09) group. In the low RMR group, the occurrence of other RED-S markers was observed, including subclinically low testosterone (<14.8 $nmol.L^{-1}$), subclinically low fT_3 (<4.3 $pmol.L^{-1}$), subclinically high cortisol (>537 $nmol.L^{-1}$), and elevated LDL (>3.0 $mmol.L^{-1}$). Among all athletes, low BMD was found in 16%, all with normal

RMR. Subclinically low testosterone and fT_3 levels were found in nine (25%) and two (5%) athletes, respectively, whereas subclinically high cortisol was found in 23% of all athletes. Finally, 34% of the athletes had elevated LDL levels. In **Study III**, baseline screening revealed healthy body composition (body fat percentage > 5%), EA (~51 ± 16 kcal.kg^{-1} FFM.day^{-1}), and RMR_{ratio} (1.03 ± 0.07). Five of the adolescent athletes (38%) were "at risk" of low bone mass at baseline. Over the three years of investigation, total (~0.03 g/cm^2/year, $p < 0.001$) and regional (0.02 g/cm^2/year, $p < 0.05$) BMD increased. However, a subanalysis revealed that none of the athletes exhibited the expected increase in their total body Z-scores. Furthermore, the lumbar Z-score only increased in 5 of 9 athletes (56%). Throughout the three-year period, fat-free mass (FFM) (2.2 kg/year, $p < 0.001$) and height (1.6 cm/year, $p < 0.001$) increased, whereas fat percentage remained stable ($p = 0.517$). No changes were observed in EA ($p = 0.475$), whereas a small decline in RMR_{ratio} (0.02/year, $p = 0.016$) was observed. Performance levels, such as VO_{2peak} (~5 mL.kg^{-1}.min^{-1}/year, $p < 0.001$) and strength (force; ~180 N/year, $p < 0.001$ and power; ~60 W/year, $p < 0.001$) increased during the three-year period.

Conclusion: In **Study I**, athletes did not seem to match the EI in conjunction with a four-week high-intensity interval training period. Despite an observed increase in overall performance, RED-S-associated markers such as decreased RMR, lowered T_3, and increased cortisol were found. These results indicate the complexity involved in periodizing EI, and that male endurance cyclists may be at risk of developing indications of RED-S even during a short four-week endurance training period. In **Study II**, seven Norwegian male Olympic-level athletes identified with low RMR also had a cluster of additional RED-S markers, strengthening the indication of LEA, emphasizing the need for regular screening and further scrutinizing of these athletes. Other symptoms related to RED-S were also found among other athletes without low RMR, including low BMD, subclinically low total testosterone, subclinically low fT_3, and subclinically high cortisol. These findings highlight the need to investigate further the clustering of RED-S risk markers among male athletes at a high-performing level. In **Study III**, 38% of the adolescent athletes had poor lumbar spine bone health at baseline. Most of the athletes either lost or did not achieve the expected pubertal bone mineral accrual during the three-year follow-up period, although all athletes increased their aerobic performance and muscle strength. Furthermore, despite three athletes

displaying LEA at three different time points, no other signs of RED-S were found among these young athletes.

The findings of this dissertation highlight that RED-S is a phenomenon present to a certain degree among Norwegian male athletes of different ages and performance levels. However, this dissertation also highlights that RED-S seems less pronounced among our Olympic-level athletes compared with similar research, as well as less prevalent among our adolescent athletes compared with the adult population investigated. Furthermore, we did identify poor bone health among all populations, highlighting that awareness of both LEA and that athletes participating in endurance sports are at risk of poor bone health is needed. However, significant gaps in the scientific literature concerning RED-S for adolescent athletes exist, and it is likely that the threshold limits of RED-S-related markers among adolescents are different compared with the adult population due to the energetic requirements of growth, development, and puberty as well as hormonal changes, as well as the need to investigate other markers of RED-S among this population. More research is needed to transfer our findings to other athletes because our results may not be generalized. Still, the knowledge presented in this dissertation should be useful for current and future athletes, coaches, sports medicine health personnel, and sports federations. Future research should embark on investigating the apparent sex difference in both prevalence and consequences of RED-S among male and female athletes.

Abbreviations

ACSM	American College of Sports Medicine
AN	Anorexia nervosa
BEDA-Q	Brief Eating Disorder in Athletes Questionnaire
BMD	Bone mineral density
DLS	Drive for leanness scale
DT	Drive for thinness
DXA	Dual-energy X-ray absorptiometry
EA	Energy availability
EAI-Y	Exercise addiction inventory – youth
ED/DE	Eating disorders/Disordered eating
EDI	Eating disorder inventory
EDS	Exercise dependency score
EEE	Exercise energy expenditure
EHMC	Exercise hypogonadal male condition
EI	Energy intake
ES	Effect size
FFM	Fat-free mass
FSH	Follicle-stimulating hormone
FTP	Functional threshold power
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
HDL	High-density lipoprotein
HPG	Hypothalamic–pituitary–gonadal
HPT	Hypothalamic–pituitary–thyroid
HR	Heart rate
IgA	Immunoglobulin A
IGF-1	Insulin-like growth factor 1
IOC	International Olympic Committee
Kcal	Kilocalorie
LBM	Lean body mass
LDL	Low-density lipoprotein
LEA	Low energy availability
LEAF-Q	Low energy availability in females questionnaire
LH	Luteinizing hormone
MD	Menstrual dysfunction
RCI	Reliable change index
RED-S	Relative energy deficiency in sport
RMR	Resting metabolic rate
SEAQ-I	Sport-specific questionnaire and clinical interview
SHBG	Sex hormone-binding globulin
$T_3/fT_3/T_4$	Triiodothyronine/free Triiodothyronine/Thyroxine
TC	Total cholesterol
TRH	Thyrotropin-releasing hormone
TRIAD	Female athlete triad
TSH	Thyroid-stimulating hormone
URS	Upper-respiratory symptoms
USG	Urine specific gravity
VO_{2peak}	Peak oxygen uptake

Definitions

BMD Z-score	The number of standard deviations above or below the mean for the person's age, sex, and ethnicity as defined by the International Society for Clinical Densitometry	(ISCD, 2019)
Disordered eating (DE)	A spectrum of attitudes and behaviors including concerns with body weight and shape, food restriction and dieting, as well as bingeing, vomiting, and abusing diuretics, laxatives, and diet pills	(American Psychiatric Association, 2013)
Eating disorders (ED)	Anorexia nervosa, bulimia nervosa, or Other Specified Feeding and Eating Disorders (OSFED) meeting the DSM-V criteria and diagnosed by the Eating Disorder Examination (EDE-16) interview	(American Psychiatric Association, 2013)
Ecological validity	The ability to generalize the situation investigated into real-world settings, e.g., controlled laboratory setting generalized into real-world settings	(Thomas et al., 2015)
Energy availability (EA)	Ingested energy remaining for all other metabolic processes after the energy cost of exercise has been subtracted expressed in $kcal.kg^{-1}$ $FFM.day^{-1}$	(Loucks & Thuma, 2003)
Exercise hypogonadal male condition (EHMC)	Exercise-trained males with lowered testosterone levels not caused by stress or strain of exercise, overtraining, or major body weight reductions, but due to being involved in long-term exercise training over several years with high-volume exercise	(Hackney, 2020)

Eumenorrhea	Menstrual cycles at intervals near the median interval for young adult women	(Nattiv et al., 2007)
Low BMD	BMD Z-score between –1.0 and –2.0 in adults	(Nattiv et al., 2007)
Low EA	Energy availability < 30 kcal.kg^{-1} FFM.day^{-1}	(Nattiv et al., 2007)
Low RMR	Ratio between measured RMR and predicted RMR defined as <0.90	(De Souza et al., 2008)
Optimal EA	Energy availability ≥ 45 kcal.kg^{-1} FFM.day^{-1}	(Nattiv et al., 2007)
Menstrual dysfunction	Ranging from anovulation, short luteal phase defect to oligomenorrhea/functional hypothalamic amenorrhea	(Melin et al., 2015)
Measured RMR	Resting metabolic rate measured by indirect calorimetry using a ventilated open canopy hood system	(Compher et al., 2006)
Osteoporosis	BMD Z-score < –2.0 together with secondary risk factors for fracture (e.g., undernutrition, prior fractures)	(Nattiv et al., 2007)
Predicted RMR	Predicted resting metabolic rate using the Cunningham (1980) equation	(Cunningham, 1980)
Primary hypogonadism	Caused by primary testicular failure. Can lead to hypergonadotropic hypogonadism, an impaired response of the gonads to GnRH, or LH and FSH stimuli	(Hackney, 2020)

Secondary hypogonadism	Known as hypogonadotropic hypogonadism and indicates a problem in the hypothalamus or the pituitary gland leading to GnRH or LH and FSH not being produced adequately. The testicles have normal functions.	(Hackney, 2020)
Underweight	Defined as either grade 1 (within the 3–10 percentile) or grade 2 (<3 percentile)	(Júlíusson et al., 2009)
VO_{2peak}	Maximal aerobic capacity measured as the peak oxygen uptake during an incremental exercise test measured in $mL.kg^{-1}.min^{-1}$	(Gore et al., 2013)

List of figures and tables

Thesis at a glance

Table 1. A brief description of the main findings and clinical implications of the three studies performed.

	Main findings	Clinical implications
Study I/ Paper I	Four weeks of high-intensity interval training, superimposed on the athletes' background training, showed a lack of increased EI during the training period, associated with adverse effects on RED-S markers such as lowered RMR and T_3, and increased cortisol, despite improved performance and increased testosterone levels.	Negative changes in RED-S parameters were observed after only four weeks of intensified endurance training. These findings substantiate the importance of periodization of EI, by increasing EA in male athletes undertaking intensified endurance training regimens, as well as increased awareness and education on RED-S among athletes and coaches.
Study II/ Paper II	Symptoms of chronic energy conservation related to RED-S were found in Norwegian male Olympic-level athletes. Seven athletes (16%) had low RMR, with the majority clustering with several additional RED-S markers, strengthening the link to LEA. Other symptoms related to RED-S were also found among other athletes without low RMR emphasizing the need to scrutinize these athletes further.	The findings indicate that RED-S is present to a limited degree among athletes at the highest performance levels in Norway, compared with research among other high-level athletes. The clustering of variables related to RED-S represents a novel approach and warrants further investigation among athletes at different ages, sports, and performance levels.
Study III/ Paper III	Athletes at elite sport high schools increased aerobic performance and strength over the three-year period. 38% were "at risk" of low bone mass, and most did not achieve the expected BMD increase. Three athletes displayed LEA at three different time points, whereas most athletes did not display signs of DE or other signs of RED-S, such as low RMR, during the study period.	An apparent low risk of RED-S among adolescent athletes was found. The improved performance, body composition, and maintenance of EA levels might indicate that the athletes achieved the necessary puberty-related increases in anabolic hormones and maintained satisfactory nutritional intake and recovery during the three-year follow-up. It is important that coaches, athletes, and sports federations have a focus on the risk of poor bone health among this group of athletes.

1 Introduction

Maintaining optimal health and performance in sport can be challenging for athletes, and sufficient energy intake (EI) is considered a key component (Burke, 2001; Mountjoy et al., 2014). Decades of research have found that female athletes performing within weight-sensitive sports have an increased risk of low energy availability (LEA), with or without eating disorders (ED), impaired bone health, and menstrual dysfunction[1] (MD) known as the female athlete triad (TRIAD) syndrome (Nattiv et al., 2007). A more comprehensive description of the syndrome was recently introduced by the International Olympic Committee (IOC), broadening the concept of the TRIAD to Relative Energy Deficiency in Sport (RED-S) (Mountjoy et al., 2018b; Mountjoy et al., 2014), and thereby recognizing that RED-S also exists in male athletes. In the 2014 RED-S consensus statement (Mountjoy et al., 2014), the IOC vastly expanded the possible negative health outcomes derived from LEA and recognized the potential decremental impact also on performance (Mountjoy et al., 2018b; Mountjoy et al., 2014). In brief, RED-S describes a syndrome with impairment of numerous physiological systems triggered by LEA, where energy availability (EA) represents the amount of energy left to support essential body functions after subtraction of exercise energy expenditure (EEE) (Loucks & Thuma, 2003). Until recently, research investigating LEA has been predominantly performed in the female population, with an emphasis on athletes from weight-sensitive sports (Dipla et al., 2020; Elliott-Sale et al., 2018; Logue et al., 2018; Logue et al., 2020; McCall & Ackerman, 2019; Melin et al., 2019; Mountjoy et al., 2018b; Mountjoy et al., 2014; Nattiv et al., 2007; Slater et al., 2017; Tenforde et al., 2016; Wasserfurth et al., 2020), where leanness and/or low body weight is perceived as important for performance, appearance, or a requirement to compete in a specific weight category (Martinsen et al., 2010). Recent research has also identified LEA among some female athletes representing sports with less focus on weight (Ackerman et al., 2019; Braun et al., 2018; Condo et al., 2019; Sygo et al., 2018; Zabriskie et al., 2019; Zanders et al., 2021). When investigating males, research has uncovered similar negative metabolic and endocrine alterations, such as reductions in testosterone levels, associated with reproductive dysfunction, impaired performance, injuries, and

[1]Menstrual dysfunction is defined in this dissertation as follows: Ranging from anovulation, short luteal phase defect to oligomenorrhea/functional hypothalamic amenorrhea.

poor bone health (Andersen et al., 2018; De Souza et al., 2019b; Elliott-Sale et al., 2018; Friedl et al., 2000; Heikura et al., 2018b; Logue et al., 2018; Nattiv et al., 2021). Before the IOC 2014 consensus statement on RED-S, research on the prevalence of RED-S among males was scarce (Mountjoy et al., 2014). Since then, RED-S-related research in males has risen steadily, but there are still several knowledge gaps to be filled including RED-S research among male athletes at different age and performance levels.

1.1 Delimitations

Research on LEA in male athletes has gained a lot of attention since the formal inclusion of male athletes in both the RED-S model (Mountjoy et al., 2018b; Mountjoy et al., 2014) and recently in the American College of Sports Medicine (ACSM) male athlete TRIAD (De Souza et al., 2019b; Nattiv et al., 2021). Thus, since starting this Ph.D., more and more research has emerged. Despite the difference between the IOC and ACSM, this dissertation will exploit the RED-S syndrome. However, the important work of the ACSM workgroup on both the female athlete TRIAD and the male athlete TRIAD must be recognized. Thus, the current discussions between the RED-S group and the TRIAD group will not affect this dissertation (De Souza et al., 2020; De Souza et al., 2014b; Kuikman et al., 2021; Mountjoy et al., 2015a; Strock et al., 2021; Williams et al., 2019), although it will be briefly commented on in the perspectives section. Furthermore, because the RED-S model is vastly expanded compared with the TRIAD, and that this dissertation does not cover all aspects of the model, the theoretical part in this dissertation will only contain the elements investigated in the studies performed. Readers interested in the aspects of the RED-S model not covered in this dissertation are encouraged to read the IOC position stands (Mountjoy et al., 2018b; Mountjoy et al., 2014), the ACSM position stands (De Souza et al., 2014a; Fredericson et al., 2021; Nattiv et al., 2021) as well as the many review papers currently published (Areta et al., 2021; Dipla et al., 2020; Elliott-Sale et al., 2018; Logue et al., 2018; Logue et al., 2020; McCall & Ackerman, 2019; Melin et al., 2019; Nattiv et al., 2007; Slater et al., 2017; Tenforde et al., 2016; Wasserfurth et al., 2020).

2 Historical background

In the 1960s, Erdelyi (1962) raised the first novel scientific concern on the potential negative influence of excessive exercise combined with low EI in female athletes, later followed by Malina et al. (1978). The nature of these cross-sectional data was, however, not able to determine any cause–effect relationships. In the 1980s and 1990s this vastly changed, fueled by Dr. Barbera Drinkwater when she investigated the negative associations between reproductive function and bone health within females (Drinkwater et al., 1984; Drinkwater et al., 1986). Other research in the same time period also identified and linked MD with reduced bone mass and disordered eating (DE) behaviors (Howat et al., 1989; Marcus et al., 1985; Warren et al., 1986). In the early 1990s, the ACSM convened an expert group, aiming to address the growing concern and evidence from the research in females (Yeager et al., 1993). This resulted in the TRIAD being characterized as a combination of DE, MD, and osteoporosis found in physically active adolescent girls and adult females (Yeager et al., 1993). The first position stand concerning the TRIAD was published in 1997 by the ACSM, aiming to provide information on screening, prevention, diagnosis, and treatment of the TRIAD targeting coaches and health personnel (Otis et al., 1997). In 2007, the ACSM released an updated version of the position stand, modifying the description of the TRIAD (Nattiv et al., 2007). The TRIAD, as shown in Figure 1, describes the interrelation between EA, menstrual function, and bone health, and revolves around a continuum ranging from optimal EA, eumenorrhea, and normal bone health, through subclinical and clinical conditions ending in LEA, severe MD, and osteoporosis (Nattiv et al., 2007).

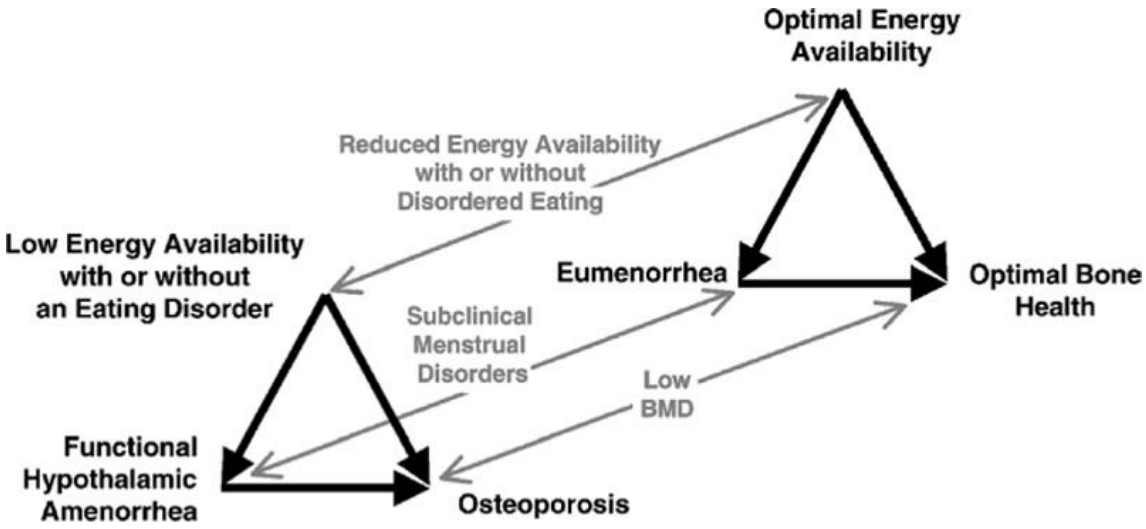

Figure 1. *The female athlete triad, as depicted in the 2007 ACSM position statement, ranging from optimal energy availability, bone health, and reproductive function, to severe low energy availability, severely impaired bone health, and menstrual dysfunction. Reproduced from Nattiv et al. (2007) with permission.*

Despite some sporadic research on males, initiated in the 1980s (Bilanin et al., 1989; Hackney et al., 1988; McColl et al., 1989; Wheeler et al., 1984), more research started to emerge around the year 2000 related to the health of male athletes including bone health and reproductive hormones (Arce et al., 1993; De Souza et al., 1994; De Souza & Miller, 1997; MacKelvie et al., 2000; Naessens et al., 1995; Rector et al., 2008; Smathers et al., 2009). However, by the end of the 2000s, research on male athletes within this field was still scarce. In 2014, the ACSM working group released a consensus statement, aimed at highlighting the diagnosis, treatment, and return to play from the TRIAD (De Souza et al., 2014a). Collectively, the IOC released a new and comprehensive position stand, introducing the new terminology RED-S, aimed to supplement the 2007 ACSM position stand, yet also describing adverse health effects of various body systems, including adverse effects on performance, in female as well as male athletes (Mountjoy et al., 2014). In 2018, the IOC released an updated position stand (Mountjoy et al., 2018b), whereas the ACSM released a new position stand in 2021 named the male athlete TRIAD (Nattiv et al., 2021). These parallel releases of the RED-S and the TRIAD position statements caused, and still cause, disruption among researchers, despite their common intention to secure the health of an athlete (De Souza et al., 2019b; De Souza et al., 2014b; Fredericson et al., 2021; Mountjoy et al., 2018b; Mountjoy et al., 2015a; Nattiv et al., 2021; Williams et al., 2019).

3 Relative Energy Deficiency in Sport

As depicted in the Mountjoy et al. (2014) position stand, one of the main goals of the IOC is to protect the health of the athletes. Overwhelming scientific evidence, as well as clinical experience, have shown that the "*aetiological factor underpinning the TRIAD is an energy deficiency relative to the balance between dietary energy intake (EI) and the energy expenditure required to support homoeostasis, health and the activities of daily living, growth and sporting activities*" (Mountjoy et al., 2014). Today, it is hypothesized that the TRIAD should no longer be limited to just the three units of the original TRIAD: EA, menstrual function, and bone health, but rather be viewed as a syndrome containing multiple characteristics that can affect various physiological functions (Mountjoy et al., 2014). Such characteristics include, but are not limited to, metabolic rate, menstrual function, bone health, immunity, protein synthesis, cardiovascular health as well as psychological health (Mountjoy et al., 2014). Therefore, the 2014 IOC consensus statement defines RED-S as a syndrome that

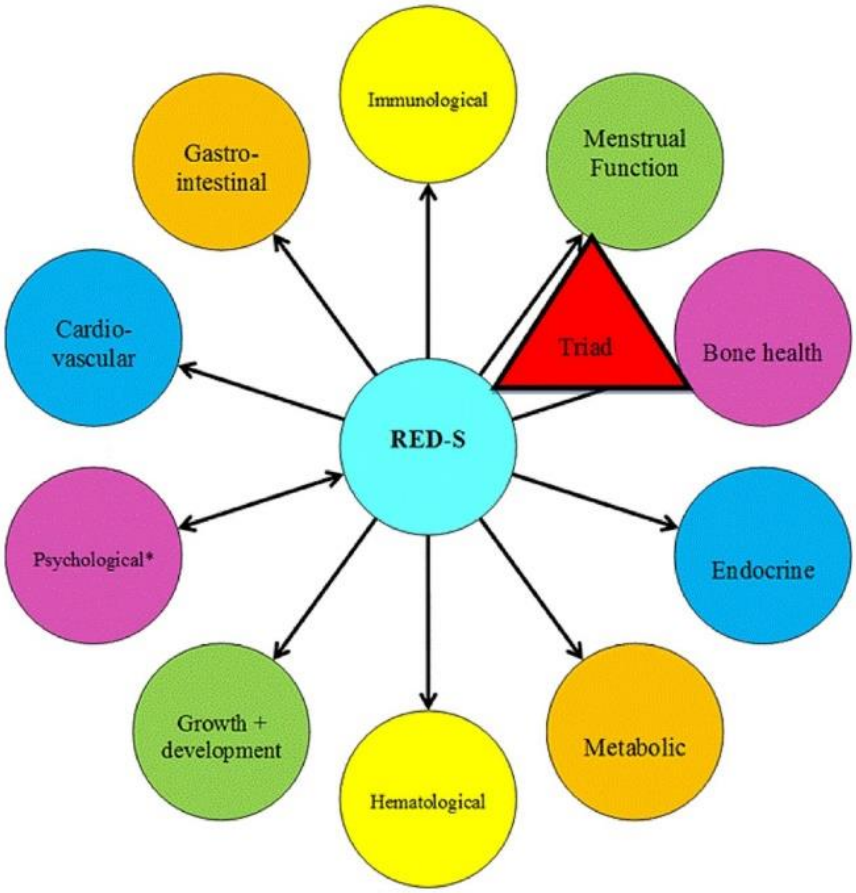

Figure 2. *Health consequences of Relative Energy Deficiency in Sport (RED-S), depicting an expanded syndrome, including the interrelationship of the female athlete triad. Reproduced from Mountjoy et al. (2014) with permission.*

"*refers to impaired physiological function including, but not limited to, metabolic rate, menstrual function, bone health, immunity, protein synthesis, cardiovascular health caused by relative energy deficiency*" (Mountjoy et al., 2014). The underlying cause of the RED-S syndrome is inadequate energy to support a range of body functions to maintain optimal health and performance as outlined in Figures 2 and 3.

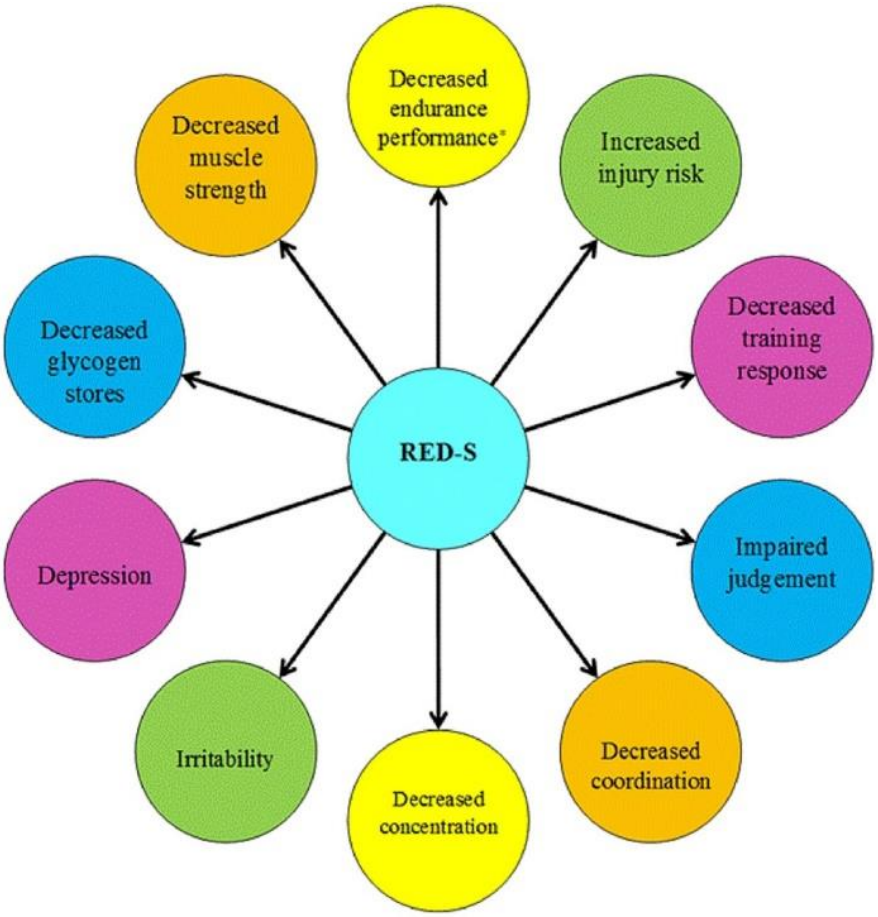

Figure 3. *Potential effects of Relative Energy Deficiency in Sport (RED-S) on various performance aspects. Reproduced from Mountjoy et al. (2014) with permission.*

3.1 Energy availability

Common to both the TRIAD and RED-S is that EA is the core of the syndrome. EA is defined as the amount of energy left to support other body functions after exercise, and is calculated as dietary EI minus EEE divided by fat-free mass (FFM) (Mountjoy et al., 2014; Nattiv et al., 2007):

$$\text{Energy availability} = \frac{\text{energy intake} - \text{exercise energy expenditure}}{\text{fat-free mass}}$$

Experimental work by Loucks and Thuma (2003) and Ihle and Loucks (2004) in sedentary women found that EA less than 30 kcal.kg^{-1} FFM.day^{-1} for five days resulted in the suppressing of the hypothalamic–pituitary axis, resulting in elevated cortisol levels, decrease in triiodothyronine (T_3) and luteinizing hormone (LH), as well as loss of bone formation markers and reduced blood glucose. LEA has also been found to cause metabolic adaptations, including lowered resting metabolic rate (RMR) and increased work efficiency in athletes with MD (Melin et al., 2015), whereas moderate or recurrent reduced EA may induce subclinical MD and impaired bone health (Nattiv et al., 2007). This threshold of 30 kcal.kg^{-1} FFM.day^{-1} was then defined and established as LEA in females but has come under some scrutiny in recent times (Areta et al., 2021; De Souza et al., 2019a; De Souza et al., 2019b; Nattiv et al., 2021), with researchers highlighting that the use of an absolute EA threshold as a strategy to prevent the development of TRIAD conditions and RED-S should be avoided, due to the presence of individual variability in regard to tolerance for EA (De Souza et al., 2019a; De Souza et al., 2019b; Nattiv et al., 2021). Calculating EA is mathematically simple, consisting of three components: EI, EEE, and FFM (Mountjoy et al., 2018b). Despite the simplicity, several caveats exist when accurately quantifying each component (Burke et al., 2018), further discussed in Section 7.2, no universal agreement currently exists on how to quantify the three components accurately, thus the methods used within the research community greatly differ (Burke et al., 2018; Logue et al., 2018) and must be taken into consideration when comparing studies. The aim is, however, to gain valid measurements of all the variables, using the most precise method that is suitable for the population studied.

3.2 Etiology

The etiology of RED-S is complex, but LEA with or without ED/DE is the central aspect of the syndrome (Gibbs et al., 2013; Mountjoy et al., 2014). DE includes various abnormal eating behaviors, such as restrictive eating, fasting, skipping meals, and using laxatives, whereas ED is a clinical mental disorder defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) (American Psychiatric Association, 2013), and characterized by abnormal eating behaviors, fear of weight gain, and false beliefs about eating, weight, and shape (American Psychiatric Association, 2013). Other factors related to LEA include excessive exercise, “making weight” before a competition, or unintentional mismatch between energy expenditure and EI resulting from, e.g., a lack of appetite, poor

nutrition knowledge, or lack of time to plan and prepare meals (Gibbs et al., 2013; Nattiv et al., 2007; Tenforde et al., 2016). Several reasons may lie behind the actions that lead to LEA, in some athletes due to well-intentioned or well-justified reasons, such as undergoing programs to optimize body weight or composition (Burke et al., 2018). However, some athletes or coaches may not be aware that rapid and/or not well-managed manipulation of body weight or body composition can lead to negative health and performance consequences (Garthe et al., 2013; Stellingwerff, 2018; Tipton, 2015). Other factors include excessive exercise behaviors (Burke et al., 2018), unawareness of the energetic cost of exercise (Burke et al., 2018), or being unable to consume required amounts of energy to compensate for the high cost of exercise (Burke, 2001), such as inadequate appetite (Larson-Meyer et al., 2012) or consuming fiber-rich and bulky foods with low energy density (Melin et al., 2016; Reed et al., 2013).

3.3 Prevalence

Research among female athletes has been extensive, and several recent reviews have outlined and summarized the prevalence of LEA in these athletes (Areta et al., 2021; Dipla et al., 2020; Elliott-Sale et al., 2018; Logue et al., 2018; Logue et al., 2020; McCall & Ackerman, 2019; Melin et al., 2019; Mountjoy et al., 2018b; Mountjoy et al., 2014; Nattiv et al., 2007; Slater et al., 2017; Tenforde et al., 2016; Wasserfurth et al., 2020). Although the scientific literature on males has grown, especially within the last couple of years (Areta et al., 2021; Logue et al., 2018; Logue et al., 2020; Schofield et al., 2020), knowledge on both the prevalence and outcomes of RED-S within this group is still wanted (Areta et al., 2021; Mountjoy et al., 2018b). DE and ED in weight-sensitive sports are found to be more prevalent among both females and males than in sports where low body weight is perceived as less important (Byrne & McLean, 2002; Chatterton & Petrie, 2013; Gibbs et al., 2013; Goltz et al., 2013; Martinsen et al., 2010; Martinsen & Sundgot-Borgen, 2013; Sundgot-Borgen, 1993; Sundgot-Borgen et al., 2013; Sundgot-Borgen & Torstveit, 2004; Torstveit et al., 2008). DE among female athletes has been reported to range between 16% and 47% compared with 5% to 21% in controls (Byrne & McLean, 2002; Sundgot-Borgen, 1993; Torstveit et al., 2008). In males, although more limited, research also identifies a higher prevalence of DE and nutrient deficits among athletes than with controls, especially within weight-sensitive sports (Bratland-Sanda & Sundgot-Borgen, 2013; Tenforde et al., 2016). Sundgot-Borgen and Torstveit (2004) found that clinical ED was more pronounced

in male elite athletes (8%) compared with nonathletic controls (0.5%), and further reported a higher prevalence of ED in antigravitation sports (22%) compared with ball-game sports (5%) and endurance sports (9%). Chatterton and Petrie (2013) found that most eating disturbances among male athletes were at subclinical levels, whereas dieting and exercise manipulation were among the most common practices for weight control, as well as more common when participating in weight-class sports compared with endurance sport or ball games. Goltz et al. (2013) reported that 28% of male athletes within ED "high-risk" sports, such as weight-class sports, sports where leanness is a key performance enhancer as well as aesthetic sports, displayed DE behaviors linked to body image dissatisfaction. Investigating adolescent elite athletes, Martinsen et al. (2010) found a higher prevalence of symptoms of DE among male controls (31%) than with athletes (13%), whereas a later study using clinical interviews, found the opposite; that the prevalence of ED was higher in athletes (3%) than in nonathletic controls (0%) (Martinsen & Sundgot-Borgen, 2013).

The prevalence of LEA in adult male athletes within various sports and performance levels is found to range between 25% and 88% (Table 2). These sports include cycling and long-distance running (Geesmann et al., 2014; Heikura et al., 2018a; Heikura et al., 2018b; Hooper et al., 2017; Jurov et al., 2021; Keay et al., 2018; Lane et al., 2019; Lane et al., 2021; Torstveit et al., 2018; Torstveit et al., 2019; Viner et al., 2015; Vogt et al., 2005; Woods et al., 2018), cross-country running (Jesus et al., 2021; McCormack et al., 2019; Tenforde et al., 2015), rowing (Woods et al., 2017), martial arts (Langan-Evans et al., 2021), dancing (Keay & Francis, 2020; Staal et al., 2018), horse-racing (Dolan et al., 2011), wrestling (McMurray et al., 1991), and soccer (Lee et al., 2020). Only a few cross-sectional studies have investigated EA among male adolescent athletes, limited to sports such as cross-country running (Matt et al., 2021), soccer (Cherian et al., 2018a), acrobatic gymnastics (Silva et al., 2018), and rink hockey (Silva & Silva, 2017). Of these four studies, only two have investigated the prevalence of LEA and identified a prevalence of ~24%–30%. As outlined in Table 2, these adolescent athlete studies have investigated athletes in different sports, at different performance levels, different ages, using vastly different methodological approaches, as well as having defined LEA as either <30 kcal.kg^{-1} FFM.day^{-1} (Cherian et al., 2018a; Matt et al., 2021) or <45 kcal.kg^{-1} FFM.day^{-1} (Silva & Silva, 2017; Silva et al., 2018).

Table 2. Summary of studies investigating LEA and/or associated markers of RED-S in male athletes.

Reference	Study type	Participants	Methods	EA assessment duration	Key findings	Prevalence of LEA
Hoeg et al. (2021)	CS	Nonelite and elite ultramarathon runners (n=83).	Identified the prevalence of male athlete triad risk factors and explored associations between sex hormones and BMD.	N/A	44.5% had an elevated risk for DE. 20.5% had a history of BSI and 30.1% had Z-scores < –1.0. None were observed with low BMI (<18.5 kg/m^2). The Triad cumulative risk assessment classified 29.2% as moderate risk and 5.6% as high risk.	N/A
Lane et al. (2021)	CS	Nonelite endurance athletes (n=60), runners (n=27), cyclists (n=21), triathletes (n=7), and others (n=5).	Investigated EA and the risk factors for RED-S, and their associations. RMR using canopy hood, BC and BMD using DXA, BS for hormonal assessment. EEE logged using 7-days training logs and EI using 4 days of diet records.	4 d	Mean EA was 28.7 ± 13.4 $kcal.kg^{-1}$ $FFM.day^{-1}$. LEA was present in 61.7% of the participants (mean EA 20.7 $kcal.kg^{-1}$ $FFM.day^{-1}$). Hormonal and bone biomarkers were within normal clinical ranges, despite LEA. RMR_{ratio} was within the normal range (0.99 ± 0.08).	62%
Matt et al. (2021)	CS	Adolescent cross-country runners (n=12).	Evaluated EA and EI among high school cross-country runners. EI was assessed using a questionnaire. BC using DXA or bioimpedance.	Questionnaire	EA among males was 35.8 ± 14.4 $kcal.kg^{-1}$ $FFM.day^{-1}$ with 30.0% of males meeting criteria for LEA (<30 $kcal.kg^{-1}$ $FFM.day^{-1}$). Male calorie intake (2614.2 ± 861.8 $kcal.day^{-1}$) fell below the estimated energy requirement for "active" boys (>3100 $kcal.day^{-1}$)	30%

Martin et al. (2021)	NRS (trial)	Recreationally active males (n=6).	Determined whether LEA, when compared with EA at levels required for normal physiological functionality, alters NEAT in a repeated measures four-way crossover design. A secondary goal was to determine whether NEAT is impacted differently when LEA is achieved solely by a reduction in EI or in combination with increased EEE.	4 d per condition	LEA (15 kcal.kg^{-1} FFM.day^{-1}), attained with dietary restriction alone or in combination with exercise, did not result in adaptive reductions in NEAT when compared with adequate EA (40 kcal.kg^{-1} FFM.day^{-1}). LEA does not seem to impact NEAT in the short term, but how it is attained may impact objectively measured physical activity behavior outside of exercise and subjective perceptions of energy state.	N/A
Jurov et al. (2021)	CS	Well-trained cyclists and triathletes (n=12).	EI was assessed using dietary diaries, including photos. EEE was estimated using heart rate. BS on day 8, whereas performance, RMR, BC (BIA), and psychological variables were assessed on day 9.	7 d	Mean EA was 29.5 kcal.kg^{-1} FFM.day^{-1}. LEA (<30 kcal.kg^{-1} FFM.day^{-1}) found in 67% of athletes. Critical cognitive restraint (≥13) was reported by 75% of participants. No differences in performance, blood values, or psychological evaluation between the LEA group and normal EA group.	67%
Jesus et al. (2021)	CS	Elite cross-country runners (n=124).	Estimated the prevalence of LEA using the LEAF-Q with adapted scoring to fit males, and to analyze demographic and physical characteristics associated with LEA.	Questionnaire	A high prevalence of athletes at risk of LEA was observed in males (54.0%). No associations were found between the risk of LEA and weight, BMI, and age for male athletes.	54%

Langan-Evans et al. (2021)	Case report	1 international-standard Taekwondo athlete.	Athlete undergoing 3 phases; Phase 1 (EA ~20 kcal.kg^{-1} FFM.day^{-1}), phase 2 (<10 kcal.kg^{-1} FFM.day^{-1}), and phase 3 (ad libitum EI). EA assessed using provided meals in phases 1 and 2, using digital photography in phase 3, EEE via Actiheart and BC via DXA. RMR via indirect calorimetry and endocrine markers via BS.	Throughout the period	BM reduced over 8 weeks (13.5%). No LEA consequences were detected in phase 1 but found in phase 2, including transient clinically low TES (4 nmol.L^{-1}) and RMR_{ratio} (0.87), with levels returning to normal at phase 3.	N/A
Taguchi et al. (2020)	CS	Collegiate long-distance runners (n=6).	Assessed energy status of runners and examined associations between energy deficiency and energy metabolism, bone health, and hormonal status, using DXA, BS, and RMR.	3 d	Mean EA was 18.9 ± 6.8 kcal.kg^{-1} FFM.day^{-1}. Five of six athletes had LEA < 30 kcal.kg^{-1} FFM.day^{-1}. Suppressed RMR in combination with low BMD suggests that energy deficiency could promote bone resorption and energy metabolism suppression.	83%
Ishibashi et al. (2020)	NRS (trial)	Long-distance runners (n=6).	Investigated the effect of LEA during 3 consecutive days of endurance training on muscle glycogen content and iron metabolism.	3 d	3 days of endurance training under LEA condition (20 kcal.kg^{-1} FFM.day^{-1}) reduced muscle glycogen content including increased serum hepcidin levels.	N/A
Murphy and Koehler (2020)	NRS (trial)	Recreational weight lifters (n=7).	Measured the impact of short-term caloric restriction on the anabolic response to a bout of resistance exercise.	3 d	3 days of LEA (20 kcal.kg^{-1} FFM.day^{-1}) induced anabolic resistance, characterized by increased GH secretion and reduced IGF-1 secretion.	N/A

Kojima et al. (2020)	NRS (trial)	Long-distance runners (n=7).	Investigated the effects of 3 consecutive days of endurance training under LEA conditions on the muscle glycogen content, muscle damage markers, endocrine regulation, and endurance capacity, consisting of two trials of LEA (18.9 ± 1.9 kcal.kg^{-1} FFM.day^{-1}) or EA (52.9 ± 5.0 kcal.kg^{-1} FFM.day^{-1})	3 days	Body weight, FFM, and skeletal muscle volume were significantly reduced in LEA. Muscle glycogen content was significantly reduced in LEA (~30%). Time to exhaustion was not significantly different between the two trials.	N/A
Keay and Francis (2020)	CS	Dancers (n=22).	Investigated awareness and indicators of LEA, using a dance-specific questionnaire	Questionnaire	Negative RED-S risk scores were reported in 29% of male dancers. 14% reported ED, whereas only 29% had awareness of the terminology of RED-S, and 37% about LEA.	29%
Lee et al. (2020)	CS	Korean collegial soccer players (n=12).	EA was investigated via digital photography and food package, EEE using HR monitors, and BC via DXA. Endocrine markers were assessed via BS, and RMR using Douglas bags.	7 d	Mean EA was 31.9 ± 9.8 kcal.kg^{-1} FFM.day^{-1}. LEA (<30 kcal.kg^{-1} FFM.day^{-1}) found in 5 athletes, showing suppressed RMR_{ratio} (0.91 ± 0.06), lower IGF-1 levels (32.6 ± 6.7 nmol/L) than with optimal EA (41.8 ± 5.7 nmol/L).	42%
Egger and Flueck (2020)	CS	Wheelchair athletes (n=8).	Investigated EA via weighed EI logs as well as training logs. BC estimated via DXA and RMR using a metabolic chart.	7 d	EA in males was 36.1 ± 6.7 kcal.kg^{-1} FFM.day^{-1}). 1 athlete had 0 days of LEA (<30 kcal.kg^{-1} FFM.day^{-1}), whereas the remaining 7 attained LEA in 1–4 of the 7 days. In total, LEA occurred in 30% of the days.	88%

McCormack et al. (2019)	CS	Cross-country runners (n=27) and nonrunning controls (n=23).	Investigated BMD, EA, and dietary restraint. EA via QA and training logs, BC and BMD via DXA. ED via questionnaire.	Questionnaire	42% of runners had LEA (<30 kcal.kg^{-1} FFM.day^{-1}), and higher BMD than controls. Runners scored significantly higher than controls in dietary restraint as well as in eating concern.	42%
Torstveit et al. (2019)	CS	Well-trained cyclists, triathletes, and long-distance runners (n=53).	Investigated exercise dependency with EA and ED.	7 d	Athletes (30%) with higher exercise dependency scores reported LEA (<30 kcal.kg^{-1} FFM.day^{-1}), whereas higher COR levels were found in the group with higher exercise dependency scores.	30%
Lane et al. (2019)	CS	Competitive, recreationally trained cyclists, runners, and triathletes (n=108).	Investigated the prevalence of LEA using an online survey with diet and exercise training logs.	3 d	47% of the athletes were classified with LEA (<30 kcal.kg^{-1} FFM.day^{-1}). Cyclists had lower EA than runners and all other sport categories.	47%
Keay et al. (2018)	CS	Well-trained competitive road cyclists (n=50).	Assessed with a sport-specific questionnaire, via BC and BMD using DXA and endocrine markers via BS.	Questionnaire	LEA in 28% of cyclists. Low BMD was found in 44% of cyclists. LEA was associated with reduced fat%. 10 cyclists with chronic LEA had lower levels of TES than those having adequate EA.	28%
Staal et al. (2018)	CS	Professional ballet dancers (n=20).	Investigated the impact of different RMR in relation to EA markers. BC and BMD were assessed via DXA, RMR via canopy hood, DE via questionnaire.	N/A	Weight and BC within normal range. 10% had DE and 25% had hypotension. 5% had low BMD. 80% had low RMR (RMR_{ratio} < 0.90) using the Cunningham equation.	80%

Heikura et al. (2018a)	CS	World-class middle- and long-distance runners and racewalkers (n=21).	Identified EA via food and training logs, during a 3- to 4-week altitude training camp. BC and BMD via DXA.	7 d	Reduced EA (36 ± 6 $kcal.kg^{-1}$ $LBM.day^{-1}$) in male athletes. No correlation between EA and hemoglobin mass changes was found.	N/A
Heikura et al. (2018b)	CS	World-class middle- and long-distance runners and racewalkers (n=35 females, n=24 males).	Identified EA via food and training logs. BC via DXA, metabolic and reproductive function via BS, and injury and illness using a questionnaire.	7 d	25% of the males (n=6) were identified as having LEA (<30 $kcal.kg^{-1}$ $FFM.day^{-1}$), whereas 42% (n=10) had low TES levels. T_3 was significantly lower in the low TES group compared with normal. Bone injuries were ~4.5-fold more prevalent in the same group.	25%
Cherian et al. (2018a)	CS	Junior national soccer players (n=21) grouped by <12 y and <16 y.	Evaluated EEE, EI, and nutrient adequacy using a portable metabolic analyzer and activity records, EI via food logs.	3 d	5 of 21 boys had LEA (24%), and 4 of these 5 (80%) were found in the <16 y group. Boys <12 y showed a positive energy balance compared with <16 y.	24%
Torstveit et al. (2018)	CS	Well-trained cyclists, triathlon, and long-distance runners (n=31).	Compared within-day energy deficiency in athletes with suppressed RMR and normal RMR.	7 d	Similar 24-h EB in both groups, the suppressed group spent more time in energy deficit > 400 kcal. Within-day energy deficiency was associated with increased COR levels and decreased TES:COR ratio.	N/A

Kojima et al. (2020)	NRS (trial)	Long-distance runners (n=7).	Investigated the effects of 3 consecutive days of endurance training under LEA conditions on the muscle glycogen content, muscle damage markers, endocrine regulation, and endurance capacity, consisting of two trials of LEA (18.9 ± 1.9 kcal.kg^{-1} FFM.day^{-1}) or EA (52.9 ± 5.0 kcal.kg^{-1} FFM.day^{-1})	3 days	Body weight, FFM, and skeletal muscle volume were significantly reduced in LEA. Muscle glycogen content was significantly reduced in LEA (~30%). Time to exhaustion was not significantly different between the two trials.	N/A
Keay and Francis (2020)	CS	Dancers (n=22).	Investigated awareness and indicators of LEA, using a dance-specific questionnaire	Questionnaire	Negative RED-S risk scores were reported in 29% of male dancers. 14% reported ED, whereas only 29% had awareness of the terminology of RED-S, and 37% about LEA.	29%
Lee et al. (2020)	CS	Korean collegial soccer players (n=12).	EA was investigated via digital photography and food package, EEE using HR monitors, and BC via DXA. Endocrine markers were assessed via BS, and RMR using Douglas bags.	7 d	Mean EA was 31.9 ± 9.8 kcal.kg^{-1} FFM.day^{-1}. LEA (<30 kcal.kg^{-1} FFM.day^{-1}) found in 5 athletes, showing suppressed RMR_{ratio} (0.91 ± 0.06), lower IGF-1 levels (32.6 ± 6.7 nmol/L) than with optimal EA (41.8 ± 5.7 nmol/L).	42%
Egger and Flueck (2020)	CS	Wheelchair athletes (n=8).	Investigated EA via weighed EI logs as well as training logs. BC estimated via DXA and RMR using a metabolic chart.	7 d	EA in males was 36.1 ± 6.7 kcal.kg^{-1} FFM.day^{-1}). 1 athlete had 0 days of LEA (<30 kcal.kg^{-1} FFM.day^{-1}), whereas the remaining 7 attained LEA in 1–4 of the 7 days. In total, LEA occurred in 30% of the days.	88%

McCormack et al. (2019)	CS	Cross-country runners (n=27) and nonrunning controls (n=23).	Investigated BMD, EA, and dietary restraint. EA via QA and training logs, BC and BMD via DXA. ED via questionnaire.	Questionnaire	42% of runners had LEA (<30 kcal.kg^{-1} FFM.day^{-1}), and higher BMD than controls. Runners scored significantly higher than controls in dietary restraint as well as in eating concern.	42%
Torstveit et al. (2019)	CS	Well-trained cyclists, triathletes, and long-distance runners (n=53).	Investigated exercise dependency with EA and ED.	7 d	Athletes (30%) with higher exercise dependency scores reported LEA (<30 kcal.kg^{-1} FFM.day^{-1}), whereas higher COR levels were found in the group with higher exercise dependency scores.	30%
Lane et al. (2019)	CS	Competitive, recreationally trained cyclists, runners, and triathletes (n=108).	Investigated the prevalence of LEA using an online survey with diet and exercise training logs.	3 d	47% of the athletes were classified with LEA (<30 kcal.kg^{-1} FFM.day^{-1}). Cyclists had lower EA than runners and all other sport categories.	47%
Keay et al. (2018)	CS	Well-trained competitive road cyclists (n=50).	Assessed with a sport-specific questionnaire, via BC and BMD using DXA and endocrine markers via BS.	Questionnaire	LEA in 28% of cyclists. Low BMD was found in 44% of cyclists. LEA was associated with reduced fat%. 10 cyclists with chronic LEA had lower levels of TES than those having adequate EA.	28%
Staal et al. (2018)	CS	Professional ballet dancers (n=20).	Investigated the impact of different RMR in relation to EA markers. BC and BMD were assessed via DXA, RMR via canopy hood, DE via questionnaire.	N/A	Weight and BC within normal range. 10% had DE and 25% had hypotension. 5% had low BMD. 80% had low RMR (RMR_{ratio} < 0.90) using the Cunningham equation.	80%

Heikura et al. (2018a)	CS	World-class middle- and long-distance runners and racewalkers (n=21).	Identified EA via food and training logs, during a 3- to 4-week altitude training camp. BC and BMD via DXA.	7 d	Reduced EA (36 ± 6 $kcal.kg^{-1}$ $LBM.day^{-1}$) in male athletes. No correlation between EA and hemoglobin mass changes was found.	N/A
Heikura et al. (2018b)	CS	World-class middle- and long-distance runners and racewalkers (n=35 females, n=24 males).	Identified EA via food and training logs. BC via DXA, metabolic and reproductive function via BS, and injury and illness using a questionnaire.	7 d	25% of the males (n=6) were identified as having LEA (<30 $kcal.kg^{-1}$ $FFM.day^{-1}$), whereas 42% (n=10) had low TES levels. T_3 was significantly lower in the low TES group compared with normal. Bone injuries were ~4.5-fold more prevalent in the same group.	25%
Cherian et al. (2018a)	CS	Junior national soccer players (n=21) grouped by <12 y and <16 y.	Evaluated EEE, EI, and nutrient adequacy using a portable metabolic analyzer and activity records, EI via food logs.	3 d	5 of 21 boys had LEA (24%), and 4 of these 5 (80%) were found in the <16 y group. Boys <12 y showed a positive energy balance compared with <16 y.	24%
Torstveit et al. (2018)	CS	Well-trained cyclists, triathlon, and long-distance runners (n=31).	Compared within-day energy deficiency in athletes with suppressed RMR and normal RMR.	7 d	Similar 24-h EB in both groups, the suppressed group spent more time in energy deficit > 400 kcal. Within-day energy deficiency was associated with increased COR levels and decreased TES:COR ratio.	N/A

Silva et al. (2018)	CS	Child and adolescent high-performance-level acrobatic gymnasts (n=21).	To evaluate sleep, BC, EI, and eating behaviors in athletes compared with population-based reference using food and training logs, BC via skinfold techniques.	3 d	Male adolescents had significantly lower EA (45.1 ± 14.7 kcal/kg FFM/day) than children (53.8 ± 9.1 kcal/kg FFM/day). Significant low intakes of important vitamins and minerals were reported. Most of the participants did not eat or drink during or immediately after training sessions.	N/A
Woods et al. (2018)	Quasi	Trained cyclists (n=13).	Investigated the effects of a 6-week training period eliciting overreaching on markers such as EI via food logs, RMR, BC, and BMD via DXA. Mood via questionnaire.	EI, 3 d, 8 times; RMR, 14 times, DXA, 3 times, blood 8 times.	Decrease in RMR and BC, that improved after a period of recovery. Overreaching among athletes were identified from reductions in aerobic and anaerobic performance as well as mood disturbances.	N/A
Woods et al. (2017)	Quasi	Male (n=10) and female (n=7) national-level rowers.	Investigated the effects of an intensified training period on markers such as EI using food logs, RMR, BC, and BMD via DXA pacing profile. Mood and sleep via questionnaire.	3 d pre and post a 4-week training period.	Aerobic performance decreased, whereas no increase in EI was observed. Decrease in BC and RMR. Increase in mood disturbance as well as sleep disturbance.	N/A

Koehler et al. (2016)	NRS (trial)	Recreationally active males (n=6).	Assessed EA's effect on hormones related to LEA during four conditions: LEA with exercise, LEA without exercise, normal EA with exercise, and normal EA without exercise.	4 d per condition	LEA (15 kcal.kg^{-1} FFM.day^{-1}) resulted in reductions in BC, leptin, insulin, and fasting glucose, whereas no reduction was observed in T_3, IGF-1, ghrelin, and TES.	N/A
Viner et al. (2015)	L	Professional and well-trained competitive cyclists (n=4 females, n = 6 males).	Identified EA via food log and EEE using METs. BC and BMD via DXA, and eating habits using questionnaires.	3 days month^{-1} across the season	LEA (<30 kcal.kg^{-1} FFM.day^{-1}) remained across the season in 70% of all cyclists. Male cyclists mean EA 20 ± 10 kcal.kg^{-1} FFM.day^{-1}, with a 40% prevalence of low BMD at the lumbar spine and 10% in femoral neck.	70%
Geesmann et al. (2014)	L	Well-trained cyclists (n=14).	Assessed EB and macronutrient intake before and during a 1,230-km bike marathon. BC was assessed before and after the event.	Continuously through the event.	EI was 25% lower than EEE in 85% of athletes, and EI decreased significantly after 618 km.	N/A
Dolan et al. (2011)	CS	National hunt and flat racing jockeys (n=27).	Identified EA using food diaries and accelerometers, BC via DXA, lifestyle practices using questionnaires.	7 d	Mean daily EI (1803 ± 564 kcal) was low and appeared to provide an insufficient availability of energy for the sustainment of usual daily and metabolic processes. Carbohydrate intake. Mean EA at race days 1 ± 12 kcal.kg^{-1} LBM.day^{-1}.	N/A

Silva et al. (2018)	CS	Child and adolescent high-performance-level acrobatic gymnasts (n=21).	To evaluate sleep, BC, EI, and eating behaviors in athletes compared with population-based reference using food and training logs, BC via skinfold techniques.	3 d	Male adolescents had significantly lower EA (45.1 ± 14.7 kcal/kg FFM/day) than children (53.8 ± 9.1 kcal/kg FFM/day). Significant low intakes of important vitamins and minerals were reported. Most of the participants did not eat or drink during or immediately after training sessions.	N/A
Woods et al. (2018)	Quasi	Trained cyclists (n=13).	Investigated the effects of a 6-week training period eliciting overreaching on markers such as EI via food logs, RMR, BC, and BMD via DXA. Mood via questionnaire.	EI, 3 d, 8 times; RMR, 14 times, DXA, 3 times, blood 8 times.	Decrease in RMR and BC, that improved after a period of recovery. Overreaching among athletes were identified from reductions in aerobic and anaerobic performance as well as mood disturbances.	N/A
Woods et al. (2017)	Quasi	Male (n=10) and female (n=7) national-level rowers.	Investigated the effects of an intensified training period on markers such as EI using food logs, RMR, BC, and BMD via DXA pacing profile. Mood and sleep via questionnaire.	3 d pre and post a 4-week training period.	Aerobic performance decreased, whereas no increase in EI was observed. Decrease in BC and RMR. Increase in mood disturbance as well as sleep disturbance.	N/A

Hooper et al. (2017)	CS	Well-trained long-distance runners (n=9) with EHMC and nonactive controls (n=8) without EHMC.	Identified EA using QA, BC via DXA, reproductive function via BS and questionnaire.	1 d	Runners had lower EA (27 ± 13 kcal.kg^{-1} FFM.day^{-1}) than controls (45 ± 18 kcal.kg^{-1} FFM.day^{-1}) as well as TES (9.2 ± 2.3 nmol.L^{-1} vs 16.2 ± 3.4 nmol.L^{-1}).	N/A
Papageorgiou et al. (2017)	NRS (trial)	Recreationally active males (n=11) and females (n=11).	Assessed EA's effect on bone turnover and regulatory hormones, with a crossover design of 2 × 9 days of optimal EA (45 kcal.kg^{-1} LBM.day^{-1}) and restricted (15 kcal.kg^{-1} LBM.day^{-1})	2 × 9 d	No difference in bone turnover in males. Specific values of regulatory hormones and blood biomarkers related to LEA not stated.	N/A
Silva and Silva (2017)	CS	Child and adolescent rink-hockey players (n=38, n=34) and controls (n=43, n=36) respectively.	Evaluated EI and BC using food and training logs. BC was assessed using skinfold techniques. LEA was defined as <45 kcal.kg^{-1} FFM.day^{-1}.	3 d	Athletes were leaner than controls. Lower EI and higher EEE in athletes compared with controls. LEA (<45 kcal.kg^{-1} FFM.day^{-1}) was observed in 10.1% of the athletes.	N/A

Koehler et al. (2016)	NRS (trial)	Recreationally active males (n=6).	Assessed EA's effect on hormones related to LEA during four conditions: LEA with exercise, LEA without exercise, normal EA with exercise, and normal EA without exercise.	4 d per condition	LEA (15 kcal.kg^{-1} FFM.day^{-1}) resulted in reductions in BC, leptin, insulin, and fasting glucose, whereas no reduction was observed in T_3, IGF-1, ghrelin, and TES.	N/A
Viner et al. (2015)	L	Professional and well-trained competitive cyclists (n=4 females, n = 6 males).	Identified EA via food log and EEE using METs. BC and BMD via DXA, and eating habits using questionnaires.	3 days month^{-1} across the season	LEA (<30 kcal.kg^{-1} FFM.day^{-1}) remained across the season in 70% of all cyclists. Male cyclists mean EA 20 ± 10 kcal.kg^{-1} FFM.day^{-1}, with a 40% prevalence of low BMD at the lumbar spine and 10% in femoral neck.	70%
Geesmann et al. (2014)	L	Well-trained cyclists (n=14).	Assessed EB and macronutrient intake before and during a 1,230-km bike marathon. BC was assessed before and after the event.	Continuously through the event.	EI was 25% lower than EEE in 85% of athletes, and EI decreased significantly after 618 km.	N/A
Dolan et al. (2011)	CS	National hunt and flat racing jockeys (n=27).	Identified EA using food diaries and accelerometers, BC via DXA, lifestyle practices using questionnaires.	7 d	Mean daily EI (1803 ± 564 kcal) was low and appeared to provide an insufficient availability of energy for the sustainment of usual daily and metabolic processes. Carbohydrate intake. Mean EA at race days 1 ± 12 kcal.kg^{-1} LBM.day^{-1}.	N/A

Vogt et al. (2005)	CS	Professional road cyclists (n=11).	Quantified the nutritional status of the cyclists during preseason training. Energy expenditure assessed using power output, and EI assessed via weighed food records.	6 d	Daily energy expenditure was 30% higher than the daily EI. EA estimated as ~8 $kcal.kg^{-1}$ $FFM.day^{-1}$	N/A
McMurray et al. (1991)	Quasi	Wrestlers (n=12).	Assessed effects of LEA via dietary recall during two conditions (normal and high carbohydrates) on performance and hormones. BC was obtained through underwater weighing.	7 d	Decline in BC, aerobic performance, growth hormones, and IGF-1 independent of the group.	N/A

Abbreviation: BC, body composition; BMD, bone mineral density; BS, blood sampling; BSI, bone stress injury; COR, cortisol; CS, cross-sectional; DE, disordered eating; DXA, dual-energy X-ray absorptiometry; EA, energy availability; EB, energy balance; ED, eating disorders; EHMC, Exercise Hypogonadal Male Condition; EI, energy intake; EXP, experimental; FFM, fat-free mass; IGF-1, insulin-like growth factor 1; L, longitudinal; LBM, lean body mass; LEA, low energy availability; MET, metabolic equivalent; NRS, nonrandomized controlled study; N/A, not available; RMR, resting metabolic rate; T_3, triiodothyronine; TES, testosterone; Quasi; quasi-experiment

3.4 Health consequences

The human body consists of a myriad of biological processes, vastly simplified in the RED-S model (Figures 2 and 3). Hence, Section 3.4 will first outline the most well-investigated and well-established health consequences of LEA in males, building on decades of excellent research. The last part of Section 3.4 will briefly outline newly added and less-established consequences of the RED-S model, while section 3.5 will outline known performance consequences.

3.4.1 Reproductive function

The male reproductive system is controlled by the hypothalamic–pituitary–gonadal axis (HPG), consisting of the hypothalamus, anterior pituitary, and testicles (Hackney, 2020; Lanfranco & Minetto, 2020). The central controlling structure of the gonadal axis is the pituitary gland, releasing LH and follicle-stimulating hormone (FSH), regulated by the hypothalamic gonadotropin-releasing hormone (GnRH) (Hackney, 2020). Secretion of GnRH is affected by several excitatory modulators such as the noradrenergic system, neuropeptide Y, and leptin as well as several inhibitory modulators such as interleukin-1, opioid peptides, dopamine, serotonin, ghrelin (Lanfranco & Minetto, 2020), and glucose availability (Loucks & Thuma, 2003). One of the important mechanisms that control the GnRH synthesis is the gonadal steroid feedback, where testosterone plays a major role in men, by inhibiting the gonadotropin secretion in negative feedback loops at the hypothalamic and pituitary level, as shown in Figure 4 (Hackney, 2020; Lanfranco & Minetto, 2020).

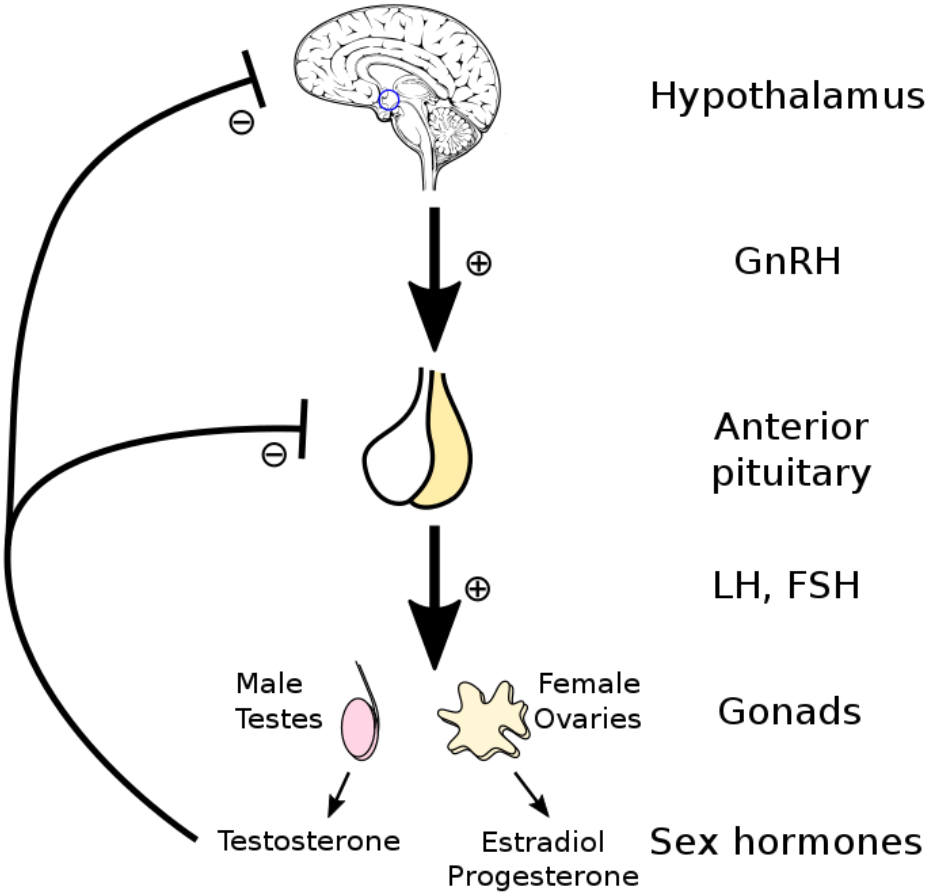

Figure 4. *Testosterone production, controlled by the hypothalamic–pituitary–gonadal axis (HPG), with the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), regulated by the hypothalamic gonadotropin-releasing hormone (GnRH). Reprinted with permission: Artoria2e5 / CC BY (https://creativecommons.org/licenses/by/3.0)*

Testosterone is an anabolic steroid, produced in the Leydig cells in the testes, stimulating growth and bodily development, increasing protein synthesis, and controlling the development and maintenance of the secondary sex characteristics as well as cognitive development (Hackney, 2020; Lanfranco & Minetto, 2020). Testosterone is also reported to facilitate physiological advantages in sport performance, such as increased muscular development, as well as increased erythropoiesis and hemoglobin, which facilitate blood oxygen content, maximal aerobic capacity, and increased muscle mass (Hackney, 2020). Both total and free testosterone are usually measured in the blood, where free testosterone represents the unbound form of ~1.5%–2.0% of the total amount of testosterone circulating in the blood (Hackney, 2020). The remaining 98% of testosterone in the blood is

weakly bound to two different carrier proteins, sex hormone-binding globulin (SHBG) carrying ~65% and albumin carrying ~33% (Hackney, 2020).

Although the health benefits of being physically active are overall considered overwhelming (Haskell et al., 2007), extensive physical activity is associated with hypogonadism (Hackney, 2020). Hypogonadism is the medical term for decreased activity of the gonads and in males is characterized as a testosterone production deficiency, leading to lowered testosterone levels (Hackney, 2020; Kumar et al., 2010; Rey et al., 2013; Sterling et al., 2015). Two types of hypogonadism exist. Primary hypogonadism is related to primary testicular failure, defined as hypergonadotropic hypogonadism, leading to impaired response in the testicles to GnRH or LH and FSH stimuli (Hackney, 2020). Secondary hypogonadism is related to the hypothalamus or the pituitary gland, leading to impaired production of GnRH, LH, and FSH (testicles are functioning as normal), and is termed hypogonadotropic hypogonadism (Hackney, 2020). Primary hypogonadism may arise from different events, such as medial syndromes, cancer, testicular injuries, or normal aging (Hackney, 2020). Secondary hypogonadism may result from diseases and medications (Hackney, 2020), LEA (De Souza et al., 2019b; Nattiv et al., 2021), or overtraining (Safarinejad et al., 2009; Stellingwerff et al., 2021). According to De Souza et al. (2019b), reports of secondary hypogonadism have been observed in several studies investigating endurance athletes, and include findings of low testosterone (MacConnie et al., 1986; McColl et al., 1989; Wheeler et al., 1984), poor semen quality (De Souza et al., 1994; De Souza & Miller, 1997), and low libido (Zekarias & Shrestha, 2019). In 2005, Hackney et al. (2005) introduced a terminology named Exercise Hypogonadal Male Condition (EHMC). This condition describes a state where exercise-trained men display lowered testosterone levels, often in a subclinical state, ranging from 25% to 50% lower than expected, with criteria not related to secondary hypogonadism (Hackney et al., 2005). EHMC seems not to be related to stress or strain of exercise, overtraining, or major body weight reductions, but is related to long-term exercise training over several years with high volumes of training (Hackney, 2020). In EHMC, persistent and chronic regular endurance exercise training induces adaptations in the HPG axis and resets this, thereby lowering testosterone levels, compared with males living a more sedentary lifestyle (Hackney, 2020). This became evident when researchers reexamined and repooled 196 male endurance-trained distance runners and reported a 30%–35% reduction in testosterone levels

in healthy male runners with ≥5 years' experience of endurance training compared with runners with <5 years' experience of endurance training (Hackney & Lane, 2018). According to the authors, EHMC seems therefore not to be related to RED-S or overtraining, and is viewed as a different condition than secondary hypogonadism (Hackney, 2020).

Reduction in testosterone levels in combination with insufficient EI has primarily been observed in studies investigating extreme situations, including high-intensity training (Heikura et al., 2018b), long-duration exercise (Berg et al., 2008), extremely low levels of EA (Langan-Evans et al., 2021), or exposure to extreme stressors in combination with severe energy deficit (Friedl et al., 2000; Kyrolainen et al., 2008). Friedl et al. (2000) identified severe endocrine responses during an 8-week special forces US Army Ranger course, performed in a multistressor environment in a state of semistarvation. One Ranger group (1) experienced four repeated bouts of normal feeding followed by 7- to 10-day periods of energy restriction, whereas another group (2) received an extra 400 kcal/day compared with group 1. Dramatic reductions in testosterone levels were observed in both groups approaching castration levels. When investigating effects of refeeding in group 2, an abrupt normalization of testosterone and other hormonal levels were observed, with levels returning to a declining trajectory when starvation was reintroduced (Friedl et al., 2000). Studying soldiers undergoing a 20-day field exercise with heavy prolonged physiological stress, Kyrolainen et al. (2008) found 25% reductions in testosterone levels during the first phase with an energy deficit of ~4000 kcal/day, with recovery to baseline values during the next two phases, consisting of ~450 and ~1000 kcal/day of energy deficit. In male elite long-distance endurance athletes, LEA has been reported to correlate strongly with reduced testosterone levels (Berg et al., 2008; Heikura et al., 2018b; Hooper et al., 2017; Keay et al., 2018; Langan-Evans et al., 2021). Berg et al. (2008) investigated nine male ultra-endurance athletes competing in the six-day Adventure Racing World Championship and estimated that three athletes experienced a combined energy deficit during the race of 40,000 kcal. Immediately after the race, free- and total testosterone levels were obtained, and severely reduced testosterone levels compared with baseline were observed (5.7 ± 2.0 vs 17.5 ± 4.0 nmol.L^{-1}, $p < 0.01$) (Berg et al., 2008). Hooper et al. (2017) found that long-distance runners, running 81 ± 14 km/week, exhibited lower total testosterone levels (9.2 ± 2.3 vs 16.2 ± 3.4 nmol.L^{-1}, $p < 0.001$) as well as lower EA (27.2 ± 12.7 vs 45.4 ± 18.2 kcal.kg^{-1}

FFM.day^{-1}, p = 0.029) compared with sedentary controls. Heikura et al. (2018b) found a 40% prevalence of low testosterone among middle- and long-distance runners and racewalkers, with lower testosterone levels (14.8 ± 3.6 vs 22.9 ± 8.0 nmol.L^{-1}, p < 0.05) observed in athletes exhibiting LEA (<30 kcal.kg^{-1} FFM.day^{-1}) compared with moderate EA (>30 kcal.kg^{-1} FFM.day^{-1}). In a case study, Langan-Evans et al. (2021) observed severe low testosterone levels (<5 nmol.L^{-1}) in a male combat athlete after five days of very low EA (3 ± 7 kcal.kg^{-1} FFM.day^{-1}), with a subsequent increase in testosterone levels the week after EA was restored to >45 kcal.kg^{-1} FFM.day^{-1}. Adequate EI seems to be a key component of the reproductive function, however, clinical symptoms of the male reproductive function are few and may require sperm analysis (De Souza et al., 2019b; Nattiv et al., 2021). To the author's knowledge, only two studies to date have tried to evaluate the effects of manipulating EA on testosterone levels. Koehler et al. (2016) exposed recreationally trained students to two four-day periods of LEA (~15 kcal.kg^{-1} FFM.day^{-1}) and two four-day periods of optimal EA (~40 kcal.kg^{-1} FFM.day^{-1}) and found no reductions in testosterone levels. The authors, however, implied that it was unclear whether a four-day period of LEA was long enough to observe changes in subclinical LEA markers. In a more recent study by Kojima et al. (2020), athletes underwent two trials consisting of LEA (18.9 ± 1.9 kcal.kg^{-1} FFM.day^{-1}) and optimal EA (52.9 ± 5.0 kcal.kg^{-1} FFM.day^{-1}) in combination with endurance training. In the LEA group, resting testosterone was reduced after four days (p < 0.05), with no significant difference between trials. Thus, more research is warranted identifying how and when LEA affects testosterone in males.

3.4.2 Bone health

Bones are a highly specialized framework, characterized by hardness, rigidity, and the ability to regenerate and repair themselves (Kini & Nandeesh, 2012). Under normal circumstances, bones are constantly being remodeled during life by osteoclasts (removes bone) and osteoblasts (replenishes bone), to help adapt to changes in biomechanical forces and to preserve bone strength (Kini & Nandeesh, 2012) (Figure 5). Physical activity, growth factors, and hormones are all important stimulants of the osteoblasts, increasing bone remodeling, with subsequent effects on the bones (Kini & Nandeesh, 2012; Kohrt et al., 2004). The greatest bone formation occurs during adolescence, facilitating and increasing bone mineral density (BMD), thereby increasing bone strength (Kini & Nandeesh, 2012; Kohrt

et al., 2004). A time window of approximately two years exists where peak bone accrual occurs, suggested to be around the time of puberty at age 13–15 years for boys (Bailey et al., 2000; Kohrt et al., 2004; Tenforde et al., 2016). Peak bone mass in males seems to reach its highest levels by the age of 20 years (Heaney et al., 2000) and seems to be followed by a subsequent decline of at least 0.5% per year, after the third decade of life (Kohrt et al., 2004). Low BMD increases the risk of bone stress injuries caused by minimal trauma (Kohrt et al., 2004). Optimizing bone strength early in life and maintaining peak bone mass is therefore important to prevent bone stress injuries during the athletic career and to decrease fracture risk and osteoporosis later in life (Kohrt et al., 2004). Several factors influence bone strength, such as size, shape, and architecture (Kohrt et al., 2004). BMD, structures of bone mineral, as well as bone protein quality are important factors for bone strength and risk of fractures (Nattiv et al., 2021), and may explain why some athletes can suffer from fractures whereas others do not, despite equal BMD.

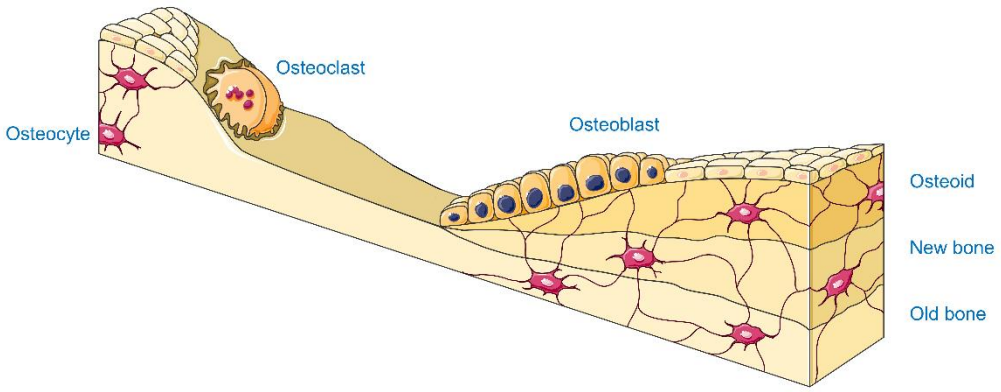

Figure 5. *Simplified overview of bone resorption and formation via osteoclasts and osteoblasts. Osteoclasts remove old and microdamaged bone, whereas osteoblasts start the replacement process by forming new and stronger bone (osteoid). Osteocytes are associated with remodeling and bone turnover. Reprinted and edited with permission: Laboratoires Servier / CC BY-SA (https://creativecommons.org/licenses/by-sa/3.0)*

To identify low BMD, the International Society for Clinical Densitometry (ISCD) recommends using age-matched Z-scores to estimate BMD in premenopausal women, males <50 years of age, and children <20 years of age, and a Z-score < –2.0 to be termed "below expected range for age" (ISCD, 2019). Athletes participating in weight-bearing sports tend to have a 5%–15% higher BMD than nonathletes (Fehling et al., 1995; Risser et al., 1990; Robinson et al., 1995). Thus, athletes participating in, e.g., high-impact loading sports, such as gymnastics, hurdles, and karate, or odd-impact sports such as soccer, basketball, racquet games,

and speed skating are observed to have a higher BMD than nonathletes (Tenforde & Fredericson, 2011). ACSM and IOC define bone health in female and male adult athletes within a continuum, ranging from normal bone health (Z-score ≥ –1.0), low BMD, or BMD below the expected range for age (Z-score < –1.0 to –1.99) including secondary clinical risk factors for fracture such as undernutrition and hypogonadism, to osteoporosis with secondary clinical risk factors for fracture present (Z-score ≤ –2.0) (De Souza et al., 2014a; Mountjoy et al., 2014; Nattiv et al., 2007). Therefore, it has been suggested that a Z-score < –1.0 might be a better threshold of suboptimum BMD for male and female athletes due to the requirements of stronger bones to tackle repetitive or higher impact activities (Hind & Hamer, 2021). In adolescent athletes, research by Barrack et al. (2010a) has defined athletes with a BMD Z-score < –1.0 as being "at risk" of low bone mass.

Athletes participating in leanness sport such as running, cycling, and horse-racing seem not to present such "above-average" levels of BMD, and it is well documented that persistent LEA is a key contributor to impaired bone health in female athletes (De Souza et al., 2014a; Mountjoy et al., 2018b; Mountjoy et al., 2014; Nattiv et al., 2007), primarily impairing bone health in the anatomical sites of the lumbar spine, femur neck, and hips (Ackerman et al., 2011; Ackerman et al., 2012; Barrack et al., 2010a; Fredericson et al., 2007; Hind et al., 2006; Papageorgiou et al., 2018; Papageorgiou et al., 2017; Tenforde & Fredericson, 2011; Tenforde et al., 2015). Even short-term LEA has negatively affected bone turnover markers in recreationally active females (Ihle & Loucks, 2004; Papageorgiou et al., 2017). Data on males are now starting to emerge, including increased risk of low BMD within various sport genres, such as running (Barrack et al., 2017; Barrack et al., 2010a; Fredericson et al., 2007; Hind et al., 2006; Tenforde et al., 2015; Tenforde et al., 2018), cycling (Andersen et al., 2018; Barry & Kohrt, 2008; Nichols et al., 2003; Nichols & Rauh, 2011; Olmedillas et al., 2012; Penteado et al., 2010; Smathers et al., 2009; Viner et al., 2015) and horse-racing (Jackson et al., 2017; Wilson et al., 2015; Wilson et al., 2018). A recent longitudinal study by Viner et al. (2015) investigated LEA and bone health across a cycling season. They found that more than 70% of the cyclists presented with LEA (<30 kcal.kg^{-1} FFM.day^{-1}) and reported a 40% prevalence of low BMD at the lumbar spine and 10% at the femur neck, although BMD levels remained constant across the season (Viner et al., 2015). In contrast, a cross-sectional study

by Heikura et al. (2018b) found no significant correlations between LEA (<30 kcal.kg^{-1} FFM.day^{-1}) and low BMD in male athletes, although athletes with reduced testosterone levels had a 4.5 times greater incidence of bone injuries. To the author's knowledge, only one study has investigated the short-term effects of LEA on BMD, bone quality, and bone metabolism in the male athlete population (Papageorgiou et al., 2017). When exposing 11 recreationally trained males to LEA (15 kcal.kg^{-1} LBM.day^{-1}) for five days, no meaningful difference was observed in either BMD or bone markers, but when considering individual responses, some of the participants responded adversely to LEA impairing bone turnover markers negatively (Papageorgiou et al., 2017). In an observational study, an even shorter duration of energy restriction showed that three days of LEA did promote bone resorption in male Japanese long-distance runners (Taguchi et al., 2020). The lack of evidence is however, not surprising because the development of BMD is multifactorial, and effects on BMD may not be detectable for years (De Souza et al., 2014a). Research overall finds that the alterations in bone metabolic markers in response to LEA seem less consistent in males than females (Nattiv et al., 2021), thus more research is required to establish a cause–effect relationship especially among male athletes (Papageorgiou et al., 2018).

3.4.3 Endocrine changes

The effects of LEA on the endocrine system are currently well-described in females but have only recently been described in males (Mountjoy et al., 2018b). In female athletes with LEA or MD, several disturbances have been observed, including, but not limited to, disruption in the hypothalamic–pituitary–thyroid (HPT) axis, changes in thyroid hormones and alterations in insulin-like growth factor 1 (IGF-1), growth hormone (GH), and cortisol (Allaway et al., 2016; Mountjoy et al., 2018b). However, many of these changes are still not fully elucidated or understood in males (Mountjoy et al., 2018b).

The HPT axis consists of the hypothalamus, anterior pituitary, and thyroid gland (Hiller-Sturmhofel & Bartke, 1998; Ylli et al., 2020). The central controlling structure of the thyroid axis is the pituitary gland, releasing the two major thyroid hormones thyroxine (T_4) and T_3, regulated by the thyrotropin-releasing hormone (TRH) (Hiller-Sturmhofel & Bartke, 1998). Secretion of TRH is controlled by the negative feedback loop from the increase in T_3 and T_4, thus declining levels of circulating T_3 or T_4 will prompt secretion of TRH as shown in Figure 6 (Ylli et al.,

2020). Thyroid hormones play a crucial role in the body with several systems and functions affected, such as skeletal and cardiac muscle functions, pulmonary performance, and metabolism, and changes in this function can cause changes in body functions during exercise and at rest (Ylli et al., 2020). The thyroid hormones are bound with thyroglobulin and stored in the thyroid gland, and when released into the bloodstream, thyroglobulin undergoes endocytosis and proteolytic digestion, under the control of thyroid-stimulating hormone (TSH) (Hiller-Sturmhofel & Bartke, 1998; Ylli et al., 2020). T_3 only constitutes ~10% of the hormones produced, whereas T_4 constitutes the remaining 90%; however, T_3 is 10–15 times more potent than T_4, and only 20% of the circulating T_3 stems from the thyroid gland, whereas the remaining 80% stems from monodeiodination of T_4 to T_3 (Hiller-Sturmhofel & Bartke, 1998; Ylli et al., 2020).

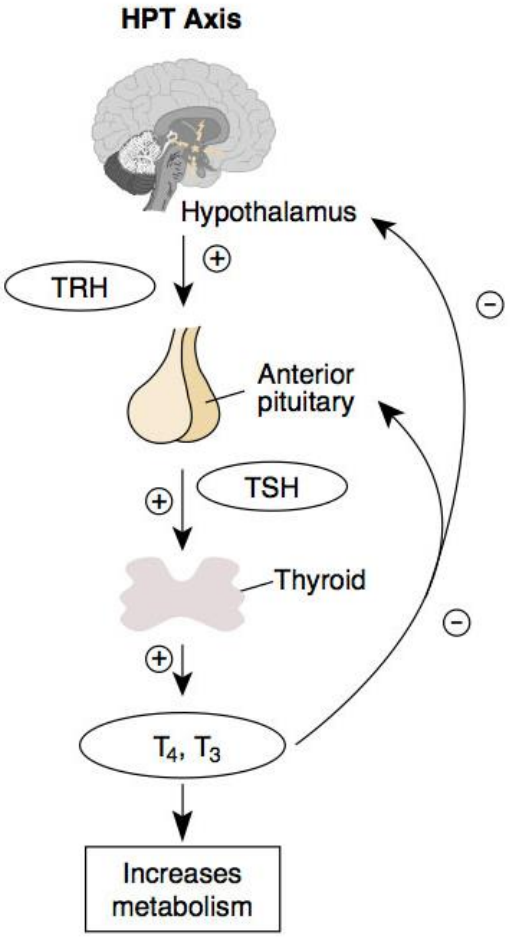

Figure 6. *Triiodothyronine (T_3) and thyroxine (T_4) production, controlled by the hypothalamic–pituitary–thyroid axis (HPT axis), with the release of thyroid-stimulating hormone (TSH), regulated by the thyrotropin-releasing hormone (TRH). Reproduced with permission from Hiller-Sturmhofel and Bartke (1998).*

Adequate EI is considered an essential component in the regulation of the HPT axis (Ylli et al., 2020). Research has shown that reduction in EI negatively impacts the HPT axis, resulting in adaptation and alteration of both T_3 and T_4 hormone secretion, to conserve energy for vital body functions (Misra & Klibanski, 2014). Several studies have investigated the impact of LEA on thyroid function in females (Heikura et al., 2018b; Papageorgiou et al., 2017) as well as in athletes with MD vs eumenorrheic athletes (Harber et al., 1998; Tornberg et al., 2017; Vanheest et al., 2014) and have consistently demonstrated lower T_3 and free T_3 (fT_3) levels, whereas the impact on TSH and T_4 in females is less reliable (Loucks & Heath, 1994b; Loucks et al., 1992; Tornberg et al., 2017).

In male patients with anorexia nervosa (AN), Skolnick et al. (2016) found reduced T_3 and T_4 levels, whereas no change in TSH was observed. In the study of the special forces, Friedl et al. (2000) observed substantial reductions of both T_3 and testosterone during elicited prolonged starvation, with a subsequent brief restoration of T_3 after refeeding, returning to a declining trajectory when starvation was reintroduced. Lower T_3 values have also been identified in male athletes with low testosterone levels (Heikura et al., 2018b). Heikura et al. (2018b) investigated male world-class middle- and long-distance runners and racewalkers and found that athletes with low testosterone levels had lower T_3 levels than athletes with normal testosterone levels. Declining T_3 levels have also been identified in athletes undergoing intensified training periods without increasing their EI, potentially due to a change in the HPT axis (Woods et al., 2018). Perseghin et al. (2009) investigated sprint track and marathon runners and found a reduced TSH:fT_3 ratio compared with sedentary controls. To the author's knowledge, only two studies have investigated the effects of LEA on the thyroid function in males. Papageorgiou et al. (2017) and Koehler et al. (2016) exposed recreationally trained males to ~15 kcal.kg^{-1} FFM.day^{-1} for four days, and found no reductions in T_3. Despite this inconsistency, it is suggested that T_3 might be a more useful marker of LEA in males, compared with T_4 and TSH (McCall & Ackerman, 2019).

GH is a pituitary peptide necessary for muscle and bone anabolism and metabolism of fuel, whereas the effect of GH is mediated by IGF-1 (Elliott-Sale et al., 2018). Studying the effects of LEA in females in a controlled setting, Loucks et al. (1998) and Loucks and Thuma (2003) found increased GH and reduced IGF-1 levels when exercising females were exposed to LEA of <20 kcal.kg^{-1} LBM.day^{-1}. In

exercising females and athletes with MD, increased GH pulsation combined with similar IGF-1 levels compared with eumenorrheic counterparts, as well as disordered secretory patterns of GH have been observed (Laughlin & Yen, 1996; Waters et al., 2001). In athletes, the impact of LEA on these markers is still understudied (Mountjoy et al., 2018b). In males, Friedl et al. (2000) observed that IGF-1 levels were halved among the special forces soldiers experiencing extreme starvation. Furthermore, they also observed a temporary normalization when soldiers were refed (Friedl et al., 2000). When investigating wrestlers during a competitive season involving energy restriction and weight loss, Roemmich and Sinning (1997) observed increases in GH secretion, with significantly increased GH and decreased IGF-1 levels at the end of the season. Investigating ultra-endurance athletes participating in a 1230 km cycling competition, Geesmann et al. (2017) also found severe reductions in IGF-1, with a strong positive correlation between energy balance and changes in IGF-1. Murphy and Koehler (2020) found a postexercise GH/IGF-1 response in resistance-trained athletes exposed to LEA (<15 kcal.kg^{-1} FFM.day^{-1}). However, in a controlled setting, Koehler et al. (2016) found no reductions in IGF-1 when exposing recreationally trained males to LEA (<15 kcal.kg^{-1} FFM.day^{-1}), with similar cross-sectional observations by Heikura et al. (2018b) indicating no difference in IGF-1 in elite male middle- and long-distance runners and racewalkers experiencing LEA (<30 kcal.kg^{-1} FFM.day^{-1}) compared with those with moderate EA (≥30 kcal.kg^{-1} FFM.day^{-1}).

Cortisol, a steroid hormone primarily related to stress response, is likely to contribute to increased adiposity during energy abundance and is an important catabolic hormone secreted to ensure glucose homeostasis during prolonged exercise, glycogen depletion, and starvation (Elliott-Sale et al., 2018; Logue et al., 2018; Schaal et al., 2011). Increases in cortisol during severe caloric restriction and fasting have been reported (Nakamura et al., 2016), and hypercortisolemia might directly affect the reproductive function or serve as a biomarker of stress and reproductive dysfunction in athletes with MD (Ackerman et al., 2013; Berga et al., 1989; Elliott-Sale et al., 2018). Despite this, cortisol alterations have not been consistently reported in the LEA research community. Research in females has suggested that EA < 30 kcal.kg^{-1} FFM.day^{-1} increases cortisol levels (Loucks & Thuma, 2003). Other research has found higher levels of cortisol among female well-trained (Schaal et al., 2011) and elite endurance athletes (Melin et al., 2015; Tornberg et al., 2017) with MD compared with eumenorrheic athletes. In the study

of the special forces, Friedl et al. (2000), found that reduced fat was associated with increased cortisol levels after four weeks of semistarvation during military training. In the study by Kyrolainen et al. (2008), increased cortisol levels as a response to heavy prolonged physiological stress with an energy deficit were found, followed by an immediate reduction when soldiers experienced a stress reduction and increase in EI. A study by Torstveit et al. (2018) found that larger single-hour energy deficit was associated with higher cortisol values among well-trained male endurance athletes, when investigating within-day energy balance. Within-day energy balance assess EI and expenditure in one-hour intervals, trying to overcome some difficulties with the traditional 24-h views of EI and expenditure (Benardot, 2013). A higher exercise dependency score (EDS) was associated with higher cortisol levels among well-trained male cyclists and runners in another cross-sectional study (Torstveit et al., 2019). However, in a study comparing nine long-distance male runners with LEA with eight nonathletes with optimal EA, cortisol was not different between the groups (Hooper et al., 2017). In case studies, Rossow et al. (2013), investigated a male bodybuilder in a one-year study, and found extreme cortisol changes, increasing 90% when EA was estimated to range between 22 and 25 $kcal.kg^{-1}$ $FFM.day^{-1}$. In an 8-week study on a male combat-sport athlete with extreme periods of LEA, no changes in cortisol were found (Langan-Evans et al., 2021). Thus, research in males, and especially in male athletes is scarce, and more in-depth work is needed to understand better the effects of LEA on cortisol levels (Elliott-Sale et al., 2018).

Insulin is a metabolic hormone involved in energy balance, and insulin secretion is correlated with visceral fat in humans, and particularly in males (Woods et al., 2003). In laboratory-controlled intervention studies among females, Loucks et al. (1998), Loucks and Thuma (2003), and Papageorgiou et al. (2017) have observed suppressed insulin concentrations when females were exposed to LEA ranging from 10 to 30 $kcal.kg^{-1}$ $LBM.day^{-1}$. Furthermore, Melin et al. (2015) found no differences in insulin between EA groups when investigating elite female endurance athletes. Investigating female elite middle- and long-distance runners and racewalkers, Heikura et al. (2018b) found no differences in insulin between athletes with MD and eumenorrheic athletes, and between LEA and optimal EA groups. In males, the study of the special forces by Friedl et al. (2000) reported a 50% reduction in insulin when soldiers underwent an eight-week military exercise with semistarvation. Kyrolainen et al. (2008) also found a 70% reduction in insulin

when soldiers were exposed to heavy prolonged physiological stress and reduced EI, followed by a normalization when soldiers experienced a stress reduction and increased EI, although EA was not calculated. In observational studies, Koehler et al. (2013) observed no significant differences in EA between quartiles of serum insulin among both males and females. In the study by Heikura et al. (2018b), no difference in insulin between males with adequate and low testosterone levels, and between LEA and optimal EA were observed. However, some controlled intervention studies have evaluated the effects of reduced EI or LEA on insulin. Chan et al. (2003) observed significantly lower insulin levels on the final day, when healthy males were exposed to three 72-h fasting states. Maestu et al. (2010) observed significantly reduced insulin levels in bodybuilders undergoing 11 weeks of restricted EI compared with controls, whereas Koehler et al. (2016) found a significant decrease in insulin of 36% when males were exposed to short periods of severe LEA (15 $kcal.kg^{-1}$ $FFM.day^{-1}$). On the other hand, Papageorgiou et al. (2017) found no reductions in males exposed to similar conditions as Koehler et al. (2016). Thus, with these inconsistencies, more research is required to understand the short- vs long-term effects of LEA and insulin in male athletes (Elliott-Sale et al., 2018).

3.4.4 Energy metabolism

The metabolic system is controlled by the HPT axis (Ylli et al., 2020), and T_3 and T_4 are often referred to as the major metabolic hormones, involved in the adjustment of RMR (Speakman & Selman, 2003). FFM is the largest determinant of RMR, accounting for up to 70% of the individual variation, and is considered as the largest component of total energy expenditure (Speakman & Selman, 2003). Adequate EI is essential for humans to maintain basic physiological processes, and when in a state of insufficient energy, the body seems to prioritize processes that are crucial for survival, such as cell maintenance, circulation, and neural activity (Wade & Jones, 2004). In female athletes, independent of reproductive function, stable body weight and body composition have been reported when displaying long-term LEA (Redman & Loucks, 2005). Redman et al. (2009) and Goldsmith et al. (2010) found that obese males and females, subjected to persistent LEA, to some extent preserved their body tissue because of metabolic adaptations such as increased work efficiency or reduced RMR. Melin et al. (2015) investigated EA in elite female endurance athletes and found lower RMR in subjects with LEA

compared with females with optimal EA, as well as lower RMR, and increased work efficiency in athletes with MD compared with eumenorrheic athletes. Similar findings have been observed in males (Torstveit et al., 2018; Woods et al., 2017; Woods et al., 2018). Woods et al. (2017) investigated elite male and female rowers undertaking four weeks of heavy endurance training, without dietary compensation, and found a 5% decrease in RMR. In males, Torstveit et al. (2018) found suppressed RMR in endurance athletes who spend more time in energy deficits exceeding 400 kcal, with larger single-hour energy deficits than athletes with normal RMR. Woods et al. (2018) investigated male cyclists and found reduced RMR in a state of overreaching after six weeks of intensified training was undertaken without adjustment of EI.

To identify low RMR, the calculation of the ratio between measured RMR and predicted RMR (RMR_{ratio}) is widely used among females and found to reflect T_3 status accurately (Strock et al., 2020b). Based on previous research by De Souza et al. (2008), an RMR_{ratio} of <0.90, defined as low RMR, has been widely used as a marker of energy deficiency in females (McCall & Ackerman, 2019; Strock et al., 2020b). In some studies investigating patients with ED, a very low RMR_{ratio} between 0.60 and 0.80 has been observed (Marra et al., 2002; Platte et al., 2000). Although the <0.90 ratio has been directly transferred to males (Schofield et al., 2019; Strock et al., 2020b; Staal et al., 2018), some concerns are raised about whether the model are representative among both sexes (Strock et al., 2020b). Research by Strock and co-workers has further identified that the equation used to predict RMR vastly influences what level the cut-off value should be in female athletes (Strock et al., 2020b). Here, they found that the current 0.90 threshold showed the highest sensitivity for the Cunningham (1980) equation, was lower (0.87) for the Harris and Benedict (1918) equation, and higher (0.94) for the dual-energy X-ray absorptiometry (DXA) method (Gallagher et al., 1998; Hayes et al., 2002). Therefore, more research is needed to establish whether the proposed RMR cut-offs for females are transferrable to males.

3.4.5 Immunological function

LEA might distort the immune system, as shown in a study of Japanese elite collegiate runners with MD, reporting higher upper-respiratory symptom (URS) and lower immunoglobulin A (IgA) secretion rates than their eumenorrheic

counterparts (Shimizu et al., 2012). Further, studying female elite athletes in preparation for the 2016 Olympic Games, researchers found that self-reported symptoms of LEA, such as injuries, menstrual and gastrointestinal dysfunction, were linked to increased risk of illness and aches, including head-related symptoms (Drew et al., 2018; Drew et al., 2017). In males, a study by Hanstock et al. (2020) explored how a one-month training period would affect URS incidence and biomarkers of immunity, stress, and nutrition, and found an inverse relationship, indicating higher EA equaled a small increase in URS as well as an increased risk of URS being associated with higher IgA secretion rates. However, research in this area is severely limited and needs to be investigated further.

3.4.6 Cardiovascular function

Among patients with severe AN, cardiovascular changes, such as bradycardia, hypotension, hypercholesterolemia, and endothelial dysfunction might become more and more life-threatening, as AN evolves (Spaulding-Barclay et al., 2016). Whether the same cardiovascular changes are found in athletes is uncertain. Among female endurance athletes, Rickenlund et al. (2005) found that MD is associated with endothelial dysfunction and unfavorable lipid profile, with higher total cholesterol (TC) and low-density lipoprotein (LDL). A study by O'Donnell et al. (2015), demonstrated lower heart rate (HR) and systolic blood pressure in recreationally trained athletes with MD compared with eumenorrheic athletes. Melin et al. (2015) found higher TC levels among female elite endurance athletes with LEA (<30 kcal.kg^{-1} FFM.day^{-1}) than reduced (30–45 kcal.kg^{-1} FFM.day^{-1}) and normal EA (>45 kcal.kg^{-1} FFM.day^{-1}), although no differences were observed in LDL levels between groups. When assessing hypotension, more subjects ($p = 0.022$) with LEA had hypotension (4/8) compared with athletes with reduced EA (2/17) and optimal EA (1/15), although no difference in blood pressure between groups was observed (Melin et al., 2015). Research among males is limited. In male judo athletes, Filaire et al. (2001) found that a seven-day dietary restriction did not influence changes in TC, low- and high-density lipoprotein (HDL), whereas increased triglycerides and free fatty acid levels were observed. Similar findings of an increase in free fatty acids were identified by Koehler et al. (2016), investigating exercising males exposed to LEA (<15 kcal.kg^{-1} FFM.day^{-1}) in a controlled setting. However, the effects of LEA on cardiovascular health among athletes are still relatively unexplored and warrant further investigations.

3.4.7 Psychological factors

Within the RED-S syndrome, psychological problems can precede, cause, or be a consequence of LEA (Figure 2) and have been linked to both female and male athletes as well as adolescents with LEA (Mountjoy et al., 2018b; Mountjoy et al., 2014). Besides the distinct connection of LEA and ED/DE as described in Section 3.3, other psychological factors have also been shown to correlate negatively with LEA in athletes (Bomba et al., 2014; Bomba et al., 2007; De Souza et al., 2007; Fagerberg, 2018; Jurov et al., 2021; Langan-Evans et al., 2021; Marcus et al., 2001; Melin et al., 2015; Petrie et al., 2014; Torstveit et al., 2019). In adolescent female athletes, studies have found a higher frequency of decreased stress-management, mild depressive traits as well as psychosomatic symptoms in athletes with MD (Bomba et al., 2007; Marcus et al., 2001). In a later study, Bomba et al. (2014) found overlapping similarities in adolescents with AN and those with MD, where both groups had increased depression, social insecurity, and fear of weight gain compared with healthy controls. Furthermore, the AN group showed more severe traits than the MD group, most likely due to more severe LEA (Bomba et al., 2014). In females, drive for thinness (DT), diagnosed using the Eating Disorder Inventory (EDI) questionnaire (Garner, 1991), may serve as a proxy indicator of LEA (De Souza et al., 2007). Investigating both sedentary and physically active females, researchers found that those scoring higher on DT had lower RMR, lower T_3 levels, higher levels of ghrelin, as well as scoring higher in domains of ineffectiveness, asceticism, had bulimic tendencies as well as cognitive restraint (De Souza et al., 2007). Another study also found a higher DT in elite female endurance athletes with MD compared with eumenorrheic athletes (Melin et al., 2016). In male athletes, Petrie et al. (2014) investigated a large cohort of athletes in various sports and found that both dietary restraint and muscle-building behaviors were related to bulimic characteristics. In a review by Fagerberg (2018), the authors concluded that male bodybuilders experiencing prolonged LEA (20–25 $kcal.kg^{-1}$ $FFM.day^{-1}$) might be pathological with negative psychological effects, such as mood disturbances. Studying well-trained endurance athletes, Torstveit et al. (2019) found that athletes with higher EDSs displayed more negative energy balance (–479 ± 657 vs 15 ± 633 kcal/day, $p = 0.008$) than athletes with lower exercise dependencies scores. Investigating well-trained male athletes, Jurov et al. (2021) found that 75% of the athletes showed critical cognitive restraint during the prerace season and found that cognitive restraint was negatively associated with energy

conservation (r = –0.549, p = 0.032). Investigating a single case combat-sport athlete, Langan-Evans et al. (2021) found no major psychological fluctuations in mood state or mood disturbance assessed via questionnaires across the weeks leading to weigh-in. However, through interviews, the athlete did display feelings of fear coupled to the loss of body weight before a weigh-in, and how this would affect his health and performance (Langan-Evans et al., 2021). An interesting study by Langbein et al. (2021) explored the consequences of RED-S on psychology using a qualitative approach, and found that athletes experienced an array of physiological impairments, accompanied by significant psychological distress, such as experiencing irritability, vulnerability, weakness, anxiety, fear, helplessness, and despair.

3.5 Performance consequences

The effects of LEA on athletic performance are understudied in both sexes, but it is hypothesized that persistent LEA can affect performance through processes such as reduced glycogen storages (Tarnopolsky et al., 2001), protein synthesis (Areta et al., 2014), and increased risk of illness and injury in both professional athletes and recreational activities (Drew et al., 2018; Drew et al., 2017; Logue et al., 2019). Recent studies have identified the impact of LEA on sports performance in both the female (Ackerman et al., 2019; Silva & Paiva, 2016; Tornberg et al., 2017; Vanheest et al., 2014) and the male athletic population (Keay et al., 2018; Woods et al., 2017; Woods et al., 2018). In elite adolescent swimmers, Vanheest et al. (2014) found a 10% decline in speed over 400 m of swimming in athletes with MD compared with their eumenorrheic counterparts after a 12-week training period. Among female elite rhythmic gymnasts, Silva and Paiva (2016) reported that EA was negatively correlated with competition rankings, most gymnasts reported LEA as well as presented poor sleep habits with consequences upon daytime sleepiness, sleep quality, and LEA. In nonweight-bearing activities, a greater power-to-weight ratio is regarded as important, and attaining an ideal body composition through persistent and severe energy restriction is likely to affect performance and health negatively (Mooses & Hackney, 2017; Tornberg et al., 2017). Investigating elite athletes, Tornberg et al. (2017) reported that athletes with MD had reduced knee muscular strength and reduced reaction time compared with eumenorrheic elite athletes, with no difference in peak oxygen uptake (VO_{2peak}), further supported in an east-African runner study by Mooses and Hackney (2017). In a recent study investigating female athletes from various sports, Ackerman et al. (2019) reported

decreased self-reported performance effects of LEA, such as decreased training response, impaired judgment, decreased coordination and concentration, depression, as well as decreased endurance performance. In males, Woods et al. (2017) investigated elite rowers undertaking a four-week intensified training period accompanied by a lack of proper dietary intake and found decreased recovery and reduced 5 km time trial performance. In a later study on trained cyclists undertaking an intensified training period eliciting overreaching, Woods et al. (2018) also found signs of reduced anaerobic and aerobic performance as well as reductions in body composition and RMR, with insufficient EI as a contributing factor. In another observational study investigating LEA in cyclists using a sport-specific questionnaire, Keay et al. (2018) found that athletes assessed as having chronic LEA had reduced testosterone levels, lower body fat, and impaired cycling performance compared with athletes assessed with normal EA.

3.6 Prevention, screening, and treatment

3.6.1 Prevention

The negative impact of RED-S on various bodily systems highlights the importance of preventing LEA among both sexes in all sports. To attain this, increased knowledge and awareness are crucial among all athletes, coaches, supporting staff, and sports federations (Mountjoy et al., 2018b). Unfortunately, there is still a way to go, despite that some progress has been made (Ackerman et al., 2020). An Australian study found that 33% of exercising females thought that periods with irregular menses were normal among exercising females, despite that almost half of them knew that MD was linked to low BMD (Miller et al., 2012). Multiple other reports have shown that less than 50% of the supporting staff, such as coaches, athletic trainers, physicians, and physiotherapists, could identify the TRIAD components (Brown et al., 2014; Curry et al., 2015; Feldmann et al., 2011; Kroshus et al., 2015; Kroshus et al., 2014; Mukherjee et al., 2016; Pantano, 2006, 2017; Troy et al., 2006). A recent study by Lodge et al. (2021) found that knowledge, confidence, and impact scores of both the TRIAD and RED-S were lowest in female cross-country athletes and highest among athletic trainers, supporting the need for education. Using a top-down approach, Mountjoy et al. (2018a) investigated sports federations and found that only 7% of the investigated Olympic federations had programs on RED-S education, showing that the unawareness of RED-S is broad-spectral. Preventing ED/DE, thereby reducing the

risk of RED-S, should include both athletes and coaching staff (Bar et al., 2016) with peer-led educational programs found to be efficient (Becker et al., 2012). Other studies suggest that prevention programs should also target individual athletes, including being sex specific and involve peers as well as influence sports regulations, and include the health care system (de Bruin, 2017; Martinsen et al., 2014a; Martinsen et al., 2015; Mountjoy et al., 2014).

3.6.2 Screening

In both a short- and long-term perspective, identifying athletes at risk of LEA is important, both from a health perspective as well as to maintain or increase athletic performance (Mountjoy et al., 2014; Nattiv et al., 2007). Athletes' supporting staff, such as coaches and athletic trainers, are in a position to identify athletes with prominent signs of RED-S such as ED/DE. Unfortunately, athlete secrecy, masking behaviors, as well as coaches' stereotypical beliefs can complicate the identification process (Plateau et al., 2013). If an ED/DE is detected, further difficulties in convincing athletes to seek treatment have been found (Plateau et al., 2017). In screening larger populations, several instruments identifying ED/DE behaviors exist (Fairburn & Beglin, 1994; Garner & Garfinkel, 1979; Garner et al., 1983; Hill et al., 2010), some developed for athletes (Hazzard et al., 2020; Hinton & Kubas, 2005; Martinsen et al., 2014b; McNulty et al., 2001; Steiner et al., 2003), although not validated for DSM-V (American Psychiatric Association, 2013). Although questionnaires are important in identifying athletes at risk of ED/DE and LEA, diagnosing is time-consuming and requires additional in-depth interviews (Fairburn & Beglin, 1994, 2008; Martinsen & Sundgot-Borgen, 2013; Sundgot-Borgen & Torstveit, 2004). Furthermore, some athletes report a high prevalence of LEA or MD without ED/DE (Gibbs et al., 2013; Melin et al., 2015). A study by Gibbs et al. (2011) found that a higher DT derived from the EDI-2 questionnaire was associated with energy deficiency (depicted as $RMR_{ratio} < 0.90$) and MD in a large cohort of exercising females. To identify athletes at risk of LEA, Melin et al. (2014) have successfully developed and validated the Low Energy Availability in Females Questionnaire (LEAF-Q), enabling the identification of female endurance athletes at risk of LEA. In males, Keay et al. (2018) successfully identified male cyclists at risk of LEA, using a sport-specific questionnaire and clinical interview (SEAQ-I). Furthermore, it has been suggested in a review by Sim and Burns (2021) that other questionnaires already developed, not maintaining female-specific questions such as in the LEAF-Q, may be used in males. These questionnaires

include the Brief Eating Disorder in Athletes Questionnaire (BEDA-Q) (Martinsen et al., 2014b), Eating Disorder Inventory (EDI) DT scores (Garner, 1991), Eating disorder Screen for Primary care (ESP) (Ackerman et al., 2019), Eating Disorder Examination Questionnaire (EDE-Q) (Fairburn & Beglin, 2008), and Three-Factor Eating Questionnaire (TFEQ) (Stunkard & Messick, 1985). However, these questionnaires still need to be validated to address LEA in male athletes (Sim & Burns, 2021). The RED-S clinical assessment tool (RED-S CAT) is another tool aimed at helping the supporting staff to screen for RED-S and manage return-to-play decisions, although not validated (Mountjoy et al., 2015a), as well as the newly developed, yet unvalidated male athlete Triad cumulative risk assessment tool (Fredericson et al., 2021).

3.6.3 Treatment

To treat RED-S, both nonpharmacologic and pharmacologic managements exist (Mountjoy et al., 2018b). Nonpharmacologic treatment involves a wide variety of methods, including an educational approach, and increasing EA via modifications of exercise in combination with an increase of EI. Regardless of the severity of LEA, involving appropriately trained experts, such as sport nutritionists, is strongly recommended, and each intervention should be individualized and periodized to each athlete (Mountjoy et al., 2018b). Furthermore, it is important to distinguish between RED-S and overtraining syndrome because these seem to have many shared pathways, symptoms, and diagnostic complications (Stellingwerff et al., 2021). LEA should be addressed in both sexes by modifying nutritional habits and/or exercise behaviors (Bhasin et al., 2018; Bhasin et al., 2010; Gordon et al., 2017). Modifications can include an array of variables, such as increased food intake, including increased intake of energy-dense foods, manipulating food choices, changing consumption patterns, as well as reductions in or changing exercise behaviors (Melin et al., 2016; Mountjoy et al., 2018b). Other methods include cognitive behavioral therapy, with positive results for female athletes (Berga & Loucks, 2006; Michopoulos et al., 2013). Pharmacological management in females using oral contraceptives in aiming at regaining menses or improving BMD is not recommended due to the potential risk of masking the return of spontaneous menses (Mountjoy et al., 2018b). Treating ED/DE is more complex, and should include a multidisciplinary team, consisting of medical, dietary, and mental health support, and athletes diagnosed with severe ED such as AN and

bulimia nervosa should not participate in normal training programs or competition (Mountjoy et al., 2018b; Mountjoy et al., 2014).

In summary, research on RED-S in males has emerged in the last couple of years (Areta et al., 2021; Dipla et al., 2020; Elliott-Sale et al., 2018; Logue et al., 2018; Logue et al., 2020; McCall & Ackerman, 2019; Melin et al., 2019; Slater et al., 2017; Tenforde et al., 2016; Wasserfurth et al., 2020) since the initial publications of the Mountjoy et al. (2014) position stand paper. Despite this, some populations are still understudied, including male adolescent and elite athletes. Furthermore, most studies are performed with a cross-sectional design, thus, a lack of both trials and longitudinal perspectives investigating health and performance consequences of RED-S exists.

4 Aims of the dissertation

The overall aim of this Ph.D. dissertation was to investigate RED-S among Norwegian male athletes of different ages and performance levels. Three independent studies including experimental and observational study designs were conducted. These studies addressed three specific aims:

I. To determine how a mesocycle of four weeks of intensified endurance training designed to increase aerobic performance would affect RMR, body composition, energy intake, total and free testosterone, cortisol, testosterone:cortisol ratio, T_3, insulin, and IGF-1 levels in well-trained male cyclists (**Study I**/paper I).

II. To investigate RED-S in a Norwegian cohort of male Olympic-level athletes using surrogate markers such as suppressed RMR, impaired bone health, and altered metabolic and endocrine variables (**Study II**/paper II).

III. To investigate RED-S in male adolescent endurance athletes attending Norwegian elite sport high schools over a three-year period, with a special focus on bone health, EA, RMR, and performance variables (**Study III**/paper III).

5 Methods

This dissertation presents data from three studies conducted from 2016 to 2020. **Study I** was performed during autumn 2016. **Study II** was performed in the spring of 2018. **Study III** was initiated in autumn 2017 as a three-year longitudinal study and completed in the spring of 2020.

5.1 Study designs

Study I was conducted as a prospective intervention study (quasi-experiment), with pre–post measurements aimed at determining how a mesocycle of four weeks of intensified endurance training, designed to increase key aerobic performance such as VO_{2peak} and functional threshold power (FTP), would affect EI, body composition, RMR, and blood biomarkers of RED-S among well-trained male cyclists.

Study II was conducted as a cross-sectional study to investigate the prevalence of RED-S in Norwegian male Olympic-level athletes using surrogate RED-S-related markers such as suppressed RMR, impaired bone health, and altered metabolic and endocrine blood biomarkers.

Study III was conducted as a longitudinal study, with six measuring points over a period of three years. The aim of the study was to monitor the possible development of RED-S and associated markers in a three-year longitudinal perspective, among elite male adolescent endurance athletes attending sport-specific high schools in Norway. Athletes were tested every six months, matching testing just before and after their competitive season with baseline testing performed in 2017. Because of the COVID-19 world-pandemic, data collection at T6 had to be canceled (Figure 7).

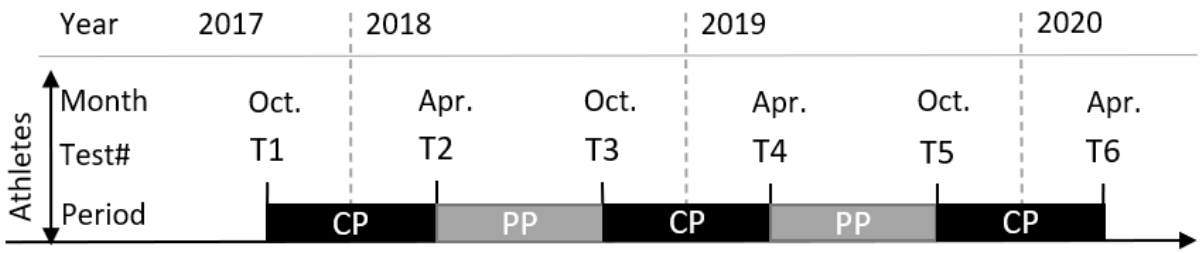

Figure 7. *Longitudinal testing and seasonal overview of Study III, with the measurement at highlighted timepoints T1–T6. CP, competition period; PP, preparation period.*

5.2 Participants

A total of 80 healthy males were recruited in all three studies and all provided informed consent. The goals and aims of the studies were thoroughly described to all participants in all studies. In **Study I**, 22 well-trained male cyclists were recruited from local sport clubs in Kristiansand. In **Study II**, 44 male Olympic-level athletes were recruited from the Norwegian Olympic and Paralympic Committee and Confederation of Sports, Oslo, Norway. In **Study III**, 14 junior endurance athletes were recruited from sport-specific high schools within the region of Agder, Norway.

A total of two participants were excluded in **Study I**, none were excluded in **Study II**, whereas five participants withdrew from **Study III**. In **Study I**, two participants were excluded, one due to failing to complete the intervention and one due to noncompliance. In **Study III**, five participants dropped out during the three years. The reasons for dropping out were injury prohibiting further participation, changing/moving to a new school (relocation), or the extra burden the study inflicted on the participants (load) (Table 3).

Table 3. Dropouts with included reasons in Study III.

	T1	T2	T3	T4	T5	T6	Total
Injuries	1*	0	0	0	1	C	2
Relocation	0	0	1	0	0	C	1
Load	0	0	0	0	2	C	2
Total	1*	0	1	0	3	C	5

T = time-point, C = Canceled due to COVID-19. *Dropped out before data collection

In **Study I**, the inclusion criteria were that participants had to be active in their sport, with a training frequency of ≥3 sessions/week during the last 12 months, compete at regional or national level, be >18 but <50 years of age with a peak oxygen uptake of ≥55 mL·kg body mass^{-1}·min^{-1}. Exclusion criteria were disease or injury that would prohibit participation or failure to complete the study intervention. In **Study II**, participants had to be elite athletes from national teams or competitive athletes from regional clubs approved and monitored by the Norwegian Olympic and Paralympic Committee and Confederation of Sports, ≥18 years old and free of injury or illness preventing athletes from training and participating in the study. In **Study III**, participants had to be first-year high school students at the beginning of the study program, study at high schools specialized

in sport, endurance athletes competing at regional or national level, and free of injuries or illness that would prohibit participation at baseline testing. For detailed descriptive data of the participants included in data analysis in all three studies, see Table 4.

Table 4. Study overview, including design, timeframe, descriptive participant characteristics included at baseline (dropouts are removed, see Table 3), and variables measured.

Study	Design (time frame)	N	Age (years)	VO_{2peak} (mL.kg body $mass^{-1}.min^{-1}$)	Training status	Body composition/ RMR	Blood variables	Energy intake and expenditure	Performance
I	Experimental (2016)	20	33.3 ± 6.7	63.5 ± 6.6	Well-trained athletes	DXA/ ventilated hood	TES, T_3, COR, IGF-1, Insulin, SHBG	EI + EEE	VO_{2peak} and FTP
II	Cross-sectional (2018)	44	24.7 ± 3.8	N/A	Olympic-level athletes	DXA/ ventilated hood	TES, T_3, COR, TC, LDL	N/A	N/A
III	Longitudinal (2017–2020)	13	16.3 ± 0.4	61.5 ± 5.3	Junior elite athletes	DXA/ ventilated hood	N/A	EI + EEE	VO_{2peak} and muscular strength and power

Data are presented as mean ± SD. COR = Cortisol, DXA = Dual-energy X-ray absorptiometry, EEE = Exercise energy expenditure, EI = Energy intake, FTP = functional threshold power, IGF-1 = Insulin-like growth factor 1, LDL = Low-density lipoprotein, N/A = Not available, RMR = Resting metabolic rate, SHBG = Sex hormone-binding globulin, T_3 = Triiodothyronine, TC = Total cholesterol, TES = Testosterone, VO_{2peak} = peak oxygen uptake

5.3 Study protocols

Study I:

This began with a one-week baseline testing period, consisting of physiological testing, including RMR, body composition, blood biomarkers, EI, and performance variables. The four-week training intervention consisted of three high-intensity interval sessions per week, each containing 20 min of warm-up at a self-regulated pace, followed by an interval period consisting of 32 min of high-intensity training. The final weeks consisted of laboratory testing of physiological variables identical to baseline (Figure 8).

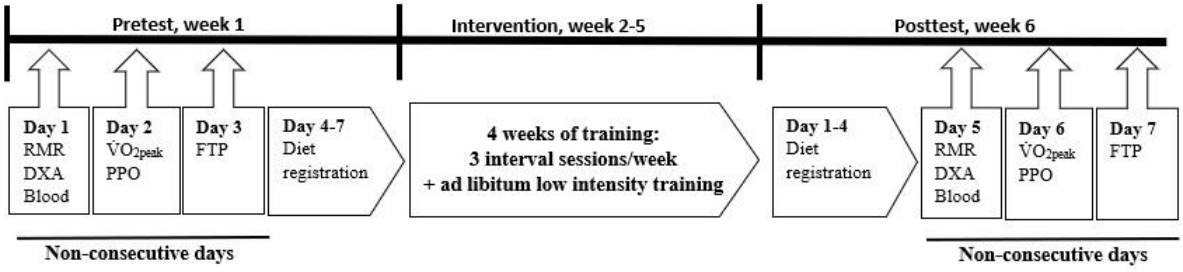

Figure 8. *Schematic overview of Study I. Pre- and posttest measures included rested and fasted resting metabolic rate (RMR), dual-energy X-ray absorptiometry (DXA), and blood sampling. An incremental exercise test for determination of peak oxygen uptake (VO_{2peak}) and peak power output (PPO) as well as a 40-min functional threshold power test (FTP) were performed in an unfasted state. Diet registration was performed for four consecutive days.*

Study II:

Testing was performed at the Norwegian Olympic and Paralympic Committee and Confederation of Sports in Oslo and initialized with an assessment of RMR early in the morning, followed by an assessment of body composition, bone health, and blood sampling in an adjacent building.

Study III:

Five days before arrival at testing, participants recorded their EEE using an HR monitor. Participants from schools outside Kristiansand arrived at the university the day before testing. At arrival, participants underwent a modified four-day retrospective dietary history interview, before being housed next to the laboratory for a sleepover. The next morning, participants underwent RMR measurement and delivered a urine sample for assessment of urine specific gravity (USG), followed by assessment of body composition and bone health. After testing, participants

underwent a five-hour waiting period, with ad libitum EI. During this period, athletes relaxed and prepared for their performance testing, including VO_{2peak} and strength testing. Participants living in Kristiansand first underwent RMR and DXA measurement, followed by a modified retrospective dietary history interview. Later during the day, athletes went back for determination of VO_{2peak} and strength testing (Figure 9).

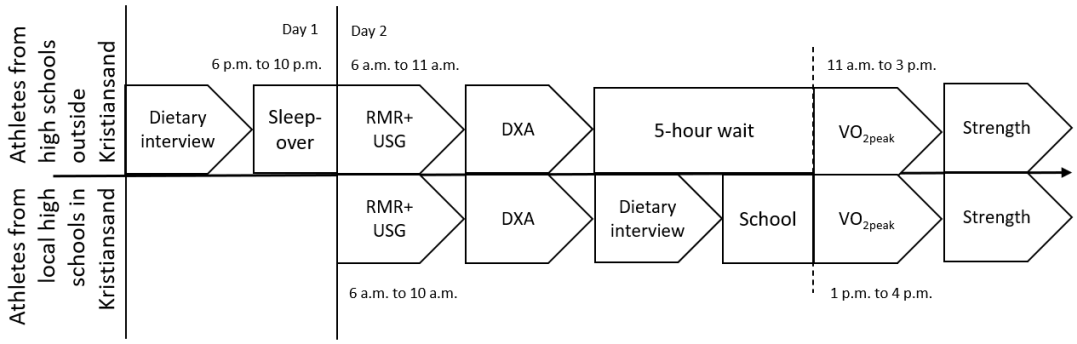

Figure 9. *Overview of the testing protocol used in Study III. The protocol included rested and fasted urine sampling, measurements of resting metabolic rate (RMR), dual-energy X-ray absorptiometry (DXA), and a four-day dietary recall interview at initial testing. Performance testing included an incremental exercise test for the determination of peak oxygen uptake (VO_{2peak}) and strength testing.*

5.4 Measurement protocols

5.4.1 Resting metabolic rate

In **Studies I**, **II**, and **III**, RMR was measured by indirect calorimetry using a canopy hood system. **Studies I** and **III** utilized the metabolic chart of Oxycon Pro (Carefusion, Höchberg, Germany) with LABManager software (v. 5.31.0.4) whereas **Study II** utilized the Vyntus CPX (CareFusion, Höchberg, Germany) with SentrySuite software (v. 2.21.4). All testing was performed in a darkened, quiet room, maintained at a constant temperature. In **Studies I** and **III**, participants living in Kristiansand were instructed to arrive at the laboratory on the morning of the test, using minimal bodily movement, either by taking the bus or arriving by car. Transportation that involved physical activity such as cycling or walking long distances was prohibited. In **Study III**, participants from schools outside of Kristiansand arrived at the lab the day before testing and were accommodated for an overnight sleep next to the lab. In **Study II**, participants either stayed overnight

in conjunction with the laboratory or arrived using motorized transport with minimal bodily movement, limited to walking <100 m to the laboratory. In all studies, every system was calibrated according to laboratory standards in advance of testing, and best-practice protocols for measurement were adhered to, which included testing in a 12-h rested and fasted state, abstaining from alcohol, nicotine, and caffeine, and limited physical activity the day before (Compher et al., 2006). Upon arrival at the lab, participants relaxed for 15 min before measurement in a supine position was initiated. VO_2 and VCO_2 were then assessed over a 30-min period, and participants were instructed to minimize movement during measurement. The last 20 min of measurements were used to assess RMR similar to Melin et al. (2015) and the measurements were accepted when a coefficient of variation (CV) < 10% was obtained (Compher et al., 2006). Measured RMR was calculated in all three studies using the Weir (1990) equation: $(3.94 \times VO_2\ [mL]) + (1.1 \times VCO_2\ [mL]) \times 1.44$. Relative RMR was calculated as measured RMR in $kcal.kg^{-1}$ $FFM.day^{-1}$. The predicted RMR was calculated using the Cunningham (1980) equation and RMR_{ratio} was calculated as measured RMR [kcal]/predicted RMR [kcal].

5.4.2 Body composition and bone mineral density

In **Studies I**, **II**, and **III**, height was measured without shoes to the nearest 0.1 cm using a wall-mounted centimeter scale (Seca Optima, Seca, Birmingham, UK). Body weight was measured in underwear to the nearest 0.01 kg with an electronic scale (Seca 1, model 861, Birmingham, UK). Body mass index (BMI) was calculated as weight in kg divided by height in meters squared (kg/m^2). Body composition and BMD were assessed using a General Electric (Madison, WI, USA) DXA narrow fan-beam scanner. A Lunar Prodigy (EnCore software v. 15) was used in **Studies I** and **III**, whereas an iDXA (EnCore software v. 16.2) was used in **Study II**, all using the combined NHANES/Lunar reference database. DXA was calibrated with a standard phantom before each morning of scanning, and scanning was performed in the following periods: **Study I**: 6–8 a.m., **Study II**: 7–9 a.m., and 6–9 a.m., in **Study III**. Participants were instructed to meet in a 12-h rested and fasted state with limited physical activity the day before as well as being encouraged to stay hydrated the day before testing in all studies. Participants were asked to void and defecate before testing and assessment of hydration status was performed with a USG test using a digital Atago refractometer (UG-α cat. no. 3464, ATAGO USA Inc., Bellevue, WA, USA). Participants were positioned in a

supine position as referred to by Nana et al. (2015) and Kerr et al. (2016), limited to underwear clothing. Body composition was assessed according to the best-practice protocol including assessment of USG (Kerr et al., 2016; Nana et al., 2015). Within each study, the same technician performed all tests with the same scanner on all participants, using the standard thickness mode as determined by the auto-scan feature in the software. BMD was assessed and calculated in the lumbar spine (L1–L4), femoral neck, and total hip using the automated analysis of the software and adjusted if necessary. Low BMD was defined as Z-score < –1.0 in one of the measured sites in adults, as recommended by Nattiv et al. (2007). Adolescent athletes were defined as being "at risk" of low bone mass with a BMD Z-score < –1.0 as recommended by Barrack et al. (2010a).

5.4.3 Blood sampling

In **Studies I** and **II**, blood samples were drawn from the cephalic vein of participants 5 min after DXA assessment. In **Study I**, two 5 mL Vacuette Z Serum Sep clot activators (BD, Plymouth, UK) were filled and centrifuged at 3100 × *g* for 10 min (Statspin Express 4, Beckman Coulter, Brea, CA, USA) within a preset limit of ≥30 min but ≤60 min from sampling. Five 2 mL Cryotube vials (VWR International, Radnor, PA, USA) were filled with serum and frozen at –80 °C, before being transported for analysis at Sørlandet's Hospital, Kristiansand and analyzed for testosterone (analytic CV: 6.7%), SHBG (4.0%), T_3 (6.9%), cortisol (8.2%), insulin (21.1%), and IGF-1 (8.0%). Free testosterone was estimated by dividing total testosterone by SHBG (free testosterone = 10 × testosterone/SHBG). In **Study II**, one 5 mL Vacuette Z Serum Sep clot activator was filled and subsequently centrifuged at 3100 × *g* for 10 min (Statspin Express 4, Beckman Coulter, Brea, CA, USA) within a limit of ≥20 min but ≤40 min. 2 mL Cryotube vials were filled with serum and cooled to 2 °C before being transported to Fürst laboratory in Oslo the same day. Blood was analyzed for LDL (analytic CV: 2.0%), TC (1.9%), fT_3 (3.0%), total and free testosterone (6.7%), and cortisol (8.2%).

5.4.4 Psychological factors

In **Study III**, three different six-item short questionnaires were distributed to assess DE, drive for leanness, and exercise addiction. The questionnaires included the BEDA-Q (Martinsen et al., 2014b), the Drive for Leanness scale (DLS) (Smolak & Murnen, 2008), and the Exercise Addiction Inventory for Youth (EAI-Y) questionnaire (Lichtenstein et al., 2018). Athletes arriving from schools outside

Kristiansand filled out the questionnaires during the 5-h wait, whereas athletes from schools in Kristiansand answered the questionnaires before performance assessment (Figure 9).

5.4.5 Energy intake

In **Study I**, participants weighed and registered their dietary intake for four consecutive days using a digital kitchen scale (OBH Nordica 9843 Kitchen Scale Color, Taastrup, Denmark). Before registration, in-depth oral and written instructions were given, and participants were asked to maintain their habitual dietary patterns and routines during the registration period. Participants logged all dietary data using Dietist Net software (Dietist Net v. 20.10.3, Kost och Näringsdata, Bromma, Sweden) with access to the Norwegian food table and an open Norwegian nutritional information database. In **Study III**, participants' dietary intake was obtained using a modified retrospective dietary history interview (Gibson, 2005). Participants were interviewed and asked to recall all food and fluid intake during the last four days. The interviewers were trained in advance, followed an interview protocol, equipped with images of various food portion sizes designed to help subjects with estimating portion sizes. A PC was used to help the interviewer and subjects to identify specific products using Google searching. After the interview, the data were logged using software from Dietist Net (Dietist Net v. 20.10.3, Kost och Näringsdata, Bromma, Sweden) with access to the Norwegian food table and an open Norwegian nutritional information database.

5.4.6 Exercise energy expenditure

In **Study III**, the participants recorded all training sessions with an HR monitor (Polar M400, Polar Electro, Kempele, Finland) five days before testing. Data were recorded as epochs of 5 s during every training session. EEE was calculated as EEE ($kcal.kg^{-1}.min^{-1}$) = ((5.95 × HRaS) + (0.23 × age) + (84 × 1) − 134)/4,186.8, where HRaS = HR above sleeping HR (beats/min). Sleeping HR was derived during RMR measurement using the following formula: Sleep HR = 0.83 × supine HR (Crouter et al., 2008).

5.4.7 Peak oxygen uptake

Peak oxygen uptake ($\dot{V}O_{2peak}$) was assessed in **Studies I** and **III**. In **Study I**, VO_{2peak} was performed on a stationary bike (Excalibur Sport, Lode B.V.,

Groningen, the Netherlands) starting with 1 min of cycling at a power output of 175 W and increased by 25 W min^{-1} until voluntary exhaustion or failure to maintain a cadence of at least 70 rounds per minute. VO_2 and VCO_2 were measured using the metabolic chart Oxycon Pro (Carefusion, Höchberg, Germany, LABManager software v. 5.31.0.4) using the mixing chamber and 30 s sampling time. In **Study III**, VO_{2peak} was measured on a treadmill (Woodway, GmbH, Weil am Rhein, Germany) starting with 1 min of running at 12 km h^{-1} on a constant incline of 6° (10.5%). Speed was increased by 1 $km.h^{-1}.min^{-1}$ until voluntary exhaustion or failure to maintain the correct position on the treadmill. VO_2 and VCO_2 were measured using a portable Metamax 3B (Cortex Biophysik GmbH, Leipzig, Germany) using breath-by-breath measurement. In **Studies I** and **III**, VO_{2peak} was defined as the average of the two highest 30-s consecutive $\dot{V}O_2$ measurements. HR was measured continuously, and blood lactate was measured one minute after completion of the test. To ensure a valid test, objective criteria for attainment of VO_{2peak} were plateau of oxygen uptake or HR ≥ 95% of known HR_{peak}, respiratory exchange ratio ≥ 1.10, and blood lactate ≥ 8.0 $mmol.L^{-1}$ (Howley et al., 1995). Before each test, all equipment was calibrated according to procedures provided by the manufacturer.

5.4.8 Functional threshold power

In **Study I**, the cycling-specific test of FTP was performed. Using their own bike, participants performed a seated 40-min all-out test on CompuTrainer Lab bike rolls (Race Mate, Seattle, WA, USA). Before the test was initialized, participants were instructed to perform a 20- to 30-min warm-up at a self-regulated load. During the FTP test, the participants were verbally encouraged to perform the all-out 40-min ride with the highest possible mean wattage. During the test, the participants were blinded for power output and HR, with only time remaining and rounds per minute displayed.

5.4.9 Strength and power testing

In **Study III**, leg strength and power were assessed using a 10-repetition leg extension test on a pneumatic Keiser leg extension machine (AIR300, Keiser Corporation, Fresno, CA, USA). Each participant had their seating position adjusted, aiming at a vertical femur, equivalent to a 90° knee angle, and feet placed with heels at the bottom end of the footplate. Initially, participants performed a short warm-up consisting of six repetitions at a moderate load with increasing

intentional velocity automatically determined by the computer software. During the 10-repetition test, participants were asked to extend both legs with maximum effort. After completion, one-repetition maximum force and power were derived from the dedicated software (A420, build 2.0.0.4).

5.5 Ethical approval and considerations

Before recruitment in **Studies I** and **III**, the usage and data storage were evaluated and approved by the Norwegian Centre for Research Data (see Appendix I). Further, all three studies were also evaluated by the Regional Committee for Medical and Health Research Ethics, which assessed **Studies I** and **III** to not require ethical approval, whereas **Study II** was evaluated and approved (Appendix II). Finally, all three studies were also approved at the local Ethical Committee of the University of Agder. In all projects, information about the study was distributed both in writing and verbally, clearly stating the intention of the study, that participation was voluntary, data would be considered confidential, all data would be treated anonymously, that participants were able to withdraw from the study at any time without any explanations and could require the deletion of their data if not already published. Finally, all studies complied with the standards set by the Declaration of Helsinki (World Medical Association, 2013).

Ethical behavior refers to the standards of protecting individuals, communities, and environments, to increase the sum of good in the world (Israel & Hay, 2006). An important element is not to inflict harm on the subjects investigated, interpreted as a means to frighten, embarrass, or negatively affect the participants (Thomas et al., 2015). **Study II** included elite and Olympic-level athletes who are publicly known, both from a national and international perspective, through their sport participation. Such factors prompted extra precautions for both securing confidentiality and anonymity, ensuring that no single athlete could be indirectly identified, by removal of variables from the published article such as the specific sport discipline athletes were engaged in. **Study III** involved adolescent athletes, and due to the risk of causing harm to the athletes, we chose a different method of assessing EI compared with **Study I**. These considerations were made based on feedback from previous experiences within the schools, where weighed food records had caused adolescent athletes unexpectedly to increase their awareness of calories consumed to an unhealthy state.

5.6 Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (v. 25; IBM Corp., Armonk, NY, USA) in **Study I**, STATA for Windows (v. 16.1; StataCorp LCC, 2019, College Station, TX, USA) in **Study II**, and Jamovi for Windows (the jamovi project, 2020, version 1.6.3, Sydney, Australia) in **Study III**. Figures were made using GraphPad Prism (Graph Pad Software, Inc., La Jolla, CA, USA). Datasets were controlled for missing data and indication of nonnormality using histograms and Quantile–Quantile plots as reference. Descriptive data in **Studies I**, **II**, and **III** are presented as mean ± standard deviation (SD) unless stated otherwise. Statistical significance level was defined as $p < 0.05$ in all three studies. In **Study I**, the difference between pre- (PRE) and posttest (POST) was assessed using the paired-samples T-test (POST-PRE), generating means, SD of differences, and 95% confidence intervals including percent change. Changes between subgroups were tested using an independent-samples T-test. In **Study II**, the difference between groups containing interval or ratio data was assessed using the Welch t test for unequal variance (Delacre et al., 2017) and contingency data were analyzed using the Fisher exact test (Yates, 1984). To interpret the meaningfulness of results, effect size (ES) using Cohen (1988) criteria were calculated in **Studies I** and **II** using the following thresholds: trivial (<0.2), small (0.2–0.5), moderate (0.5–0.8), and large (>0.8). In **Study III**, longitudinal changes were analyzed using a Linear Mixed Model with restricted maximum likelihood (REML) estimation, with time set as fixed effects and random intercepts and linear slopes. To interpret the magnitude of bone health changes at various time points for each athlete, the reliable change index (RCI) was calculated using the following formula: $\mathrm{RCI} = \frac{x^2 - x^1}{\mathrm{SE}}$ (Jacobson & Truax, 1992; Maassen, 2004). In the above equation, X^1 and X^2 represent the individual scores at two time points, with the standard error (SE) calculated as follows: $\mathrm{SE} = \sqrt{(S_X^2 + S_Y^2)(1 - r_{XY})}$, were S_X^2 and S_Y^2 are the variances at the timepoints, and r_{XY} is the test–retest reliability (Maassen et al., 2009). Changes were interpreted as statistically significant when RCI was greater than 1.96 in both directions, whereas values between –1.96 and 1.96 indicated no reliable change between time points (Jacobson & Truax, 1992).

6 Summary of findings

This section briefly summarizes the most important findings in **Studies I**, **II**, and **III**. Each paper is presented at the end of this document.

6.1 Study I – paper I

The impact of a four-week intensified endurance training program on markers of RED-S was investigated in well-trained male cyclists, using pre- and postintervention testing. Testing protocols included assessment of RMR, body composition and bone health, endocrine changes, EI, as well as aerobic performance. At pretest, 15% of the athletes were identified with low BMD (Z-score < –1.0). In total, the athletes' aerobic performance increased, resulting in a gain in relative VO_{2peak} (2.4%, p = 0.005), absolute VO_{2peak} (2.1%, p = 0.026), and FTP (6.5%, p < 0.001) indicating a successful training intervention. No changes were observed in EI (0.2%, p = 0.965), bodyweight (–0.1%, p = 0.342), or FFM (0.0%, p = 0.764), despite four weeks of intensified training (Figure 10).

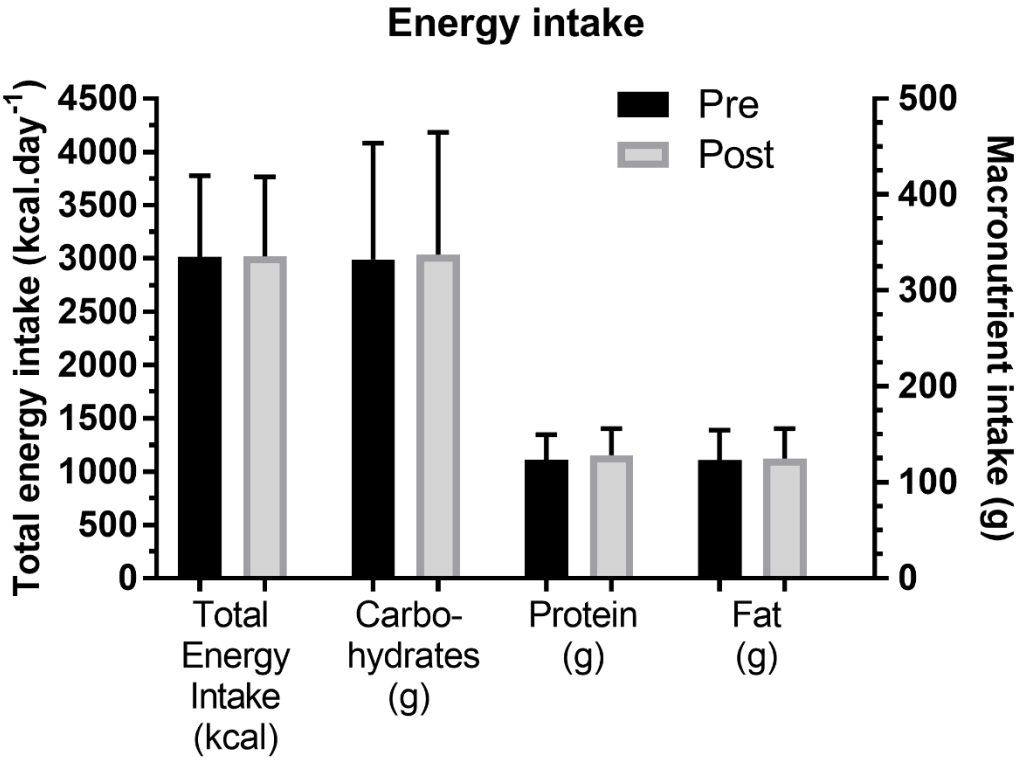

Figure 10. *Changes in energy and macronutrient intake from pre- and posttest, with mean and standard deviation.*

Assessing changes in RED-S-related parameters, total testosterone levels increased (8.1%, p = 0.011), whereas reductions in both relative RMR (–2.6%, p = 0.013) and RMR_{ratio} (–3.3%, p = 0.011), and T_3 levels (4.8%, p = 0.008), as well as an increase in cortisol levels (12.9%, p = 0.021) were observed (Figure 11). No significant changes were observed in IGF-1 (–0.6%, p = 0.740) and insulin (–10.6%, p = 0.121). At pretest, a 40% prevalence of low RMR was observed, increasing to 65% at posttest.

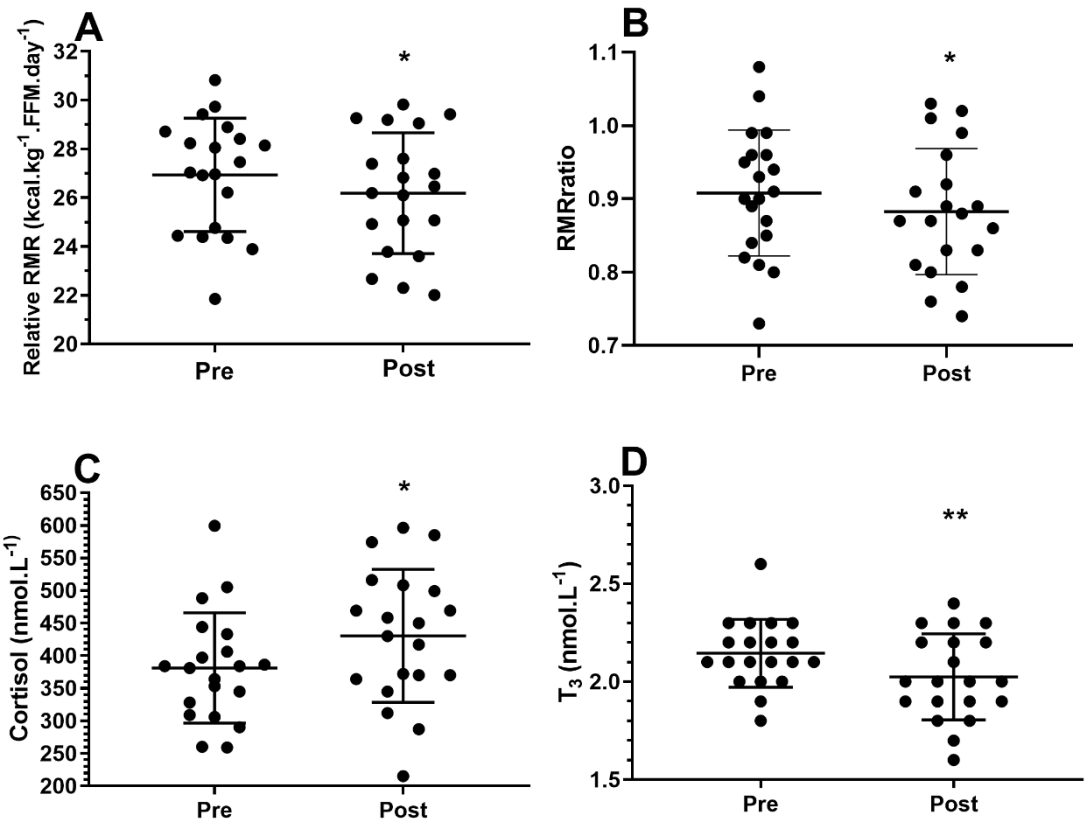

Figure 11. *Plots with individual values with mean and standard deviation in four RED-S markers from pre- and posttest of A) Relative RMR, B) RMR_{ratio}, C) Cortisol, and D) Triiodothyronine (T_3). *p < 0.05, **p < 0.01.*

When assessing training stress, no changes were observed in total testosterone:cortisol ratio (1.6%, p = 0.789) or testosterone:cortisol ratio (–3.2%, p = 0.556). A subanalysis of the five participants with the largest increase in testosterone:cortisol ratio revealed greater improvements in FTP (9.5% vs 2.5%, p = 0.037) as well as higher relative RMR (0.6% vs –4.2%, p = 0.39) than the group with the largest decrease.

6.2 Study II – paper II

Surrogate markers of RED-S in a cohort of Norwegian male Olympic-level athletes using a cross-sectional design were investigated. Assessment of RMR, body composition, bone health, and venous blood variables was performed (Figure 12). In total, 7 of 44 athletes (16%) were identified as energy deficit (RMR_{ratio} < 0.90). The energy deficit group (RMR_{ratio} 0.81 ± 0.07 vs 1.04 ± 0.09, p < 0.001, ES 2.6) showed lower testosterone (12.9 ± 5.3 vs 19.0 ± 5.3 nmol.L^{-1}, p = 0.020) than the normal RMR group. Furthermore, the majority of the energy deficit group also clustered with several additional RED-S markers, including subclinically low testosterone (<14.8 nmol.L^{-1}) and/or subclinically low fT_3 (<4.3 pmol.L^{-1}) levels, and/or low BMD (Z-score < –1.0) and/or subclinically high cortisol (>537 nmol.L^{-1}) and/or elevated LDL levels (>3.0 mmol.L^{-1}). Some athletes showed either low RMR (n = 2, 5%) or low BMD (n = 4, 9%) without the presence of any other RED-S markers (Table 5).

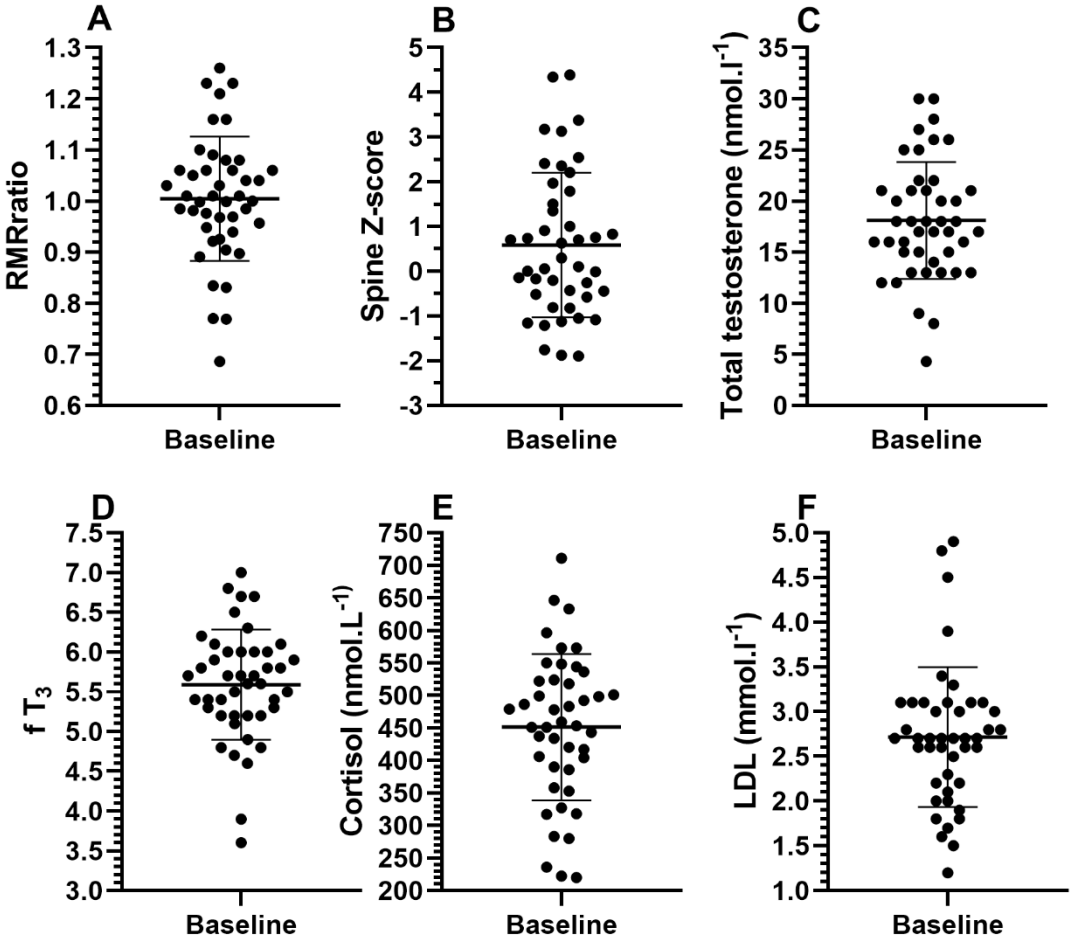

Figure 12. *Baseline values, with individual values with mean and standard deviation for all the associated RED-S parameters measured of A) RMR_{ratio}, B) lumbar spine Z-score, C) total testosterone, D) free triiodothyronine (fT_3), E) cortisol, and F) low-density lipoprotein (LDL).*

Table 5. A detailed description of athletes with one, two, and ≥three RED-S markers.

Athlete	**Low RMR Ratio** < 0.90	**Low BMD Z-score** < –1.0	**Subclinical low TES** <14.8 nmol·L^{-1}	**Subclinical low fT$_3$** <4.3 pmol·L^{-1}	**Subclinical high COR** >537 nmol·L^{-1}	**Elevated LDL** >3.0 nmol·L^{-1}
1 RED-S marker						
1	**YES (0.89)**	NO (+4.3)	NO (21.0)	NO (5.3)	NO (479)	NO (2.7)
2	**YES (0.68)**	NO (–0.4)	NO (17.0)	NO (5.2)	NO (483)	NO (2.6)
3	NO (1.06)	**YES (–1.2)**	NO (16.0)	NO (6.3)	NO (459)	NO (2.6)
4	NO (1.06)	**YES (–1.1)**	NO (22.0)	NO (6.7)	NO (283)	NO (2.7)
5	NO (0.98)	**YES (–1.1)**	NO (30.0)	NO (5.9)	NO (390)	NO (1.6)
6	NO (1.08)	**YES (–1.9)**	NO (18.0)	NO (6.0)	NO (406)	NO (2.2)
2 RED-S markers						
7	**YES (0.77)**	NO (+3.2)	**YES (13.0)**	NO (4.8)	NO (404)	NO (2.0)
8	**YES (0.89)**	NO (+0.3)	**YES (9.0)**	NO (6.5)	NO (386)	NO (2.6)
9	NO (1.03)	**YES (–1.2)**	NO (20.0)	NO (5.8)	NO (478)	**YES (3.9)**
10	NO (1.06)	**YES (–1.8)**	NO (27.0)	**YES (3.6)**	NO (518)	NO (1.9)
11	NO (0.96)	NO (+0.8)	**YES (13.0)**	NO (5.3)	NO (451)	**YES (3.1)**
12	NO (0.92)	NO (–0.8)	NO (25.0)	NO (5.1)	**YES (544)**	**YES (3.1)**
13	NO (1.04)	NO (+1.5)	**YES (13.0)**	NO (5.4)	NO (236)	**YES (4.9)**
≥3 RED-S markers						
14	**YES (0.77)**	NO (–0.1)	**YES (4.3)**	**YES (3.9)**	**YES (573)**	NO (2.8)
15	**YES (0.83)**	NO (+2.4)	**YES (13.0)**	NO (4.9)	**YES (711)**	NO (2.8)
16	**YES (0.83)**	NO (+3.4)	**YES (13.0)**	NO (5.4)	NO (222)	**YES (4.5)**
17	NO (1.05)	**YES (–1.9)**	**YES (12.0)**	NO (5.7)	NO (417)	**YES (3.1)**
18	NO (1.08)	NO (–0.5)	**YES (8.0)**	NO (5.4)	**YES (633)**	**YES (3.1)**

Abbreviations: BMD: bone mineral density, RMR: resting metabolic rate, TES: total testosterone, fT$_3$: free triiodothyronine, COR: cortisol, LDL: low-density lipoprotein, ( ) represent a**ctual** values of measurements

Low BMD was found in seven of the athletes (16%). Subclinically low testosterone and fT$_3$ levels were found in 11 (25%) and 2 (5%) athletes, respectively. Subclinically high cortisol levels were found in 10 (23%) whereas 15 athletes (34%) had elevated LDL cholesterol levels (Figure 12). When clustering RED-S criteria, 32 athletes (73%) had either 0 or 1, seven athletes (16%) had 2, four athletes (9%) had 3, and one athlete (2%) had 4 RED-S criteria.

6.3 Study III – paper III

RED-S was monitored among a small group of adolescent endurance athletes attending regional elite sport high schools in a three-year longitudinal setting. Testing was performed five times during the period, with six-month intervals. Protocols included assessment of RMR, body composition and BMD, EA, aerobic, and strength performance. At baseline, body composition (fat; 11.5% ± 3.3%), EA (~51 ± 16 kcal.kg^{-1} FFM.day^{-1}), and RMR_{ratio} (1.03 ± 0.07) were within the normal range (Figure 13). None of the athletes exhibited low RMR. One athlete displayed one-time LEA at T1, a second at T3, and a third at T4, and all climbed above the LEA threshold at the next measuring point. None of the athletes displayed unhealthy body fat storage (<5%), whereas three athletes (23%) were defined as grade-1 underweight. However, 5 of 13 athletes (38%) had poor bone health and were "at risk" of low bone mass (Z-score ≤ –1) at baseline (Figure 13), including all three athletes defined as underweight.

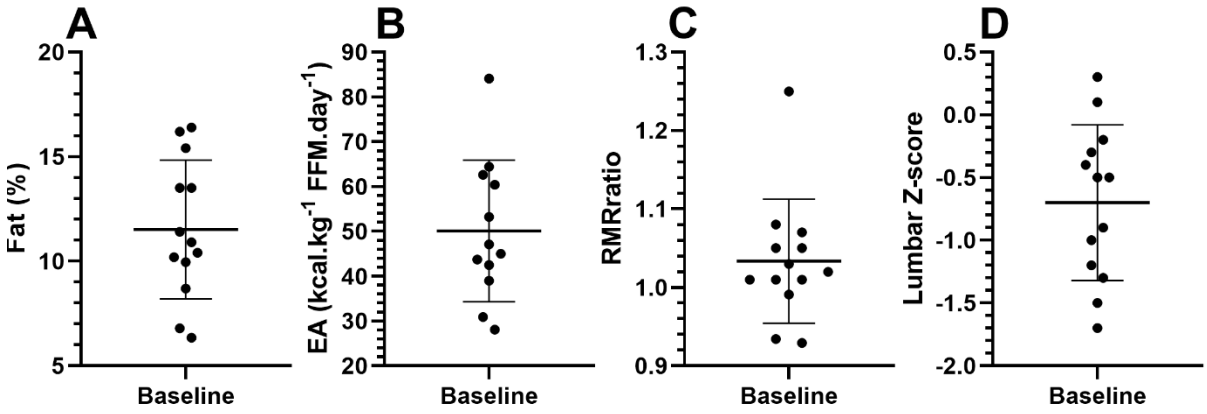

Figure 13. *Baseline values, with individual values with mean and standard deviation of A) fat percentage, B) energy availability (EA), C) RMR_{ratio}, and D) lumbar Z-score.*

Throughout the three-year period, an increase in FFM (2.2 kg/year $p < 0.001$) and height (1.6 cm/year $p < 0.001$) were observed, whereas fat percentage remained stable ($p = 0.517$). No changes were observed in EA ($p = 0.475$), whereas a small decline in RMR (0.02/year, $p = 0.016$) was observed, although all subjects remained within normal reference values. A positive development of aerobic performance (VO_{2peak}; ~5 mL.kg^{-1}.min^{-1}/year, $p < 0.001$) and strength (force; ~180 N/year, $p < 0.001$ and power; ~60 W/year, $p < 0.001$) were observed (Figure 14). No signs of DE behavior were observed for all athletes (mean scores 0.0, $p = 0.321$), the drive for leanness scores remained constant ($p = 0.782$), whereas the

exercise addiction scores decreased (p = 0.005). One athlete showed signs of exercise addiction at baseline, followed by a subsequent decrease below threshold.

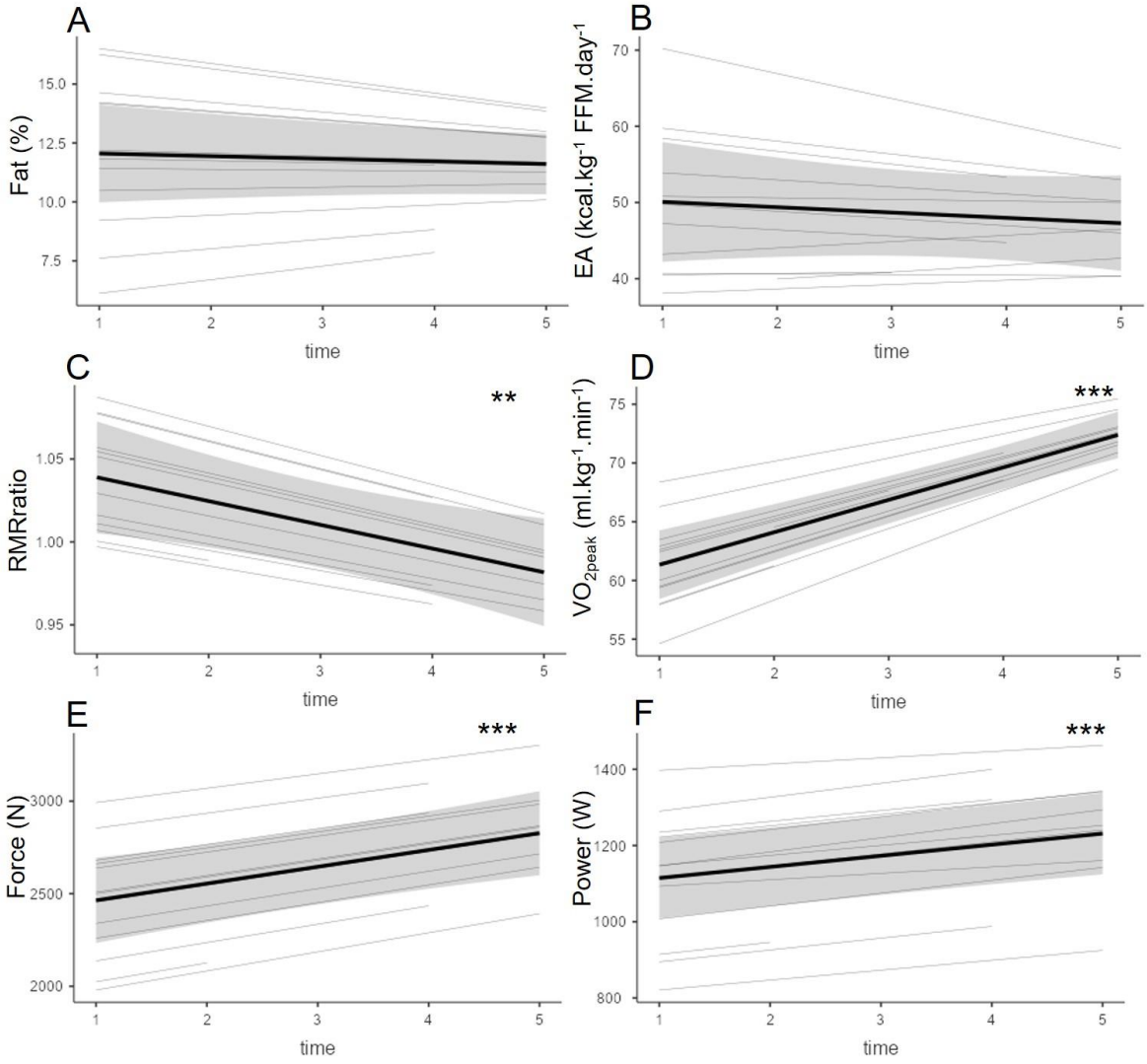

Figure 14. *Effect-plots from the linear mixed effect model of selected RED-S-related variables. The plots include individual linear trajectories (light gray lines), the slope mean (thick black line), and the 95% confidence interval around the slope mean (grayed area) for A) fat percentage, B) energy availability (EA), C) RMR_{ratio}, D) peak oxygen uptake (VO_{2peak}), E) force, and F) power. **p < 0.01, ***p < 0.001.*

When investigating individual bone health values for each athlete using the RCI, most of the athletes either lost or did not achieve the expected pubertal bone mineral accrual during the 3-year period.

7 Discussion

In the following, the main findings from **Studies I**, **II**, and **III** will be discussed in Section 7.1 according to the overall aim of the dissertation, whereas Section 7.2 will discuss the methodological perspectives used in all three studies.

7.1 Discussion of main findings

7.1.1 Reproductive function

Indisputable evidence shows that shorter periods of LEA cause suppression of the reproductive function in females (Loucks & Thuma, 2003). However, the effects of LEA on male reproductive function are still not fully understood (Areta et al., 2021), although exercising males at risk of LEA may show signs of secondary hypogonadism (Arce et al., 1993; De Souza et al., 1994; Tenforde et al., 2016). Arce et al. (1993) and De Souza et al. (1994) were the first to report findings of lower total and free testosterone levels in moderate to high mileage male runners compared with sedentary controls. Subclinical testosterone levels were associated with decreased sperm motility and morphological changes that may compromise fertility (Arce et al., 1993). These findings were confirmed by Safarinejad et al. (2009) in a large, randomized training study, demonstrating that strenuous long-term high-intensity exercise with significant weight loss resulted in a significant decrease in plasma sex hormone concentrations and impaired reproductive capacity. Thus, several conditions in male athletes can result in subclinically low testosterone levels, including secondary hypogonadism as a result of LEA (De Souza et al., 2019b; Nattiv et al., 2021) or overtraining (Safarinejad et al., 2009; Stellingwerff et al., 2021), or EHMC as a result of many years of exercise with no apparent health problems (Hackney, 2020). In our **Study I**, mean total testosterone increased, presumably as a positive response from the intensified endurance training protocol (Hackney, 2020). However, a decrease in the testosterone:cortisol ratio of 30% has been suggested as an indicator of poor recovery (Banfi et al., 1993; Vervoorn et al., 1991) and a catabolic state (Lee et al., 2017; Urhausen et al., 1995), whereas a value of 0.35×10^{-3} has been suggested as a threshold of overtraining (Vervoorn et al., 1991). In **Study I**, two athletes (10%) were identified with a testosterone:cortisol ratio decrease of >30%. When comparing the five athletes with the highest testosterone:cortisol ratio increase (indicating better recovery) with the five athletes with the greatest testosterone:cortisol ratio decrease (indicating poor recovery), a greater improvement in FTP was found in

the better recovery group compared with the poor recovery group. Furthermore, although no changes in EI between the groups were observed, an ~4% reduction in RMR was found in the poor recovery group indicating LEA, supported by higher cortisol levels, as well as lower performance increase compared with the better recovery group. In **Study II**, 11 athletes (25%) had subclinically low testosterone levels (<14.8 nmol.L^{-1}), and one had clinically low levels (<8 nmol.L^{-1}). Transient clinically low testosterone values have been observed among soldiers undergoing prolonged starvation in a multistressor environment (Friedl et al., 2000), in a case study of a male combat-sport athlete with extreme levels of LEA (3 kcal.kg^{-1} FFM.day^{-1}) (Langan-Evans et al., 2021), and in participants in ultra-endurance events (Geesmann et al., 2017; Hooper et al., 2018). Interestingly, several reportings of reduced testosterone levels (Heikura et al., 2018b; Hooper et al., 2018; Kupchak et al., 2014; McColl et al., 1989) fall within the subclinically low range, newly proposed as being a "gray zone" ranging from ~8 to 12 nmol.L^{-1} (Nattiv et al., 2021), thus questioning whether it is due to secondary hypogonadism (LEA induced) or EHMC. However, in **Study II**, lowered testosterone levels, which mostly fell within the subclinically low range, were present among almost all athletes with low RMR, strengthening the indication of LEA among these athletes. However, it may be argued that the other athletes only displaying subclinically low testosterone values could arise from EHMC because no other RED-S-related parameters were found (Hackney, 2020). The EHMC, however, does not seem to address the metabolic adaptations that persistent LEA can inflict on the body, such as stabilizing body weight and body composition found in females, potentially also affecting males (Redman & Loucks, 2005). In a new study by Logue et al. (2021), the risk of EHMC was found among 23% of male athletes and associated with lower-than-normal sex drive and fewer morning erections per week compared with athletes not at risk. Thus, the authors suggest that these symptoms may be related to RED-S (Logue et al., 2021), but confounding factors such as overtraining (Stellingwerff et al., 2021) must be considered. Nonetheless, a possible way of assessing if lowered testosterone levels are due to secondary hypogonadism or EHMC is to interpret testosterone values in relation to FSH/LH (Sterling et al., 2015). Unfortunately, this was not possible in **Study II**. Interestingly, when examining effects of short-term LEA (five days or less with an EA of 15 kcal.kg^{-1} FFM.day^{-1}) on testosterone levels in controlled trials, less agreement exists, including significant reductions (Kojima et al., 2020) and no reductions (Koehler et al., 2016). What is evident is that testosterone

reductions are observed in nonexperimental field studies often investigating more "extreme" situations. These includes prolonged high-intensity training (Heikura et al., 2018b), long-duration exercise (Berg et al., 2008), shorter duration extreme events (Geesmann et al., 2017; Hooper et al., 2018; Kraemer et al., 2008; Kupchak et al., 2014), or in military studies with severe energy deficit (Friedl et al., 2000; Kyrolainen et al., 2008), highlighting the associations of LEA with the reproductive function in males. Thus, when investigating RED-S outside the laboratory, measuring testosterone levels seems important, specifically to screen for the risk of LEA, the development of secondary hypogonadism and to distinguish this from EHMC. However, more laboratory research is needed in trying to establish a dose–response relationship between different length of LEA, simulating athletes' exposure in the field, and the effects on testosterone production, as well as the potential different origins of secondary hypogonadism and EHMC.

7.1.2 Bone health

The development and accumulation of BMD during adolescence and early adulthood is multifactorial and influenced by several parameters, such as endocrine aspects, energy and nutrient intake, mechanical loading, and genetics (De Souza et al., 2014a; Hind & Hamer, 2021; Kohrt et al., 2004). LEA is strongly correlated with impaired bone health in female athletes (Barrack et al., 2008; Barrack et al., 2010b; Ihle & Loucks, 2004; Melin et al., 2015), and is a well-established phenomenon within the female athlete TRIAD (De Souza et al., 2014a) and RED-S (Mountjoy et al., 2018b). In males, observational studies have reported impaired bone health in athletes with negative energy balance (Zanker & Swaine, 2000), LEA (Taguchi et al., 2020; Viner et al., 2015), and in athletes with markers of LEA (Barrack et al., 2017; Heikura et al., 2018b; Kraus et al., 2019). However, there is still uncertainty regarding the severity of EA that can inflict negative effects on bone turnover markers in adolescent and adult males, and there are in general few studies available regarding bone turnover in males (Papageorgiou et al., 2017; Taguchi et al., 2020). Only one study seems to have investigated the cause–effect relationship of LEA and bone markers in males (Papageorgiou et al., 2017). In a randomized controlled trial, Papageorgiou et al. (2017) found no negative changes in markers related to impaired bone health and speculated whether the five-day induced LEA restriction was insufficient in males to affect bone turnover markers negatively as observed in females in the same study

(Papageorgiou et al., 2017) and earlier (Ihle & Loucks, 2004). In an observational study, Taguchi et al. (2020) investigating Japanese male long-distance runners reported a mean EA of 18.9 ± 6.8 kcal.kg^{-1} FFM.day^{-1}, where researchers linked LEA to increased bone resorption. In contrast, Wilson et al. (2018) investigated male flat jockeys, a sport where low body weight is beneficial, and reported that low BMD or RMR did not differ between novice and senior jockeys, and did not progressively decrease with years of racing. Hence, the researchers suggested that low BMD in jockeys is not due to LEA per se but rather the lack of an osteogenic stimulus associated with riding (Wilson et al., 2018). It could be argued that this may be one reason why we identified several leanness sport athletes in **Studies II** and **III** with low BMD as the only marker of RED-S. However, higher risks of low BMD and bone stress injuries using a modified female athlete Triad cumulative risk assessment score were found among adult male runners, highlighting that low body weight, nutritional deficits, and believing that being thinner improves performance, is common among these types of athletes (Kraus et al., 2019). Among adolescent male runners, a 21% prevalence of low bone mass (Z-score < –1.0) has been identified (Tenforde et al., 2015). Researchers further found that BMI ≤ 17.5 kg/m^2 and believing that being thinner improves performance were significantly linked to low bone mass in these athletes (Tenforde et al., 2015). These results are in agreement with the results in **Study III**, where we identified five adolescent athletes (38%) being "at risk" of low bone mass at baseline, where three of these were also grade-1 underweight (Júlíusson et al., 2009). This is concerning because poor bone health was identified during a peak window of bone mineral accrual (Kohrt et al., 2004) (mean age of athletes in **Study III** at baseline was 16.3 ± 0.4 years). Even more worrying is that only one of these five athletes increased his BMD Z-score to above –1, for two athletes the BMD Z-score remained stable, whereas two athletes were lost to follow-up. Hence, the two athletes being "at risk" of low bone mass at T5 will initiate their senior athletic career with increased risk of bone stress injury, as well as potential early onset of osteopenia and osteoporosis. Thus, it is important that health care personnel, teachers, and the management at elite sport high schools as well as athletes and coaches are aware of the associations between poor bone health and low body weight, nutritional deficits, and believing that being thinner improves performance (Kraus et al., 2019; Lodge et al., 2021; Tenforde et al., 2015). However, more research is warranted in trying to confirm previous findings that LEA may not

affect bone health in males in the same manner as in females because the current evidence is weak (Nattiv et al., 2021; Papageorgiou et al., 2017).

On the other hand, impaired bone health has been linked to specific sports disciplines in adults. Observational studies in males have identified an increased risk of bone stress injuries among runners (Barrack et al., 2017; Fredericson et al., 2007; Kraus et al., 2019; Tenforde et al., 2015; Tenforde et al., 2018), low BMD among cyclists (Barry & Kohrt, 2008; Guillaume et al., 2012; Nichols et al., 2003; Nichols & Rauh, 2011; Olmedillas et al., 2011, 2012; Penteado et al., 2010; Smathers et al., 2009; Viner et al., 2015), runners (Hetland et al., 1993; Hind et al., 2006), both cyclists and runners (Klomsten Andersen et al., 2018; Rector et al., 2008; Stewart & Hannan, 2000), swimmers (Gomez-Bruton et al., 2016; Taaffe & Marcus, 1999), and jockeys (Dolan et al., 2012; Jackson et al., 2017; Wilson et al., 2015; Wilson et al., 2018). In all three of our studies, we identified a prevalence of low BMD, ranging from 15% in **Study I** among well-trained adult cyclists, 16% among adult Olympic-level athletes (rowers, triathletes, cyclists, and kickboxers) in **Study II**, to 38% being "at risk" of low bone mass among adolescent cross-country skiers and biathletes in **Study III**. These findings are similar to earlier findings among athletes competing in low-impact and nonweight-bearing sports (Barry & Kohrt, 2008; Guillaume et al., 2012; Klomsten Andersen et al., 2018; Nichols et al., 2003; Nichols & Rauh, 2011; Olmedillas et al., 2011, 2012; Penteado et al., 2010; Rector et al., 2008; Smathers et al., 2009; Stewart & Hannan, 2000; Viner et al., 2015). Thus, it cannot be ruled out that some of the cases of low BMD in **Studies I** and **II** may arise due to other factors than LEA, such as genetics and lack of osteogenic stimulus. Unfortunately, this was not possible to assess in these samples. However, **Study III** appears to be the first study investigating BMD in male cross-country skiers and biathletes, and research related to females seems limited (Gulsvik et al., 2018; Heinonen et al., 1993; Pettersson et al., 2000). Therefore, more studies are needed to investigate the long-term effect of cross-country skiing and biathlon on BMD. Furthermore, among adolescent athletes, research has identified that participating in osteogenic sports (football) yielded higher bone acquisition than with athletes participating in nonosteogenic sport (swimming and running) during a one-year longitudinal study (Vlachopoulos et al., 2017), highlighting the vulnerability of developing poor bone health in athletes participating in nonosteogenic sports. Despite **Study III** having a low sample size, these findings are still concerning. Athletes and coaches in non- or low-impact

sport such as cross-country skiing and biathlon need to be aware that performing high-load exercise could dampen the effects of bone loss in these sport disciplines (Vlachopoulos et al., 2018a, 2018b). Thus, our findings highlight the importance of elite endurance sport high schools focusing on the risk of poor bone health among these athletes and may consider implementing specific bone-loading exercises targeting sites such as spine and femur to decrease the risk of bone stress injury and poor bone health in their athletes performing low-impact repetitive and nonweight-bearing sports.

7.1.3 Endocrine changes

The hormone T_3 is essential for growth and metabolism, and is closely related to LEA, including suppressed RMR (Loucks & Callister, 1993; Trexler et al., 2014). Low total and free T_3 values were first observed in athletes with MD and the studies demonstrated that it was EA, and not the stress of exercise, that was the determining factor of hormone concentrations (Loucks & Callister, 1993). When athletes were exposed to LEA of ~11 kcal.kg^{-1} LBM.day^{-1}, reductions in T_3 were found (Loucks & Callister, 1993), and another study identified that a threshold of 25 kcal.kg^{-1} LBM.day^{-1} suppressed the thyroid hormone productions of total and free T_3 (Loucks & Heath, 1994b). Furthermore, RMR_{ratio} has been found to predict and correlate with T_3 in exercising females, making it a useful marker of LEA (Strock et al., 2020b). In **Study I**, a reduction in T_3 was observed among our cyclists in combination with reduced RMR and increased cortisol levels during the intervention period. Such findings underline the indication of athletes not increasing their EI during an intensified training intervention, resulting in reduced EA. However, when investigating the subgroup of athletes with poor recovery compared with athletes with better recovery (see Section 7.1.1), both groups reduced their T_3 levels equally, despite a significant decrease in RMR only in the poor recovery group. This apparent difference compared with the result on a group level between pre- and posttest, may be due to a much smaller sample size in the subanalysis. In **Study II**, two athletes were identified with subclinically low fT_3. One athlete (a professional cyclist), categorized in the energy deficit group (low RMR_{ratio}), displayed very low RMR (RMR_{ratio} 0.77), clinically low testosterone levels (4.3 nmol.L^{-1}), and subclinically high cortisol (573 nmol.L^{-1}), indicating long-term LEA. The second athlete (cyclist) with subclinically low fT_3 did not display low RMR but had low BMD. This may be due to individual differences and that some athletes are more sensitive or robust to LEA (Koehler et al., 2016;

Papageorgiou et al., 2017) or coupled with cycling being a nonosteogenic sport (Olmedillas et al., 2012). However, the effects of short-term LEA on T_3 remain unclear among males and research is lacking in establishing a cause–effect relationship (Areta et al., 2021). Only two experimental studies have investigated the effects of LEA on the thyroid function in males (Koehler et al., 2016; Papageorgiou et al., 2017). Both studies investigated how LEA (15 kcal.kg^{-1} FFM.day^{-1}) for four or five days through diet restriction with or without exercise would affect hormone production and found no impact on T_3 (Koehler et al., 2016; Papageorgiou et al., 2017). However, these studies are to some extent different from the benchmark study performed in females by Loucks and Thuma (2003). The latter investigated sedentary females compared with recreationally active people in the male studies, different EA thresholds (10/20/30/45 kcal.kg^{-1}LBM.day^{-1} compared with 15/40/45 kcal.kg^{-1} FFM.day^{-1}), and a much longer period between each condition (two months vs 4–10/28 days). This highlights that athletes engaged in regular exercise may respond differently to LEA compared with a sedentary or recreationally active population, perhaps due to individual differences such as genetics, age, training volumes, training status, as well as the magnitude and time frame of LEA. These differences may also explain some of the findings in **Studies I** and **II**. In field studies in males, Friedl et al. (2000) have demonstrated that severe energy restrictions lead to plummeting T_3 values close to and beyond clinically low levels, with immediate normal-level recovery when refeed, yet returning to low levels when severe energy restriction are reinstated. Furthermore, low T_3 in combination with reduced EI (Woods et al., 2018), or low testosterone levels (Heikura et al., 2018b) have been reported in observational studies among well-trained and elite male athletes. This apparent discrepancy between short-term well-controlled laboratory-based settings and real-world observational studies of short- and long-term LEA or severe energy restriction is challenging and warrants further investigation.

Low IGF-1 levels are linked to starvation and chronic undernutrition (Elliott-Sale et al., 2018). Decreased IGF-1 levels have been observed among females exposed to LEA ~20 kcal.kg^{-1} FFM.day^{-1} or less (Loucks & Heath, 1994a; Loucks & Thuma, 2003; Loucks et al., 1998; Papageorgiou et al., 2017). IGF-1 is considered a reliable marker of short-term LEA among females (Heikura et al., 2021), although that may not be the case in males. In males, observational studies have found reduced IGF-1 concentrations in soldiers with extreme starvation (Friedl et

al., 2000), in wrestlers with reduced EI (Roemmich & Sinning, 1997), and in male cyclists performing ultra-endurance events (Geesmann et al., 2017). However, controlled laboratory studies are few, and not in agreement (Koehler et al., 2016; Murphy & Koehler, 2020). Research performed by Koehler et al. (2016) showed no reduction in IGF-1 when males were exposed to LEA < 15 $kcal.kg^{-1}$ $FFM.day^{-1}$ for four days, whereas Murphy and Koehler (2020) found an 18%–27% reduction in IGF-1 in males also exposed to LEA of <15 $kcal.kg^{-1}$ $FFM.day^{-1}$ for three days. In our **Study I**, no changes were observed in IGF-1, however, it is interesting to observe that mean IGF-1 levels (18.1 ± 4.3 $nmol.L^{-1}$) were within the lowest quartile (<28.5 $nmol.L^{-1}$) of the reference range and remained stable during the posttest. Thus, in combination with the mean RMR_{ratio} being 0.91 ± 0.08 at pretest and falling to 0.88 ± 0.09 at posttest, this may indicate the presence of persistent LEA among this group of athletes. More research is, however, needed to establish how IGF-1 may be used as a marker of short- or long-term LEA in males (Heikura et al., 2021).

Increases in cortisol during severe caloric restriction and fasting have been observed, and hypercortisolemia might directly affect the reproductive function or serve as a biomarker of stress and reproductive dysfunction in athletes (Elliott-Sale et al., 2018). In military soldier studies, increased cortisol levels have been seen during exercise in a stressful environment, in combination with starvation, and have been associated with reduced body fat storages (Friedl et al., 2000; Kyrolainen et al., 2008). In athletes, Torstveit et al. (2018) found that a larger single-hour energy deficit was associated with higher cortisol and additionally that higher EDSs were associated with a more negative energy balance and higher cortisol levels (Torstveit et al., 2019). In contrast, cortisol did not differ between a group of nine male long-distance runners with LEA compared with eight nonathletes with optimal EA (Hooper et al., 2017). In our **Study I**, cortisol increased by 12.9% from pre- to posttest but remained within normal laboratory-specific reference values. This increase may be used as a proxy indicator of reduced EA, especially because we also observed lowered T_3 levels and RMR in this group of athletes. It could be argued that the increase in cortisol may be due to the stress induced by the intervention (Schaal et al., 2011). However, the blood samples were taken in a rested and fasted state five days after the intervention, and not immediately after exercise, limiting the impact of stress and exercise (Rubin, 2020). Thus, the increase may rather be a sign of the need to catabolize alternate

energy sources and preserve glycogen because no athlete increased their EI, which was also shown in the soldier studies (Friedl et al., 2000; Kyrolainen et al., 2008). The testosterone:cortisol ratio, discussed in Section 7.1.1, further serves as an indication of reduced EA in this group of athletes. In **Study II**, 23% of the athletes were identified with subclinically high cortisol levels. Although the use of subclinical values ("gray zone") to investigate LEA recently has been debated (Nattiv et al., 2021), the use may function as a secondary marker of RED-S. In fact, higher cortisol levels, ranging from 573 to 711 nmol.L^{-1} were present among three (one clinical and two subclinical) of five athletes with three or more markers of RED-S in **Study II**. These markers include low RMR in two, subclinically low testosterone levels in all three, subclinically low fT_3 in one, and elevated LDL in one of the athletes (Table 5), indicating long-term LEA. Thus, cortisol may not be suited as a single marker of LEA, and should in general be interpreted with care, due to the variety of response reasons (St-Pierre & Richard, 2013). More in-depth research is therefore needed to understand better the effects of LEA on cortisol especially in the male population (Areta et al., 2021; Elliott-Sale et al., 2018).

Insulin is strongly related to energy storage and is typically downregulated during LEA conditions (Elliott-Sale et al., 2018), improving the availability of fuel substrates (Martin et al., 2008). In females, reduced insulin levels have been observed in athletes with MD (Laughlin & Yen, 1996; Rickenlund et al., 2004) compared with controls. In males, both observational studies (Langan-Evans et al., 2021; Maestu et al., 2010) and a well-controlled trial (Koehler et al., 2016) have shown a decrease in insulin in response to LEA or decreased EI in exercising males as well as in soldiers (Friedl et al., 2000; Kyrolainen et al., 2008). In a controlled setting, Koehler et al. (2016) found reduced insulin levels (34%–38%) when exercising males were exposed to LEA with or without exercise (15 kcal.kg^{-1} FFM.day^{-1}). However, another controlled trial found no reductions in insulin levels when males were exposed to similar levels of LEA (Papageorgiou et al., 2017). In an observational study, Maestu et al. (2010) found that male bodybuilders exposed to 11 weeks of reduced EI also decreased insulin and body fat storage. Similar findings were observed in a case study of a male combat-sport athlete (Langan-Evans et al., 2021). In soldiers experiencing prolonged low EI, insulin levels dropped 50%–70% (Friedl et al., 2000; Kyrolainen et al., 2008). In **Study I**, no significant decrease was observed in insulin levels during the intensified training intervention, without an apparent increase in EI. One

explanation could be that the athletes' energy deficit was not large enough to induce significant changes, or that the athletes were able to refeed properly before posttest, as earlier observed in other studies (Kyrolainen et al., 2008; Langan-Evans et al., 2021). However, more research is needed to investigate discrepancies of LEA and insulin response in male athletes because most research has been done in soldiers and exercising males.

7.1.4 Energy metabolism

An RMR_{ratio} of <0.90 is often used as a definition of low RMR and has been recognized as a surrogate marker of LEA in exercising females (De Souza et al., 2008). Research has further identified that RMR_{ratio} accurately reflects T_3 status in females, making it a useful marker of prolonged energy deficiency (Strock et al., 2020a; Strock et al., 2020b). However, using RMR_{ratio} in males as a single indicator of LEA is problematic, and it is recommended to be combined with other biomarkers such as subclinically low testosterone levels (Staal et al., 2018). In **Study I**, we observed an ~3.3% reduction of RMR_{ratio} and relative RMR during the four-week period of intensified interval training. These findings are similar to studies investigating athletes during intensified training periods, such as in elite rowers (Woods et al., 2017) and trained cyclists (Woods et al., 2018). Common to these studies is the apparent lack of increased EI during the training period, leading to reduced EA with a subsequent reduction in RMR. As outlined in Section 3.4.4, FFM is the largest determinant for RMR, and changes in FFM are likely to affect overall energy expenditure (Donahoo et al., 2004). However, in **Study I**, no significant changes in FFM were observed, despite several hormonal indications of a more catabolic state linked to RED-S. The lowered RMR might therefore be a protective mechanism to prevent weight reduction and changes in body composition as shown in females (Redman & Loucks, 2005). It is, however, interesting to observe the overall mean RMR_{ratio} at baseline in **Study I** being close to the threshold of low RMR (0.91 ± 0.08), with eight of the athletes (40%) having low RMR at baseline, whereas three of these had subclinically low testosterone. After the training period, the mean RMR_{ratio} decreased to 0.88 ± 0.09, with a subsequent higher frequency of athletes (13 athletes, 65%) having low RMR, with several eliciting very low levels (RMR_{ratio} 0.73 to 0.82). This highlights the potential impact of improper adjustment of EI in relation to total energy requirements of exercise and daily living on RMR, something that is crucial for recovery (Misra & Klibanski, 2014). Low RMR was also observed in **Study II**,

where seven athletes (16%) had low RMR_{ratio}, and five of these ranged between 0.68 and 0.83. Interestingly, most of the athletes with low RMR in **Study II** also had subclinically low testosterone, strengthening the link to LEA (Section 7.1.1). In **Study III**, none of the adolescent athletes had low RMR at baseline (1.03 ± 0.07). One athlete had low RMR at T2 but was unfortunately lost to follow-up before T3, due to an injury. For the remaining athletes, only a small decrease in RMR_{ratio} (0.02/year, $p < 0.001$) was seen during the three-year period, and none of the athletes were defined with low RMR at any other time-point. However, monitoring and assessing RMR among adolescents can be problematic due to several factors potentially biasing the results. First, the equations used to calculate predicted RMR are derived from adult populations (Schofield et al., 2019). Second, the current cut-off value established for low RMR ($RMR_{ratio} < 0.90$), was originally established in adult women (De Souza et al., 2008). To the author's knowledge, only few studies have investigated measured and predicted RMR among adolescent athletes, all performed among male soccer players (n = 30–45) (Cherian et al., 2018b; De Lorenzo et al., 1999; Kim et al., 2015; Oliveira et al., 2021). In the studies by Kim et al. (2015) and Oliveira et al. (2021), the reported mean RMR_{ratio} was ~0.99 ± 0.11. None was however controlled for EA status or energy deficiency before inclusion, limiting the usefulness of the results in regard to RED-S assessment. Furthermore, RMR_{ratio} seems to fluctuate between a minimum of 0.84 to a maximum of 1.33 among adolescents in these studies (Kim et al., 2015; Oliveira et al., 2021), similar to the findings in our **Study III** (RMR_{ratio} ranging from 0.86 to 1.25). Potentially, the threshold limits among adolescents are higher than with adults due to the energetic requirements of growth, development, and puberty (Heikura et al., 2021). However, a significant gap in the scientific literature concerning RED-S thresholds for adolescent athletes exists (Heikura et al., 2021), and characterizing adolescent athletes with LEA based on measuring RMR and/or other RED-S markers should therefore be interpreted with caution. Furthermore, it is questionable whether the low RMR cut-off point (< 0.90) applies to adult male athletes, who generally have a higher body mass and FFM than females (Malina & Geithner, 2011). Despite this, RMR is still a widely used tool when investigating LEA in adult males (Egger & Flueck, 2020; Jurov et al., 2021; Lane et al., 2021; Langan-Evans et al., 2021; Lee et al., 2020; Staal et al., 2018; Torstveit et al., 2018; Torstveit et al., 2019; Woods et al., 2017; Woods et al., 2018) and is negatively associated with LEA among males (De Souza et al., 2019b; Mountjoy et al., 2018b; Nattiv et al., 2021). To complicate matters even more,

several prediction equations for RMR exist (Schofield et al., 2019), and it is important to understand the relation between the predictive equations and low RMR threshold usage because this can vastly influence the results as demonstrated by Strock et al. (2020b). Thus, it may seem a bit arbitrary that we used the Cunningham (1980) equation in all our studies. This is, however, based on research by Thompson and Manore (1996), indicating that the Cunningham (1980) equation yields a more precise estimate of RMR among highly active individuals, particularly because of higher LBM and FFM. Furthermore, recent studies have found the Cunningham (1980) equation to be a better choice in adult males (Staal et al., 2018; ten Haaf & Weijs, 2014) and adolescents (Cherian et al., 2018b; De Lorenzo et al., 1999; Kim et al., 2015; Oliveira et al., 2021). Using the Cunningham equation also makes our results comparable to the current research literature (Lane et al., 2021; Langan-Evans et al., 2021; Staal et al., 2018; Torstveit et al., 2018; Torstveit et al., 2019; Wilson et al., 2015; Wilson et al., 2018), compared with studies using other standard equations (Jurov et al., 2021; Lee et al., 2020). To understand better how RMR in males is affected by LEA, more research is needed, especially in understanding and developing male-specific thresholds, potentially making this a reliable biomarker of LEA in males as well.

7.1.5 Cardiovascular function

Cardiovascular consequences in both male and female athletes related to LEA are understudied. In athletes with MD, unfavorable lipid profiles have been reported, including elevated TC and LDL levels (Ackerman et al., 2019; Melin et al., 2015; Rickenlund et al., 2005). In males, increased TC and LDL levels with LEA or severe reductions in EI have been found among soldiers (Friedl et al., 2000) and in a combat-sport athlete (Langan-Evans et al., 2021). However, in judo athletes, seven-day dietary restriction did not affect TC, LDL, or HDL levels (Filaire et al., 2001). In **Study II**, we identified one-third of the total sample having elevated LDL levels. Of notice, elevated LDL levels were present among the majority of athletes with low testosterone levels. However, we were not able to investigate the athletes' family history, genetics, or diet to explore potential dietary causes of elevated blood lipids, thus it is difficult to conclude with certainty the associations between LEA and LDL in our sample. More research on risk factors for cardiovascular health among male athletes is needed to improve the understanding of the complexity and possible link to RED-S.

7.1.6 Psychological factors

LEA can be present with or without DE behaviors and is more prevalent in sports where leanness is associated with performance than in nonleanness sports (Gibbs et al., 2013). Hence, those more prone to developing DE behaviors seem to be athletes within sports where maintaining a specific appearance or having an "ideal" body type is important, or in athletes exposed to pressure to increase performance (Sundgot-Borgen & Torstveit, 2010). In **Study III**, none of the athletes showed any signs of DE behavior during the three-year period, indicated by low BEDA-Q scores at baseline (0 at baseline for all athletes), which remained stable during the period. However, the BEDA-Q was developed for female athletes, and it is therefore unclear whether results can be generalized to male athletes (Martinsen et al., 2014b), which may bias our results. It could be argued that different male-specific questionnaires should have been used in all three studies, such as the EDE-Q or the SEAQ-I. However, EDE-Q is only validated in nonactive males, and the SEAQ-I was not available when we performed our studies. Furthermore, it has been found that questionnaires trying to assess DE may not always work in the adolescent population, as shown by two studies (Martinsen et al., 2010; Martinsen & Sundgot-Borgen, 2013). In their first study, Martinsen et al. (2010) found a higher prevalence of symptoms of DE among male controls (31%) than in male athletes (13%) when using questionnaires, whereas their second study using clinical interviews found the opposite (Martinsen & Sundgot-Borgen, 2013). Regarding psychological parameters, we also assessed drive for leanness in **Study III** and identified baseline DLS scores to be 3.8 ± 1.1, ranging from 1.8 to 5.3 (a maximum score of 6), remaining stable throughout the period ($p = 0.782$). Baseline values were lower than what has been observed among female weight lifters (mean DLS 4.6 ± 0.8) (Hartmann et al., 2018) and female students 4.0 ± 0.8 (Smolak & Murnen, 2008), but identical to what has been reported in male students (mean DLS 4.0 ± 0.8) (Smolak & Murnen, 2008). Hence, a lean body type may be idealized by some of the adolescent athletes in **Study III**. This may show that our male adolescent endurance athletes relate more to the DLS attributes because this refers to an interest in having relatively low body fat and toned muscles (Smolak & Murnen, 2008) compared with the BEDA-Q attributes, possibly due to the latter having a greater focus on excessive concern with dieting, preoccupation with weight, and fear of weight gain (Garner, 1991; Martinsen et al., 2014b). Our findings are further in agreement with other research, indicating stable DE scores

in adolescent athletes (Krentz & Warschburger, 2013) and nonathletic adolescents (Hautala et al., 2008) during both three-year and one-year periods, respectively. However, the DLS is yet to validated among athletes, but may be relevant to include as a screening tool for LEA (Nattiv et al., 2021).

Exercise addiction is often associated with ED and perfectionism among women (Bratland-Sanda et al., 2011; Muller et al., 2015), but only one study has tried to investigate exercise addiction and association with biomarkers of RED-S among male athletes (Torstveit et al., 2019). This study identified associations between higher exercise addiction scores, ED symptoms, and biomarkers of RED-S, including a more pronounced negative energy balance and higher cortisol levels among well-trained male endurance athletes (Torstveit et al., 2019). Further, the study also identified that higher subscale exercise addiction scores were associated with lower blood glucose, lower testosterone:cortisol ratio, and higher cortisol:insulin ratio (Torstveit et al., 2019). In **Study III**, only one athlete displayed exercise addiction behavior at baseline, with subsequent decline at T2. Further decrease was seen among all athletes during the three-year period, indicating no apparent exercise addiction in this small group of adolescent athletes. These findings support previous research on the prevalence of exercise addiction among adolescents ranging from 4% to 8% (Hautala et al., 2008; Lichtenstein et al., 2018; Villella et al., 2011), however, none of these studies has investigated possible associations with RED-S. Unfortunately, in **Study III**, we were not able to investigate blood biomarkers in relation to exercise dependency as done in the Torstveit et al. (2019) study. Thus, more research is needed in investigating exercise dependency among both adolescent and adult male athletes.

7.1.7 Performance

The effects of LEA on athletic performance are understudied among both males and females. However, it is hypothesized that persistent LEA may affect performance (Areta et al., 2014; Drew et al., 2018; Drew et al., 2017; Tarnopolsky et al., 2001). Despite this, only a few studies have investigated the relationship of EA and sports performance in adult female endurance athletes (Harber et al., 1998; Tornberg et al., 2017), female swimmers (Vanheest et al., 2014), male rowers (Woods et al., 2017), and male cyclists (Keay et al., 2018; Woods et al., 2018). In **Study I** we assessed VO_{2peak} and FTP among the well-trained cyclists, no performance testing was available in **Study II**, whereas we assessed VO_{2peak} and

muscular strength among adolescent athletes in **Study III**. VO_{2peak} is considered one of the most important factors for determining success in aerobic endurance sports (Åstrand et al., 2003). In **Study I**, the athletes undertook a four-week intensified endurance training period, designed to improve performance with similar high-intensity interval training sessions as the study by Seiler et al. (2013) and Sylta et al. (2016). As expected, VO_{2peak} increased (~3%) in **Study I**, similar to what has been reported in other studies showing a 3%–6% increase (Seiler et al., 2013; Sylta et al., 2016). However, because our study was shorter in duration (four vs seven and 12 weeks) with similar participants' characteristics, we did not expect to see an identical increase in aerobic performance compared with these studies (Seiler et al., 2013; Sylta et al., 2016). Other studies have observed similar increases in VO_{2peak} during intensified training interventions, ranging from 5% to 10% in soccer players (Helgerud, 1994) to 5%–8% in moderately trained males (Helgerud et al., 2007). However, improvements in VO_{2peak} seem to be dependent on fitness level, thus, the higher the performance level, the smaller the improvement in VO_{2peak} (Helgerud et al., 2007). The FTP test serves as a valid and reliable test that closely replicates the demands of competition (Jeukendrup et al., 1996). In **Study I**, FTP increased by ~7%, which is equivalent to similar studies ranging from 5% to 10% (Seiler et al., 2013; Sylta et al., 2016). Thus, the intensified training period was successful in the matter of performance increase, despite the apparent lack of matching EI to energy requirements. In contrast, a study investigating rowers performing a four-week intensified training period without an apparent increase in EI found significantly worsened rowing performance (Woods et al., 2017). Furthermore, this performance decrease was associated with reduced RMR (Woods et al., 2017), similar to the findings in our **Study I**. When analyzing athletes with poor recovery vs those with better recovery in **Study I** (see Section 7.1.1), we identified significant differences in performance improvement in the athletes with a poor recovery in combination with several other RED-S markers. Although **Study I** was not designed to investigate the effects of LEA on performance, but rather to investigate how an endurance training period would affect EI and RED-S markers, impairments on markers related to RED-S were observed. These included reduced RMR and T_3 and increased cortisol, highlighting the potential negative effects on RED-S-related markers of a short, yet successful intensive training program, without an apparent increase in EI. These findings indicate that well-trained male athletes may underestimate the importance of increasing their EI when undertaking an intensified endurance

training protocol, and the importance of proper periodization of EI (Stellingwerff et al., 2019). Thus, athletes, coaches, and practitioners should be aware that male athletes are also prone to develop indications of RED-S even during a short intensified four-week endurance training period. In **Study III**, both absolute and relative endurance capacity and muscle strength improved significantly during the three-year period among the adolescent athletes. Most importantly, VO_{2peak} improved by ~3 $mL \cdot kg^{-1} \cdot min^{-1}$, equivalent to an increase of ~10% per year, similar to Eastwood et al. (2009). Longitudinal studies among adolescent athletes are scarce (Eastwood et al., 2009; Krahenbuhl et al., 1989; Landgraff et al., 2021). Eastwood et al. (2009) found an increase in relative VO_{2peak} of 11.3% ± 8.9% among adolescent cyclists over a period of one year of training, and although these athletes were much younger (13.8 ± 1.0 years old) than the athletes in our **Study III** (16.3 ± 0.4 years old) they had similar baseline relative VO_{2peak} at baseline (57.8 ± 7.6 vs 61.5 ± 5.3 $mL.kg^{-1}.min^{-1}$). Although other studies have identified improvement over several years in absolute VO_{2peak}, improvement in relative VO_{2peak} has not been reported among young athletes (Krahenbuhl et al., 1989; Landgraff et al., 2021). The improvements in performance variables among the athletes in **Study III** were, however, expected because these athletes attended elite sport high schools, aiming at developing their physique and sporting career. Thus, these adolescent athletes experienced an increase in training volume of ~25% from their first to their last year (unpublished), while simultaneously increasing their FFM. The improvement in aerobic performance and strength, in combination with the increased growth, the maintenance of EA levels as well as no apparent ED behavior, may indicate that the athletes in **Study III** achieved the necessary puberty-related increases in anabolic hormones, such as GH, IGF-1, and testosterone (Eliakim & Nemet, 2020), as well as kept a satisfactory nutritional intake and recovery, during the three-year follow-up. However, two athletes were lost to follow-up due to injury and **Study III** lacks further information (due to withdrawal, and not being willing to answer further questions) on these athletes, including types of injuries and assessment of RED-S markers. Thus, we do not know whether LEA among these athletes might have contributed to the injuries as seen in other studies (Drew et al., 2018; Drew et al., 2017). Well-controlled trials are warranted to investigate the effects of LEA on performance, both in short- and long-term settings, among different performance levels, and among different age groups. Furthermore, more observational studies are needed to investigate performance and LEA in a field-based setting.

7.2 Methodological considerations, strengths, and limitations

The studies included in this dissertation used multiple study designs to address the aims of the dissertation as well as including athletes at different age and performance levels, as outlined in Section 0. However, all designs and protocols have their strengths and limitations and are discussed in the following section.

7.2.1 Study designs

Study I was designed as a quasi-experiment, with pre- and posttest testing, without a control group. The purpose of a quasi-experiment is to fit the design of the intervention, to mirror the real world, while still controlling as many variables as possible (Thomas et al., 2015). This allowed the investigation of the RED-S syndrome in an "in situ" intensified endurance training setting among well-trained athletes. Because this study did not aim at investigating the effects of LEA on performance, randomization of athletes was not relevant. We do, however, acknowledge that a lack of a control group makes it difficult to conclude with certainty that the changes observed are a result of the intervention. However, such control groups were not possible to recruit in this study, mainly due to limitations in the laboratory due to available equipment, space, and testing personnel, as well as **Study I** being a part of a larger training study. However, more well-controlled trials are needed to understand better the effects of LEA on health and performance under both short- and long-term conditions, depicting field situations and behavior, and thereby increasing the ecological validity (the ability to generalize) of these studies (Thomas et al., 2015).

Study II was designed as a cross-sectional study, with a narrowly defined population (Olympic-level athletes) examining the prevalence of RED-S markers at a single time-point. A cross-sectional design does not enable the establishment of any cause–effect relationships, gives poor estimates of means and proportions in the more generalized population, although the design can investigate relationships within the sample, and are most likely not related to only the group studied (Bland, 2015). Despite the limitations, cross-sectional studies are easier to perform, require less funding (Bland, 2015), and are among the most used study designs in the RED-S literature (Areta et al., 2021). Furthermore, elite athletes at the highest performance level are difficult to gain access to because of strict and heavy training schedules, traveling, and competitions. Thus, the selected design was the only possible one to use, based on the population studied.

In **Study III**, we investigated RED-S in a cohort of adolescent athletes in a three-year longitudinal perspective. In this group, we aimed to observe whether they developed any signs of RED-S, and although the results cannot be extrapolated as estimates for the athletic population, our results can be compared with similar studies, slowly increasing the understanding of the phenomena (Bland, 2015). The main concern regarding longitudinal studies is the risk of attrition from participants leading to a high risk of drop-out (Altman, 1990), something we did experience, with a 31% drop-out rate during the three-year period in **Study III**. However, we are, to our knowledge, the first researchers to investigate the prevalence of RED-S in a longitudinal three-year setting at elite sport high schools, something that is warranted in the RED-S literature (Heikura et al., 2021; Mountjoy et al., 2018b).

7.2.2 Study samples and sizes

The samples in all three studies are considered as having convenience sample characteristics (Altman, 1990). Although convenience sampling is a common research practice, it is also the weakest form of sampling, where researchers merely select the most convenient sample available (Polit & Beck, 2014). In our type of research, this problem can be difficult to overcome, often due to a relatively small number of athletes with specific traits of interest available within a defined region or population. Hence, athletes in **Studies I** and **III** were recruited in the southern part of Norway, a region that does not contain a large proportion of the athletes of interest, whereas athletes in **Study II** were Olympic-level athletes from the whole country, being part of the Norwegian Olympic and Paralympic Committee. Furthermore, research is voluntary, making it impossible to include all athletes of a specific regional population. Thus, we invited available athletes, and accepted the risk of convenience sample bias, and recognize that such readily available participants may not be typical of the whole population (Polit & Beck, 2014). A power calculation is essential in experiments to ensure the detection of the smallest true difference (Altman, 1990). In **Study I**, power was calculated in advance, to ensure an appropriate number of participants to gain sufficient statistical power (> 80%) to see the effects of an intervention (Altman, 1990). In **Studies II** and **III**, we did not perform a power calculation due to the limited number of participants at these performance levels available for recruitment, limited laboratory capacity in all studies, and funding. Neither did we perform post hoc power calculations, an approach that has been deemed flawed with errors (Hoenig & Heisey, 2001;

Levine & Ensom, 2001), thus a possible low power in **Studies II** and **III** may have led to a type II error, and results must therefore be interpreted with care (Altman, 1990). Furthermore, we are aware that the limited sample sizes in all studies must be taken into consideration, and that we cannot generalize our results to other populations (Polit & Beck, 2014). However, in all three studies, we maximized the capacity available in the laboratories, although funding prohibited the use of multicenter studies to increase the number of participants. Thus, we encourage other researchers to perform similar studies to ours, with increased sample size, to try to overcome some of the challenges a limited sample size faces.

7.2.3 Protocols

To reduce limitations in all three studies, we implemented best-practice protocols where available, including guidance and advice, such as standard operating procedures (SOPs) from renowned laboratories, strict guidelines from the blood analysis laboratories, and written preparations for the participants with instructions to adhere strictly to them. In the assessment of RMR, a SOP from the metabolic lab at the Department of Nutrition, Exercise and Sports at the University of Copenhagen was used as well as best-practice protocols from Compher et al. (2006). BMD was assessed via DXA, the gold standard method of assessing bone health (Lewiecki, 2005), as well as body composition assessment as recommended in athletes (Sundgot-Borgen et al., 2013). Protocols included the sampling of urine to assess USG to monitor for proper hydration and limiting the amount of allowed clothing, thus improving the comparison of body composition (Nana et al., 2015). To ensure consistent positioning at each scan, positioning aids were used (Kerr et al., 2016), while the same experienced DXA technician scrutinized and analyzed all measurements, ensuring consistency as recommended (Nana et al., 2015). All blood samples were taken using a trained phlebotomist, in a rested and fasted state, adhering to strict guidelines from the blood analysis laboratory. When assessing EI, we used weighed food records in **Study I** and a modified retrospective dietary history interview in **Study III** (Gibson, 2005). We do, however, recognize that the protocol used in **Study III** is not ideal, and could be considered less precise than weighed food dietary records. However, in this group of young athletes, the method selected was chosen due to ethical considerations because the elite sport high schools reported that weighed food records earlier had triggered DE behavior among students. To assess performance in **Studies I** and **III**, we used best-practice protocols derived by the Norwegian Olympic and Paralympic Committee and

Confederation of Sports to ensure satisfactory comparison between studies. These protocols are based on many years of experience with training and testing of Norwegian elite and Olympic-level athletes.

7.2.4 The three components of energy availability

Obtaining valid and reliable information on EI, whether it is habitual or periodic, is difficult, and various approaches have been used throughout the literature, with the most recommended being the prospective method of food records (Burke et al., 2018; Gibson, 2005). Such methods, however, whether it is food weighing, electronic aids, or photo assessment are known to cause underreporting of meal sizes and foods considered "unhealthy," overreporting of foods considered "healthy," as well as subjects changing their habitual intake (Burke et al., 2001; Burke et al., 2018; Capling et al., 2017; Gibson, 2005). A recent meta-analysis study by Capling et al. (2017) found a mean bias of 19% underreporting of EI in athletes, equivalent to approximately 600 kcal per day. From the athletes' perspective, estimating EI whether in a prospective or retrospective way, adds a burden on the subject, making it prone to affect compliance (Burke et al., 2018). In **Study I**, we utilized weighed food records to estimate EI over a period of four days, designed to mirror participants' typical food patterns both pre- and postintervention. Periods of seven days of EI registration are often recommended, to minimize the effects of day-to-day variation, but provides the subjects with an extra burden (Sjödin et al., 1994). Therefore, to increase compliance, as well as to minimize the overall burden on the subjects, we chose four days in both **Studies I** and **III**, as highlighted in Sjödin et al. (1994). In **Study I**, participants were provided with a detailed description of how to weigh and register their EI, in addition, researchers were available for questions and help. In **Study II** we were unable to obtain any data on EI due to the athletes investigated. In **Study III**, we initially planned to assess EI using weighed food records. However, ethical considerations, as mentioned in Section 5.5, prevented us from using such. To minimize errors during the nutrition interview, interviewers were rigorously trained in advance and used technical aids, including pictures of different portion sizes of the most commonly eaten items, and the Google search engine to identify specific products of interest.

Measuring EEE is also prone to compliance issues due to errors dependent on the method used, which vary greatly in the literature (Burke et al., 2018). Some

methods can provide individualized objective feedback on EEE such as GPS units, HR monitors, power meters, and oxygen consumption measurements in exercises that contain simple tasks, such as cycling and running (Burke et al., 2018). Limited data exist within more complex exercise tasks such as strength training, swimming, and team sports (Burke et al., 2018). Other methods rely on deriving EEE from activity logs using the Metabolic Equivalent of Task (Ainsworth et al., 2000), despite this being a much less accurate method of estimation (Burke et al., 2018). Another methodological discrepancy in the literature is whether to subtract RMR in the calculation of EEE, as originally intended in the early definition of EA (Loucks et al., 1998). This discrepancy may lead to an overestimation of EEE, thus underestimating the true EA in athletes engaged in prolonged or long-lasting exercises, yet only a few studies to date have clearly implemented this in their EEE calculation (Heikura et al., 2018b; Koehler et al., 2013; Lane et al., 2021; Melin et al., 2015; Torstveit et al., 2018; Torstveit et al., 2019; Viner et al., 2015). In **Study I**, we aimed at measuring EEE using training diaries provided by the athletes, however, we experienced low compliance regarding the details of the training diaries, thus making them irrelevant to calculate EEE and EA. In **Study III**, we obtained EEE using HR monitors. Athletes were instructed to record all training sessions within the last five days before testing. Epochs of five seconds during every training session were then utilized to calculate EEE using the validated equations described by Crouter et al. (2008) and RMR was subtracted, as described in other studies from our research group (Torstveit et al., 2018; Torstveit et al., 2019). However, although those data from HR monitors are likely to be superior compared with the use of METs as described earlier, it is not the best method of calculating EEE (Heikura et al., 2021). Data have shown potential error rates of ~100 to 600 kcal/day with the use of HR monitors (Heikura et al., 2021; O'Driscoll et al., 2020). Although no gold standard methods exist for determining EEE, the use of laboratory-based measures where HR is plotted against indirect calorimetry data is considered better than the methods used in **Study III** (Heikura et al., 2021). However, this method is more time-consuming for athletes as well as costly and was not feasible to perform in **Study III** due to the longitudinal perspective as well as the limited amount of time available for testing athletes.

Several ways of determining FFM exist, all have their challenges, and currently, no universal gold standard exists (Ackland et al., 2012). The techniques differ and can include the use of electrical impedance, ultrasound, skinfold techniques, and

DXA (Ackland et al., 2012). Currently, recommendations for assessing body composition in athletes are either to use skinfold measures or DXA (Sundgot-Borgen et al., 2013). The skinfold measures are cheap to perform but require skilled and experienced operators licensed by the International Society for the Advancement of Kinathropometry (Sundgot-Borgen et al., 2013). However, skinfold measures do not provide information on bone health, a crucial marker of LEA in females (De Souza et al., 2014a; Mountjoy et al., 2018b; Mountjoy et al., 2014; Nattiv et al., 2007). DXA is another common method to estimate body composition, yet it is costly, not readily available for the majority of athletes, as well as the use of strict best-practice protocols is advised to detect true changes, not influenced by hydration status, food intake, prior exercise, or operator error (Kerr et al., 2016; Nana et al., 2012; Nana et al., 2016; Nana et al., 2015). Discrepancies also exist when using different DXA machine manufacturers or even different machines from the same manufacturer (Burke et al., 2018; Nana et al., 2015). In all three studies, we used DXA located at the campus to assess BMD and body composition with strict best-practice protocols, including strict standardized preparation protocols, position aids, and the assessment of USG (Kerr et al., 2016; Nana et al., 2012; Nana et al., 2016; Nana et al., 2015). To limit discrepancies among the different machines used (GE Lunar Prodigy and GE Lunar iDXA), the same experienced senior technician analyzed data from all participating athletes (**Studies I**, **II**, and **III**). Thus, inconsistencies were minimized when performing a DXA scan, providing as accurate results as possible for the FFM component.

Finally, the calculation of EA is mathematically easy, as outlined in Section 3.1, however, the caveats with each of the components of the equation must be taken into consideration when comparing results within this field of research. Thus, it is possible that we overestimated EA in **Study III** because the method chosen seems to overestimate EI (Gibson, 2005) as well as the errors reported when using HR monitors to assess EEE in free-living athletes (Heikura et al., 2021). Thus, our EA estimation must be viewed with caution. Furthermore, adolescent athletes may have different thresholds for EA and other markers of RED-S due to the energetic requirements of growth, development, and puberty (Heikura et al., 2021). Thus, the EA thresholds used in **Study III**, and similar adolescent studies (Cherian et al., 2018a; Silva & Silva, 2017; Silva et al., 2018), must be interpreted with caution,

and more research is needed to understand EA and its thresholds in adolescent populations better.

7.2.5 Biomarkers of RED-S

Measuring EA is not the sole way of assessing RED-S in athletes (Heikura et al., 2018b) because research has shown the unfavorable health and physiological effects of LEA (Mountjoy et al., 2018b). To overcome the difficulties described regarding the determination and estimation of EA, we chose to include recognized biomarkers (see Sections 5.4.3 and 7.1.1 – 7.1.5) to assess RED-S. These biomarkers included objective short-term markers strongly linked to energy deficiency such as low RMR, low body fat, and being underweight, as well as blood biomarkers including reduced testosterone, T_3, IGF-1, and insulin, and increased cortisol levels, as well as long-term markers such as low BMD, described in several position stands (De Souza et al., 2019a; De Souza et al., 2019b; De Souza et al., 2014a; Mountjoy et al., 2018b; Mountjoy et al., 2014; Nattiv et al., 2021), in a large number of review papers (Areta et al., 2021; Dipla et al., 2020; Elliott-Sale et al., 2018; Fagerberg, 2018; Logue et al., 2018; Logue et al., 2020; McCall & Ackerman, 2019; McGuire et al., 2020; Melin et al., 2019; Papageorgiou et al., 2018; Schofield et al., 2020; Tenforde et al., 2016; Wasserfurth et al., 2020) and found in several studies investigating soldiers undergoing extreme starvation in prolonged multistressor environments (Friedl et al., 2000; Kyrolainen et al., 2008). Unfortunately, not all biomarkers related to RED-S were possible to include in **Studies I** and **II**, such as GH, leptin, ghrelin, and markers of bone formation and resorption, due to lack of funding because blood analyses are expensive. Furthermore, we chose to not include blood biomarkers in **Study III**, mainly due to the changing hormonal profiles of males during their growth stages (Lanfranco & Minetto, 2020). Despite the inconsistency in the effects of short-term LEA on bone metabolism in males compared with females (Papageorgiou et al., 2017), there is an established link between low BMD and energy deficiency within the LEA groups (Mountjoy et al., 2018b; Nattiv et al., 2021), making it a useful marker to include when assessing for RED-S. However, the levels and cut-offs of such biomarkers and their relation to LEA are still debated. Recently, Heikura et al. (2021) evaluated the use of blood biomarkers and concluded that they most likely provided an objective measure of short to moderate (days/weeks) exposure to LEA in females. These markers included leptin, IGF-1, and T_3, as well as bone formation and resorption markers (Heikura et al., 2021). It should be noted,

however, that the authors questioned whether these markers are transferable to males, due to limited research performed. At present, research is limited to five well-controlled trials, resulting in six published papers; two from the same trial (Koehler et al., 2016; Martin et al., 2021) and four others (Ishibashi et al., 2020; Kojima et al., 2020; Murphy & Koehler, 2020; Papageorgiou et al., 2017). Notably, these studies have a low sample size (<10 participants) and they have all tried to investigate different components of the RED-S model (see Section 3.0). When trying to identify the effects of LEA on blood biomarkers in males, discrepancies have also been observed regarding T_3, IGF-1, and leptin as well as a lack of research regarding cortisol and GH (Koehler et al., 2016; Kojima et al., 2020; Murphy & Koehler, 2020; Papageorgiou et al., 2017). However, the major limitations of these studies are that they have only investigated short-term effects of LEA over periods ranging from three to five days, a time period that does not reflect true behavior in the field, leading to poor ecological validity (Heikura et al., 2021), and may not necessarily discover traits of RED-S that usually develop over months and years such as poor bone health. Thus, there is a discrepancy between well-controlled trials in the laboratory and field-based research. In fact, the field study by Friedl et al. (2000) showed some of the massive impact severe energy deficit may have on body composition and endocrine markers in healthy adult men. Body composition including body weight, BMI, fat mass, and FFM declined, in conjunction with reductions of several blood biomarkers, falling outside of normal reference levels (Friedl et al., 2000). This included testosterone levels close to levels observed in castrated males, low T_3 values, severely reduced IGF-1 levels, as well as high TSH, cortisol, and SHBG (Friedl et al., 2000). These findings are supported by a case study showing some of the same detrimental effects in a male combat athlete experiencing severe LEA over several weeks (Langan-Evans et al., 2021). However, markers such as body weight and body composition should be scrutinized further, due to stable body weight and body composition reported in female athletes with long-term LEA (Redman & Loucks, 2005). Furthermore, research has also identified that obese males and females with persistent LEA preserved their body tissue because of metabolic adaptations (Goldsmith et al., 2010; Redman et al., 2009), warranting further research in healthy male athletes. Overall, these findings still highlight the potential usefulness of a variety of objective markers in discovering energy deficits. However, more research, specifically well-controlled laboratory trials aimed at mimicking field settings in athletes at different age and performance levels is needed. This will improve the

understanding of the usefulness of markers of LEA; however, establishing a dose–response relationship, aiming at increasing the ecological validity, that the current laboratory studies (Ishibashi et al., 2020; Koehler et al., 2016; Kojima et al., 2020; Martin et al., 2021; Murphy & Koehler, 2020; Papageorgiou et al., 2017) are lacking is important.

8 Conclusion

This dissertation aimed to investigate RED-S among Norwegian male athletes of different ages and performance levels. The conclusions derived from the main aims in the three studies are presented below.

I) Investigating well-trained male athletes undertaking a four-week intensified endurance training period, we observed increases in performance and testosterone levels, yet also observed negative changes in RED-S-related markers, such as reductions in RMR and T_3, and an increase in cortisol levels.

II) Investigating Olympic-level athletes, most athletes displayed none or only a few single RED-S-related markers, and we identified a lower prevalence of RED-S than with other comparable studies. However, a total of 16% were identified with a major symptom of chronic energy conservation related to RED-S, depicted as low RMR. The majority of these athletes did also show the presence of several other RED-S-related markers.

III) Investigating adolescent endurance athletes attending elite sport high schools, we observed an overall improvement in aerobic performance and strength over a three-year period. Few athletes displayed single case prevalence of LEA, and no other RED-S-related markers, including DE behavior, drive for leanness, or exercise addiction were observed among the athletes during the three-year period. This indicates that RED-S is not particularly prevalent among this group of athletes. However, several athletes (38%) had poor bone health and were "at risk" of low bone mass.

In sum, and based on these main findings, several RED-S-related markers were found in all samples investigated in this dissertation:

1. Signs of perturbation of the reproductive function:
    a. In well-trained cyclists (**Study I**), three athletes (15%) had subclinically low testosterone at pretest, decreasing to two athletes (10%) at posttest. Furthermore, overall testosterone levels increased

during the training intervention, despite no apparent EI increase. Among Olympic-level athletes (**Study II**), 25% had subclinically low testosterone levels, clustering with multiple other RED-S variables.

2. Poor bone health:
    a. Among adults, 15% of the well-trained cyclists (**Study I**) and 16% of the Olympic-level athletes (**Study II**) had low BMD (Z-score < –1.0). Among adolescent athletes (**Study III**), 38% were "at risk" of low bone mass (Z-score < –1.0). Furthermore, the majority of the adolescent athletes either lost or did not achieve the expected pubertal bone mineral accrual during the three-year period investigated.
3. Perturbation of the endocrine system:
    a. Well-trained athletes (**Study I**) did not display subclinically low T_3, but we found a 5% decrease in T_3 during the training intervention. When identifying a subgroup of athletes with poor vs better recovery, no difference in T_3 levels was found between the groups. In Olympic-level athletes (**Study II**), subclinically low T_3 was identified in 5% of the athletes.
    b. Among well-trained athletes (**Study I**), subclinically high cortisol levels were not found, although cortisol increased by 12% during the intensified training intervention. Furthermore, two athletes had >30% reduction in their testosterone:cortisol ratio, indicating poor recovery. In Olympic-level athletes (**Study II**), 23% were identified with subclinically high cortisol levels, including one with a clinically high level. Of the athletes with subclinically high cortisol levels, 30% also had other RED-S parameters.
    c. No changes were observed in IGF-1 (**Study 1**), none were identified with low values, but mean IGF-1 levels (18.1 ± 4.3 $nmol.L^{-1}$) were within the lowest quartile (<28.5 $nmol.L^{-1}$) of the reference range.
4. Metabolic perturbation:
    a. The prevalence of low RMR ($RMR_{ratio} \leq 0.90$) ranged from 8% to 65%, with the lowest prevalence observed among adolescent athletes (**Study III**) and the highest among well-trained athletes (**Study I**). Very low RMR ($RMR_{ratio} < 0.8$) was identified among well-trained (15%) (**Study I**) and Olympic-level athletes (7%) (**Study II**).

5. Cardiovascular perturbation (**Study II**):
    a. Signs of perturbation in the cardiovascular system were observed in Olympic-level athletes. A 34% prevalence of subclinically high LDL levels among these athletes was identified, with the majority also having subclinically high testosterone levels.
6. Psychological factors (**Study III**):
    a. No apparent sign of DE behavior was observed among adolescent athletes.
    b. Drive for leanness remained constant, but our athletes may attribute more to DLS attributes compared with the BEDA-Q tributes.
    c. One athlete displayed signs of exercise addiction at baseline with a subsequent lasting decrease.
7. Performance levels:
    a. Well-trained athletes (**Study I**) undergoing four weeks of intensified interval training increased their performance, including VO_{2peak} (~3%) and FTP (~7%) despite negative changes in markers related to RED-S being found.
    b. Adolescent athletes (**Study III**) increased their VO_{2peak} and muscle strength during their stay at elite sport high schools in Norway (~10% per year), whereas no apparent RED-S-related markers were observed.

Thus, in **Study I**, the findings indicate the complexity involved in the RED-S syndrome and highlight that male athletes may be at risk of developing subclinical indications of RED-S even during a short four-week endurance training period. In **Study II**, the findings emphasize a lower prevalence of RED-S than with similar studies and the usefulness of scrutinizing high-performance athletes. However, the findings also highlight the need to investigate further the use of clustering of such RED-S risk factors among various groups of athletes. In **Study III**, the findings highlight an apparent low risk of RED-S among adolescent athletes. However, they also highlight the importance of coaches, athletes, and sports federations focusing on the risk of poor bone health, and gaining more knowledge on specific bone-loading exercises, within low-impact repetitive and nonweight-bearing endurance sports, to ensure that athletes have the best possible bone health when transitioning to adulthood.

9 Perspectives and future directions

The findings in this dissertation could be useful for current and future athletes, coaches, health personnel, supporting staff, sports federations, and researchers. This dissertation highlights that RED-S is present to varying degrees among different ages and performance levels among Norwegian male athletes. Position stands have established that RED-S is multifactorial and may induce serious and detrimental health and performance consequences (Mountjoy et al., 2018b; Mountjoy et al., 2014). However, various individual differences between athletes seem to exist and indicate that some athletes might tolerate LEA better than others, as shown in laboratory studies (Ishibashi et al., 2020; Koehler et al., 2016; Kojima et al., 2020; Martin et al., 2021; Murphy & Koehler, 2020; Papageorgiou et al., 2017), and males may tolerate LEA better than females (Koehler et al., 2016). Hence, we observed an increase in performance in **Study I**, despite potentially reduced EA because the athletes did not increase their EI in conjunction with several related RED-S parameters being negatively affected. Furthermore, **Study II** identified a lower prevalence of RED-S in Norwegian Olympic-level athletes than reported in other studies (Table 2). In **Study III**, we did not seem to identify adolescent athletes being at risk of RED-S, except for poor bone health, to some extend supported by the findings of a limited cause–effect relationship between short-term LEA and the endocrine system in males (Ishibashi et al., 2020; Koehler et al., 2013; Kojima et al., 2020; Martin et al., 2021; Murphy & Koehler, 2020; Papageorgiou et al., 2017; Taguchi et al., 2020) compared with females (Ihle & Loucks, 2004; Loucks & Heath, 1994b; Loucks & Thuma, 2003; Papageorgiou et al., 2017). This may be because the RED-S assessment, including a plan for return to play (Mountjoy et al., 2015b), is well implemented within the Norwegian Olympic and Paralympic Committee and Confederation of Sports and within several Norwegian sports federations. Furthermore, Norway has a long tradition in implementing education as well as individual and within-team interventions around healthy food cultures (Skårderud et al., 2012). Despite this, these findings do not absolve anyone of responsibility of monitoring for RED-S in the future. Nonetheless, it must still be highlighted that some studies (Friedl et al., 2000; Langan-Evans et al., 2021; Woods et al., 2017) investigating long-term LEA or extreme energy deficiencies have clearly demonstrated detrimental effects on health and performance in males as described in the RED-S model (Mountjoy et al., 2018b). These findings emphasize the need for more research investigating

RED-S in male athletes including long-term consequences of LEA. Athletes, coaches, and sports federations should therefore strive to ensure that the health of athletes is a priority. Stable long-run performance increases should be prioritized compared with short-term performance increases, which may introduce hazardous weight-control behaviors to gain e.g., a higher power-to-weight ratio (Werner et al., 2013). Low BMD may arise from other factors than LEA, such as lack of osteogenic manipulation during childhood or genetics. Although only a few cases of apparent LEA were observed among adults in both **Studies I** and **II** and among our adolescent athletes in **Study III**, it is worrying that several athletes in **Study III** were at risk of low bone mass and did not increase their bone strength during an age where peak bone mass is achieved. This highlights the importance of elite sports high schools and sports federations in low- and nonimpact sports focusing on the risk of poor bone health. Thus, increased knowledge among coaches, sports medicine personnel, sports federations, clubs, and elite athlete schools, on awareness of the associations between poor bone health and low body weight and nutritional deficits, as well as knowledge on how specific bone-loading exercises can improve bone health among athletes, including nutritional education, is needed to ensure that athletes have the best possible bone health when transitioning to adulthood, where bone accrual stops (Bailey et al., 2000; Kohrt et al., 2004; Tenforde et al., 2016).

The term EA is well-established in the research environment and functions well in a laboratory setting, where most elements can be controlled. However, trying to estimate EA in free-living individuals in the field may not work well. This dissertation along with existing literature highlights that screening for objective markers associated with RED-S, such as low RMR, poor bone health, and impaired endocrine function, can be used in assessing the risk of RED-S. Such screening can be implemented every 6–12 months (Mountjoy et al., 2015b), increasing the chance of early detection of athletes at risk of LEA, which is critical in preventing long-term consequences. To make screening easier and to reduce costs, researchers should try to develop screening aids, similar to the LEAF-Q in females (Melin et al., 2014), as well as the SEAQ-I (Keay et al., 2018) that can identify male athletes at risk of RED-S. Such instruments may help practitioners to interpret and monitor EA and identify athletes that need to be screened and aided further. Furthermore, more research is needed in trying to establish whether the currently used cut-offs for several RED-S parameters are transferable to male athletes because these were

originally developed in recreational females. Future research should also investigate the effects of LEA on markers of RED-S in a longer perspective than the short perspective (5 days or less) published to date, and researchers should target time frames, if possible, that most likely reflect situations in the field, such as weeks and months, thereby increasing the ecological validity (Heikura et al., 2021).

Finally, it must be recognized that the RED-S model is new compared with the female athlete TRIAD. Thus, some discrepancies between the TRIAD research group (De Souza et al., 2020; De Souza et al., 2014b; Strock et al., 2021; Williams et al., 2019) and the RED-S research group (Kuikman et al., 2021; Mountjoy et al., 2015a) have emerged. The main difference between the models is that the female athlete TRIAD model builds on several decades of well-established research, coupled to three distinct conditions (De Souza et al., 2014a) compared with the vastly expanded RED-S model (Mountjoy et al., 2018b). The vast expansion of the RED-S model does, however, have its weaknesses, not always being directly supported by well-controlled trials, thereby only linking, and not establishing cause–effect relationships of LEA on all these systems (Mountjoy et al., 2018b). Interestingly, the authors of the TRIAD consensus paper stated back in 2014, that the "*scientific evidence of RED-S as it applies to men, non-Caucasians and disabled individuals, is in its infancy and is not sufficiently developed to warrant a new theoretical model*" (De Souza et al., 2014b). This has to some extent been confirmed in the recent controlled trials performed in males (Ishibashi et al., 2020; Koehler et al., 2013; Kojima et al., 2020; Martin et al., 2021; Murphy & Koehler, 2020; Papageorgiou et al., 2017; Taguchi et al., 2020). However, despite this ongoing discrepancy between research groups of the TRIAD and RED-S, it must be recognized that RED-S is not a faulty model per se because it is important to never stop asking questions and developing new hypotheses (Mountjoy et al., 2015a). Thus, rather than viewing the RED-S model as a proven theoretical model, it could be seen as a framework model, continuously being adjusted as the scientific evidence improves, importantly being a model that does not exclude athletes based on gender or disability. Furthermore, despite the authors of the TRIAD consensus paper initially claiming back in 2014 that it was in its infancy to include males (De Souza et al., 2014b), one could also view the inclusion as a gateway for gaining new attention to the field. This may increase the research, hopefully leading to improvements in the model, including the possibility of a

differentiated male/female model, similar to the ACSM male and female TRIAD. Thus, the author of this dissertation embraces the RED-S model but is also aware of and recognizes its weaknesses.

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Paper I

Impact of a 4-Week Intensified Endurance Training Intervention on Markers of Relative Energy Deficiency in Sport (RED-S) and Performance Among Well-Trained Male Cyclists

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Impact of a 4-Week Intensified Endurance Training Intervention on Markers of Relative Energy Deficiency in Sport (RED-S) and Performance Among Well-Trained Male Cyclists

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Cyclists often apply block periodization to high training volumes in meso- and macrocycles to optimize training adaptation and to prepare for competition. Body mass influences performance in many sports, including endurance disciplines, and conditions related to the syndrome Relative Energy Deficiency in Sports (RED-S) such as metabolic adaptations and premature osteoporosis have also been reported in male cyclists. This study aimed to determine how a 4-week mesocycle of intensified endurance training designed to increase performance, would affect markers of RED-S in well-trained male cyclists. Twenty-two participants (age: 33.5 ± 6.6 years, height: 181.4 ± 5.2 cm, weight: 76.5 ± 7.4 kg, peak oxygen uptake (VO_{2peak}): 63.5 ± 6.6 mL·kg^{-1}·min^{-1}) were recruited and instructed to maintain their background training load and to follow a supervised training protocol consisting of three high-intensity interval training sessions per week with a work duration of 32 min per session. Protocols included pre- and postintervention assessment of resting metabolic rate (RMR) using a ventilated hood, body composition and bone health by dual-energy X-ray absorptiometry (DXA), blood samples, energy intake, and aerobic performance. The interval training increased participants' aerobic performance—peak power output [4.8%, $p < 0.001$], VO_{2peak} [2.4%, $p = 0.005$], and functional threshold power [6.5%, $p < 0.001$] as well as total testosterone levels [8.1%, $p = 0.011$]—while no changes were observed in free testosterone [4.1%, $p = 0.326$]. Bodyweight, body composition, and energy intake were unchanged from pre- to post-test. Triiodothyronine (T_3) [4.8%, $p = 0.008$], absolute RMR [3.0%, $p = 0.010$], relative RMR [2.6%, $p = 0.013$], and RMR_{ratio} [3.3%, $p = 0.011$] decreased, and cortisol levels increased [12.9%, $p = 0.021$], while no change were observed in the total testosterone:cortisol ratio [1.6%, $p = 0.789$] or the free testosterone:cortisol (fT:cor) ratio [3.2%, $p = 0.556$]. A subgroup analysis of the five participants with the largest increase

in fT:cor ratio, revealed a greater improvement in functional threshold power (9.5 vs. 2.5%, $p = 0.037$), and higher relative RMR (0.6 vs. −4.2% $p = 0.039$, respectively). In conclusion, 4 weeks of intensified endurance interval training increased the athletes' aerobic performance and testosterone levels. However, negative changes in markers related to RED-S, such as a reduction in RMR and T_3, and an increase in cortisol were observed. These results indicate the complexity involved, and that male athletes are at risk of developing clinical indications of RED-S even during a short 4-week endurance training mesocycle.

Keywords: endurance athletes, energy availability, hormonal response, male cyclists, resting metabolic rate, testosterone, training intervention

INTRODUCTION

Preparing for a competitive cycling season often involves high volumes of training, quantified over several periods, ranging over micro-, meso-, and macrocycles, designed to induce specific physiological adaptations (1). If a planned overload is followed by a well-matched recovery strategy, functional overreaching with the intended physiological adaptation occurs (1). However, large training volumes that are combined with insufficient recovery strategies can trigger the development of non-functional overreaching and overtraining syndrome, with symptoms of fatigue and decreased performance (2, 3). Monitoring changes in an athletes' hormone concentrations, including testosterone and cortisol, have previously been used to assess athletes' anabolic-catabolic balance (4). However, monitoring athletes' testosterone-to-cortisol ratio is considered more sensitive to training stress than is merely measuring testosterone and cortisol separately (5).

Several parameters such as body mass and nutritional intake affect cycling performance, and low energy availability is frequently reported among cyclists (6, 7). Energy availability is the amount of energy relative to fat-free mass (FFM) left to support basic body functions after subtraction of the energy used during exercise; energy availability = (energy intake [kcal]—exercise energy expenditure [kcal])/(FFM [kg])/day (8–12). Low energy availability combined with large training volumes, can cause negative consequences such as impaired protein synthesis, impaired hormonal and training response, and increased risk of fatigue; these may lead to performance impairment (5, 9, 10). Research in females has also shown a variety of health parameters being negatively affected by both short- and long-term low energy availability (8–13). Clinical trials exposing eumenorrheic females to low energy availability (<30 kcal·kg^{-1} FFM·day^{-1}) for only 5 days found reductions in levels of insulin-like growth factor-1 (IGF-1), leptin, insulin, triiodothyronine (T_3), and luteinizing hormone (12, 14). Furthermore, long-term low energy availability has been found to increase the risk of premature osteoporosis and to give elevated cardiovascular risk factors (10, 13).

Research reports that male athletes are also vulnerable to the negative health and performance consequences of low energy availability as outlined in the Relative Energy Deficiency in Sports (RED-S) model (10). Not all health and performance aspects of RED-S are, however, fully elucidated, and recent research in male athletes has shown inconsistent findings (15–17). One possible reason for this inconsistency is believed to be the methodological difficulties of assessing energy availability (8, 18). Measurements of resting metabolic rate (RMR), implicating the energy expended on basic bodily functions have therefore been proposed to, and to some extent used as, a potential objective indicator of energy availability (9, 19). However, only two studies to date, have investigated the impact of different training regimens on RMR as a surrogate marker, where one study investigated trained cyclists eliciting overreaching (20), and the other investigated elite rowers during an intensified training period (19). These studies, however, did not include an assessment of hormonal responses when monitoring athlete's responses to changes in energy intake, training regimen or the combination of both.

Therefore, the aim of this study was to determine how a mesocycle of 4 weeks of intensified endurance training designed to increase aerobic performance, would affect RMR, body composition, energy intake, total and free testosterone, cortisol, testosterone:cortisol ratio, T_3, insulin and IGF-1 levels in well-trained male cyclists.

METHODS

Study Design

This prospective intervention study was part of a larger training study (clinicaltrials.gov; NCT04075929) with no control group. The training intervention consisted of three supervised high-intensity interval sessions per week, for 4 weeks. Athletes were instructed to maintain their current background training load while enrolled in the study. Each interval training session contained 20 min of self-regulated warm-up, followed by an interval work period with a total accumulated work duration of 32 min of high-intensity training, followed by a 20-min self-regulated cool-down. The total accumulated amount of exercise during the 4-week training intervention was 384 min of high-intensity training and 480 min of self-regulated warm-up and cool-down. Bone mineral density (BMD) was assessed before the intervention, while RMR, body composition, hormone levels, performance variables (peak oxygen consumption and time trial), and energy intake were assessed before and after the intervention period.

Participants

To be included in the study, participants had to be at least 18 years old but younger than 50 years, with a peak oxygen uptake (VO_{2peak}) $\geq$ 55 mL·kg body mass^{-1}·minutes^{-1} and a training frequency of at least three sessions per week during the last year. Furthermore, absence of disease and injury was required. All participants' were classified at performance level 3–4 (21). Recruitment was accomplished through social media and local online newspapers. Before inclusion, all participants received information about the study and test procedures, and signed an informed consent agreement. The study protocol was approved by the University Faculty Ethics Committee and the Norwegian Center for Research Data (no. 46706). All testing complied with the Declaration of Helsinki. Initially, 22 well-trained male cyclists aged between 22 and 45 years who competed at a regional or national level were recruited (**Figure 1**). Throughout the intervention, two participants were excluded from the analysis: one failed to complete the intervention, and one was excluded because of non-compliance; hence 20 participants were included in the final analysis.

Procedures and Measures

Training volume from the last 4 weeks before pretesting, as well as during the intervention, was collected via written training diaries. During a 2-week period before and after the intervention, participants completed physiological testing, and logged their dietary intake. Participants arrived at the university laboratory during three non-consecutive days for physiological testing. On the first day, participants arrived using motorized transport in a fasted and rested state. RMR, body composition, BMD, and blood sampling were assessed at 06:00–09:00 a.m. to control for diurnal variation. On the second day, participants completed a maximum aerobic exercise testing protocol at 12:00–05:00 p.m. in an unfasted state. On the third test day, the participants performed a 40-min time trial to assess their functional threshold power. During the last week before, and just after the intervention, participants weighed, and registered their dietary intake for four consecutive days (**Figure 2**).

Performance Variables

VO_{2peak} and peak power output measurements were performed on a stationary bike (Excalibur Sport, Lode B.V., Groningen, the Netherlands) starting with 1 min of cycling at a power output of 175 W and increased by 25 W per minute until voluntary exhaustion or failure to maintain a cadence of at least 70 rounds per minute. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) was measured using Oxycon Pro™ with mixing chamber and 30 s sampling time (Oxycon, Jaeger GmbH, Hoechberg, Germany) and was calibrated according to standard laboratory procedures. Mean power during the last minute of the test decided the 'cyclist's peak power output, and the mean from the two highest VO_2 measurements determined VO_{2peak}. Heart rate was measured continuously, and blood lactate was measured 1 min after test completion. Objective criteria, such as plateau of the oxygen uptake, heart rate $\geq$ 95% of known heart rate peak, respiratory exchange ratio $\geq$ 1.10, and blood lactate $\geq$ 8.0 mMol·L^{-1} were used to ensure a valid test (22). To assess functional threshold power, participants performed a seated 40-min all-out test using their own bike on CompuTrainer Lab bike rolls (Race Mate, Seattle, WA, USA). The test started with a 20–30-min warm-up at a self-regulated load, followed by a 40-min ride with the highest possible mean wattage. All participants were blinded for power output and heart rate, with only time remaining and rounds per minutes displayed.

Resting Metabolic Rate

Indirect calorimetry using a canopy hood system was used to assess RMR (Oxycon Pro, Jaeger, Germany), and systems were calibrated before each test according to standard laboratory procedures. Participants rested for 15 min before measurement. VO_2 and VCO_2 were assessed over a 30-min period. The last 20 min of measurements were used to assess RMR as described elsewhere (23). Measured RMR was calculated using the Weir equation (24) (3.94 × VO_2 [ml]) + (1.1 × VCO_2 [ml]) × 1.44. Relative RMR was calculated as measured RMR in kcal·kg^{-1} FFM·day^{-1}. Predicted RMR was calculated using the Cunningham equation (25) (500 + (22 × FFM [kg]), and RMR_{ratio} was calculated as measured RMR [kcal]/predicted RMR [kcal]. Resting heart rate (V800, Polar Elektro Oy, Kempele, Finland) was defined as the lowest heart rate measured during RMR measurement.

Energy Intake and Macronutrients

Participants weighed and registered their dietary intake for four consecutive days using a digital kitchen scale (OBH Nordica 9843 Kitchen Scale Color, Taastrup, Denmark). In-depth oral and written instructions were given before registration, and participants were asked to maintain their habitual dietary patterns and routines during the registration period. All dietary data were logged using software from Dietist Net (Dietist Net, Kost och Näringsdata, Bromma, Sweden) with access to the Norwegian food table and an open Norwegian nutritional information database.

Body Composition and Bone Mineral Density

Height was measured without shoes to the nearest 0.1 cm using a wall-mounted centimeter scale (Seca Optima, Seca, Birmingham, UK). Body weight was measured in underwear to the nearest 0.01 kg with an electronic scale (Seca 1, model 861, Birmingham, UK). Body mass index (BMI) was calculated as weight in kg divided by height squared in meters (kg/m^2). Body composition and BMD were assessed using dual-energy X-ray absorptiometry (DXA) (GE-Lunar Prodigy, Madison, WI, USA, EnCore software version 15). The same technician performed all tests with the same scanner on all participants. BMD was assessed in the lumbar spine (L1–L4), femoral neck, and total hip. Low BMD in athletes was defined as a Z-score of < -1.0 in one of the measured sites, as recommended by Nattiv et al. (11). Body composition was assessed according to a best-practice protocol (26), including assessment of hydration status (USG) before DXA measurement using a digital refractometer (Atago UG-α cat. no. 3464, Atago U.S.A. Inc., Bellevue, WA).

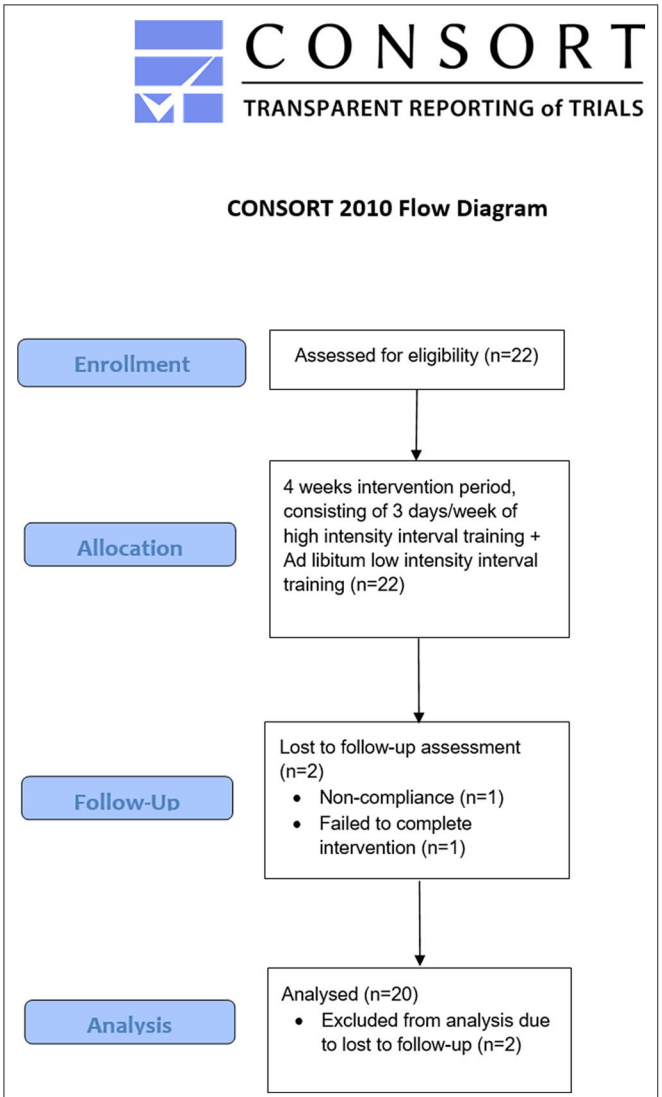

FIGURE 1 | Participation flow. The study was conducted in Kristiansand, Norway.

Blood Sampling

Blood samples were drawn from the cephalic vein of participants 5 min after completion of DXA. Two 5 mL Vacuette Z Serum Sep clot activators (BD, Plymouth, UK) were filled and centrifuged at 3,100 × g for 10 min (Statspin Express 4, Beckman Coulter, Inc. 250 S. Kraemer Blvd. Brea, CA, USA) within the limit of at least 30 min but <60 min. Five 2 mL Cryotube vials (VWR International, Radnor, Penn, USA) were filled with serum and frozen to −80°C. Serum was analyzed at Sørlandets Hospital, Kristiansand and analyzed for testosterone (analytic CV: 6.7 %), sex hormone-binding globulin (SHBG 4.0%), T_3 (6.9%), cortisol (8.2%), insulin (21.1%), and IGF-1 (8.0%). Free testosterone was calculated by dividing total testosterone with SHBG.

Statistics

Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows (v. 25; IBM Corp., Armonk, NY, USA). The dataset was controlled for missing data and signs of non-normality using histograms as reference, and the assumption of normality of variance was found to be satisfied. Difference and relative changes between pre- (PRE) and posttest (POST) were assessed using paired-samples *t*-test (POST-PRE), generating mean, standard deviation of difference, and 95% confidence interval including percent change. Changes between groups were found using independent sample *t*-test. Effect size (ES) was calculated to interpret the meaningfulness of results using Cohen (27) criteria (0.2 = small effect, 0.5 = medium effect, 0.8 = large effect). Statistical significance level was defined as $p < 0.05$. A priori power analysis was calculated based on an expected standard deviation of 2.0 (19), and we had 80% power to detect a true mean group difference at 1.9 kcal·kg^{-1} FFM·day^{-1} in relative RMR with a minimum of 11 participants (alpha: 0.05; two-tailed).

RESULTS

Descriptive characteristics of the participants are presented in **Table 1**. Comparing total accumulated training load (including background training) from before pretesting with total accumulated training during the intervention, no significant increase was found ($p = 0.497$).

Performance

Athletes improved their VO_{2peak} (2.4%, $p < 0.01$), peak power output (4.8%, $p < 0.001$) and functional threshold power (6.5%, $p < 0.001$) from pre- to post-test (**Table 2**).

Resting Metabolic Rate, Energy Intake, Body Composition, and Bone Health

A 3.0% reduction was found in both absolute RMR, relative RMR, and RMR_{ratio} from pre- to post-test ($p < 0.05$) (**Table 3**). No changes were observed in energy intake (kcal/day) or intake of macronutrients (g per kg, E%). Body weight, fat mass, and FFM was assessed during stable urine specific gravity (0.001 ± 0.006 kg.m^3, $p = 0.420$), and did not differ from pre- to post-test (**Table 3**). L1-L4 average Z-score was 0.1 ± 1.1, while average femoral neck and total hip Z-scores were 0.2 ± 1.0 and 0.3 ± 0.9, respectively. Three athletes (15%) had low BMD in either L1-L4, femoral neck, or total hip, respectively: participant 1 (Z-scores: −3.6, −2.2, and −2.0, 26 years old, 17.4% fat); participant 2 (+0.2, −1.1 and −1.1, 36 years old, 15.9% fat); and participant 3 (−1.8, +1.2, and +0.9, 43 years old, 24.7% fat).

Blood Markers

Total testosterone increased 8.1% ($p = 0.011$) from pre- to post-test while no significant changes in free testosterone (4.1%, $p = 0.326$) were found. Cortisol levels increased 12.9% ($p = 0.021$) while total testosterone:cortisol ratio (1.6%, $p = 0.789$), and free testosterone:cortisol ratio (−3.2%, $p = 0.556$) remained unchanged from pre- to post-test. Mean T_3 levels decreased 4.8% ($p = 0.008$) while no significant changes

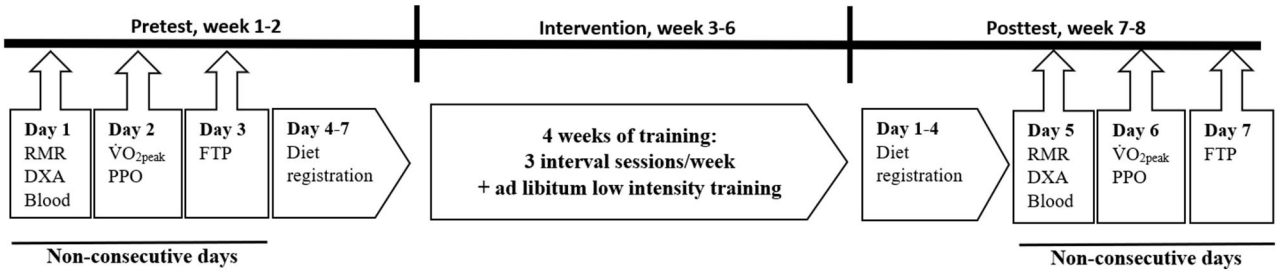

FIGURE 2 | Schematic overview of study design. Pre- and posttest measures included rested and fasted resting metabolic rate (RMR), dual-energy X-ray absorptiometry (DXA), and blood sampling. An incremental exercise test for determination of peak oxygen uptake (VO_{2peak}) and peak power output (PPO) as well as a 40-min functional threshold power-test (FTP) were performed in an unfasted state. Diet registration were performed during four consecutive days.

TABLE 1 | Descriptive characteristics of athletes included in the final analysis.

Variables	All ($n = 20$)
Age (years)	33.3 ± 6.7
Height (cm)	180.8 ± 4.9
Weight (kg)	75.8 ± 7.3
BMI (kg/m^2)	23.2 ± 1.9
Body fat (kg)†	11.1 ± 4.5
Body fat (%)†	14.9 ± 5.2
FFM (kg)†	65.5 ± 5.2
Resting HR (beats/minute)	48.0 ± 8.0
VO_{2peak} (mL.kg^{-1}.minute^{-1})	63.5 ± 6.6
VO_{2peak} (L.minute^{-1})	4.8 ± 0.4
Exercise (h/year)	395 ± 171
Active within cycling (years)	12.9 ± 9.7

Data are presented as mean ± SD. †measured by DXA. BMI, body mass index; DXA, dual-energy X-ray absorptiometry; FFM, fat-free mass; HR, heart rate; VO_{2peak}, peak oxygen uptake.

were observed in insulin and IGF-1 levels from pre- to post-test (**Table 4**).

A subanalysis that included the five participants with the largest increase and the five participants with the largest decrease in their free testosterone:cortisol (fT:cor) ratio from pre- to post-test revealed quantitatively quite similar changes in both total and free testosterone. In the group with an increased fT:cor ratio, there was a pronounced increase in testosterone (19 and 25%, total and free testosterone, respectively) and a 7% decrease in cortisol. This contrasted the group with decreased fT:cor ratio, where there was a decrease in total and free testosterone of 4 and 8%, respectively, combined with a 32% increase in cortisol. Furthermore, a greater improvement in functional threshold power was observed in the high fT:cor ratio group vs. the low fT:cor ratio group (9.5 vs. 2.5%), and similarly a higher relative RMR (0.6 vs. −4.2%, respectively) (**Table 5**). No differences were found when comparing training volume before or during the intervention in the high vs. low fT:cor ratio subgroups ($p = 0.609$).

DISCUSSION

In this study, we have demonstrated that 4 weeks of high-intensity training for 32 min, three times a week, superimposed on the athletes' background training, resulted in increased aerobic peak power output, VO_{2peak}, functional threshold power, as well as increased testosterone levels. In contrast, markers associated with low energy availability such as decreased RMR, lowered T_3, and increased cortisol, were found. Thus, our findings suggest positive performance responses of the exercise program used in the present study, however negative responses related to health, potentially caused by lowered energy availability were observed. This is a worrying sign, that a relative short period of 4 weeks can induce such changes, and athletes need to take this seriously.

Resting Metabolic Rate, Energy Intake, Body Composition, and Bone Mineral Density

In the present study, cyclists undertook a 4-week intensified endurance training intervention, which without any apparent increase in their energy intake, led to reduced energy availability, and a 3% reduction in RMR. This is similar to the findings of other studies (19, 20); indeed a 5% decrease in RMR was reported by Woods and co-workers (19) when elite male and female rowers undertook 4 weeks of heavy endurance training, without dietary compensation. Meanwhile, the same group reported that male cyclists achieved a state of overreaching and reduced RMR when 6 weeks of intensified training was undertaken without adjustment of energy intake (20). Meanwhile, other studies of increases in training workloads in endurance-trained male cyclists (28) or healthy males undertaking resistance and endurance training (29) reported an increase, or no change in RMR, respectively. However, in these studies, energy intake was either not assessed (28), or measured using a suboptimal protocol of a 3-day recall (29), and it is uncertain whether energy compensation accounted for the divergent results. RMR is mostly affected by body composition, with FFM as the largest determinant accounting for up to 70% of the individual variation in RMR, and is considered one of the largest components of total

TABLE 2 | Aerobic performance variables at pre- and posttest. Results from paired-sample *t*-tests (post-pre).

Outcome measure	Pre	Post	Mean ± SD of difference	95% CI	*P*-value	Δ Post-Pre (%)	ES
PPO (Watt)	397	416	18.5 ± 12.4	12.7–24.3	<0.001	4.8	1.49
VO_{2peak} (mL.kg^{-1}.minute^{-1})	63.5	65.0	1.5 ± 2.1	0.5–2.5	0.005	2.4	0.72
VO_{2peak} (L.minute^{-1})	4.8	4.9	0.1 ± 0.2	0.01–0.2	0.026	2.1	0.54
FTP (Watt)	261	278	17.0 ± 11.8	11.5–22.5	<0.001	6.5	1.44
FTP (Watt/kg)	3.5	3.7	0.2 ± 0.2	0.2–0.3	<0.001	6.9	1.48

Data are presented as mean ± SD of difference, 95% CI, percent change from pre to posttest and effect size (Cohen's D). PPO, aerobic peak power output; VO_{2peak}, peak oxygen uptake; FTP, functional threshold power.

TABLE 3 | RMR, energy intake, macronutrients, and body composition at pre- and posttest. Results from paired-sample *t*-tests (post-pre).

Outcome measure	Pretest	Posttest	Mean ± SD of difference	95% CI	*P*-value	Δ Post-Pre (%)	ES
Absolute RMR (kcal·day^{-1})	1,768	1,716	−52 ± 81	−90.3 to −14.1	0.010	−3.0	0.64
Relative RMR (kcal·kg^{-1} FFM·day^{-1})	26.9	26.2	−0.8 ± 1.2	−1.3 to −0.2	0.013	−2.6	0.67
RMR_{ratio}	0.91	0.88	−0.03 ± 0.04	−0.1 to 0.0	0.011	−3.3	0.75
Energy intake (kcal)	3,015	3,021	5.6 ± 560.6	−256.7 to 268.0	0.965	0.2	0.01
Carbohydrate intake (g)	332	338	5.2 ± 74.2	−30.6 to 40.9	0.766	1.8	0.07
Relative carbohydrate intake (g/kg)	4.4	4.5	0.1 ± 1.1	−0.4 to 0.6	0.607	2.2	0.09
Protein intake (g)	124	128	4.7 ± 25.0	−7.4 to 16.7	0.428	3.2	0.19
Relative protein intake (g/kg)	1.6	1.7	0.07 ± 0.4	−0.1 to 0.2	0.388	6.3	0.17
Fat intake (g)	123	125	1.7 ± 29.8	−12.6 to 16.1	0.803	1.6	0.06
Relative fat intake (g/kg)	1.6	1.7	0.03 ± 0.5	−0.2 to 0.2	0.741	1.8	0.06
Body weight (kg)†	75.8	75.7	−0.16 ± 0.7	−0.5 to 0.2	0.342	−0.1	0.23
FFM (kg)†	65.5	65.5	−0.05 ± 0.8	−0.4 to 0.3	0.764	0.0	0.06
Fat mass (kg)†	11.1	11.0	−0.09 ± 0.7	−0.4 to 0.2	0.563	−0.9	0.13

Data are presented as mean ± SD of difference, 95% CI, percent change from pre- to post-test and effect size (Cohen's D). †measured by DXA. DXA, dual-energy X-ray absorptiometry; FFM, fat-free mass; RMR, resting metabolic rate.

energy expenditure (30). In the present study, body composition, including FFM, remained unchanged from pre- to post-test and was therefore unlikely to contribute to the reduced RMR, despite several RED-S-related hormonal indications of a more catabolic state. It is unclear whether the increase in testosterone levels, possibly triggered by the endurance interval training, acted as a protective mechanism to prevent increased proteolysis. Hence, the lowered RMR might be a protective mechanism to prevent weight reduction and changes in body composition. Similar findings have been reported in elite male endurance athletes with low energy intake compared with athletes with adequate energy intake, where RMR was calculated to be 8% lower in the low energy intake group, suggesting an energy-conserving mechanism for maintaining body function and stable body weight (31).

Poor bone health develops over a long period with several influential factors, where a lack of loading due to the mode of exercise and poor nutrition are key factors (8, 10, 11). It is well-documented that long-term low energy availability is linked to poor bone health in both male and female athletes (8, 10, 11, 13), and road cycling does not induce significant osteogenic benefits compared with weight-bearing sports (32). Olmedillas et al. (33) reported lower BMD in young cyclists compared with recreationally active age-matched controls, and a recent Norwegian study showed that as many as 53% of elite cyclists had low BMD in the lower extremities, despite reporting regular resistance training (34). In our study 15% of the athletes had low BMD in either the lumbar spine, femoral neck, or total hip. Despite not having information on our athletes previously athletic history, it still raises concerns of athletes being unaware of the potentially negative effects of the lack of bone-loading involved in non-weight-bearing exercise, not performing high-load exercise that dampens the effects of bone loss as well as the intake of insufficient amounts of macro- and micronutrients.

The etiology of low energy availability is complex and may include excessive exercise, "making weight" before a competition, eating disorders, or unintentional mismatch between energy expenditure and energy intake resulting from a lack of appetite, poor nutrition knowledge, or lack of time to plan and prepare meals (11). In the present study, carbohydrate intake was lower and protein intake was higher than recommended (35, 36) and remained unchanged from pre- to post-test. In weight reduction periods, a higher protein intake at the expense of carbohydrates has been shown to improve the amount of fat loss and to preserve lean tissue (37), and this may contribute to the explanation of maintained FFM, despite unchanged energy intake during the intensified endurance training period in the present study. Nonetheless, the importance of periodizing energy intake to make changes in nutritional demands during different phases of training has previously been demonstrated (19); this should be emphasized to help support and enhance endurance training adaptations, especially

TABLE 4 | Blood markers at pre- and posttest. Results from paired-sample *t*-tests (post-pre).

Outcome measure	Pretest	Posttest	Mean ± SD of difference	95% CI	*P*-value	Δ Post-Pre (%)	ES
Total testosterone (nmol/L) [7.2–24.0]	17.4	18.8	1.35 ± 2.13	0.35–2.35	0.011	8.1	0.63
Free testosterone (nmol/L) [0.168–0.607]	0.459	0.478	0.020 ± 0.087	−0.021 to 0.060	0.326	4.1	0.23
Cortisol (nmol/L) [138.0–690.0]	381.1	430.3	49.25 ± 87.31	8.39–90.11	0.021	12.9	0.56
Free testosterone:cortisol ratio	0.00125	0.00121	0.0001 ± 0.0003	−0.0001 to 0.0001	0.556	−3.2	0.06
Total testosterone:cortisol ratio	0.047	0.046	0.001 ± 0.012	−0.007 to 0.005	0.789	1.6	0.06
SHBG (nmol/L) [8.0–60.0]	39.7	40.2	0.45 ± 4.23	−1.53 to 2.43	0.640	2.8	0.11
T_3 (nmol/L) [1.2–2.8]	2.1	2.0	−0.12 ± 0.18	−0.02 to −0.04	0.008	−4.8	0.67
Insulin (pmol/L) [≤160.0]	34.7	31.0	−3.70 ± 10.20	−8.48 to 1.08	0.121	−10.6	0.36
IGF-1(nmol/L) [17.0–63.0]	18.1	18.0	−0.16 ± 2.06	−1.12 to 0.81	0.740	−0.6	0.08

Data are presented as mean ± SD of difference, 95% CI, percent change from pre to post-test and effect size (Cohen's D). [xx-xx] indicates reference values. IGF-1, insulin-like growth factor-1; SHBG, sex hormone-binding globulin; T_3, triiodothyronine.

TABLE 5 | Relative changes in hormonal and performance variables from pre- to post-test in participants with highest increase vs. highest decrease in free testosterone:cortisol ratio. Results from independent sample *t*-test.

Relative change (%)	Highest increase ($n = 5$)	Highest decrease ($n = 5$)	*P*-value
Total testosterone	18.7 ± 20.6	−4.1 ± 8.9	0.053
Free testosterone	24.7 ± 26.0	−7.8 ± 9.0	0.030
Cortisol	−6.9 ± 17.7	32.3 ± 15.5	0.006
SHBG	−4.1 ± 6.1	4.2 ± 7.4	0.088
T_3	−10.0 ± 3.5	−11.0 ± 7.4	0.803
Insulin	−8.1 ± 17.6	−1.3 ± 30.0	0.675
IGF-1	−7.2 ± 3.0	−3.9 ± 6.8	0.352
PPO	6.3 ± 4.1	4.2 ± 3.2	0.388
VO_{2peak}	3.8 ± 3.8	2.4 ± 3.8	0.557
FTP	9.5 ± 5.4	2.5 ± 3.1	0.037
Training volume (h/week)	−5.1 ± 31.5	2.7 ± 18.9	0.650
Energy intake	6.6 ± 22.6	10.2 ± 38.2	0.860
Relative RMR	0.6 ± 2.8	−4.2 ± 3.3	0.039
Body weight	−0.4 ± 0.7	−0.5 ± 1.2	0.901
FFM	−0.7 ± 1.1	0.3 ± 0.6	0.126

Data are presented as mean ± SD. FFM, fat free mass; FTP, functional threshold power; IGF-1, insulin like growth factor-1; PPO, peak power output; relative RMR (kcal/kg FFM/day), resting metabolic rate; SHBG, sex hormone-binding globulin; T_3, triiodothyronine; VO_{2peak}, peak oxygen uptake.

when athletes undergo strenuous meso- and macrocycle training (38).

Blood Markers

We observed an increase in total testosterone levels from pre- to post-test, presumably as a positive response from the intensified endurance training protocol. We measured testosterone directly, and calculated free testosterone as well, by dividing total testosterone with SHBG. Based on the old free hormone hypothesis, free testosterone should be the bioavailable form of testosterone. However, this hypothesis has been debated for three decades, without definite conclusion. Thus, a recent comprehensive review by Goldman et al. (39) concluded that no measure of testosterone is ideal, and that both total and free testosterone should be considered. The calculated free testosterone, found by dividing total testosterone with SHBG, is also hampered by assumptions of association constants, and further accuracy and precision are affected negatively by the need for using two analyses. In the literature on the effect of training on testosterone levels, most studies have reported only total testosterone levels. Therefore, we chose to report both measures. The increase in total testosterone observed, could partly be a result of an observed small, however insignificant increase in SHBG. Testosterone, an anabolic steroid, stimulates growth, increases protein synthesis, and controls the development and maintenance of the secondary sex characteristic. Previous studies have demonstrated acute changes in testosterone in resistance training and high volumes of exercise using large muscle mass (40). Severe reductions in testosterone have been reported in male soldiers undergoing prolonged starvation (41), while Koehler et al. (16) found no reduction in testosterone when males were exposed to short periods of very low energy availability (∼15 $kcal \cdot kg^{-1}$ $FFM \cdot day^{-1}$) for 4 days.

In the present study, cortisol increased by 12.9% from mean values of 381–430 nmol/L. Cortisol is likely to contribute to increased adiposity during energy abundance, and is an important catabolic hormone secreted to ensure glucose homeostasis during prolonged exercise, glycogen depletion, stress, and starvation (13, 42). A meta-analysis of human studies by Nakamura et al. (43) investigating fasting and severe caloric restriction found increased cortisol levels followed by a long-term normalization, while another study by Kyrolainen et al. (17) found increased cortisol as a response to heavy prolonged physiological stress in soldiers, followed by an immediate reduction when soldiers experienced a stress reduction. However, in a study comparing nine long-distance male runners with low energy availability with eight non-athletes with optimal energy availability, cortisol was not different between the groups (44). The increase in cortisol in our athletes could, therefore,

be a combination of a natural response to a sudden increase in high-intensity training as well as an increased need to catabolize alternate energy sources and preserve glycogen, as shown previously (17).

Increased training volumes, combined with insufficient recovery strategies, increases the risk of non-functional overreaching (2, 3). A decrease in the testosterone:cortisol ratio of 30% has been suggested as an indicator of poor recovery (45, 46) and a catabolic status (4, 5), while a value of 0.35×10^{-3} has been suggested as a threshold of overtraining (46). In the present study 50% of the participants increased their free testosterone:cortisol ratio during the intervention period, while 50% had a reduced free testosterone:cortisol ratio, including two athletes who had a decrease of > 30%. In the exploratory subanalysis where we looked at the five athletes with the highest increase and five athletes with the greatest decrease from pre- to post-test values of the fT:cor ratio, the changes in total and free testosterone were quantitatively similar, and the ratio was not affected by changes in SHBG to a major degree. Of particular interest, we also found a greater improvement in functional threshold power in those with the highest fT:cor ratio increase compared with those with the largest decrease. Due to a combined increase in free testosterone and decrease in cortisol levels and maintained RMR, this indicates a highly improved anabolic state from pre- to post-test in our study. Although no differences were found in the changes in energy intake between the groups, a > 4% reduction in RMR indicates low energy availability in the participants with the largest decrease the in fT:cor ratio (19). Interestingly, none of the participants in this group showed any signs of preexisting low energy availability on endocrine markers, body composition, BMD, or markers related to RMR; hence, the changes in RMR could potentially be linked to inadequate recovery in this group. Unfortunately, no information regarding heredity of low BMD, history of earlier eating disorder behavior, or what type of training the athletes did before starting being active within cycling were available. Furthermore, when examining the training diaries from before the intervention with the diaries from during the intervention, we found no differences between subgroups. Unfortunately, we do not know the exact distribution of their low- and high-intensity training before the intervention, due to low compliance regarding intensity distribution.

IGF-1 is a pro-insulin-like structure with broad anabolic properties, and low levels are linked to starvation and chronic undernutrition (47). Insulin is a metabolic hormone involved in energy balance, and insulin secretion is correlated with visceral fat in humans, and particularly in males (48). In an eight-week military-exercise study with extreme starvation, Friedl et al. (41) reported a 50% reduction in both IGF-1 and insulin, suggesting improved insulin sensitivity, with a normalization of IGF-1 after a refeeding period halfway through the intervention; however, IGF-1 returned to its declining trajectory when energy again was restricted. Research by Koehler and co-workers (16) showed no reduction in IGF-1, while a decrease in insulin of 36% was observed during short periods of severe low energy availability. These results are similar to the findings in the present study, although we found a non-significant decrease in insulin of 11%. It is possible that the athletes' energy deficiency was not large enough to initiate significant changes, or that the athletes in our study were able to refeed and recover in the week between the last exercise bout and testing.

We did, however, observe a reduction in T_3, an important hormone for growth, reproduction, and metabolism (13), and a suggested surrogate marker of low energy availability, widely associated with suppressed RMR (49, 50). However, in the study by Koehler et al. (16) where they exposed males to very low energy availability, they found no reduction in T_3, and therefore questioned whether exercising men are more robust to short bouts of low energy availability compared with sedentary and exercising women. A reduction in T_3 among soldiers experiencing prolonged starvation has been reported (41), and a recent study reported lower T_3 levels in males with testosterone levels within the lowest quartile of the reference range compared with males with testosterone levels above this threshold (51).

In the present study, the intensified endurance training protocol could potentially have induced the increase in testosterone levels, while subclinical low energy availability could have induced the lowered RMR and T_3 and increased cortisol levels. Although indications of low energy availability with an increased catabolic state and a less positive response of the training intervention were found in a subgroup of participants, it is possible that the intensified mesocycle superimposed on their habitual training load, was not strenuous enough to induce widespread hormonal changes. Other reasons could be that the participants' overall energy deficit was not large enough to induce the severe endocrine changes associated with clinical low energy availability in males earlier reported (16, 41). Unfortunately, we were not able to obtain a thoroughly detailed training load from the participants' habitual training pattern, or energy availability, since the details of the participants' training diaries were of inadequate quality to distinguish between high-intensity and low-intensity training.

Limitations

To minimize limitations in this study, we used strict best-practice protocols developed for RMR and body composition assessments, including urine specific gravity tests to secure reliable results for comparison (26, 52, 53). Furthermore, we had an appropriate number of participants to gain sufficient statistical power, and we used a 4-day consecutive dietary record period mirroring participants typical food patterns, including weighed dietary records to assess energy intake. Although most assessments in the present study were performed in a controlled laboratory-based setting, some limitations must still be acknowledged. First, the sample was classified as having some convenience sample characteristics. Second, we acknowledge that RED-S is a complex field of research, and the results presented in this study should be interpreted with care, given that: (1) various individual responses to intensive exercise occurs, (2) the cyclists were not matched according to training/hormonal status, (3) the study design did not include measurement of energy intake, exercise energy expenditure, and changes in RMR during the intervention period, only pre- and posttest, (4) we experienced low compliance regarding the details of training diaries, making it difficult to assess total accumulated high- and low-intensity training prior to and during the intervention, and

(5) we had no control group. We acknowledge that the lack of a control group makes it difficult to conclude with certainty that the changes are due to the intervention. We therefore also chose a more exploratory approach, by investigating the participants with the highest increase/decrease in fT:cor ratio, aiming at generating new hypotheses. Regarding the analysis of testosterone, it should be emphasized that this analysis has inherent and until now unsolved problems, as discussed earlier. Finally, we also acknowledge that the participants in this study were free-living, well-trained athletes, not elite athletes. This makes them prone to stresses outside of our control, including those associated with obligations to family and friends, work and study loads, as well as lifestyle factors that may have influenced their training load.

NOVELTY STATEMENT

Periods with increased training loads are common as part of an attempt to increase aerobic performance. Today, only a few studies have examined how various intensified endurance training regimens expose male athletes to the risk of RED-S, and this study contributes to new knowledge on a group of athletes not previously investigated; it also uses blood markers, as called for in recent studies (19, 20). The present study demonstrated that 4 weeks of high-intensity endurance training superimposed on their regular training increased athletes' aerobic performance and testosterone levels. However, adverse changes in markers related to low energy availability, such as a reduction in RMR and T_3, and an increase in cortisol were observed. It is, however, unclear whether these changes resulted from a lack of increase in energy intake *per se,* if the length of the intervention period was too short to identify more severe clinical changes in markers of low energy availability, or a combination of both. It is worrying, that negative changes in RED-S-related parameters were observed after only 4 weeks of intensified endurance training, and our findings substantiate the importance of further understanding and monitoring RED-S in male athletes undertaking intensified endurance training regimens, as well as increased awareness and education among athletes and coaches.

PRACTICAL IMPLICATIONS

The present study indicates that well-trained male athletes seem to underestimate the importance of matching their energy intake when undertaking a mesocycle of intensified endurance training. This is challenging, and practitioners should be aware that male athletes are also prone to develop indications of RED-S even during a short intensified 4-week endurance mesocycle. Investigating and understanding RED-S, especially in male athletes, is a complex and difficult task. Several markers exist to help researchers and practitioners to interpret energy availability among athletes. The use of blood markers as one of several measures should be included in future research to better understand how males respond to various levels of endurance exercise regimens in combination with assessing their RMR and energy availability. Furthermore, to prevent RED-S-associated conditions in athletes, established and available tools, such as the RED-S clinical assessment tool (RED-S CAT), may be of value for practitioners and health personnel (8, 54).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University Faculty Ethics Committee and the Norwegian Centre for Research Data (No. 46706). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The study was conceptualized and designed by TS, MT, and AM. Data were collected and analyzed by TS. Contribution were made to materials analysis by TS, MT, JF, and AM. Visualization was performed by TS. Writing of the original draft was performed by TS. Reviewing and editing were done by TS, MT, JF, and AM. All authors approved the final version of the paper.

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Paper II

Prevalence of surrogate markers of relative energy deficiency in male Norwegian Olympic-level athletes

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ORIGINAL RESEARCH

Prevalence of Surrogate Markers of Relative Energy Deficiency in Male Norwegian Olympic-Level Athletes

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The syndrome of relative energy deficiency in sport (RED-S) includes wide-ranging effects on physiological and psychological functioning, performance, and general health. However, RED-S is understudied among male athletes at the highest performance levels. This cross-sectional study aimed to investigate surrogate RED-S markers prevalence in Norwegian male Olympic-level athletes. Athletes ($N = 44$) aged 24.7 ± 3.8 years, body mass 81.3 ± 15.9 kg, body fat 13.7% ± 5.8%, and training volume 76.1 ± 22.9 hr/month were included. Assessed parameters included resting metabolic rate (RMR), body composition, and bone mineral density by dual-energy X-ray absorptiometry and venous blood variables (testosterone, free triiodothyronine, cortisol, and lipids). Seven athletes (16%) grouped by the presence of low RMR ($RMR_{ratio} \leq 0.90$) (0.81 ± 0.07 vs. 1.04 ± 0.09, $p < .001$, effect size 2.6), also showed lower testosterone (12.9 ± 5.3 vs. 19.0 ± 5.3 nmol/L, $p = .020$) than in normal RMR group. In low RMR_{ratio} individuals, prevalence of other RED-S markers (—subclinical—low testosterone, low free triiodothyronine, high cortisol, and elevated low-density lipoprotein) was (N/number of markers): 2/0, 2/1, 2/2, 1/3. Low bone mineral density (z-score < −1) was found in 16% of the athletes, all with normal RMR. Subclinical low testosterone and free triiodothyronine levels were found in nine (25%) and two (5%) athletes, respectively. Subclinical high cortisol was found in 23% of athletes while 34% had elevated low-density lipoprotein cholesterol levels. Seven of 12 athletes with two or more RED-S markers had normal RMR. In conclusion, this study found that multiple RED-S markers also exist in male Olympic-level athletes. This highlights the importance of regular screening of male elite athletes, to ensure early detection and treatment of RED-S.

Keywords: body composition, low energy availability, metabolic rate, hormonal response

Relative energy deficiency in sport (RED-S) describes a syndrome with impairment of numerous physiological systems, triggered by low energy availability (LEA; Mountjoy et al., 2014, 2018). The LEA with or without disordered eating (DE) behaviors, impose serious health risks potentially with clinical manifestations, such as endocrine alterations, reproductive function, impaired bone health, and cardiovascular risk factors (De Souza et al., 2014; Elliott-Sale et al., 2018; Gibbs et al., 2013; Logue et al., 2020; McCall & Ackerman, 2019; Melin et al., 2019; Mountjoy et al., 2014, 2018; Nattiv et al., 2007). Until recently, research related to LEA has been predominantly performed in female athletes (De Souza et al., 2014; Logue et al., 2020; Mountjoy et al., 2014, 2018; Nattiv et al., 2007), competing in sport disciplines where leanness and/or a low body weight is directly (power-to-weight ratio) or indirectly (appearance) related to performance or a specific body weight as a requirement to compete (weight category sports) (Gibbs et al., 2013; Martinsen et al., 2010; Mountjoy et al., 2018; Sundgot-Borgen, 1993, 2013; Sundgot-Borgen & Torstveit, 2010).

In males, similar negative metabolic and endocrine alterations have been observed, as well as reductions in testosterone levels, which may be associated with reproductive dysfunction, impaired performance, injuries and poor bone health (De Souza et al., 2019; Elliott-Sale et al., 2018; Friedl et al., 2000; Heikura et al., 2018b; Klomsten Andersen et al., 2018). Elite athletes often have high training loads and energy expenditure, demanding an increase in energy intake which, if not addressed by an accompanying increase in energy intake, may amplify the risk of LEA (Burke et al., 2018). Furthermore, elite athletes in leanness sports may be particularly vulnerable to LEA due to the desire to remain light and lean, with many acknowledging the use of increased training load to facilitate body composition adaptations (Gibbs et al., 2013; Martinsen et al., 2010; Sundgot-Borgen, 1993, 2013; Sundgot-Borgen & Torstveit, 2010). The incidence of LEA in world-class male elite endurance athletes has been reported to be 25% (Heikura et al., 2018b). Due to potential adverse implications, the development of tools to identify male athletes at risk for RED-S is therefore warranted (Mountjoy et al., 2018). Preliminary research suggests that males may withstand a lower threshold of LEA compared with females (Koehler et al., 2016; Papageorgiou et al., 2017); however, EA is difficult to assess, making it challenging to use as a practical and reliable measure (Areta et al., 2021; Burke et al., 2018; De Souza et al., 2019; Heikura et al., 2018b). Furthermore, no validated screening tools like the "Low Energy Availability in Females Questionnaire" currently exists for use with males. In total, RED-S in male athletes is understudied with only a few studies investigating RED-S among elite male endurance athletes (Heikura et al., 2018a, 2018b; Logue et al., 2021), including nonleanness athletes (Logue et al., 2020, 2021; Tenforde et al., 2016).

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The aim of this study was to investigate RED-S in a Norwegian cohort of male Olympic-level athletes using surrogate markers, such as suppressed resting metabolic rate (RMR), impaired bone health, and altered metabolic and endocrine variables.

Material and Methods

Study Design and Recruitment

This study was designed as a cross-sectional study. Athletes were recruited through the Norwegian Olympic and Paralympic Committee and Confederation of Sports. The study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (2017/2160) and the Norwegian Centre for Research Data (56937/3/STM/LR) and conducted following the 2013 Declaration of Helsinki. Inclusion criteria were senior athlete ≥18 years of age, competing at a national team level in road cycling, long- and middle-distance running, triathlon, race walking, rowing, wrestling, biathlon, Nordic combined, cross-country skiing, boxing, powerlifting, soccer, or handball. The exclusion criteria were injuries preventing athletes from participating in their regular training regimen. The recruitment process involved announcements and distributions of invitations via email to both national coaches and athletes, intending to encourage participation. Interested athletes received written information about the study, and those interested in participation signed an informed consent. In total, 44 Olympic-level male athletes accepted participation, competing in the following sports: road cycling, triathlon, race walking, light-weight rowing, wrestling, biathlon, Nordic combined, cross-country skiing, kickboxing, powerlifting competing in high weight classes (≥93 kg), and handball.

Assessment Protocol

All tests were performed from January to March 2018, between 5 and 9 a.m. starting with RMR measurements, followed by body composition and BMD assessment before blood sampling.

Resting Metabolic Rate

Athletes either slept overnight at the laboratory in Oslo, Norway or arrived in a 12-hr fasted and rested state using motorized transport with minimal bodily movement. On arrival, subjects were placed in a quiet and dimly lit room maintained at a constant temperature (21 °C). For a detailed description of measurement, see Table 1.

Body Composition and Bone Health

Following RMR assessment, stretch stature, body weight, body composition, and BMD were measured as described in Table 1.

Biochemical Markers

A venous blood sample was drawn as described in Table 1, and serum was analyzed at a commercial clinical laboratory (Fürst, Oslo, Norway).

RED-S Criteria

Following the procedure of Heikura et al. (2018b), athletes were given a score based on a positive (1 point) or a negative (0 points) prevalence related to the following symptoms of RED-S; low body fat, defined as <5% (Sundgot-Borgen et al., 2013), underweight defined as BMI < 18.5 kg/m^2 (Sundgot-Borgen et al., 2013), low BMD defined as a z-score < −1 in lumbar spine or femur neck (Nattiv et al., 2007), low RMR defined as an RMR_{ratio} < 0.90 using the Cunningham (1980) equation (Strock et al., 2020b), subclinical low testosterone, defined as within the lowest quartile of clinical range defined by the laboratory (<14.8 nmol/L) or fT_3 (<4.3 pmol/L), subclinical high cortisol, defined as within the highest quartile of clinical range (>537 nmol/L), or elevated low-density lipoprotein (LDL) levels (>3.0 mmol/L).

Statistics

Data were analyzed using Stata for Windows (version 16; Stata Corp LCC, College Station, TX). The data set was controlled for signs of nonnormality using histograms, Q–Q plot, and the Shapiro–Wilk test. Athletes ($n = 44$) were included and divided into two groups based on energetic status (low vs. normal RMR) (Strock et al., 2020b). Differences between energetic status were assessed using the welch test for unequal variances. Contingency data were analyzed using the Fisher exact test. Between-group differences are expressed with Cohen's d effect size (ES) with the following threshold; trivial (<0.2), small (0.2–0.5), moderate (0.5–0.8), and large (>0.8). Relationships between RED-S variables were investigated using linear regression. Statistical significance level was defined as $p < .05$, and data are presented as mean ± SD.

Results

Descriptive data are presented in Table 2.

RED-S Criteria

Of the 44 athletes, 32 (73%) had either 0 or 1 RED-S criteria present seven athletes (16%) presented with two criteria, four athletes (9%) with three criteria, and one athlete (2%) with four criteria (Figure 1). Detailed criteria points, including absolute values for all athletes with low RMR are presented in Table 3, including all athletes with low BMD independent of the presence of other markers, as well as two athletes with three simultaneously present criteria other than low RMR.

RED-S Surrogate Markers

Table 4 summarizes the RED-S surrogate markers investigated according to energetic status, while Figure 2 summarizes RED-S markers. Overall, the low RMR group had lower testosterone compared with the normal RMR group (Table 4). No significant linear relationship was found between RMR_{ratio} and surrogate biochemical markers of RED-S ($p > .05$).

None of the athletes had low body fat or were underweight. Of the 44 athletes included, seven (16%) had low RMR_{ratio}. Of these seven athletes, two athletes had no other RED-S marker present, two athletes had one marker present, two athletes had two markers present, while one athlete had three other RED-S markers present simultaneously. Seven athletes (16%) had low BMD in the lumbar spine, with four of them having no other RED-S marker present. A total of 11 athletes (25%) had subclinical low testosterone levels, including one athlete with clinically low levels (<8 nmol/L). Two athletes (5%) had subclinical low fT_3. Ten athletes (23%) had subclinical high cortisol, and 15 athletes (34%) had elevated LDL levels.

Leanness Versus Nonleanness Athletes

Thirty-four of the athletes participated in leanness sports, while the remaining 10 were involved in nonleanness sports. No significant

Table 1 Overview of Methods Used to Assess and Evaluate RED-S Surrogate Markers

Component	Summary of method	Comments/references
RMR		
mRMR	Indirect calorimetry using an automated system with a ventilated canopy hood (SentrySuite version 2.21.4; Vyntus CPX, CareFusion, Hoechberg, Germany). The system was calibrated before each test following manufacturer directions. Participants laid in supine position for 5 min, before canopy was positioned. All were instructed to remain still and not fall asleep. VO_2 and VCO_2 were assessed over a 25-min period, and the last 20 min of measurements used to assess RMR. Typical error of measurement (CV%) for this methodology in the laboratory was 4.5% (95% confidence limits, 3.5%–6.2%)	Compher et al. (2006) Areta et al. (2019) Weir (1990)
pRMR	$500 + 22 \times$ LBM (in kilograms)	Cunningham (1980) based on Thompson and Manore (1996)
RMR ratio	Calculated as mRMR/pRMR	De Souza et al. (2008)
Physique		
Body composition + BMD (femur neck and lumbar spine L1–L4)	Via DXA, strictly adhering to protocol. Urinary specific gravity was measured using a digital refractometer (Atago UG-α cat. no. 3464, ATAGO USA Inc., Bellevue, WA). Scans were performed in the total body mode on a narrow fan-beam DXA scanner (EnCore version 16.20 software; Lunar iDXA, GE Healthcare, Madison, WI with the combined NHANES/Lunar reference database). The coefficient of variation for the laboratory was 0.0%, 1.0%, 0.3%, 0.3% for body mass, fat mass, lean mass, and bone mass, respectively. All scans were conducted by the same technician using the standard thickness mode as determined by the auto scan feature in the software and analyzed automatically by the DXA software	Kerr et al. (2016) Nattiv et al. (2007) Mountjoy et al. (2014)
Height	Measured without shoes to the nearest 0.1 cm using a wall-mounted centimeter scale (Seca Optima; seca Ltd, Birmingham, United Kingdom)	
Body weight	Measured in underwear to the nearest 0.01 kg with an electronic scale (model 861; seca Ltd)	
BMI	Total body weight (in kilograms)/body height squared (in meter), kg/m^2	
Q3 FFMI	FFM (in kilograms)/body weight squared (in meter), kg/m^2	
FMI	Fat mass (in kilogram)/body weight squared (in meter), kg/m^2	
Biochemical markers		
Blood sampling	A venous blood sample was drawn from an antecubital forearm vein by a qualified nurse. 5-ml Vacuette Z Serum Sep clot activators were filled and subsequently centrifuged at 3000 RPM for 10 min (Statspin Express 4; Beckman Coulter, CA) within a limit of ≥20 min but ≤40 min. 2-ml Cryotube vials were filled with serum and cooled to 2 °C before being transported for analysis	Blood was centrifuged at $1500 \times g$ for 12 min and serum was analyzed for total and free testosterone (analytic CV 7.6%), fT_3 (3.0%), cortisol (8.2%), LDL (2.0%), and TC (1.9%)

Note. BMD = bone mineral density; BMI = body mass index; FFM = fat-free mass; FFMI = fat-free mass index; FMI = fat mass index; RED-S = relative energy deficiency in sport; LBM = lean body mass; RMR = resting metabolic rate; mRMR = measured RMR; pRMR = predicted RMR; fT_3 = free triiodothyronine; DXA = dual-energy X-ray absorptiometry; NHANES = National Health and Nutrition Examination Survey; RPM = rotations per minute.

differences in prevalence were observed between leanness and nonleanness athletes (Figure 2).

Discussion

This is one of the few studies investigating surrogate markers of RED-S in a larger group of Olympic-level male athletes, including both leanness and nonleanness sports athletes (Drew et al., 2018, 2017). The primary findings of this investigation were that most athletes displayed none or few single markers related to RED-S independent of current low RMR. However, seven athletes (16%) were identified with low RMR with the majority of these displaying additional RED-S markers. The LEA can be present with or without DE behaviors and is more prevalent among female athletes, especially in sports where leanness is associated with

Table 2 Descriptive Characteristics of Athletes in Total and Categorized According to Energetic Status

Measurement	Total ($n = 44$)	Low RMR ($n = 7$)	Normal RMR ($n = 37$)	p value	ES (95% CI)
Age (years)	24.8 ± 3.8	26.0 ± 3.3	24.6 ± 3.9	.338	0.2 [−1.1, 0.4]
Stature (cm)	181.3 ± 8.4	177.9 ± 8.8	181.8 ± 8.2	.297	0.5 [−0.3, 1.3]
Weight (kg)	81.3 ± 15.9	80.5 ± 19.1	81.5 ± 15.5	.907	0.1 [−0.8, 0.9]
BMI (kg/m^2)	24.7 ± 4.4	25.3 ± 4.4	24.6 ± 4.4	.724	0.1 [−0.9, 0.7]
FFM (kg)[a]	69.4 ± 11.2	71.2 ± 12.9	69.0 ± 10.9	.682	0.2 [−1.0, 0.6]
FFMI (kg/m^2)	21.6 ± 2.7	22.4 ± 2.9	21.4 ± 2.7	.425	0.2 [−1.2, 0.4]
FMI (kg/m^2)	3.6 ± 2.4	3.2 ± 1.8	3.7 ± 2.5	.567	0.2 [−0.6, 1.0]
Body fat (%)[a]	14.7 ± 6.9	12.2 ± 4.5	15.2 ± 7.2	.167	0.4 [−0.6, 1.0]
Training volume (hr/month)	76.1 ± 22.9	72.9 ± 18.6	76.7 ± 22.7	.638	0.2 [−0.6, 1.0]
L1–L4, z-score[a]	0.59 ± 1.62	1.86 ± 1.92	0.35 ± 1.46	.083	1.0 [0.2, 1.8]
Femur z-score[a]	0.96 ± 1.14	1.33 ± 0.82	0.89 ± 1.19	.280	0.3 [−0.3, 0.5]

Note. Values are presented as mean ± *SD*. The p value and ES indicates difference between low and normal RMR group. The ES expressed as Cohen's d with 95% CI. BMI = body mass index; CI = confidence interval; ES = effect size; DXA = dual-energy X-ray absorptiometry; FFM = fat-free mass; FFMI = fat-free mass index; FMI = fat mass index; RMR = resting metabolic rate.
[a]Measured by DXA.

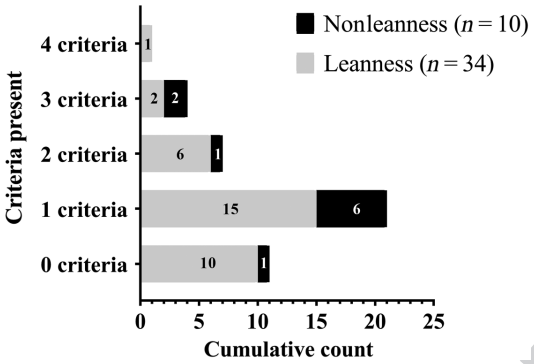

Figure 1 — Between-group and cumulative count (x-axis) of the numbers of RED-S criteria present among the athletes divided into leanness and nonleanness groups. RED-S = relative energy deficiency in sport.

performance (Gibbs et al., 2013; Mountjoy et al., 2014; Sundgot-Borgen, 1993, 2013; Sundgot-Borgen & Torstveit, 2010; Tenforde et al., 2016). Hence, screening and identifying athletes at risk of DE behaviors is therefore important; however, it is time consuming and requires the expertise of a multidisciplinary team (Wells et al., 2020).

Prevalence of Clustered RED-S Markers

The prevalence of RED-S in athletes has been reported to range between 22% and 58% (Logue et al., 2020). However, few of these studies have investigated male athletes at elite or Olympic levels. In a study by Heikura et al. (2018b), 25% of their world-class male middle- and long-distance runners and racewalkers were identified with LEA, with significant lower testosterone levels in the LEA group. Assessing RED-S related markers, 40% of their population also had lower testosterone and T_3 levels, including a 4.5 times greater incidence of bone injury in these athletes, despite BMD being unimpaired, but did not assess RMR (Heikura et al., 2018b). Woods et al. (2017) reported reduction of ~2 kcal·kg FFM^{-1}·day^{-1} in RMR and body weight in elite rowers undertaking a 4-week intensified training period, without an apparent increase in EI. We recently reported a case study on a male combat athlete cutting weight for competition during 7 weeks of EA ~20 kcal·kg FFM^{-1}·day^{-1} and 1 week ~3 kcal·kg FFM^{-1}·day^{-1}, showing a clear concomitant decrease of RMR_{ratio} under 0.9 (Cunningham, 1980) and RED-S markers falling outside clinical reference ranges (Langan-Evans et al., 2020). Similarly, in the current study, we identified seven athletes (16%) with low RMR, five of whom had multiple other RED-S markers, such as subclinical low testosterone and fT_3, subclinical high cortisol, and elevated LDL. Interestingly, we also identified two athletes without low RMR, yet with three other RED-S markers present, such as subclinical low testosterone, low BMD, subclinical high cortisol, and elevated LDL, warranting further scrutiny (Table 4). However, our findings provide preliminary data suggesting that RMR_{ratio} may be a practical tool to identify athletes at risk of RED-S, representing a novel approach attempting to overcome the difficulties of assessing EA (Areta et al., 2021; Burke et al., 2018; De Souza et al., 2019).

Metabolic Alterations

The FFM is one of the most significant determinants of RMR, and reductions in RMR have been reported in male athletes with LEA (Torstveit et al., 2018; Woods et al., 2017, 2018). When energy availability is insufficient for basal physiological processes, the body prioritizes processes essential for survival, reducing RMR to conserve energy, including suppression of reproduction, growth, metabolism, and bone formation (De Souza et al., 2019; Mountjoy et al., 2014; Nattiv et al., 2007). An RMR_{ratio} of <0.90 has been recognized as a surrogate marker of LEA in exercising females (McCall & Ackerman, 2019; Strock et al., 2020a, 2020b). Furthermore, research by Strock et al. has identified that RMR_{ratio} accurately reflects total T_3 status in females, making it a useful marker of prolonged energy deficiency (Strock et al., 2020a, 2020b). In our study, seven athletes had low RMR, with five of them also having subclinically low testosterone. Interestingly, five out of seven of these athletes had very low RMR, ranging from 0.68 to 0.83 (Table 3), with similar deficits to that observed in females with anorexia nervosa (Marra et al., 2002). Most athletes with low RMR also presented subclinically low testosterone levels, strengthening a link to LEA, similar to the findings of Heikura et al. (2018b). However, rather than using RMR_{ratio} as a sole diagnostic tool, a

Table 3 A Detailed Description of Athletes With 1, 2, and ≥3 RED-S Points

Athlete	Sport	Low RMR ratio < 0.90	Low BMD *z*-score <−1.0	Subclinical low TES < 14.8 nmol/L	Subclinical low fT_3 < 4.3 pmol/L	Subclinical high COR > 537 nmol/L	Elevated LDL > 3.0 nmol/L	Fat %
1 RED-S point								
1	Wrestling	**YES** (0.89)	NO (+4.3)	NO (21.0)	NO (5.3)	NO (479)	NO (2.7)	8.1
2	Kickboxing	**YES** (0.68)	NO (−0.4)	NO (17.0)	NO (5.2)	NO (483)	NO (2.6)	11.6
3	Triathlon	NO (1.06)	**YES** (−1.2)	NO (16.0)	NO (6.3)	NO (459)	NO (2.6)	9.7
4	Triathlon	NO (1.06)	**YES** (−1.1)	NO (22.0)	NO (6.7)	NO (283)	NO (2.7)	13.4
5	Rowing	NO (0.98)	**YES** (−1.1)	NO (30.0)	NO (5.9)	NO (390)	NO (1.6)	17.9
6	Rowing	NO (1.08)	**YES** (−1.9)	NO (18.0)	NO (6.0)	NO (406)	NO (2.2)	15.5
2 RED-S points								
7	Kickboxing	**YES** (0.77)	NO (+3.2)	**YES** (13.0)	NO (4.8)	NO (404)	NO (2.0)	9.7
Q4 8	Powerlift	**YES** (0.89)	NO (+0.3)	**YES** (9.0)	NO (6.5)	NO (386)	NO (2.6)	21.5
9	Cycling	NO (1.03)	**YES** (−1.2)	NO (20.0)	NO (5.8)	NO (478)	**YES** (3.9)	13.3
10	Cycling	NO (1.06)	**YES** (−1.8)	NO (27.0)	**YES** (3.6)	NO (518)	NO (1.9)	9.0
11	Rowing	NO (0.96)	NO (+0.8)	**YES** (13.0)	NO (5.3)	NO (451)	**YES** (3.1)	8.1
12	Nordic combined	NO (0.92)	NO (−0.8)	NO (25.0)	NO (5.1)	**YES** (544)	**YES** (3.1)	9.0
13	Powerlift	NO (1.04)	NO (+1.5)	**YES** (13.0)	NO (5.4)	NO (236)	**YES** (4.9)	26.1
≥3 RED-S points								
14	Cycling	**YES** (0.77)	NO (−0.1)	**YES** (4.3)	**YES** (3.9)	**YES** (573)	NO (2.8)	8.6
15	Kickboxing	**YES** (0.83)	NO (+2.4)	**YES** (13.0)	NO (4.9)	**YES** (711)	NO (2.8)	14.1
16	Powerlift	**YES** (0.83)	NO (+3.4)	**YES** (13.0)	NO (5.4)	NO (222)	**YES** (4.5)	26.1
17	Powerlift	NO (1.05)	**YES** (−1.9)	**YES** (12.0)	NO (5.7)	NO (417)	**YES** (3.1)	35.4
18	Rowing	NO (1.08)	NO (−0.5)	**YES** (8.0)	NO (5.4)	**YES** (633)	**YES** (3.1)	10.7

Note. Values in parenthesis represent absolute values of measurements. BMD = bone mineral density; RMR = resting metabolic rate; TES = total testosterone; fT_3 = free triiodothyronine; COR = cortisol; LDL = low-density lipoprotein; RED-S = relative energy deficiency in sport.

Table 4 Reproductive and Metabolic Hormones of Athletes in Total and Categorized According to Energetic Status

Measurement	Total (*n* = 44)	Low RMR (*n* = 7)	Normal RMR (*n* = 37)	*p* value	ES (95% CI)
RMR_{ratio}	1.00 ± 0.13	0.81 ± 0.07	1.04 ± 0.09	<.001	2.6 [1.6, 3.6]
Relative RMR (kcal·kg FFM^{-1}·day^{-1})	29.4 ± 4.1	23.6 ± 1.8	30.4 ± 3.3	<.001	2.2 [1.2, 3.1]
Total testosterone (nmol/L)	18.1 ± 5.9	12.9 ± 5.3	19.0 ± 5.3	.020	1.2 [0.3, 2.0]
Free testosterone (nmol/L)	0.37 ± 0.11	0.28 ± 0.13	0.39 ± 0.10	.061	1.1 [0.3, 1.9]
Free T_3 (pmol/L)	5.6 ± 0.7	5.1 ± 0.8	5.7 ± 0.7	.127	0.8 [0.0, 1.6]
Cortisol (nmol/L)	451 ± 115	465 ± 154	449 ± 106	.789	0.2 [−1.0, 0.7]
TC (mmol/L)	4.7 ± 0.8	5.0 ± 0.8	4.6 ± 0.8	.270	0.5 [−0.3, 1.3]
LDL (nmol/L)	2.7 ± 0.8	2.9 ± 0.8	2.6 ± 0.8	.606	0.2 [−1.0, 0.6]

Note. Values are presented as mean ± *SD*. The *p* value and ES indicates the difference between low and normal RMR group. The ES expressed as Cohen's *d* with 95% CI. ES = effect size; FFM = fat-free mass; CI = confidence interval; T_3 = triiodothyronine; RMR = resting metabolic rate; TC = total cholesterol; LDL = low-density lipoprotein.

combination with other markers, such as hypotension, underweight, and subclinically low testosterone levels in males are recommended (Staal et al., 2018). Furthermore, the 0.90 cutoff point was initially established in exercising females (De Souza et al., 2008), making it to some extent challenging to apply to athletes, who generally have a higher fat-free mass compared with nonathletes. Finally, though we acknowledge that selecting the Cunningham (1980) equation among different predictive formulas for the RMR_{ratio} cutoff of 0.90 may appear arbitrary, a strong rationale for the use of this predictive equation exists: (a) the few studies in males in this area also utilized the Cunningham (1980) equation, making our results comparable with others in the current literature (Langan-Evans et al., 2020; Torstveit et al., 2018, 2019; Wilson et al., 2018), and (b) we observed a very large ES (Cohen's *d* 2.6; 95% CI [1.6, 3.6], Table 4) in the low RMR_{ratio} group compared with the normal RMR which would yield similar results using other formulas giving slightly different RMR_{ratio} values. We are aware of the importance of comparison of different equations

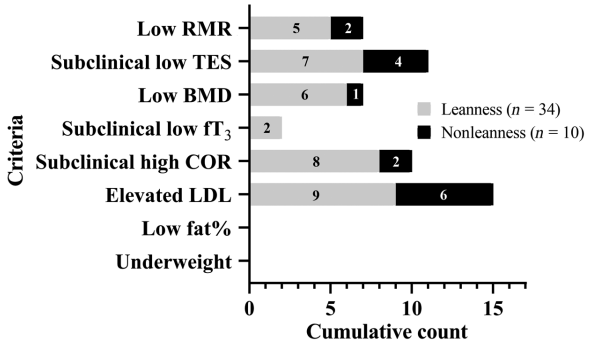

Figure 2 — Individual RED-S criteria cumulative represented (*x*-axis) and numbers present within each athlete group (numbers displayed in each bar). BMD = bone mineral density; COR = cortisol; LDL = low-density lipoprotein; RED-S = relative energy deficiency in sport; RMR = resting metabolic rate; fT_3 = free triiodothyronine; TES = testosterone.

and the need for further exploration of cutoff values in males to define presence of adaptive thermogenesis. However, such exploration is beyond the scope of the current work and we hope that the findings of this study provide evidence to substantiate further research to establish whether the proposed cutoffs are transferrable to males (Strock et al., 2020a, 2020b) as well as how RED-S markers are related to low RMR in males.

The T_3 is essential for growth, metabolism, and reproduction with ties to LEA (Elliott-Sale et al., 2018). As a result of reduced energy intake, the hypothalamic–pituitary–thyroid axis adapts and alters levels of both T_3 and thyroxine to conserve energy for vital functions (Logue et al., 2020; McCall & Ackerman, 2019). The T_3 might also be a more useful marker of LEA than other thyroid function tests in males (McCall & Ackerman, 2019). Furthermore, low T_3 levels have frequently been linked to low testosterone levels (De Souza et al., 2019; Friedl et al., 2000; Heikura et al., 2018b; McCall & Ackerman, 2019). In our study, two athletes displayed subclinical low fT_3. Only one of these athletes belonged to the energy deficit group, and also displayed very low RMR_{ratio} (0.77) and clinical low testosterone levels (4.3 nmol/L). In a study on male special forces soldiers experiencing prolonged starvation, researchers observed substantial reductions of both T_3 and testosterone during the 8-week course (Friedl et al., 2000). In the Heikura et al. (2018b) study, athletes with low testosterone had lower T_3 levels compared with athletes with normal testosterone levels, while no difference was observed between the groups of LEA and moderate EA. Similar T_3 findings are observed in studies were recreational trained males are exposed to short periods of LEA (~15 kcal·kg FFM^{-1}·day^{-1}) compared with optimal EA (40–45 kcal·kg FFM^{-1}·day^{-1}), possibly due to males being less sensitive to short periods of LEA compared with females (Koehler et al., 2016; Papageorgiou et al., 2017). In our study, athletes with severe low RMR did not show signs of subclinical low fT_3, warranting more research to explore the relation between LEA, RMR, and fT_3 in males.

Reproductive Function

Indisputable evidence shows that shorter periods of LEA causes suppression of reproductive and metabolic functions in females (Loucks & Thuma, 2003); however, this is not fully understood in male athletes, and evaluation is difficult and may require sperm analysis (De Souza et al., 2019; Elliott-Sale et al., 2018; Tenforde et al., 2016). It has been stated that testosterone in males plays a critical role in both sexual, bodily development, and cognitive aspects as well as physiological advantage in sports performance (Hackney, 2020). Research on male soldiers undergoing prolonged starvation has shown dramatic reductions in testosterone levels (Friedl et al., 2000). In male long-distance runners, race walkers and cyclists, LEA has been reported to strongly correlate with reduced testosterone levels (Heikura et al., 2018b; Keay et al., 2018; Melin et al., 2019). Experimental data have shown a causal effect between LEA and reduced testosterone only in one (Kojima et al., 2020) out of two studies (Koehler et al., 2016). In our study, a total of 11 athletes (25%) had subclinically low testosterone. However, our subclinical low testosterone levels findings may arise from hypogonadotropic hypogonadism (Arce et al., 1993; De Souza et al., 1994, 2019; Tenforde et al., 2016) or the Exercise Hypogonadal Male Condition, a maladaptation within the reproductive system due to athletes persistent and chronic exposure to large volumes of exercise training (Hackney, 2020). The first findings of lower total and free testosterone levels in male athletes compared with sedentary controls were reported by Arce et al. (1993) and De Souza et al. (1994). The subclinical testosterone levels were associated with low normal sperm count, decreased motility, and morphological changes that may compromise fertility (Arce et al., 1993). These findings were confirmed in a large, randomized training study ($n = 286$) where subjects were assigned to five 120-min sessions per week of moderate-intensity exercise (60% of VO_2max) or high-intensity exercise (80% VO_2max) (Safarinejad et al., 2009). The results demonstrated that strenuous long-term exercise with significant weight loss resulted in a significant decrease in plasma sex hormone concentrations and impaired reproductive capacity. Re-analyzing previous data, Hackney and Lane (2018) found a approximately 30%–35% reduction in testosterone levels in endurance-trained distance runners with ≥5 years compared with those with <5 years of endurance training experience; although, the reduction was unlikely to be caused by LEA, since no other health problems were reported (Hackney, 2020). In the Heikura et al. (2018b) study, low testosterone was found in 40% of participants. However, no differences in EA between the groups were reported, although athletes with LEA had significant lower testosterone levels compared with the moderate EA group. In the Koehler et al. (2016) study, no reductions in testosterone levels between groups were found. It is unclear whether the 4-day period of LEA was long enough to observe changes in subclinical markers in the latter study (Koehler et al., 2016). Establishing baseline values for endocrine markers may be warranted, where sudden and unexpected drops in values should trigger further investigations into the cause to distinguish between the potential onset of RED-S or Exercise Hypogonadal Male Condition. However, broad scientific evidence supports the fact that LEA causes reduction in testosterone, and that low testosterone levels are detrimental for performance (Hackney, 2020; Hackney et al., 2017). Thus, it is interesting to observe that subclinically low testosterone is present among almost all athletes with low RMR (Table 4), strengthening the association to LEA among these athletes (Arce et al., 1993; De Souza et al., 1994, 2019; Hackney, 2020; Tenforde et al., 2016).

Impaired Bone Health

Several parameters influence bone health, mostly endocrine and nutritional aspects, as well as mechanical loading. Long-term LEA is strongly linked to impaired bone health in female athletes (De Souza et al., 2014; Mountjoy et al., 2018, 2014; Nattiv et al., 2007)

and data on male athletes are now emerging (Barrack et al., 2017; Heikura et al., 2018b; Klomsten Andersen et al., 2018; Kraus et al., 2019; Papageorgiou et al., 2017; Tenforde et al., 2018; Viner et al., 2015). This includes increased risk of bone stress injuries among runners (Barrack et al., 2017; Kraus et al., 2019; Tenforde et al., 2018), as well as high prevalence of low BMD among cyclists (Klomsten Andersen et al., 2018; Viner et al., 2015). Viner et al. (2015) found a high prevalence of both LEA (70%) and low BMD (40%) across a professional cycling season, and Klomsten Andersen et al. (2018) found that 58% of elite cyclists had low BMD. In a randomized controlled trial, Papageorgiou et al. (2017) found decreased bone formation and increased bone resorption in females exposed to LEA, but not in males. Researchers speculate whether the 5-day LEA restriction among males was insufficient to see such changes, emphasizing the need for more research in this field (Papageorgiou et al., 2017). In a study by Heikura et al. (2018a), they reported no associations between the incidence of LEA and low BMD among world-class male endurance athletes. In our study, seven athletes (16%) were identified with low BMD, with or without other RED-S markers, highlighting the importance of screening athletes for low BMD independent of the presence of other signs of RED-S. The BMD is, affected by an array of variables, such as a chronic energy deficiency in the past, family history of osteoporosis, physical activity level, sedentary lifestyle, and dietary intake (Nattiv et al., 2007), variables which we did not assess. Finally, screening and early detection of declining BMD are especially important in athletes at risk of LEA due to the detrimental effects and the lengthy process of regaining lost BMD (De Souza et al., 2014).

Cortisol

Cortisol, a steroid hormone related to stress, is likely to contribute to increased adiposity during energy abundance and is an essential catabolic hormone secreted to ensure glucose homeostasis during prolonged exercise and starvation (Elliott-Sale et al., 2018). Increases in cortisol during severe caloric restriction and fasting has been observed in humans, and hypercortisolemia might directly affect reproductive function or serve as a biomarker of stress and reproductive dysfunction in amenorrheic athletes (Elliott-Sale et al., 2018). The role of cortisol in relation to LEA in male athletes is not fully understood. Studying American soldiers, Friedl et al. (2000) suggested that augmented cortisol levels were associated with reduced body fat after 4 weeks of semistarvation during military training. In support of this, the soldier with the highest observed levels of cortisol began the course with minimal fat reserves and lost most bodyweight (Friedl et al., 2000). In a recent study by Torstveit et al. (2018), a larger single-hour energy deficit was associated with higher cortisol values among well-trained male endurance athletes. Another study found that higher exercise dependency scores were associated with a more negative energy balance and higher cortisol levels among well-trained male cyclists and runners (Torstveit et al., 2019). In contrast, cortisol did not differ between a group of nine male long-distance runners with LEA compared with eight nonathletes with optimal EA (Hooper et al., 2017). We observed a 23% prevalence of athletes with subclinically high cortisol levels in our study. Furthermore, high cortisol levels (one clinical and two subclinical) were present among three athletes in combination with other RED-S markers (Table 3). However, cortisol as a marker itself of LEA should be interpreted with care, especially since stress and exercise per se is known to acutely increase cortisol levels (Hackney, 2020) with elite athletes exhibit large training volumes (Woods et al., 2017). More in-depth research is needed to better understand the effects of LEA on cortisol especially in the male population (Elliott-Sale et al., 2018).

Cardiovascular Health

Cardiovascular risk factors in both male and female athletes related to LEA is understudied. In females, unfavorable lipid profiles in amenorrhoeic athletes, with elevated TC and LDL levels, have been reported (Melin et al., 2019; Rickenlund et al., 2005). The mechanism for an impaired lipid profile in amenorrhoeic athletes is suggested to be related to estrogen deficiency, since increased levels of LDL have been associated with hypogonadotropic hypogonadism in anorexia nervosa patients (Meczekalski et al., 2013), and athletes with amenorrhea (Rickenlund et al., 2005). However, elevated TC and LDL levels has also been reported in female eumenorrheic athletes with current low or reduced EA and/or DE behavior, suggesting that alterations in cholesterol synthesis might be triggered by energy deficiency, despite normal weight and normal estrogen levels (Melin et al., 2015). Therefore, more research is needed to establish whether cardiovascular outcomes in female athletes can occur independent of estrogen deficiency. Research on male athletes is even more limited. Friedl et al. (2000), observed a progressive increase in both total-, LDL-, and high-density lipoprotein during the 8-week military course, potentially related to changes in thyroid hormones and insulin-like growth factor 1. Male judo players ($n = 11$) undergoing a self-selected 7-day energy restriction prior to competition showed no changes in TC-, LDL-, or high-density lipoprotein (Filaire et al., 2001). In our study, one third of the total sample displayed elevated LDL levels. We were, however, not able to investigate the athletes' family history or diet to explore for potential dietary causes of elevated blood lipids. More research on risk factors for cardiovascular health among male athletes is needed to improve the understanding of the complexity and possible link to RED-S.

Leanness Versus Nonleanness Athletes

Most of the investigated RED-S signs were also present among the investigated nonleanness athletes. These signs included low RMR, low BMD, subclinical low testosterones, subclinical high cortisol, and elevated LDL (Figure 2). A priory, we expected that athletes belonging to leanness sports would be more prone to exhibit a higher prevalence of surrogate markers of RED-S. Therefore, we hypothesized that male leanness athletes would exhibit both higher incidence and more severe cases of RED-S. Unfortunately, the small sample size in this study makes the sample highly biased and should be taken into consideration when interpreting the results. Despite this, it is still interesting to observe that some nonleanness athletes displayed signs of energetic deficit in combination with other RED-S markers, warranting further investigations among this group of athletes.

In conclusion, symptoms of chronic energy conservation related to RED-S were found in this group of Norwegian male Olympic-level athletes. Seven athletes (16%) had low RMR among this group of athletes, with the majority clustering with several additional RED-S markers, emphasizing the needs to further scrutinize these athletes. Furthermore, several RED-S markers were identified independent of current low RMR, including low BMD, subclinical testosterone, subclinical low fT_3, and subclinical high cortisol, emphasizing the need to further investigate the use of clustering of such RED-S risk factors among other groups of athletes.

Strengths and Limitations

Although LEA underpins RED-S, it is well recognized that EA is notoriously difficult to assess and evaluate on free living athletes (Areta et al., 2021; Burke et al., 2018; De Souza et al., 2019; Heikura et al., 2018b). As an alternative approach to identify athletes at risk of RED-S, we chose to accurately quantify variables, known to reflect adaptations to chronic energetic stress, such as RMR using a canopy hood, BMD, and body composition using dual-energy X-ray absorptiometry, as well as blood sampling, as described in recent studies (Elliott-Sale et al., 2018; Heikura et al., 2018b; Koehler et al., 2016; Lee et al., 2020; Logue et al., 2020; Staal et al., 2018; Woods et al., 2017, 2018). The limitations of this study are: (a) a cross-sectional design does not enable establishing any cause–effect relationships, (b) lack of data on EA and no assessment of whether athletes prior to testing had attempted to moderate body mass, thus actively facilitating a state of LEA, (c) being weight stable at the time of testing were not part of the inclusion criteria, (d) the prevalence of athletes with clustering of RED-S markers may be influenced by athletes current training phase at time of testing (Heikura et al., 2018b; Woods et al., 2017), which was not controlled for, (e) the two groups representing low and normal RMR, as well as leanness and nonleanness differ in size; hence, comparison should be interpreted with care, (f) not all athletes were tested during preseason, due to practical reasons and (g) excluding injured athletes from participation may have induced a survivorship bias, and future research may include injured athletes in their analysis to get a better understanding of the RED-S syndrome. Finally, the use of upper and lower quartiles for normative ranges, compared with using clinical cutoffs, when interpreting hormones must be taken into consideration, as research applying this method is very limited (Heikura et al., 2018b).

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Paper III

Prevalence of Relative Energy Deficiency in Sport in male adolescent endurance athletes: A 3-year longitudinal study

Stenqvist, T. B., Melin, A. K., & Torstveit, M. K.

Submitted to Scandinavian Journal of Medicine & Science in Sports

Appendix I

Thomas Stenqvist
Institutt for folkehelse, idrett og ernæring Universitetet i Agder
Serviceboks 422
4604 KRISTIANSAND S

Vår dato: 20.10.2016 Vår ref: 49943 / 3 / BGH Deres dato: Deres ref:

TILBAKEMELDING PÅ MELDING OM BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 12.09.2016. Meldingen gjelder prosjektet:

49943	*Effekten av ulike treningsintervensjoner på fysiologiske parametere – en eksperimentell studie i idrettsvitenskap*
Behandlingsansvarlig	*Universitetet i Agder, ved institusjonens øverste leder*
Daglig ansvarlig	*Thomas Stenqvist*

Personvernombudet har vurdert prosjektet, og finner at behandlingen av personopplysninger vil være regulert av § 7-27 i personopplysningsforskriften. Personvernombudet tilrår at prosjektet gjennomføres.

Personvernombudets tilråding forutsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldeskjemaet, korrespondanse med ombudet, ombudets kommentarer samt personopplysningsloven og helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.

Det gjøres oppmerksom på at det skal gis ny melding dersom behandlingen endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering. Endringsmeldinger gis via et eget skjema, http://www.nsd.uib.no/personvern/meldeplikt/skjema.html. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet.

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database, http://pvo.nsd.no/prosjekt.

Personvernombudet vil ved prosjektets avslutning, 01.10.2020, rette en henvendelse angående status for behandlingen av personopplysninger.

Vennlig hilsen

Kjersti Haugstvedt

Belinda Gloppen Helle

Kontaktperson: Belinda Gloppen Helle tlf: 55 58 28 74
Vedlegg: Prosjektvurdering

Dokumentet er elektronisk produsert og godkjent ved NSDs rutiner for elektronisk godkjenning.

Personvernombudet for forskning

Prosjektvurdering - Kommentar

Prosjektnr: 49943

I utgangspunktet var prosjektet meldt inn som to prosjekter, et doktorgradsprosjekt og et masterprosjekt, på samme prosjektmelding. De to prosjektene har ulike formål, men skal gjennomføre like tester på samme utvalg, men studere ulike parametere ved testene. Det ble derfor avklart med stipendiaten at prosjektene skulle meldes inn på to separate meldeskjemaer og at dette meldeskjemaet skulle gjelde for doktorgradsprosjektet.

FORMÅL
I følge prosjektmeldingen er formålet med doktorgradsprosjektet å se på effekten av en intensiv oppkjøringsperiode på parametere som kroppssammensetning, energitilgjengelighet, blodtrykk og blodvariabler hos godt trente mannlige utholdenhetsutøvere.

Studien er et delprosjekt i en treningsintervensjon som sammenligner tre ulike typer intervalltrening på prestasjonsutfall. I dette delprosjektet tar en sikte på å kartlegge forekomsten av lav energitilgjengelighet og undersøke effekten av en intensiv oppkjøringsperiode på utvalgte prestasjons- og helseutfall.

UTVALG OG DATAINNSAMLING
Utvalget består av mannlige aktive utøvere som driver med sykling på høyt nivå, i alderen 16 til 40 år. Utvalget består av 30 personer.

Data samles inn ved bruk av elektronisk spørreskjema og medisinske tester.

Personvernombudet forstår det slik at metoden for datainnsamling er intervensjonsstudie. Hvor deltagerne skal gjennomføre et treningsprogram, med ulik intensitet. Videre vil det bli tatt ulike medisinske tester/mål av utøverne.

INFORMASJON OG SAMTYKKE
Utvalget informeres skriftlig og muntlig om prosjektet og samtykker til deltakelse. Revidert informasjonsskriv mottatt 17.10.16 er godt utformet.

Personvernombudet er enig i at 16-åringene kan samtykke selv i dette prosjektet. Vi har lagt vekt på at det er nødvendig for prosjektets formål å innhente opplysningene fra ungdommene selv. Videre har vi vurdert at omfanget av sensitive opplysninger er lite og at prosjektet har kort varighet.

SENSITIVE PERSONOPPLYSNINGER
Det behandles sensitive personopplysninger om fysiske og psykiske helseforhold.

INFORMASJONSSIKKERHET
I følge meldeskjemaet blir hver deltager gitt et ID-nummer som alle tester og besvarelser knyttes til.

Koblingsnøkkelen blir oppbevart av prosjektleder nedlåst i et skap. Personvernombudet legger til grunn at forsker etterfølger Universitetet i Agder sine interne rutiner for datasikkerhet. Siden det skal behandles sensitive personopplysninger anbefaler vi at disse krypteres.

PROSJEKTSLUTT OG ANONYMISERING
Det er avklart med stipendiaten (jf. epost 17.10.2016) at dato for prosjektslutt er 01.10.2020. Deretter skal datamaterialet oppbevares avidentifisert i 10 år og koblingsnøkkelen skal oppbevares på UiA i tilsvarende periode for eventuelt longitudinelt studie og/eller oppfølgingsstudier.

Innen det er gått 10 år skal datamateriale anonymiseres. Anonymisering innebærer å bearbeide datamaterialet slik at ingen enkeltpersoner kan gjenkjennes. Det gjøres ved å:
- slette direkte personopplysninger (som navn/koblingsnøkkel)
- slette/omskrive indirekte personopplysninger (identifiserende sammenstilling av bakgrunnsopplysninger som f.eks. bosted/arbeidssted, alder og kjønn)
- destruere blodprøver etc.

Vi minner om at eventuelle oppfølgingsstudier eller ny forskning på datamaterialet krever ny melding til personvernombudet.

José Lisandro Areta
Seksjon for fysisk prestasjonsevne
Norges idrettshøgskole
Postboks 4014
0806 OSLO

Vår dato: 22.01.2018 Vår ref: 56937/3/STM/LR Deres dato: Deres ref:

AVSLUTTET SAKSBEHANDLING

Personvernombudet for forskning viser til meldeskjema mottatt 31.10.2017, samt godkjenning fra Regional komité for medisinsk og helsefaglig forskningsetikk (REK) mottatt 19.01.2018 for prosjektet:

56937 *Resting metabolic rate as a screening tool for relative energy deficiency in elite athletes*

Personvernombudet tar til orientering at prosjektet faller inn under helseforskningslovens bestemmelser, og at prosjektet er godkjent av REK.

Personvernombudet avslutter dermed saksbehandlingen av meldingen uten å realitetsbehandle denne. Vi avslutter også all videre oppfølgning av prosjektet.

Ta gjerne kontakt dersom noe er uklart.

Vennlig hilsen

Marianne Høgetveit Myhren

Siri Tenden Myklebust

Kopi:
Seksjon for fysisk prestasjonsevne, Norges idrettshøgskole

Monica Klungland Torstveit
Serviceboks 422
4604 KRISTIANSAND S

Vår dato: 16.08.2017 Vår ref: 54496 / 3 / STM Deres dato: Deres ref:

Tilbakemelding på melding om behandling av personopplysninger

Vi viser til melding om behandling av personopplysninger, mottatt 22.05.2017.
All nødvendig informasjon om prosjektet forelå i sin helhet 16.08.2017.
Meldingen gjelder prosjektet:

54496	*Energitilgjengelighet og idrettslig prestasjon - Forekomst og utvikling av relativ energimangel og assosierte helse- og prestasjonsvariabler blant unge mannlige og kvinnelige idrettsutøvere i Sør-Norge*
Behandlingsansvarlig	*Universitetet i Agder, ved institusjonens øverste leder*
Daglig ansvarlig	*Monica Klungland Torstveit*

Personvernombudet har vurdert prosjektet, og finner at behandlingen av personopplysninger vil være regulert av § 7-27 i personopplysningsforskriften. Personvernombudet tilrår at prosjektet gjennomføres.

Personvernombudets tilråding forutsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldeskjemaet, korrespondanse med ombudet, ombudets kommentarer samt personopplysningsloven og helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.

Det gjøres oppmerksom på at det skal gis ny melding dersom behandlingen endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering. Endringsmeldinger gis via et eget skjema. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet.

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database.

Personvernombudet vil ved prosjektets avslutning, 30.11.2020, rette en henvendelse angående status for behandlingen av personopplysninger.

Dersom noe er uklart ta gjerne kontakt over telefon.

Vennlig hilsen

Dokumentet er elektronisk produsert og godkjent ved NSDs rutiner for elektronisk godkjenning.

Katrine Utaaker Segadal

Siri Tenden Myklebust

Kontaktperson: Siri Tenden Myklebust tlf: 55 58 22 68 / Siri.Myklebust@nsd.no
Vedlegg: Prosjektvurdering

Personvernombudet for forskning

Prosjektvurdering - Kommentar

Prosjektnr: 54496

FORMÅL
Formålet med prosjektet er å undersøke sammenhengen mellom energitilgjengelighet (EA) og idrettslige prestasjoner hos unge idrettsutøvere over tid. Tilstrekkelig EA (samsvar mellom inntak og forbruk) er viktig både for helse og god prestasjon for idrettsutøvere. For lav EA har vist seg uhensiktsmessig for helse og prestasjon, og forskningen er mangelfull i forhold til unge talentfulle utøvere. Intens trening i kombinasjon med energimangel kan føre til økt risiko for sykdom og skader, overtrening og nedsatt prestasjon. Man ønsker gjennom prosjektet å få innsyn i og forståelse for hvordan unge utøvere og deres trenere kan sikre grunnlaget for best mulig trening og prestasjon på kort og lang sikt, slik at kroppen tåler den økende treningsmengde over tid for å bli god.

REK har vurdert at prosjektet faller utenfor helseforskningslovens virkeområde (2017/738/REK sør-øst A).

UTVALG OG DATAINNSAMLING
Det skal rekrutteres ca. 100 konkurranseaktive elever fra VG1 på idrettsgymnas. Disse må være konkurranseaktive innen idretten sin på regionalt og/eller nasjonalt nivå. Det skal også inkluderes en kontrollgruppe bestående av elever fra den lokale videregående skolen. Elevene i kontrollgruppen skal ha ulikt aktivitetsnivå, ikke trene spesifikt mot en konkurranse, men trene maksimalt fire timer i uken.

Når prosjektet starter inkluderes kun elever fra VG1, og disse følges longitudinelt gjennom den videregående skole. Er deltaker 15 år ved prosjektstart, involveres foreldre i informasjon og samtykke. Elever mellom 16-18 år samtykker på egen hånd. Personvernombudet er enig i at 16-åringene kan samtykke selv i dette prosjektet. Vi har lagt vekt på at det er nødvendig for prosjektets formål å innhente opplysningene fra ungdommene selv.

Data samles inn ved bruk av elektronisk og papirbasert spørreskjema og medisinske tester. Deltakerne vil gjennomgå idretts-spesifikke fysiologiske tester (maksimalt oksygenopptak, laktat-profiltest, anaerob kapasitet, reaksjonstest og styrketest). I tillegg samles det inn helsevariabler, ved bruk av ergo-spirometri, blodprøver, blodtrykk, høyde, vekt, DXA (beinhelse og kroppssammensetning) samt målinger knyttet til energiomsetning (aktivitetsmåling, pulsmåling samt hvilemetabolisme samt kostholdsregistrering).

INFORMASJON OG SAMTYKKE
Utvalget informeres skriftlig og muntlig om prosjektet og samtykker til deltakelse. Informasjonsskrivet mottatt 16.08.2017 er godt utformet.

SENSITIVE PERSONOPPLYSNINGER
Det behandles sensitive personopplysninger om helseforhold.

INFORMASJONSSIKKERHET
Personvernombudet legger til grunn at forskerne etterfølger Universitetet i Agder sine interne rutiner for datasikkerhet. Siden det skal behandles sensitive personopplysninger, anbefaler vi at disse krypteres.

INNSAMLING AV BIOLOGISK MATERIALE
Ifølge forsker skal biologisk materiale ikke oppbevares i prosjektperioden, men vil destrueres fortløpende. Så lenge biologisk materiale destrueres innen tre måneder er det ikke nødvendig å søke om opprettelse av forskningsspesifikk biobank. Vi viser for øvrig til korrespondanse den 08.08.2017 og den 16.08.2017.

PROSJEKTSLUTT
Forventet prosjektslutt er 30.11.2020. Deretter skal datamaterialet oppbevares avidentifisert i 10 år og koblingsnøkkelen skal oppbevares på UiA i tilsvarende periode for eventuelt longitudinelt studie og/eller oppfølgingsstudier. Innen det er gått 10 år skal datamateriale anonymiseres. Anonymisering innebærer å bearbeide datamaterialet slik at ingen enkeltpersoner kan gjenkjennes. Det gjøres ved å:
- slette direkte personopplysninger (som navn/koblingsnøkkel)
- slette/omskrive indirekte personopplysninger (identifiserende sammenstilling av bakgrunnsopplysninger som f.eks. bosted/arbeidssted, alder og kjønn)

Vi minner om at eventuelle oppfølgingsstudier eller ny forskning på datamaterialet krever ny melding til personvernombudet.

Appendix II

Emne: Ikke framleggingspliktig
Fra: post@helseforskning.etikkom.no
Dato: 09.09.2016 12:02
Til: monica.k.torstveit@uia.no
Kopi:

Hei.

Viser til din forespørsel om framleggingsvurdering mottatt 02.09.2016 for prosjektet "Energitilgjengelighet og prestasjon; et treningseksperiment" (vår ref. 2016/1544).

Komiteens leder Finn Wisløff har nå vurdert henvendelsen.

Formålet med studien er å kartlegge forekomsten av lav energitilgjengelighet, samt undersøke effekten av en intensiv treningsperiode på energitilgjengelighet samt assosierte fysiologiske parametere blant mannlige utøvere i krevende utholdenhetsidretter.

Basert på opplysningene som gis i skjema for fremleggingsvurdering, protokoll og spørreskjema, vurderer komiteens leder at det fremlagte prosjektet ikke vil gi ny kunnskap om sykdom og helse som sådan. Prosjektet faller dermed ikke inn under helseforskningsloven som forutsetter at formålet med prosjektet er å skaffe ny kunnskap om helse og sykdom.

Det kreves ikke godkjenning fra REK for å gjennomføre prosjektet. Prosjektet kommer inn under de interne regler som gjelder ved forskningsansvarlig virksomhet.

Jeg gjør oppmerksom på at konklusjonen er å anse som veiledende jfr. forvaltningsloven § 11. Dersom du likevel ønsker å søke REK vil søknaden bli behandlet i komitémøte, og det vil bli fattet et enkeltvedtak etter forvaltningsloven.

Med vennlig hilsen
Silje U. Lauvrak

Rådgiver
REK Sør-Øst
Tlf: 22 84 55 20

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Hege Cathrine Finholt, PhD	22857547	20.12.2017	2017/2160 REK sør-øst D
			Deres dato:	Deres referanse:
			31.10.2017	

Vår referanse må oppgis ved alle henvendelser

Gøran Paulsen
Norges idrettshøgskole

2017/2160 Hvilestoffskiftet og energitilgjengelighet hos toppidrettsutøvere

Forskningsansvarlig: Norges idrettshøgskole
Prosjektleder: Gøran Paulsen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst D) i møtet 29.11.2017. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektleders prosjektbeskrivelse
Studien består av to deler. Del 1: Undersøkelse av reprodusertbarheten for måling av hvilestoffskiftet (resting metabolic rate, RMR). Dette anses viktig for å få innblikk i hvor små endringer/forskjeller man kan forvente å avdekke med metoden. Del 2: Teste hypotesen om at hvilestoffskiftet er lavere hos utøvere med lav energitilgjengelighet enn hos utøvere med god energitilgjengelighet. Konsekvensene av langvarig lav energitilgjengelighet er endringer i hormonspeilet og redusert beinmineraltetthet. Følgelig vil vi også undersøke om det er assosiasjoner mellom hvilestoffskiftet og beinmineraltetthet og hormoner, som tyroideahormoner og kjønnshormoner. I det daglige arbeidet med utøvere med lav energitilgjengelighet i Olympiatoppen anser vi det som nyttig å bruke hvilestoffskiftemålinger, fordi metoden har svært lav risiko, forholdsvis enkel å utføre i våre lokaler, samtidig som det ikke påvirker treningen til utøverne nevneverdig.

Vurdering
Prosjektet skal studere hvilestoffskiftet hos toppidrettsutøvere med lav energitilgjengelighet. Konsekvenser av langvarig lav energitilgjengelighet er endringer i hormonspeilet og redusert beinmineraltetthet. Prosjektet vil derfor også undersøke om det er en sammenheng mellom hvilestoffskifte og beinmineraltetthet og hormoner. På grunnlag av dette mener komiteen at prosjektet vil kunne gi ny kunnskap om helse og sykdom, og at det dermed faller innenfor helseforskningslovens virkeområde.

Komiteen har vurdert søknaden og har ingen innvendinger til studien som sådan. Komiteen har imidlertid følgende kommentarer:
- Det må være en beredskap i prosjektet dersom det for noen deltagere skulle påvises for lav beinmineraltetthet.
- Informasjonsskrivet må formuleres som en forespørsel om mottaker av skrivet ønsker å delta i studien, og hvorfor akkurat de forespørres.

På denne bakgrunn setter komiteen følgende vilkår for godkjenning:
- Det må utarbeides en beredskapsplan som ettersendes komiteen.
- Informasjonsskrivet må revideres i tråd med komiteens kommentar og ettersendes til orientering.

Vedtak
Med hjemmel i helseforskningsloven § 9 jf. 33 godkjenner komiteen at prosjektet gjennomføres under forutsetning av at ovennevnte vilkår oppfylles.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2020. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2025. Forskningsfilen skal oppbevares atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren».

Dersom det skal gjøres vesentlige endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Prosjektet skal sende sluttmelding på eget skjema, senest et halvt år etter prosjektslutt.

Komiteens avgjørelse var enstemmig.

Klageadgang
REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst D. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Hege Cathrine Finholt, PhD
Rådgiver

Kopi til: turid.sjostedt@nih.no
Norges idrettshøgskole ved øverste administrative ledelse: postmottak@nih.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Hege Cathrine Finholt, PhD	22857547	31.01.2018	2017/2160/REK sør-øst D
			Deres dato:	**Deres referanse:**
			29.01.2018	

Vår referanse må oppgis ved alle henvendelser

Gøran Paulsen
Norges idrettshøgskole

2017/2160 Hvilestoffskiftet og energitilgjengelighet hos toppidrettsutøvere

Forskningsansvarlig: Norges idrettshøgskole
Prosjektleder: Gøran Paulsen

Vi viser til søknad om prosjektendring datert 29.01.2018 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst D på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringen innebærer:
- legge til målinger av hvilestoffskiftet (RMR) og kroppssammensetningen (DXA) i reliabilitetsstudien (Experiment 1 in the Protocol). Det vil si 3 målinger av RMR og DXA og ikke 2, slik vi søkte om i utgangspunktet.

Vurdering
REK har vurdert den omsøkte endringen, og har ingen forskningsetiske innvendinger til endringen slik den er beskrevet i skjema for prosjektendring.

Vedtak
REK godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11, annet ledd.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad, endringssøaknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

Klageadgang
REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Eventuell klage sendes til REK sør-øst D. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Hege Cathrine Finholt, PhD
Rådgiver

Kopi til: *turid.sjostedt@nih.no*
Norges idrettshøgskole ved øverste administrative ledelse: postmottak@nih.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anne S. Kavli	22845512	19.05.2017	2017/738/REK sør-øst A
			Deres dato:	**Deres referanse:**
			28.03.2017	

Vår referanse må oppgis ved alle henvendelser

Monica K Torstveit
Universitetet i Agder

2017/738 Energitilgjengelighet og idrettslig prestasjon

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 04.05.2017. Vurderingen er gjort med hjemmel i helseforskningsloven § 10, jf. forskningsetikkloven § 4.

Forskningsansvarlig: Universitetet i Agder
Prosjektleder: Monica K Torstveit

Prosjektbeskrivelse (revidert av REK)

Formålet med prosjektet er å undersøke sammenhengen mellom energitilgjengelighet og idrettslige prestasjoner hos unge idrettsutøvere.

Tilstrekkelig energitilgjengelighet (samsvar mellom inntak og forbruk) er viktig både for helse og god prestasjon for idrettsutøvere. For lite energitilgjengelighet har vist seg uhensiktsmessig for helse og prestasjon, og forskningen er mangelfull i forhold til unge talentfulle utøvere. Intens trening i kombinasjon med energimangel kan føre til økt risiko for sykdom og skader, overtrening og nedsatt prestasjon. Man ønsker gjennom prosjektet å få innsyn i og forståelse for hvordan unge utøvere og deres trenere kan sikre grunnlaget for best mulig trening og prestasjon på kort og lang sikt, slik at kroppen tåler den økende treningsmengden som kreves over lang tid for å bli god i sin idrett.

Det skal rekrutteres ca. 100 konkurranseaktive elever fra VG1 på idrettsgymnas. Disse må være konkurranseaktive innen idretten sin på regionalt og/eller nasjonalt nivå.

Det skal også inkluderes en kontrollgruppe bestående av elever fra den lokale videregående skolen. Elevene i kontrollgruppen skal ha ulikt aktivitetsnivå, men trene maksimalt fire timer i uken.

Det planlegges å orientere elevene om prosjektet via et informasjonsmøte på skolen, og alle aktuelle elever vil få et skriftlig informasjonsskriv.

Deltakelse i prosjektet innebærer to testdager etterfulgt av fire dager med registrering av fysisk aktivitet (med pulsklokke og akselometer) og kostholdsregistrering (all mat og væske veies og registreres).

Testdag 1 gjøres følgende undersøkelser (deltagerne møter fastende): Måling av hvilemetabolisme via indirekte kalorimetri, måling av blodtrykk som måles liggende og stående, røntgen absorbsjonsmetri for å måle benhelse og kroppssammensetning, blodprøver for måling av biomarkører (stress – og kjønnshormoner, glukose, insulin, T3, jernprofil og vitamin D), samt spyttprøver for vurdering av immunologiske faktorer (IgA).

Etter undersøkelsene vil deltakerne bli bedt om å besvare spørreskjema der spørsmålene omhandler temaer som treningsmengde, konkurranseerfaring, motivasjon, forhold til trening, skader/sykdommer, restitusjon, søvn, velvære samt spørreskjema om forstyrret spiseatferd, treningsavhengighet og relativ energimangel.

På testdag 2 gjøres følgende tester: fysiologisk test av laktatprofil, måling av maksimalt oksygenopptak(VO2maks), måling av anaerob kapasitet, måling av maksimal styrke og reaksjonstest.

Kontrollgruppen vil gjennomføre testdag en og de fire dagene med registrering av kost og aktivitet en gang hvert år i tre år, mens elevene på idrettsgymnas vil gjennomføre begge testdagene og registreringen to ganger pr år i tre år. For kontrollgruppen vil testene gjøres før skoletid eller i helger, mens det for elevene på idrettsgymnas vil gjøres i løpet av skoletiden.

Det planlegges også en delstudie hvor man prøver ut spørreskjemaet Low Energy Availability among MalesQuestionnaire (LEAM-Q) og Low Energy Availability among Female-Questionnaire (LEAF-Q).

Vurdering

Formålet med prosjektet, slik det fremkommer av søknad og protokoll, er å undersøke sammenhengen mellom energitilgjengelighet og idrettslige prestasjoner hos unge idrettsutøvere. Prosjektet har etter komiteens vurdering ikke som formål å skaffe til veie ny kunnskap om helse og sykdom.

Av den grunn faller prosjektet det her søkes om utenfor virkeområdet til helseforskningsloven. Helseforskningsloven gjelder for medisinsk og helsefaglig forskning, definert som forskning på mennesker, humant biologisk materiale og helseopplysninger, som har som formål å frambringe ny kunnskap om helse og sykdom, jf. helseforskningsloven §§ 2 og 4a. Formålet er avgjørende, ikke om forskningen utføres av helsepersonell eller på pasienter eller benytter helseopplysninger.

Prosjekter som faller utenfor helseforskningslovens virkeområde kan gjennomføres uten godkjenning av REK. Det er institusjonens ansvar på å sørge for at prosjektet gjennomføres på en forsvarlig måte med hensyn til for eksempel regler for taushetsplikt og personvern.

Vedtak

Prosjektet faller utenfor helseforskningslovens virkeområde, jf. § 2, og kan derfor gjennomføres uten godkjenning av REK.

Klageadgang

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK Sørøst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anne S. Kavli
Seniorkonsulent

Kopi til: Universitetet i Agder ved øverste administrative ledelse: post@uia.no

Appendix III

Informasjon og forespørsel om deltakelse i forskningsprosjekt

«Effekten av ulike treningsintervensjoner på fysiologiske parametere, prestasjon og helsevariabler»

– en eksperimentell studie i idrettsvitenskap.

Andreas M. Pedersen; 952 99 695 eller Ole E. Wåle; 980 39 396. Felles epost; uiaprosjekttao@gmail.com

Kjære syklist!

Vi søker syklister til å bli med på et treningsprosjekt i forbindelse med en masteroppgave og et doktorgradsprosjekt i idrettsvitenskap ved Universitetet i Agder (UIA).

Bakgrunn og hensikt

For å prestere på høyt nivå innen utholdenhetsidrett er det viktig at treningsvariablene intensitet, varighet og frekvens implementeres i treningsopplegget på en hensiktsmessig måte, i tillegg til en hensiktsmessig fordeling av rolig (LIT), moderat (MIT) og hard (HIT) trening. I tillegg til nevnte variabler, er det vanlig blant utøvere å manipulere økt-design på HIT økter gjennomført som intervalltrening, dvs. for eksempel om intervaller skal gjennomføres med kort eller lang lengde på dragene. Videre ses et økt fokus i en oppkjøringsperiode på blant annet vekt og kroppssammensetning for å optimalisere kroppen mest mulig inn mot en konkurranseperiode. Et slikt fokus på vekt og kroppssammensetning har hos kvinner blitt assosiert med mulige negative prestasjons- og helsekonsekvenser, men det finnes veldig lite forskning knyttet til mannlige utøvere.

Hensikten med denne studien er å undersøke effekten av ulike økt-design på HIT økter, gjennomført som langintervall eller kortintervall på ulike fysiologiske parametere og prestasjon, samt undersøke effekten av en tøff treningsperiode på parametere som kroppssammensetning, energitilgjengelighet, blodtrykk og blodvariabler hos godt trente mannlige utholdenhetsutøvere.

Forsøkspersoner

Vi ønsker å rekruttere 30 forsøkspersoner som oppfyller følgende inklusjonskriterier:

- Mann < 40 år
- Maksimalt oksygenopptak > 60 $ml \cdot kg^{-1} \cdot min^{-1}$
- Treningsfrekvens pr nå >3 økter/uke innen sykling det siste året (minimum 6 timer)
- Fravær fra sykdom og skader

Som forsøksperson må du være villig til å bli tilfeldig plassert i en av tre treningsgrupper og gjennomføre treningsopplegget på prosjektets premisser. Som førsøksperson må du ha mulighet til å stille på samtlige intervalløkter og tester i løpet av perioden.

Andreas M. Pedersen; 952 99 695 eller Ole E. Wåle; 980 39 396. Felles epost; uiaprosjekttao@gmail.com

Hva innebærer deltakelse i studien?

Dette er en eksperimentell studie som totalt vil foregå over en periode på 11 uker, fra uke 39-49. Periodene deles inn i flere ulike faser (**se figur 1 for oversikt**):

Tilvenningsfasen (uke 39-40): Hensikten med tilvenningsperioden er å gjøre deg kjent med prosedyrer og utstyr samt de ulike intervaller som benyttes under intervensjonen. Dette innebærer at du må sette av én dag til testing i lab i uke 39 og tre dager (mandag, onsdag og fredag) i uke 40 for tilvenning av tre intervalløkter.
Nedtreningsfasen (uke 41-43): Denne perioden er ment som en nedtreningsperiode hvor du kun har lov til å gjennomføre rolig trening. Det vil ikke bli noen fellesøkter i denne perioden.
Testfasen/pre-test (uke 44): Testfasen består av to testdager. På dag 1 skal du møte fastende i laboratoriet for måling av hvilestoffskiftet, blodtrykk, blodprøve, skanning av kroppssammensetningen din (dobbel røntgen absorpsjonsmetri; DXA) samt utfylling av spørreskjemaer.

> ***NB:*** *De siste 24 timer før testdagen må du ikke utføre intensiv eller utmattende trening/konkurranser eller drikke alkohol. Du har ikke tillatelse til å spise de siste 12 timene før testene (disse gjennomføres tidlig på morgenen). De siste tre timer før testene må du ikke drikke te, kaffe eller annen koffeinholdig drikke. Som forsøksperson vil du bli nøye overvåket av testledere.*

På dag 2 skal vi måle fysiologiske parametere knyttet til prestasjon. Du skal gjennomføre en laktatprofiltest, VO_{2maks} test samt en 30 sekunders all-out Wingate-test.

> **NB**: *De siste 48 timene før denne test (dag2) kan du ikke utføre intensiv trening eller konkurranser. Som forsøksperson vil du bli nøye overvåket av testledere.*

Videre vil du bli bedt om å registrere kostholdet ditt samt trenings- og aktivitetsnivået ditt i 4 dager før intervensjonen starter, samt 4 dager ved intervensjonsslutt. All kostholdsregistrering gjøres elektronisk via PC eller Mac med et kostholdsprogram som også benyttes av Olympiatoppen. Du vil få låne en vekt hvor du skal veie all mat og væske du inntar disse 4 dagene. Aktivitet og trening registreres med en utlevert pulsklokke fra Polar (M400) samt et lite akselerometer montert på armen (Sensewear).

Intervensjonsfasen (uke 45-48): Deretter vil du som forsøksperson bli tilfeldig fordelt i en av tre grupper som skal gjennomføre et 4 ukers eksperiment (uke 45-48) fordelt som følger;

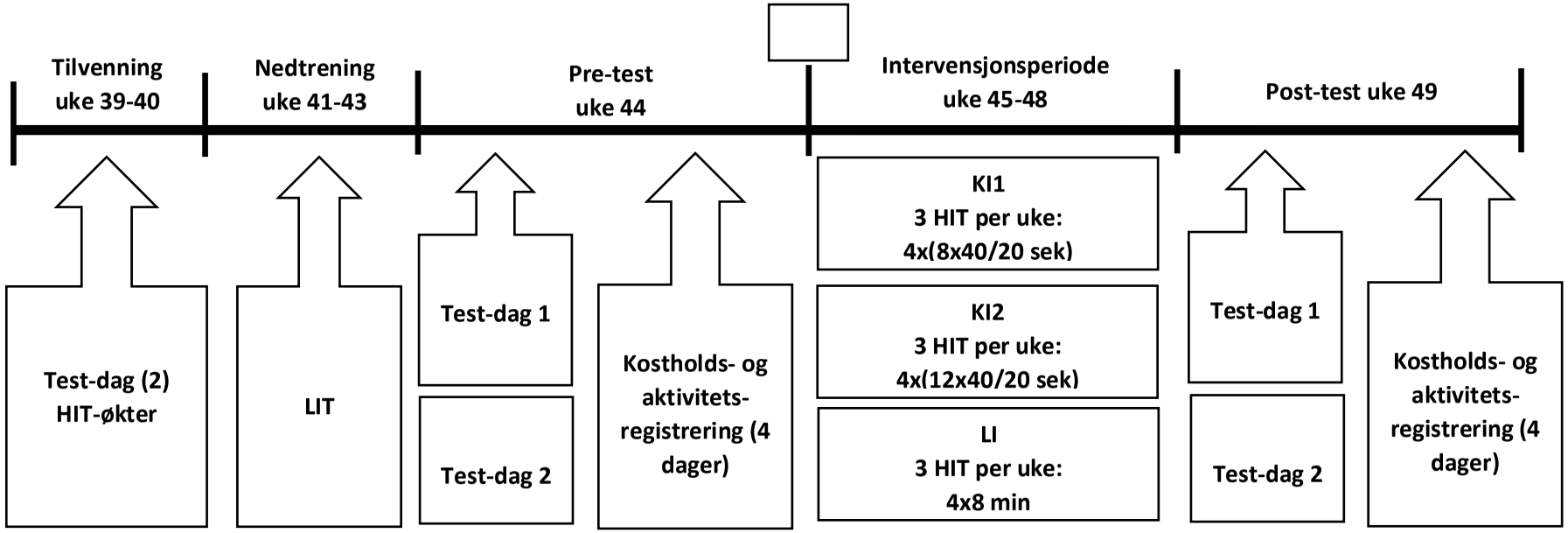
- Kortintervall-gruppe 1 (KI1) (4x(8x40/20sek) med 2 min seriepause)
- Kortintervall-gruppe 2 (KI2) (4x(12x40/20) med 2 min seriepause)
- Langintervall-gruppe (LI) (4x8 min med 2 min seriepause)

Du skal totalt gjennomføre 12 HIT økter i løpet av en fire ukers intervensjonsperiode. Det vil si tre HIT økter per uke i tillegg til 2-3 rolige økter, med en anbefalt treningsmengde på 10-12 timer per uke eller mer. HIT øktene skal gjennomføres i grupper på 10 stk. mandag, onsdag og fredag i UIAs lokaler på Spicheren treningssenter. Klokkeslett for treningen er satt til 16.00, 18.00 og 20.00 avhengig av hvilken gruppe du blir plassert i. «Heart rate variability» (HRV) vil bli målt på utvalgte forsøkspersoner før og etter utvalgte intervalløkter for å undersøke variasjonen i tidsintervallene mellom hvert hjerteslag. Dette gir en indikasjon på hvor stressende den aktuelle økta er på det autonome nervesystemet. Målingen gjøres med Polar V800 og krever ingen fysisk anstrengelse eller ubehag.

NB: *I løpet av hele perioden (uke 39-49) må du som forsøksperson fylle ut treningsdagbok som dere får utdelt. Du vil bli utstyrt med Polar M400 til bruk og innsamling av data fra både fellesøkter og individuelle økter.*

Testperiode/post-test (uke 49): Her gjennomføres samme tester i samme rekkefølge som i den første testperioden (pre-test).

Tidslinje (uke 39-49):



***Figur 1**: Studiens faser. To ukers tilvenningsfase består av en test-dag (laktatprofil-, VO_{2maks}- og Wingatetest) og tre HIT-økter (4x8x40/20 sek, 4x12x40/20 sek og 4x8 min). Tre uker nedtreningsperiode består av kun lavintensiv trening (LIT) etterfulgt av to test-dager i uke 44 (pre-test), 4 dagers kostholds- og aktivitetsregistrering i kortintervall 1 (KI1), kortintervall 2 (KI2) og langintervall (LI). Deretter følger 4 ukers intervensjonsperiode med 3 intervensjonsgrupper etterfulgt av to test-dager (post-test), samt 4 dagers kostholds- og aktivtetsregistrering.*

Mulige fordeler og ulemper:

Som deltaker vil du:

- Skaffe kunnskap for å utvikle toppidretten i samarbeid med Olympiatoppen og UIA.
- Få delta på et vitenskapelig eksperiment som kan bidra til å skaffe ytterligere kunnskap for å utvikle vår forståelse av ulik trening.
- Få mulighet til å teste din fysiske kapasitet uten kostnad på UIA.
- Få kartlagt din energitilgjengelighet med muligheter for tilbakemelding på kostholdet ditt og utvalgte helsevariabler.
- Få målt din kroppssammensetning uten kostnad med gullstandard målemetode (DXA) med detaljerte opplysninger om din fett-, muskel- og beinmasse.
- Få målt ditt hvilestoffskifte som sier noe om din forbrenning i hvile.
- Få være med på et sosialt og spennende treningsprosjekt som kan gi inspirasjon til hvordan trene videre i etterkant av intervensjonen.
- Få delta på et effektivt treningsprogram med god oppfølging.

Mulige ulemper:

- Må møte på fellesøkter og tester til fastsatte tider i løpet av perioden.
- Kan ikke trene intensive økter utover det som er inkludert i intervensjonsperioden. Det er kun lavintensive økter som kan gjennomføres valgfritt.
- All trening må dokumenteres etter gitte krav i treningsdagbok.
- Kostholdet og aktivitetsnivået må kartlegges ved to anledninger (4 dager hver).
- Må være opplagt til hver trening/test og gjennomføre disse med god innsats.
- Risiko for overbelastning både ved testing og HIT-økter.

Hva skjer med informasjon om deg?

Data som blir registrert skal kun brukes slik som beskrevet i hensikten med studien. Opplysningene vil bli behandlet uten navn og fødselsnummer, eller andre direkte gjenkjennende opplysninger. Som deltaker vil du få et ID nummer som representerer ditt navn. Tester som blir gjennomført og data som blir innhentet, vil knyttes til dette ID nummeret. Det er kun autorisert personell knyttet til prosjektet som har adgang til ID nummeret. Innsamlet data vil bli benyttet i masterprosjektet og doktorgradsprosjektet, men alltid anonymt. Dataene vil også kunne bli brukt til publisering i tidsskrift, undervisning og kongresser. Som deltaker har du rett til å få innsyn i data som er registrert på deg selv. Data vil oppbevares avidentifisert på prosjektlederes passordbelagte PC. Data vil bli oppbevart i opptil 10 år etter at prosjektet er avsluttet.

Rett til innsyn og sletting av opplysninger om deg

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner

Frivillig deltakelse:

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte prosjektleder/ kontaktperson (se under).

Ytterligere detaljert informasjon om prosjektet og de ulike testene kan utleveres ved å kontakte Andreas eller Ole.

Annet:

Som forsøksperson må du også delta på et obligatorisk informasjonsmøte onsdag 14. september kl. 1930 eller tirsdag 20. september kl. 18 i UIAs lokaler på Spicheren treningssenter.

Hvordan bli med?

Dersom du ønsker å være en del av dette prosjektet kan du sende en mail til uiaprosjekttao@gmail.com der du beskriver følgende:

- Hvem du er
- Nivå
- Treningsmengde det siste året
- Dine muligheter for å delta på samtlige økter og tester

Mvh

Andreas M. Pedersen, Ole E. Wåle og Thomas B Stenqvist.

Kontaktinfo:

Prosjektledere

Andreas M. Pedersen
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Fakultet for helse- og idrettsvitenskap
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Prosjektveiledre

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Monica K. Torstveit
Førsteamanuensis
Fakultet for helse- og idrettsvitenskap
monica.k.torstveit@uia.no

Samtykke til deltakelse i undersøkelsen:

Ved å signere samtykkeerklæringen bekrefter du også at du ikke har kjent hjertesykdom eller andre lidelser/sykdom som medfører at din fastlege har frarådet deg å trene intensivt. Alle deltakere i studien er for øvrig forsikret via UIAs egen forsikringsordning for forskningsprosjekter.

Jeg bekrefter å ha fått og forstått informasjon om studien

(Signert av prosjektdeltaker evt. foresatt, dato)

Jeg er villig til å delta i studiet?

Ja _____

(Signert av prosjektdeltaker evt. foresatt hvis under 18 år, dato)

Forespørsel om deltagelse i forskningsprosjekt

- Hvilestoffskiftet og energitilgjengelighet hos toppidrettsutøvere -

Bakgrunn og formål med studien:

Hvilestoffskiftet er energien kroppen omsetter i hvile. Denne energiomsetningen påvirkes bl.a. av treningstilstand og energitilgjengelighet (energiinntak i forhold til energiforbruk). I denne studien ønsker vi å måle hvilestoffskiftet til toppidrettsutøvere fra to grupper. En gruppe utøvere som normalt har god energitilgjengelighet, og en gruppe utøvere som (periodevis) har lav energitilgjengelighet. Den siste gruppen omfavner idretter som stiller krav til lav vekt for å prestere, typisk vektklasseidretter som kampsport og roing, samt utholdenhetsidretter som sykling og langdistanseløping.

Hensikten med studien er å undersøke om hvilestoffskiftemålinger kan brukes som et verktøy for hjelpe utøvere med å justere energitilgjengelighet innenfor det som er helse- og prestasjonsmessig gunstig. For å studere dette vil vi i tillegg til å måle hvilestoffskiftet, registrere energiinntak, beregne energiforbruk, analysere kroppssammensetning og beinmineraltetthet, samt måle hormoner i blodet. De statistiske analysene i etterkant vil avgjøre om det er forskjeller mellom utøvergruppene og om det er sammenhenger mellom de ulike variablene som er målt.

Viser det seg at hvilestoffskiftemålinger kan gi oss nyttig informasjon om hvordan energitilgjengeligheten til en utøver har vært i tiden fram til målingen, er dette en undersøkelse som går raskt å gjøre samtidig som den ikke medfører ubehag eller påvirker treningen til en utøver.

Hvem kan delta?

For å delta i denne studien må du være toppidrettsutøver med tilknytning til Olympiatoppen. Det vil si landslagsutøver og/eller stipendutøver.

Du kan ikke delta i studien om du har en sykdom og/eller går på noen form for medisin eller kosttilskudd som kan tenkes å påvirke resultatene i testene. I tvil om dette, må det avklares med lege ved Olympiatoppen om du kan delta i studien. Du kan ikke ha noen form for symptomer på sykdom på testdagen, f.eks. sår hals eller tett nese. Som kvinne, må du utelukke graviditet.

Hva innebærer studien?

Hvis du velger å delta som forsøksperson i denne studien må du møte fastende tidlig om morgen på Toppidrettssentret i Oslo én gang (mellom kl 0600 og 0700). Du sover over på hotellet og går fastende til hvilestoffskiftemålingen. Måling av hvilestoffskiftet foregår ved at du ligger på en seng i rolige omgivelser. Du får en «hood» (kuppel) over hodet og puster normalt. Etter 10 min tilvenning til situasjonen starer målingen av oksygenopptak og karbondioksidproduksjon (slik som under tradisjonell oksygenmåling på tredemølle/sykkel). Testen tar 25 minutter. Etter hvilestoffskiftemålingen tappes det blod på legesenteret (tradisjonell veneprøve). Dernest går du til Norges idrettshøgskole for å ta en kroppssammensetningsmåling (DXA), som tar ca 15 minutter. Til slutt får du frokost på Toppidrettssenteret, samtidig kan du fylle ut noen spørreskjema om din trening og ditt kosthold.

Mulig ulemper og risiko ved å delta som forsøksperson
Dagen før testene kan du kun trene rolig. For utholdenhetstrening betyr det maksimum 1 time i intensitetssone 1 (hjertefrekvens under 72%; Borgs skala under 11). Du kan ikke trene styrketrening. Bevegelighetstrening og motorisk trening, som balansetrening, er det ingen begrensinger for. Du kan ikke drikke alkohol dagen før testene, og du må innta dagens siste måltid senest kl 2200. Du kan kun drikke vann i fasteperioden. Du kan med andre ord ikke innta koffein eller nikotin i fasteperioden.

Målingen av kroppssammensetningen gjøres med DXA (Dual energy X-ray Absorptiometry). DXA måler fettmasse og beinmasse, samtidig som den analyserer beinmineraltettheten i korsrygg og lårhals. Metoden medfører en røntgenstrålingsdose. Dosen anses som lav og kan sammenliknes med strålingsdosen man utsettes for under en interkontinental flyreise.

Blodprøve ved venepunktasjon kan oppleves som ubehagelig. Blodprøver innebærer også en viss infeksjonsrisiko, men den anses som svært lav. Hormonene som analyseres er bl.a. tyroideahormoner, testosteron, østrogen og kortisol.

Hva skjer med informasjonen om deg?
Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og resultater gjennom en navneliste. Det er kun forskerne knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Alle forskerne er underlagt taushetsplikt og data behandles konfidensielt. All informasjon og prøvene som samles inn slettes senest i 2020. Det vil ikke være mulig å identifisere deg i resultatene når studien publiseres. Prosjektet er meldt til Norsk senter for forskningsdata.

Frivillig deltakelse
Det er frivillig å delta i studien, og du kan når som helst trekke ditt samtykke uten å oppgi noen grunn. Dersom du trekker deg, vil alle opplysninger om deg slettes.

Samtykke til deltakelse i studien

Jeg, _ _ _ _ __ _ _ _ __ _ _ _ __ _ _ _ _, bekrefter at jeg har mottatt både muntlig og skriftlig informasjon og samtykker herved i å delta i prosjektet, og har muligheten til å trekke meg når som helst uten å oppgi grunn og uten at det gir noen som helst form for konsekvenser.

Oslo, _ _ _ _ _ _ _ _ _ _ _ _ _

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Forsøksperson

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Prosjektmedarbeider

Dersom det er noe som du lurer på, kan du kontakte:
Ina Garthe: ina.garthe@olympiatoppen.no; mob.: 99003916
Gøran Paulsen: goran.paulsen@olympiatoppen.no; mob.: 93429429

Vennlig hilsen
Ina Garthe, PhD,
leder av Ernæringsavdelingen i Olympiatoppen

Informasjon og forespørsel om deltakelse i et forskningsprosjekt ved Olympiatoppen Sør og Universitetet i Agder

«Energitilgjengelighet og idrettslig prestasjon»

Forekomst og utvikling av relativ energimangel og assosierte helse- og prestasjonsvariabler blant unge mannlige og kvinnelige idrettsutøvere i Sør-Norge

UNIVERSITETET I AGDER

OLYMPIATOPPEN
Sør

Kjære unge idrettsutøver!

Vi søker talentfulle unge utøvere innen sykling, langrenn, skiskyting, langdistanseløping, fotball, volleyball og håndball til å bli med på et forskningsprosjekt i forbindelse med en doktorgrad i idrettsvitenskap ved Universitetet i Agder (UIA) og i samarbeid med Olympiatoppen Sør.

Bakgrunn og hensikt

For utøvere i alle aldre kan det være vanskelig å finne den gode balansen mellom trening, kosthold og restitusjon. I dette forskningsprosjektet ønsker vi å kartlegge en rekke variabler som vi antar har en sammenheng med idrettslig prestasjon og helse. Vi har en del kunnskap om disse variablene blant voksne mannlige og kvinnelige utøvere på toppnivå, men vi vet mindre om tilsvarende variabler blant unge utøvere. Vi har spesielt lite kunnskap om hva som skjer i løpet av perioden hvor unge jenter og gutter går på idrettsgymnas. I denne perioden er det mange som opplever økte treningsmengder, mindre tid til restitusjon og utfordringer med å få i seg nok og riktig mat. I dette prosjektet ønsker vi derfor å måle variabler som treningsmengde, fysisk kapasitet (eks. utholdenhet, muskelstyrke og reaksjonstid), kostholdsvaner, kroppssammensetning og andre helsevariabler som blodtrykk, sykdom og skader, nivåer av stress- og kjønnshormoner samt andre kostholdsmarkører som jern og D-vitamin. Vi ønsker å måle disse variablene to ganger i sesongen over den perioden man er elev ved idrettsgymnaset.

Dette ønskes gjort for å få et større innsyn i, og forståelse for, hvordan utøvere og trenere kan legge til rette for, og sikre grunnlaget for best mulig trening og prestasjon ikke bare på kort sikt, men også sikre at kroppen bygges opp for å tåle den økende treningsmengde som kreves over lang tid for å bli god i sin idrett.

Med bakgrunn i dette er det i kommende forskningsprosjekt ønskelig å kartlegge fysiologiske helse- og prestasjonsvariabler som trenings- og kostholdsvaner, kroppssammensetning, blodtrykk, hvilemetabolisme, fysiologisk kapasitet, sykdom og skader samt psykologiske variabler som motivasjon, velvære, treningsavhengighet og forstyrret spiseatferd to ganger i sesongen over tre år.

Vi håper at du har lyst til å hjelpe oss med å skaffe slik unik kunnskap og bidra til forskning innen idrettsvitenskap.

Forsøkspersoner

Vi ønsker å rekruttere utøvere som oppfyller følgende inklusjonskriterier:

(1) Elev ved VG1 på idrettsgymnas ved prosjektet begynnelse
(2) Konkurranseaktiv innen idretten sin på regionalt og/eller nasjonalt nivå
(3) Fravær fra sykdom og skader som hindre deltakelse i prosjektet.

Deltakelsen i prosjektet innebærer derfor for deg som deltaker, at du må være villig til å gjennomføre et testbatteri over to dager, samt registrere kosthold, trening og aktivitetsnivå i en periode på fire dager før og etter sesong (to ganger pr. år) i tre år (totalt seks ganger).

Hva innebærer deltakelse i prosjektet?
Dette er en kartleggingsstudie som vil inneholde to målepunkter fordelt over en sesong (før og etter sesong). Prosjektet vil gjennomføres over tre sesonger, hvilket innebærer seks måle- og registreringsperioder (se figur 1 for oversikt). Prosjektet er lagt opp slik at det ikke skal forstyrre treningsopplegget ditt hvis du ønsker å delta.

Testfasen:
Testfasen består av to testdager med etterfølgende fire dager med kostholdsregistrering (se figur 2).

- Dag 1; Her skal du møte fastende i laboratoriet for måling av kroppssammensetning, beinhelse, hvilestoffskiftet, blodtrykk, samt en blodprøve og en spyttprøve. I tillegg vil du bli spurt om å besvare noen spørreskjemaer om mat, kropp og helse. En gang i løpet av perioden vil du blive bedt om å svare på samme spørreskjema med to ukers mellomrom (se figur 1 i vedlegg)

NB: *De siste 24 timer før testdagen må du ikke utføre intensiv eller utmattende trening/konkurranser eller drikke alkohol. Du har ikke tillatelse til å spise de siste 12 timene før testene (disse gjennomføres tidlig på morgenen). De siste tre timer før testene må du ikke drikke te, kaffe eller annen koffeinholdig drikke. Som forsøksperson vil du bli godt ivaretatt av testledere.*

- Dag 2; Her får du målt dine fysiologiske parametere knyttet til prestasjon. Du skal gjennomføre en laktatprofiltest, test av maksimalt oksygenopptak (VO_{2maks}), en 30 sekunders all-out Wingate-test, en maksimal styrketest samt en reaksjonstest.

NB: *De siste 48 timene før denne test (dag2) kan du ikke utføre intensiv trening eller konkurranser.*

- Dag 3-6; Du vil bli bedt om å registrere kostholdet ditt samt trenings- og aktivitetsnivået ditt i løpet av fire sammenhengende dager. All kostholdsregistrering gjøres elektronisk via PC/Mac eller APP på telefon med et kostholdsprogram som også benyttes av Olympiatoppen. Du vil få låne en vekt hvor du skal veie all mat og væske du inntar disse fire dagene. Aktivitet og trening registreres med en utlevert pulsklokke fra Polar (M400) samt et lite akselerometer montert på armen (Sensewear). Alle målinger er knyttet til dette er smertefrie og uten sjener.

Mulige fordeler og ulemper:

Mulige fordeler:

- Bidra til å skaffe ytterligere kunnskap rundt energitilgjengelighet blant unge idrettsutøvere og ikke-konkurranseaktive ungdom
- Få mulighet til å teste fysisk kapasitet uten kostnad på UIA/OLT Sør
- Få kartlagt helsevariabler av betydning for idrettslig prestasjon uten kostnad på UIA/OLT Sør
- Få kartlagt energitilgjengelighet med muligheter for tilbakemelding på egne kostholdsvaner og utvalgte helsevariabler over tid
- Få målt hvilestoffskiftet og kroppssammensetning med gullstandard målemetoder og kunne følge disse over tid

Mulige ulemper:

- Må møte til testing to dager hver 6. måned i 3år, hvorav en av testdagene i hver periode må være fastende. Slike testinger kan ligge i skoletiden, da primært ved å erstatte andre treningsøkter, men forventes ikke å ha varighet på mer enn 1,5 time pr. test.
- Kan ikke trene intensive økter dagene før testing
- Må være opplagt til hver test og gjennomføre disse med god innsats
- Blodprøvetaking og måling av hvilestoffskiftet kan oppleves ubehagelig for enkelte
- Risiko for overbelastning ved testing
- Må kartlegge kostholdet og aktivitetsnivået hver 6. måned i tre år (fire dager ved hver anledning).

Hva skjer med informasjon om deg?

Data som blir registrert skal kun brukes slik som beskrevet i hensikten med prosjektet. Opplysningene vil bli behandlet uten navn og fødselsnummer, eller andre direkte gjenkjennende opplysninger. Som deltaker vil du få et ID nummer som representerer ditt navn. Tester som blir gjennomført og data som blir innhentet, vil knyttes til dette ID nummeret. Det er kun autorisert personell knyttet til prosjektet som har adgang til ID nummeret og nøkkelfilen vil oppbevares nedlåst hos prosjektansvarlig. Innsamlet data vil bli benyttet i masterprosjekt og doktorgradsprosjekt, men alltid anonymt. Dataene vil også kunne bli brukt til publisering i tidsskrift, undervisning og kongresser. Som deltaker har du rett til å få innsyn i data som er registrert på deg selv. Data vil oppbevares avidentifisert på prosjektlederes passordbelagte PC. Data vil bli oppbevart i opptil 10 år etter at prosjektet er avsluttet.

Rett til innsyn og sletting av opplysninger om deg

Hvis du sier ja til å delta i prosjektet, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Frivillig deltakelse:

Det er frivillig å delta i prosjektet. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på som medfølger. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige deltakelse. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte prosjektleder/ kontaktperson (se under).

Ytterligere detaljert informasjon om prosjektet og de ulike testene kan utleveres ved å kontakte stipendiat Thomas Birkedal Stenqvist.

Annet:

Datainnsamling forventes avsluttet senest i uke 17, 2019. Datamateriale forventes oppbevart i 10 etter endt datainnsamling.

Hvordan bli med?

Dersom du ønsker å være en del av dette prosjektet kan du sende en mail til thomas.b.stenqvist@uia.no der du beskriver følgende:

- Hvem du er
- Idrettsgren og nivå
- Skole og klasse

Med vennlig hilsen
Thomas Birkedal Stenqvist
PhD stipendiat

Fakultet for helse- og idrettsvitenskap
Institutt for folkehelse, idrett og ernæring
Universitetet i Agder
Tlf: + 47 38142416
Mobil: + 47 45290621
thomas.b.stenqvist@uia.no

Konsulent, Test- og laboratorietjenester
Olympiatoppen Sør

Prosjektansvarlig og veileder
Monica Klungland Torstveit
Førsteamanuensis

Fakultet for helse- og idrettsvitenskap
Institutt for folkehelse, idrett og ernæring
Universitetet i Agder
Tlf: + 47 3814 1831
monica.k.torstveit@uia.no

Fagansvarlig Idrettsernæring og restitusjon,
Olympiatoppen Sør

Vedlegg:

Detaljert beskrivelse av de ulike testene

Testdag 1:

Ved ankomst i laboratoriet ønsker vi aller først å måle kroppssammensetningen og beinhelse ved hjelp av lav-dose røntgenstråling (stråledosen du blir utsatt for er svært liten og tilsvarer samme mengde du vanligvis får ved å fly fra Oslo til New York).

Benhelse og kroppssammensetning: DXA (dobbel røntgen absorpsjonsmetri) er gullstandard måling for vurdering av din kroppssammensetning. Ved DXA måling vil du foruten å få målt muskelmasse og fettmasse også få målt din beinmineraltetthet (indikator på hvor sterkt skjelettet ditt er). Du vil få resultater både totalt for hele kroppen, men også i spesielt interessante områder som rygg og hofter. Selve målingen er helt smertefri og gjennomføres fullt påkledd ved å ligge på en benk/seng. Det vil kun ta ca. 15 minutter å gjennomføre målingen.

Energitilgjengelighet er den mengden av energi som er igjen til alle andre funksjoner i kroppen etter at energikostnaden ved trening er trukket fra. For å kunne måle energitilgjengelighet må vi estimere energiforbruk ved trening og fysisk aktivitet (som dere gjør ved hjelp av pulsklokkene), energiinntak (som dere estimerer via kostholdsregistreringen), fettfri masse (som vi måler ved hjelp av DXA) og til slutt måling av **hvilestoffskiftet**. Vi vet at det kan være store forskjeller i hvilestoffskiftet mellom individer og de aller færreste vet hvor mye energi de bruker i hvile da målemetodene sjelden er tilgjengelig.

Som forsøksperson skal du ligge avslappet på en benk i ca. 30 minutter med en «hette» (som vist på bildet). Målingen medfører ingen smerte eller ubehag. Hvilepulsen vil bli registrert og vi vil se til at du ikke sovner underveis i målingen.

Mens dere ligger på benken vil vi også måle **blodtrykket** liggende og deretter i stående posisjon. Dere vil så bli bedt om å ta en **blodprøve** for å analysere enkelte hormoner og kostfaktorer. Dette vil kun ta få minutter. Avslutningsvis bes dere om å besvare noen spørreskjema før dere er ferdige med dagens testbatteri. Spørsmålene omhandler temaer som demografi, treningsmengde, konkurranseerfaring, forhold til trening, mat og kropp, skader/sykdommer og restitusjon/søvn/velvære.

Kosthold og aktivitetsmåling:
Prinsippet i kostregistreringen er å beskrive når, hva og hvor mye du spiser og drikker så presist som mulig. Vi benytter et kostanalyseprogram som også benyttes av Olympiatoppen hvor vi kan få detaljerte opplysninger om eksempelvis hvilke næringsstoffer du inntar tilstrekkelig av og om du har eventuelle mangler knyttet til kostholdet ditt. Du vil få låne en kjøkkenvekt slik at du kan veie matvarene. På denne måten får vi nøyaktige data til å beregne blant annet energitilgjengelighet. Du vil måtte registrere kostholdet ditt søndag til onsdag i en gitt uke som bestemmes på forhånd. Nødvendig veiledning vil bli gitt i forkant. Samme dager som du registrerer kostholdet ditt må du også ha på deg en aktivitetsmåler (Sensewear, som festes på armen, og gir ingen ubehag). Pulsbeltet må benyttes på alle treningsøkter disse fire dagene. Dette gjøres for at vi så nøyaktig som mulig skal kunne kartlegge energiforbruket til deltakerne. Dersom du ikke selv har egnet pulsklokke vil du kunne låne dette i de fire dagene registreringen foregår.

NB: *I løpet av de 4 dager du registrerer kosthold, vil du bli utstyrt med en pulsklokke (Polar M400) til bruk og innsamling av pulsdata fra samtlige økter du har.*

Testdag 2:
Fysiologisk test av laktatprofil: Testen starter ved at du gjennomfører 5 minutters submaksimale bolker med økende belastning for å finne arbeidsbelastningen på 4 mMol laktat. Du vil begynne med 5 minutters arbeid på en lett belastning. Deretter vil belastningen øke hvert 5. minutt. Dersom laktatkonsentrasjonen i blodet stiger til over 3 mMol/L, økes belastningen mindre. Oksygenopptaket (VO_2) og hjertefrekvens måles i løpet av de siste 2,5 minuttene under hvert drag. Laktatkonsentrasjonen blir målt etter 4,5 min på hver belastning.

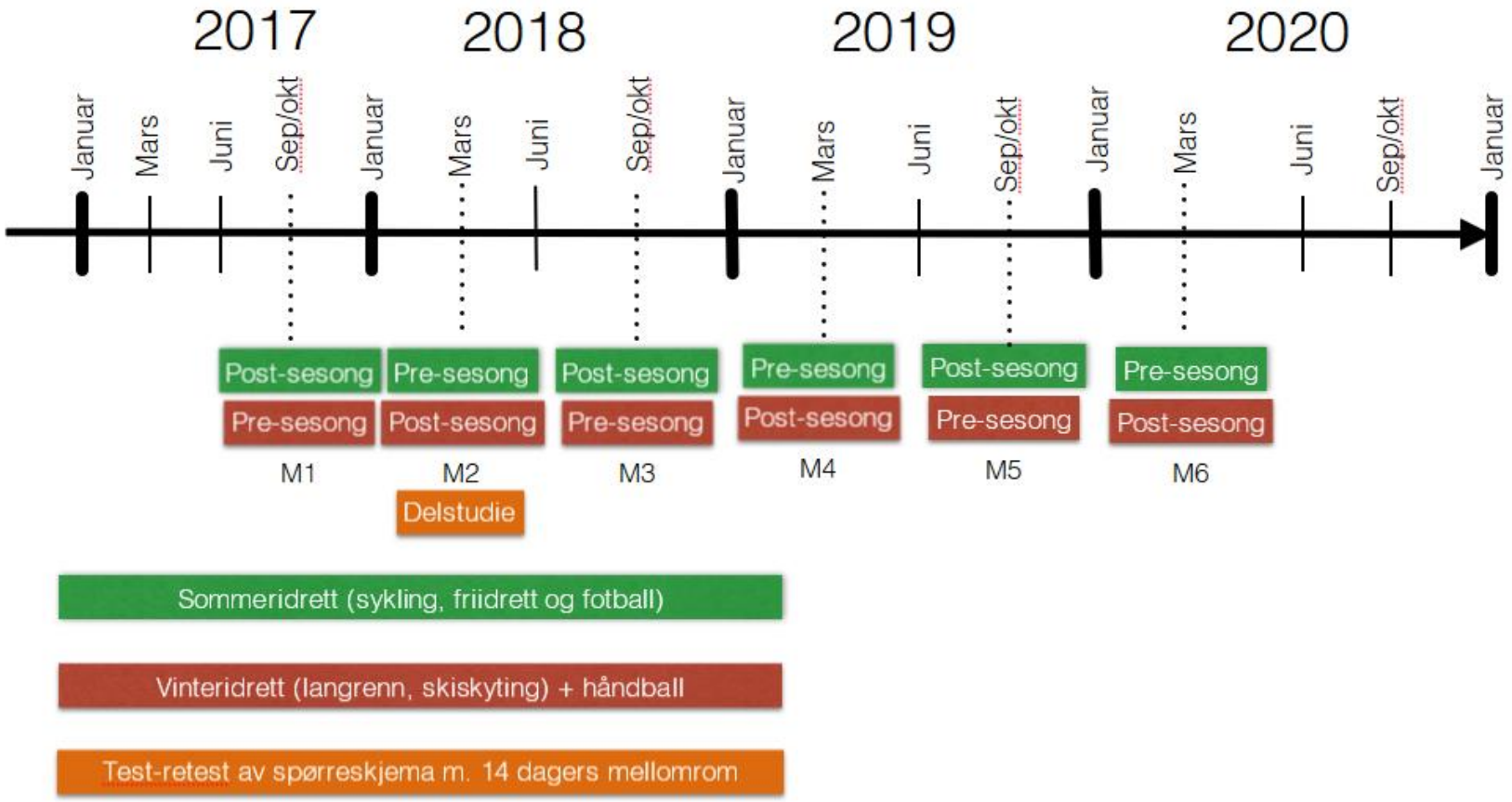
VO_{2maks}: Under testen måles oksygenopptaket til utmattelse. Du vil bli bedt om å begynne arbeidet på en gitt belastning som vil økes hvert minutt inntil utmattelse inntrer og du ser deg nødsaget til å avslutte testen. De to høyeste målinger du oppnår danner grunnlag for dit maksimale oksygenopptak.

Anaerob kapasitet (30-sek Wingate-test): Du skal heretter igjennom en 30 sekunders all-out wingate test for å måle hvor mye kraft du klarer å levere over en periode på 30 sekunder. Testen starter ved at du blir bedt om å tråkke på en sykkel med en frekvens under 120 RPM i 20 sekunder med en gitt motstand på 120 watt. Deretter følger 3 sekunders nedtelling før en bremsemotstand tilsvarende 0.7 Nm pr. kg kroppsmasse blir påført sykkelen og forblir konstant gjennom de påfølgende 30 sekundene testen varer. Du skal her sykle så hardt du overhode kan. Du kan selv velge om du vil sitte eller stå underveis i testen.

Maksimal styrke: Her vil vi måle din maksimale muskelstyrke ved hjelp av isokinetisk dynamometri. Du vil bli plassert i en behagelig sittestilling med borrelåsbånd plassert på tvers av låret, bekken, og brystet for å minimere bevegelser under test, og for å isolere bevegelse av kneleddet. Du vil da bli bedt om å holde armene i kryss over brystet for å begrense bevegelse i løpet av testen. Utvalget av bevegelsen vil variere fra 10° til 100° for knefleksjon. Utholdende styrke måles etter 60-sekunders hvile, hvor du vil bli bedt om å utføre 30 påfølgende maksimal fleksjoner av kneet med så stor kraft du klarer.

Reaksjonstest: Reaksjonstiden du bruker måles ved hjelp av en bærbar PC som er forbundet til en bærbar PC. Reaksjonstiden testes ved å måle tiden du bruker på å trykke mellomroms-tasten ned på tastaturet når PC-skjermen skifter farge.

Tidslinje for hele prosjektet:



Figur 1: *Oversikt over prosjektet. Prosjektet består av seks målepunkter (M1 – M6) hver 6. måned, samt hvor i sesongen hhv. vinteridrett og sommeridretter befinner seg. En gang i løpet av prosjektet sendes det samme spørreskjema med 14 dagers mellomrom.*

Tidslinje pr. målepunkt:

Dag 1: 06.00 - 11.00 (1,5 time avsatt pr. deltaker til test)

Høyde/vekt	DXA skan	30 min. RMR-test	Blodtrykk	Blodprøve	Spyttprøve	Instruksjon og spørreskjemaer

Dag 2: 08.00 - 20.00 (2 timer avsatt pr. deltaker til test)

Vekt	Laktat-profiltest	VO2maks	30s all-out	Maksimal styrke	Reaksjonstest

Dag «3-6 (4 dager)» : 24.00 - 24.00

Registrere energiinntak, daglig energiforbruk samt energiforbruk under trening i 4 sammenhengene dager

Figur 2: *Testprotokollen. På dag 1 måles beinhelse, kroppssammensetning og hvilemetabolisme. Videre tas blod- og spyttprøve samt at deltakerne får instruksjon og spørreskjemaer. På dag 2 måles fysiologiske parametere som laktatprofil, VO2maks, anaerob kapasitet, maksimal styrke og reaksjonstest. Deretter, over 4 sammenhengene dager veier og logger deltakerne energiinntak, daglig energiforbruk og energiforbruk under trening*

Samtykke til deltakelse i prosjektet

«Energitilgjengelighet og idrettslig prestasjon»

Ved å si ja til å delta i prosjektet, har du rett til å få innsyn i hvilke opplysninger som er registrert på deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Ved å signere samtykkeerklæringen bekrefter du også at du ikke har kjent hjertesykdom eller andre lidelser/sykdom som medfører at din fastlege har frarådet deg å teste intensivt.

Som deltaker i prosjektet er du for øvrig forsikret via at staten er selvassurandør for universitetene.

Jeg er villig til å delta i prosjektet

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om prosjektet

,Testleder

(Signert, rolle i prosjektet, dato)

Appendix IV

UNIVERSITETET I AGDER

Manual for semistructured dietary interview

Energy availability and sports performance

Incidence and development of relative energy deficiency among young female and male athletes in Southern Norway

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1. Introduction and aim

The aim of the semi-structured dietary interview is to assess habitual dietary pattern and to estimate energy intake in adolescent athletes from three different high schools in Southern Norway. Semistructured interviews allow for structure but are not so rigid that they limit the participant from sharing tangential and often relevant information.

For the purpose of this study, the interview aims to assess habitual meal patterns and dietary intake with specification of intake during the last seven days. There are several limitations compromising the validity of this method compared to the prospective weighed food record. Therefore, it is extremely important that the interviews are carried out as standardized as possible. The wording of the questions and how they are presented to the participants are crucial for the quality of the collected data. The language must be open-ended, unbiased, and nonjudgmental.

Be curious and get as much details about the respondent's meal pattern as possible. If he/she has difficulties in remembering, give him/her a little time to think back.
Make the respondent feel important. He/she has very important information we need in our research.

The interviewer must be completely objective. There are no "right" or "wrong" foods and it is important that the interview is reflected by this. Closed questions (where the answer can be "yes" or "no") should be avoided. Instead, questions often begin with "when" or "what". When you ask for details, it is okay to begin with "is this…", e.g. "is this a with or without sugar?"

For many people, talking about their dietary habits can be very intimidating, especially when they are face by health professionals. Maybe they are nervous when coming in to the interview. The interviewer must be natural in his questioning technique and when answers are received by the respondent. It is the interviewer's task to create a comfortable environment, where the respondent feels, he/she can be 100% honest. Nodding and smiling are simple and good ways to manage this. First step is to ask an ice-breaker question for instance: "Hi and welcome. I really appreciate that you want to participate in this study. What are your experiences so far?" or "what a nice weather today – how are you going to enjoy it later today?"

The interview guide serves the interviewer as a help to get the needed information but the order of the questions may depend on how the respondent answers and maybe you need to ask additional questions. Many sports are seasonal; therefor the interview is performed twice for each athlete.
Use the interview guide and write down the respondent's answers in the form.

2. Interview guide

Once again thank you for your participation in this study. Your participation is very valuable to us, and your participation help us with increased knowledge and to help you and other young athletes to optimize performance.

Now I will appriciate to know about you habitual eating habits. Our conversation will take about an hour. It is very important to me that you know, that there are not any "right" or "wrong" foods. Right foods are what you eat and it is important that you are honest. It is important that you tell me everything you eat and drink – also snacks and also if you eat or drink during the night.
What you tell me here is anonymously and will only be used for research purposes.
I will help you, if you are having trouble remembering and here beside me I have a little book with pictures of foods and portion sizes where you can identify which one is most equal to what you eat.

Do you have any questions before we begin?
So let us begin.

I will ask you to think back on what you have eaten during the last week.

1. From midnight; when is the first you eat or drink?
    a. What do you eat?
        i. Do you know the brand of this product?
        ii. Is this with sugar or a light version? (e.g. if the respondet answers youghurt)
        iii. Is this a full fat or a low fat version (e.g. if the respondet answers cheese, youghurt, or butter)
        iv. Is this a regular type or with whole grain? (e.g. if the respondet answers rice, pasta, or bread)
        v. How many slices/pieces do you eat? (e.g. if the respondet answers bread, crackers, or potatoes)
        vi. What size is this portion you eat? (e.g. if the respondet answers oat meal, pasta, rice, stew. Use the pictures)

        If e.g. the participant tells you he/she had 2 dl oat meal 5 times for breakfast during the week and 2 slices of knekkebrød with cheese the other 2 days:
        - *((40g/dl x 2) x 5)/7 =* ***57 g oat***
        - *((11g/slice x 2) x2/7 =* ***6.3 g Knekkebrød***
        - *((35g/slicex2) x2)/7 =* ***20 g cheese***

        What is written in bold should be entered in Dietist Net.

    b. Thank you. And what else do you eat at this time a day? (repeat section a, until the respondent tells you he/she does not eat anything else at this meal)

    c. What do you drink?
        i. Do you know the brand of this product?

ii. Is this with sugar or a light version? (e.g. if the respondet answers drinkingyoughurt, chocolate milk, soda or lemonade. If the respondent tells you he/she drinks self-mixed sportsdrink, remember to ask about the concentration; how many scoops/grams per ½ liter?)
iii. Is this a full fat or a low fat version (e.g. if the respondet answers milk or chocolate milk)
iv. What size is this portion you drink? (small glass, large glass, a can, ½ liter?)

2. When do you eat next? (Repeat section a, b, and c)
   - Repeat untill midnight

3. Regarding you training; what do you eat and drink there?

4. How about weekends; does weekends differ from what you have told me here? In what way?

5. You may need to add questions like «How often do you eat...?», «How often do you drink sports drink during training?», «How often do you eat after a training session?»

6. Thank you very much. Now I will read to you everything I have written of what you have told me so far.

7. Are there anything we have missed? (give the respondent time to think. In general people tend to forget snacks, alcohol and special foods they eat in the weekends. Athletes tend to forget what they drink/eat during training and supplements in general. Therefore, you may help the respondent by asking:

- How about during training sessions – what do you drink/eat during this time?
- Do you take any other supplements? For instance of vitamin/minerals?

After the interview: enter in Dietist Net and safe the filled-out form.
On page 5 you see examples of how to fill out the form. Page 6 contains the form, you need to print and fill out during the interview (you will probably need more than one).

Subject ID:_____

Meal-type: Breakfast

Date: _____

Time	**Food/beverage item** (Preparation/cooking)	**Brand** (if known)	**Specify** (e.g. fat or fiber content, if known)	**Amount (portion size/grams/slices/pieces)** Use pictures
Monday @6:30	*Oat meal*	*Solgryn*	*10% fiber*	*Medium portion*
6:30	*Milk*	*Tine*	*1,5% fat*	*1 big glass*
6:30	*Biola*	*Tine*		*1 small glass*
Tuesday @6:30	*Bread*	*Kiwi brand*	*Grov*	*3 slices*
6:30	*Spekepølse*	*Gilde jubilæum*		*6 slices*
6:30	*Milk*	*Tine*	*Lett*	*1 medium glas*

Subject ID:_____

Meal-type: _____

Date: _____

Time	**Food/beverage item** (Preparation/cooking)	**Brand** (if known)	**Specify** (e.g. fat or fiber content, if known)	**Amount (portion size/grams/slices/pieces)** Use pictures

Appendix V

BEDA-Q Introduksjon

I punktene nedenfor spørres det om dine holdninger, følelser og atferd. Noen av punktene handler om mat og spising. Andre punkter dreier seg om dine følelser i forhold til deg selv. Du skal ved hvert punkt bestemme deg for i hvilken grad utsagnet passer på deg: ALLTID, VANLIGVIS, OFTE, IBLANT, SJELDEN eller ALDRI. Hvis du mener at ditt svar på et utsagn er ofte, sett da et kryss i ruten i kolonnen under ofte for det gjeldende utsagn.

Svar på alle punktene idet du forvisser deg om at du setter kryss i den ruten som best gjenspeiler hvordan du føler det nå for tiden.

ID-nummer:

Dato:

SETT KUN ETT KRYSS FOR HVERT SPØRSMÅL

		Alltid	Vanligvis	Ofte	Iblant	Sjelden	Aldri
1	Jeg får dårlig samvittighet når jeg har spist for mye.	☐	☐	☐	☐	☐	☐
2	Jeg er svært opptatt av å bli tynnere.	☐	☐	☐	☐	☐	☐
3	Jeg synes at magen min er for stor.	☐	☐	☐	☐	☐	☐
4	Jeg er fornøyd med figuren min.	☐	☐	☐	☐	☐	☐
5	Foreldrene mine har krevd topp-prestasjoner av meg.	☐	☐	☐	☐	☐	☐
6	Som barn anstrengte jeg meg mye for ikke å skuffe mine foreldre og lærere.	☐	☐	☐	☐	☐	☐

Del 4, DLS, forhold om kropp og kroppsbilde

Nedenfor er det noen meninger om kropp. Hvor ofte stemmer disse for deg?

Aldri = 1
Sjeldent = 2
Noen ganger = 3
Ofte = 4
Nesten alltid= 5
Alltid= 6

6-point scale, ranging from never (1) to always (6). (aldri = 1, sjeldent = 2, noen ganger = 3, ofte = 4, nesten alltid= 5, alltid= 6)

1. Jeg synes de kroppene som ser finest ut er de som er veldefinerte*

2. Personer som har en fast og veldefinert kropp er svært disiplinerte*

3. Målet mitt er å ha veldefinerte muskler*

4. Personer som har en veltrent kropp og ser atletiske ut er de mest attraktive*

5. Det er viktig å ha veldefinerte magemuskler*

6. Klær ser finere ut på personer som har veldefinerte muskler*

Takk for svarene i del 4

ID-nummer:

Dato:

EAI - Y – unge (13-20 år)

	Meget uenig	Uenig	Hverken enig/uenig	Enig	Meget enig
1. Trening er det viktigste i mitt liv.	1	2	3	4	5
2. Min familie eller venner er bekymret for meg, fordi jeg trener så mye.	1	2	3	4	5
3. Jeg bruker trening til at endre humør (f.eks. for å bli mer glad eller glemme problemer).	1	2	3	4	5
4. I løpet av det siste året har jeg økt min daglige trening.	1	2	3	4	5
5. Hvis jeg ikke trener hver dag, blir jeg urolig, hissig eller lei meg.	1	2	3	4	5
6. Jeg har forsøkt at kutte ned på min trening, men ender med at trene like så mye som før.	1	2	3	4	5

Ekstra spørsmål:

7. Jeg trener ofte på tross av smerter og skader.	1	2	3	4	5
8. Jeg har skyldfølelse over ikke at trene nok.	1	2	3	4	5
9. Jeg er alt for avhengig av min trening, og den kontrollerer livet mitt.	1	2	3	4	5