Women in Motion.

Exploring the Dynamic Relationship of the Menstrual Cycle with Physical Activity and Exercise.

Inauguraldissertation der Philosophisch-humanwissenschaftlichen Fakultät zur Erlangung der Doktorwürde

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Abstract

The menstrual cycle (MC), a monthly series of changes the body goes through to prepare for a possible pregnancy, is crucial to females' reproductive lives. Despite its significance in female life, a substantial 80% of females encounter MC-related challenges at some point in their reproductive age. MC-related symptoms and disorders have the potential to impact women's overall health negatively. Concurrently, physical activity (PA) and exercise is recognized for its positive influence on well-being and health. While suggestions exist regarding the reciprocal relationship between PA and the MC, inadequate research exists on this interplay, particularly in recreationally active females. This dissertation addresses this gap by investigating the association between PA, exercise and MC-related symptoms and disorders in recreationally active females through a cross-sectional survey. Additionally, it explores the effects of MC-adapted endurance training on performance, cardiovascular health, and premenstrual syndrome through two randomized-controlled trials.

The cross-sectional study highlights elevated prevalences of premenstrual syndrome, oligomenorrhea, and secondary amenorrhea among recreationally active females, underscoring the critical need for menstrual health considerations in this population. Although marginal associations were observed between light/moderate PA, total training volume, and MC disorders, no significant relationship was found concerning PA and premenstrual syndrome.

Furthermore, the training interventions of the randomized-controlled trials significantly improved aerobic capacity in naturally menstruating females, yet no additional benefits were observed for MC phase-adapted training in terms of performance, cardiovascular health, or premenstrual symptoms. The results suggest that periodized training adapted to the MC may not yield distinct advantages over traditional training in this population. However, the substantial individual variability in training responses in all intervention groups must be emphasized.

The observed variability underscores the necessity for replications with extended intervention periods, larger sample sizes, and improved accuracy in MC determination, guiding the refinement of training strategies for females. Future research should explore diverse populations, considering those at risk for MC-related health issues or with comorbidities, and analyze various outcomes, including MC health, well-being, and enjoyment, to enhance our understanding and contribute to long-term PA adherence.

The following three manuscripts will be submitted for the cumulative dissertation:

I. Kubica, C., Zimmermann S., Ketelhut, S. & Nigg, C. R. (under review). Self-reported physical activity intensity and training volume are related to menstrual health among recreationally active Swiss females.

II. Kubica, C., Ketelhut, S., Querciagrossa, D., Burger, M., Widmer, M., Bernhard, J., Schneider, M., Ries, T. & Nigg, C. R. (2024). Effects of a training intervention tailored to the menstrual cycle on endurance performance and hemodynamics. *The Journal of Sports Medicine and Physical Fitness, 46(1), 45-54.* https://doi.org/10.23736/S0022-4707.23.15277-7

III. Kubica, C., Ketelhut, S. & Nigg, C. R. (2024). Polarized running training adapted to versus contrary to the menstrual cycle phases has similar effects on endurance performance and cardiovascular parameters. *European Journal of Applied Physiology* , *124*(11), 3433-3444. https://doi.org/10.1007/s00421-024-05545-9

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Abbreviations

ANOVA	Analysis Of Variance
CON	Control Group
FSH	Follicle stimulating hormone
GnRH	Gonadotropin Releasing Hormone
HPO	Hypothalamic-Pituarity-Ovarian
INT	Intervention Group
LH	Luteinizing Hormone
MC	Menstrual Cycle
PA	Physical Activity
PMS	Premenstrual Syndrome
RMSSD	Root Mean Square Of Successive Differences
SDNN	Standard Deviation of the NN Intervall
VO_2max	Maximum Oxygen Uptake
VO_2peak	Peak Oxygen Uptake

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1. Introduction

The menstrual cycle (MC) is an enduring biological phenomenon accompanying females from the onset of puberty until menopause (Schmalenberger et al., 2021). With an average reproductive lifespan of approximately 36 years, females undergo around 350 MCs, influenced by factors such as the number of pregnancies, individual MC length, and regularity (Mihm et al., 2011). Despite its significance in female life, a substantial 80% of females encounter MC-related challenges at some point in their reproductive age (Clayton, 2008; Hylan et al., 1999). These challenges may range from mild premenstrual symptoms (Direkvand-Moghadam et al., 2014) to severe disorders (Bachmann & Kemmann, 1982), which, over time, can adversely affect fertility, increase the risk of cardiovascular diseases, reduce bone mass, induce osteoporosis, and contribute to mental health issues such as depression and anxiety disorders (De Souza & Williams, 2004; Mihm et al., 2011; O'Donnell et al., 2011; Shufelt et al., 2017).

Many factors can impact the MC, such as physical activity (PA) (Ahrens et al., 2014). Regrettably, research investigating the interaction between the MC and PA in recreationally active females is scarce, leaving many questions unanswered (Ahrens et al., 2014). This knowledge gap places physically active females in a challenging position - from recognizing potential health risks to devising solutions for existing health issues. While it is known that many females in the general population suffer from MC-related symptoms, such as oligomenorrhea (~11%) or secondary amenorrhea (~3%) (Bachmann & Kemmann, 1982), these numbers appear to increase among physically active females, particularly athletes or those engaged in high levels of PA, up to 24% for oligomenorrhea, and 27% for secondary amenorrhea (Gibbs et al., 2013; Ravi et al., 2021). Athletes with high training volumes and those participating in "lean" sports, perpetually teetering on the edge of low-energy availability, are particularly vulnerable (Ryterska et al., 2021; Sundgot-Borgen & Torstveit, 2004; Torstveit & Sundgot-Borgen, 2005). However, the landscape for recreationally active females, who constitute the majority of active females, remains less explored. Recreationally active females might be particularly vulnerable, compared to high-performance athletes, due to the lack of support by the coaching staff or medical team. This raises crucial questions considering the interaction of MC and PA. Even though low-energy availability is considered one of the leading causes of MC disorders such as amenorrhea, it is still discussed controversially if PA only contributes to the risk of low-energy availability or whether it might be an independent stress factor negatively affecting the MC (Bullen et al., 1985; Fourman & Fazeli, 2015; Williams et al., 2015). Moreover, the positive impact of PA on MC-related symptoms, such as premenstrual symptoms, has been acknowledged, suggesting potential benefits for the well-being of physically active females (Ahrens et al., 2014; Liu et al., 2004). However, the optimal dose of PA for recreationally active females, striking a balance between reaping the positive impacts of PA and mitigating the risk of MC disorders, remains a critical question.

Additionally, overlooking the potential collaboration between the MC and PA might result in missed opportunities for designing PA interventions or training programs. As previously known, the hormonal fluctuations over the MC are not only relevant for reproduction, but the hormonal changes might also alter physiological responses to exercise (Ansdell et al., 2020) by impacting overall performance (Meignié et al., 2021), the metabolism (Hackney et al., 2022), and exercise behavior and exercise avoidance (Kolić et al., 2021; Prado et al., 2021b).

Although current research on resistance training suggests a positive impact of training adapted to the MC on training responses (Thompson et al., 2020), less is known about the effects of endurance training and the potential impact of MC-adapted training on overall well-being (Kissow et al., 2022). Adapting exercise to the MC, considering individual needs such as varying energy levels, subjective PA readiness, or MC-related symptoms, is suggested to enhance long-term PA participation by reducing barriers and positively impacting performance and overall well-being (Julian & Sargent, 2020; Prado et al., 2021a).

Despite the continuous increase in the number of female participants in recreational and high-performance sports (Fink, 2015) and growing awareness of the health-related significance of the MC (De Souza & Williams, 2004; Mihm et al., 2011; O'Donnell et al., 2011; Shufelt et al., 2017), females in research are still considered "invisible" (Cowley et al., 2021) and MC-related research is in its infancy. It is imperative to eliminate the "invisibility" of women in research and further analyze the interaction between the MC and PA. By doing so, we could contribute to preventing long-term MC and PA-related health problems and empower physically active women to establish a positive and beneficial relationship between the MC and PA. To initiate further steps and contribute to understanding the interaction of MC and PA, this dissertation aims to analyze the interaction between the MC and PA in recreationally active females. Are PA and MC-related symptoms and disorders related in this population? Further, the second aim is to explore the effects of MC-adapted endurance training on performance and health-related parameters, including cardiovascular parameters and PMS.

2. Theoretical Background

2.1. The Menstrual Cycle

From the onset of menarche to menopause, females experience cyclic ovarian function. Ovarian activity allows reproduction, which increases during puberty and decreases during perimenopause, as transitional periods, reaching maximum in-between (Hackney, 2017). The fluctuating production and release of the reproductive hormones regulate the MC. Despite inter- and intra-individual variations, the average MC spans over 28 days, ranging from 21 to 35 days (Hackney, 2017). The MC can be divided into two basic phases: the follicular and the luteal phase (de Jonge et al., 2019) (s. Fig. 1). Regular hormonal fluctuations in reproductive hormones occur in eumenorrheic females showing an ovulatory MC. The onset of menstruation marks the start of a new MC with the follicular phase. On average, the early follicular phase lasts 5 days (Elliott-Sale et al., 2021) and is characterized by low estrogens and progesterone concentrations. Within the first days, concentrations of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) begin to rise slowly, which leads to the growth of a new follicle and estrogen release from the ovaries (Khonsary, 2017). As the follicular phase progresses, the dominant follicle is selected and begins to secrete estrogen, which marks the mid-follicular phase. Just before ovulation, the highest estrogens levels of the MC are observable, while a significant increase in LH level occurs (Elliott-Sale et al., 2021). The peak in estrogens levels indicates the late follicular phase. The simultaneous rise in LH is essential, as it triggers ovulation (Khonsary, 2017). At ovulation, the mature egg is released from the follicle, and the corpus luteum is formed, which marks the beginning of the luteal phase (de Jonge et al., 2019), the early luteal phase. During the mid-luteal phase, progesterone and estrogens are secreted in large quantities. Those rising hormonal concentrations of estrogens and progesterone inhibit the secretion of FSH and LH (de Jonge et al., 2019).

If fertilization occurs, the embryo remains in the endometrium and develops into a fetus. If

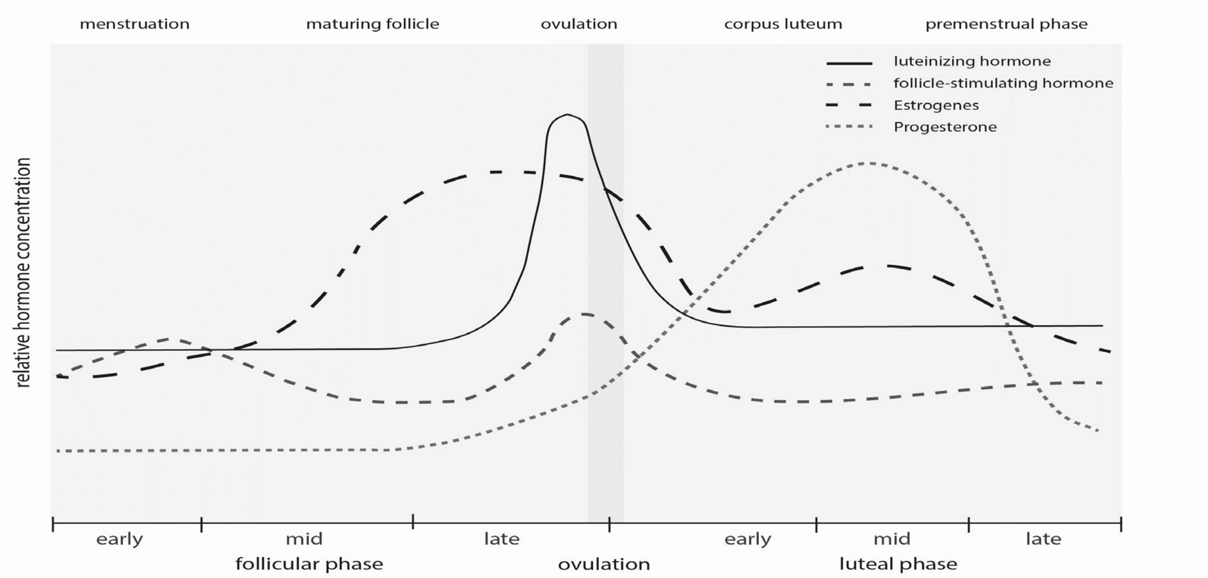

Figure 1. Key regulatory hormone changes over one menstrual cycle in a healthy eumenorrheic female, including the identified phases of the menstrual cyle. Adapted from Hackney et al. (2017, p.7)

fertilization does not occur, the corpus luteum begins to atrophy, and the secretion of the reproductive hormones decreases (Hackney, 2017). This is accompanied by a fall of estrogen and progesterone in the late luteal phase until the onset of menstruation, indicating a new MC (Fig. 1). However, several factors can affect hormonal profiles, and individual hormonal profiles may not be identical from one MC to another (Alliende, 2002).

The regular MC results from a highly coordinated hypothalamic-pituitary-ovarian (HPO) axis (s. Fig. 2), which regulates complex hormonal feedback loops. Those feedback loops lead to the formation of a dominant follicle, ovulation, and, in the absence of fertilization, shedding of the endometrial lining (Itriyeva, 2022). All three neuroendocrine glands, the hypothalamus, the pituitary, and the ovaries, must work together to ensure proper functioning (Sam & Frohman, 2008). The signaling process for the MC starts within the hypothalamus. In the hypothalamus, a set of brain peptides, also known as kisspeptin, regulate the production of the gonadotropin-releasing hormone (GnRH) (Skorupskaite et al., 2014) and serve, therefore, as a “gatekeeper” for the secretion of gonadotropins, the release of ovulation, and the metabolic regulation of fertility (Pinilla et al., 2012). The secreted GnRH is released from the hypothalamus into the bloodstream and travels to the pituitary glands. The pituitary glands respond to the increasing GnRH concentrations by releasing LH and FSH, which enter the bloodstream until FSH and LH reach the ovaries and bind to the ovarian receptors. The binding of FSH and LH to the ovarian receptors finally stimulates the production of estrogens and progesterone (Hackney, 2017). A negative feedback loop exists to downregulate the secretion of GnRH in the hypothalamus and LH in the pituitary. Estrogens combined with ovarian inhibin B mainly modulate the amplitude of pulsatile GnRH release in the hypothalamus (Meethal et al., 2009; Plant & Zeleznik, 2014). The inhibition of GnRH secretion results in diminished FSH and LH secretion within the pituitary (Stamatiades et al., 2019). In contrast to the effects of estrogen on GnRH, the indirect effect of progesterone on the GnRH pulse oscillator neurons appears to decrease GnRH pulse frequency, resulting in a decreased LH and FSH pulse frequency (Goodman et al., 2007; Hurd, 2017).

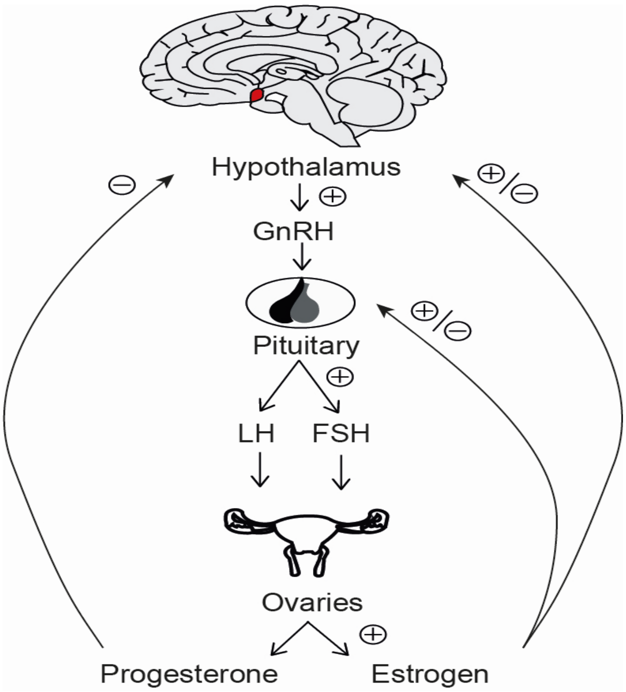

Figure 2. Endocrine feedback loops between the hypothalamus, the anterior pituitary, and the ovaries. Adapted from Popat et al. (2008, p.44).

The HPO axis is an entity that orchestrates the cyclic production of gonadotropic and steroid hormones (Mikhael et al., 2019). Various reasons can disturb the proper functioning of the HPO axis, such as hypothalamic-pituitary failure, most commonly caused by a congenital absence of GnRH (Mikhael et al., 2019). Further, endocrine disorders, such as polycystic ovary syndrome or endocrine disruptions caused by excessive weight or underweight, can also affect GnHR pulsatility (Mikhael et al., 2019). Additionally, sufficient functioning of the HPO-axis feedback loops depends on adequate energy and nutrient availability and is regulated by stress (Veldhuis et al., 1985). Stress, which affects the HPO-axis, can be either emotional and/or physical or caused by conditions such as low energy availability (Elliott-Sale et al., 2018; Hakimi & Cameron, 2017).

2.1.1. Ovarian hormones

The main ovarian hormones, whose release is regulated by the HPO-axis, are estrogens and progestogens (Hackney, 2017).

The term estrogens represents a group of similarly structured steroid hormones, which are produced by the ovaries stimulated by FSH. Three estrogens are mainly present in the human female: estradiol-β-17, estrone, and estradiol (Hackney, 2017). Given that Estradiol-β-17 holds the highest relative estrogenic potency compared to other estrogens, which contribute to the reproductive function (Wierman, 2007), this dissertation will primarily focus on it and refer to it as “estrogen” in the following chapters. Serum estrogen levels rise during the follicular phase of the MC, parallel to the growth of the follicle. A positive feedback loop exists in the estrogen-primed pituitary to augment LH release and trigger ovulation (Buffet et al., 1998; Fink, 2000). With the occurrence of ovulation, estrogen concentrations drop due to the negative feedback loop, and a second rise in the luteal phase can be identified (s. Fig. 1). Maximum estrogen concentrations are reached in the late follicular phase, reflecting the estrogen secretion from the follicle. Estrogen has a negative feedback effect on FSH-secretion (Hurd, 2017). Next to its role in reproduction, estrogen also affects soft tissue, skeletal muscle, and the epidermis (Wierman, 2007). Due to the reduced oxidative stress under high estrogen concentrations, estrogen has a protective effect on cardiovascular diseases (Xiang et al., 2021) and regulates immune response (Ma et al., 2021). Further, estrogen modulates insulin sensitivity and glucose metabolism by increasing insulin sensitivity and glucose uptake into type I muscle fibers (Oosthuyse & Bosch, 2010). Estrogen also impacts fat metabolism by increasing the availability and cellular oxidation capacity for fatty-free acids (Oosthuyse & Bosch, 2010).

Progesterone, a major progestogen, is classified as a steroid hormone predominantly produced by the ovaries (Hackney, 2017). After ovulation, the corpus luteum begins to secrete progesterone, which leads to a differentiation in the epithelial cells of the endometrium into secretory cells (Buffet et al., 1998). Peak progesterone levels occur during the mid-luteal phase (s. Fig. 1). If no pregnancy occurs, the corpus luteum regresses, leading to a fall in progesterone secretion. If pregnancy occurs, progesterone maintains the uterus's gestational sac, modulating the maternal immune system (Czyzyk et al., 2017). Progesterone also causes a depletion of estrogen receptors to protect against endometrial hyperplasia (Hurd, 2017). Further, progesterone downregulates LH pulse frequency and prevents a second LH surge within the MC (Kokawa et al., 1996). Next to its role in reproduction, progesterone also affects the central nervous system and other target tissues (Mani et al., 1997), as well as the metabolism (Redman et al., 2005), leading to a glycogen-sparing effect and increased protein catabolism (Oosthuyse & Bosch, 2010). Further, progesterone has immunomodulatory, anti-inflammatory, and neuroprotective effects (Rafiee Zadeh et al., 2018).

2.1.2. Menstrual Dysfunction and Disorders

Even though a regular MC with optimal steroid hormone concentrations is a relevant vital sign of health in females in their reproductive age, not all MCs reflect the modeled MC as described in chapter 2.1. as women show a high variability in MC length and hormonal concentrations (Bull et al., 2019; Fehring et al., 2006; Itriyeva, 2022). Epidemiological studies indicate that approximately 80% of women have to deal with symptoms associated with their MC along their reproductive ages (Hylan et al., 1999). These symptoms can manifest in different dimensions, such as the premenstrual syndrome (PMS), oligomenorrhea, or secondary amenorrhea, all of which will be discussed in the following sections.

Premenstrual Syndrome

PMS describes a wide collection of psychological, physical, and behavioral symptoms that occur during the MC (Yonkers & Simoni, 2018). The severity of the symptoms can vary from normative, mild premenstrual to severe and disabling symptoms. Criteria for PMS are not stringent in the literature, but some relevant points of agreement exist. First, symptoms are expressed mainly during the luteal phase of the MC with significant impairments, followed by a symptom-free period for at least one week when menstruation begins (Yonkers & Simoni, 2018). Symptoms of PMS can include physical and/or emotional symptoms (Yonkers & Simoni, 2018). The main affective symptoms are angry outbursts, anxiety, confusion, depression, irritability, and social withdrawal. Somatic symptoms include abdominal bloating, breast tenderness or swelling, headaches, joint or muscle pain, swelling of extremities, or weight gain (Beckmann et al., 2013). PMS prevalence rates range between 20-30% among the general population (Borenstein et al., 2007; Qiao et al., 2012). However, the prevalence rates vary greatly from study to study, as different methods are used for diagnosis. Women experiencing PMS often incur elevated indirect costs for employers, manifested through diminished work productivity, increased medical expenses, and a compromised health-related quality of life (Mishell Jr, 2005)

To diagnose PMS, retrospective questionnaires such as the premenstrual symptoms screening tool (Steiner et al., 2003) or the premenstrual assessment form (Lee et al., 2002) can be utilized. These questionnaires are based on the criteria outlined in the Diagnostic and Statistic Manual of Mental Disorders (American Psychiatric Association & Association, 2013). However, retrospective assessments are remarkably prone to bias of false positive reports and the influence of individual beliefs about the PMS (Schmalenberger et al., 2021). Therefore, prospective diaries assessments are recommended (Gnanasambanthan & Datta, 2019). These assessments should include daily ratings of the criteria defined in the Diagnostic and Statistic Manual of Mental Disorders over two consecutive MCs. The underlying causes of PMS are still debated in the literature. However, the occurrence of PMS seems to be linked to the individual response to the normal fluctuations in reproductive hormone levels (Schmalenberger et al., 2021). Two theories are postulated for the aetiology of PMS: increased sensitivity to progesterone and reduced serotonin levels caused by estrogen and progesterone (Gnanasambanthan & Datta, 2019).

Oligomenorrhea

Another common menstrual disorder affecting females in their reproductive age, alongside PMS, is oligomenorrhea. Oligomenorrhea is defined as an MC length of 35 days or more (Elliott-Sale et al., 2021). Studies from China and Iran indicate a prevalence rate of oligomenorrhea in 12-13% of females in the general population (He et al., 2020; Samani et al., 2018). Oligomenorrhea increases the risk of infertility and metabolic syndrome (He et al., 2020; Polotsky et al., 2011).

Questionnaires are used to retrospectively determine MC characteristics, including menstruation frequency and MC length in the past 12 months, to diagnose oligomenorrhea (He et al., 2020).

Mechanisms causing oligomenorrhea can be multifaceted. The leading causes discussed in the literature are chronic anovulatory disorders such as premature ovarian failure and ovarian insufficiency, and hyperprolactinemia (Seshadri et al., 1994), or endocrine disorders, which are possibly caused by hypothalamic inhibition or hyperandrogenism (Koltun et al., 2020).

Secondary Amenorrhea

A more severe form of MC disorder is secondary amenorrhea, defined as the absence of more than three consecutive periods in non-pregnant premenopausal women with past menses

(Elliott-Sale et al., 2021). The World Health Organization estimates that secondary amenorrhea is the sixth largest major cause of female infertility, and it is suggested to affect around 3% of women from the general population in the reproductive age (Bachmann & Kemmann, 1982). Furher, secondary amenorrhea increases the risk for cardiovascular diseases, osteopenia, depression, anxiety and leads to difficulties coping with daily stress (Shufelt et al., 2017).

To evaluate the presence of amenorrhea, a comprehensive history of the MC characteristics needs to be collected (Brady & Ginsburg, 2016). Causes that are mainly discussed in the literature are end-organ or outflow tract abnormalities, endocrine disorders, chromosomal abnormalities, or disruptions in the HPO-axis (Brady & Ginsburg, 2016; Dutta et al., 2013; Kriplani et al., 2017; Popat et al., 2008).

2.1.3. Hormonal contraceptives

Next to MC dysfunction and disorder, hormonal contraception needs to be briefly addressed in the context of the MC. The exogenous hormones contained in hormonal contraceptives have a detrimental effect on the natural MC (Read, 2010). Hormonal contraceptives are widely used by females in their reproductive age, mainly to prevent unintended pregnancy (Hall & Trussell, 2012), and are used worldwide by more than 150 million women (Baeten & Heffron, 2015). According to a study from Norway, 40% of 16-49 –year-old females are using hormonal contraceptives (Furu et al., 2021). Hormonal contraceptives mimic a regular MC (Read, 2010), but the steroids used in hormonal contraceptives are synthetic, and therefore, their actions within the female body may differ from endogenous hormones (Sims & Heather, 2018). Depending on the type of hormonal contraceptives (combined contraceptives with ethinyl estradiol and progestins, progestogen-only contraceptives, or intrauterine devices), these contraceptives prevent fertilization or implantation through different or combined mechanisms. These mechanisms include the prevention of ovulation, inhabitation of follicular development, reduction in the pulse frequency of GnRH, and/or changes in the cervical mucus (Hackney, 2017). The bleeding that occurs during the inactive days, or days without exogenous hormones, cannot be considered "menstrual bleeding", but is rather referred to as "withdrawal bleeding" caused by the drop in exogenous hormone levels.

As hormonal contraceptives alter the natural MC, participants with and without hormonal contraceptives should be analyzed separately. In studies considering the natural MC, participants should experience at least two natural MCs without hormonal contraception to limit the influence of exogenous hormones (Schmalenberger et al., 2021).

2.1.4. Verification and definition of the menstrual cycle

As the MC is highly individual, with a large intra-individual variability (Bull et al., 2019), accurate methods are necessary to verify and determine MC-phases (Schaumberg et al., 2017). To account for the high inter- and intra-individual variability, it is advisable to incorporate daily or multi-daily ratings of the outcome as the preferred data collection method. Additionally, a specific determination of the participant characteristics is recommended (Schmalenberger et al., 2021).

2.1.4.1. Participants characteristics

To account for the diversity among females in matters related to MC, it is crucial to distinctly assess and outline the characteristics of the participants (Elliott-Sale et al., 2021):

- Time-point of the participants within their reproductive age: puberty, reproductive age/pre-menopause, menopausal transition/perimenopause or menopause
- Individual MC-characteristics: eumenorrheic, regularly menstruating, or MC disorders such as amenorrhea, anovulation, luteal phase deficiency
- Usage and type of hormonal contraceptives
- Current pregnancy or postpartum and previous pregnancies

2.1.4.2. Menstrual cycle phase verification

Further, it is necessary to verify the MC phases comprehensively. Different methods exist to verify the MC and identify MC phases, which differ in scope, accuracy, and effort.

Calendar-based counting

The calendar-based counting method is an indirect method to determine the MC. A high feasibility characterizes this method, but it also has low accuracy (Johnson et al., 2018; Wideman et al., 2013). According to the counting method, a new MC starts with the onset of menstruation on day one, and the following days are counted until the next menstruation occurs. The MC phases are then determined retrospectively by counting backward from the last day of the MC (de Jonge et al., 2019). Usually, a fixed luteal phase length of 14 days is assumed to determine the time point of ovulation, follicular phase, and luteal phase length (Emmonds et al., 2019). The calendar-based counting method offers high practicability, but assuming a fixed luteal length can misidentify the time point of ovulation, as luteal phase length varies between individuals (Bull et al., 2019). Moreover, this method makes it impossible to distinguish between ovulatory and anovulatory MCs or identify a luteal phase deficiency, as these conditions often occur in females with regular bleeding (Schaumberg et al., 2017).

Basal body temperature

The basal body temperature measurement is another indirect method used to determine the MC, which is also characterized as feasible and inexpensive. However, its accuracy is limited (Barron & Fehring, 2005; Moghissi, 1976). The wakening basal body temperature is measured every morning with a sensitive thermometer to determine the MC based on the basal body temperature. Due to the thermogenic effects of progesterone, a biphasic temperature pattern over the MC is usually observed, with an increase in body temperature of approximately 0.3° Celsius after ovulation (de Jonge et al., 2019). The assessment of the basal body temperature helps determine the approximate day of ovulation and, therefore, distinguish between the two main MC phases. However, despite it being a widely used method, the measurement is prone to influences from other factors such as stress, illness, or alcohol consumption, all of which can also affect basal body temperature (Bauman, 1981). Furthermore, not all ovulatory MCs exhibit a rise in basal body temperature or a concurrent rise in temperature after ovulation (Barron & Fehring, 2005). Further, this method does not recognize participants with a luteal phase deficiency (Schaumberg et al., 2017).

Urinary LH measurements

The measurement of LH concentration in the urine is a non-invasive method that directly indicates hormonal fluctuations. To determine LH concentrations, participants collect their urine at a regular time point from day 8 of an MC. The LH test strip is inserted into the urine and will display a negative or a positive test result for LH concentration. Measurements are repeated daily until a positive test result occurs (de Jonge et al., 2019). Usually, ovulation occurs 10-26 hours after a urinary LH peak (Miller & Soules, 1996; Park et al., 2002). Even though this method directly indicates the LH concentration and can enhance the likelihood of accurately determining ovulation, this method cannot detect MCs with a luteal phase deficiency (Schaumberg et al., 2017).

Salivary hormone analysis

To differentiate between normal and abnormal MCs, as well as to verify MC phases based on hormonal concentrations, salivary hormone measurements of estrogen and progesterone are recommended (de Jonge et al., 2019). However, hormonal concentrations in the saliva are much lower than in the blood serum and, due to their pulsatile pattern, exhibit greater variations over 24 hours compared to serum measurements (Chatterton et al., 2005; Delfs et al., 1994).

Serum hormone analysis

Determining serum estrogen and progesterone concentrations is recommended as gold-standard for research purposes considering the MC (de Jonge et al., 2019). Based on venous blood samples, estrogen and progesterone concentrations are analyzed using kits or a pathology laboratory. This measurement enables the direct determination of MC-phases, verified by hormonal concentrations. Further, participants with specific MC patterns or disorders can be detected based on the serum hormone analysis, such as participants with a luteal phase deficiency (Schaumberg et al., 2017). However, determining the MC with serum hormone analysis is an invasive method and, compared to the other methods, the most expensive one.

2.1.4.3. Menstrual cycle phase definition

Several methods exist to define MC phases based on the method of MC verification. Following the recommendations from Schmalenberger et al. (2021), MC phases can be defined according to the verification method: calender-based counting, basal body temperature, LH-measurements, and salivary or serum hormone analysis, as displayed in Table 1.

Table 1. *Menstrual cycle phasing. Adapted from Schmalenberger et al. (2021, p.6)*

MC verification method	**Recommended Phasing Procedure**			
MC phase	Perimenstrual	Mid-follicular	Periovulatory	Mid-luteal
Counting method	Day -3 before menstrual onset to Day +2 after menstrual onset	Day +4 until +7 after menstrual onset	Day -15 to -12 before menstrual onset	Day -9 until -5 before menstrual onset
Basal body temperature	N/A	Day -7 until -3 prior nadir	Day -2 prior nadir to Day +1 following nadir	Day +6 to +10 following nadir
LH-Test	N/A	Day -7 until -3 prior positive test	Day -2 prior a positive test to Day +1 following a positive test	Day +6 to +10 following a positive test
Hormonal status	Falling Estrogen/ Progesterone, low Estrogen/Progesterone	Slight rise in estrogen, very low progesterone	Strong rise and fall of estrogen, slight increase of progesterone	High and stable Estrogen/Progesterone

2.1.5. Summary

In summary, the MC, characterized by its recurrent hormonal fluctuations, holds a crucial role in the female life (Mihm et al., 2011). Beyond its primary relevance for reproduction, the key reproductive hormones, estrogen and progesterone, exert influences on various functions within the female body, such as the central nervous system (Mani et al., 1997), metabolism (Oosthuyse & Bosch, 2010; Redman, 2006) or the immune system (Rafiee Zadeh et al., 2018). Unfortunately, MC-related symptoms and disorders, such as PMS or amenorrhea, are pervasive in the general population (Bachmann & Kemmann, 1982; Gnanasambanthan & Datta, 2019). Due to the intricate interplay of reproductive hormones within the body, these conditions can lead to significant health-related complications, including diminished health-related quality of life, infertility, reduced bone mineral density, and heightened risks of cardiovascular diseases, depression or anxiety (He et al., 2020; Mishell Jr, 2005; Shufelt et al., 2017). As a comprehensive indicator of overall health, the MC exhibits significant inter- and intra-individual variability (Bull et al., 2019) and requires specific considerations in the design of studies focusing on the MC, particularly regarding precise phase verification and definition (de Jonge et al., 2019; Elliott-Sale et al., 2021; Schaumberg et al., 2017; Schmalenberger et al., 2021; Sims & Heather, 2018). The intra-individual MC is influenced by various lifestyle and environmental factors, such as PA (Liu et al., 2004). However, a bidirectional link exists between PA and MC. Therefore, PA and the interaction between PA and MC will be explored in the following chapters.

2.2. Physical activity and exercise training

2.2.1. Definition of Physical activity, exercise, and physical fitness

According to Caspersen et al. (1985) PA is "any bodily movement produced by skeletal muscles that results in energy expenditure over the basal level". This definition has become widely accepted, as it acknowledges PA as a behavior conceptualized on a continuum from minimal to maximal movement (Smith & Biddle, 2008). However, due to the dose-response relationship between total energy expenditure and all-cause mortality, a broader definition is proposed, including that bodily movement causes a substantial increase in energy expenditure (Lee & Skerrett, 2001; Smith & Biddle, 2008).

As PA is a broad concept and includes a great variety of activities, it is important to classify and quantify PA with the essential factors of frequency, intensity, duration, type, and domain of PA (Norton et al., 2010; Smith & Biddle, 2008):

Frequency: the frequency describes the number of times the PA is performed within a specific time period, for example during a week or month.

Intensity: the intensity refers to the magnitude of the physiological response to PA. Different methods exist for describing or estimating intensity, such as the percentage of oxygen uptake reserve, heart rate reserve, volume of oxygen consumed per minute, heart rate, or metabolic equivalents (Liguori & Medicine, 2020). Due to the difficulties in measuring metabolic work directly, intensity often captures physiological surrogates, such as the heart rate, or perceptual categories, such as the rate of perceived exertion (RPE) (Liguori & Medicine, 2020). PA intensity can be clustered into five categories, which reflect similar relative physiological stress within each category on the exercising individual (Norton et al., 2010). The categories are sedentary, light, moderate, vigorous, and high intensity (s. Table 2). These categories are established according to the energy demands and represent the gradient in metabolic and neuro-humoral responses during the PA.

Table 2. *Physical activity intensity categories. Adapted from Norton et al (2009, p. 497)*

PA category	Sedentary	Light	Moderate	Vigorous	High intensity
METs	< 1.6 METs	1.6 - 2.9 METs	3 - 5.9 METs	6 - 8.9 METs	≥ 9 METs
% VO_2max	< 20% VO_2max	20 - 39% VO_2max	40 - 59% VO_2max	60 - 84% VO_2max	≥ 85% VO_2max
% of HR_{max}	< 40% HR_{max}	40 - 54% HR_{max}	55 - 69% HR_{max}	70 - 89% HR_{max}	≥ 90% HR_{max}
% of HRR	< 20% HRR	20 - 39% HRR	40 - 59% HRR	60 - 84% HRR	≥ 85% HRR
RPE	< 8	8-10	11-13	14-16	≥17
Description	Activities that usually involve sitting or lying, with little additional movement	Aerobic activity that does not cause a noticeable change in breathing rate; can be sustained for at least 60min	Aerobic activity that is able while maintaining a conversation uninterrupted; intensity may last between 30-60 min	Aerobic activity in which a conversation generally cannot be maintained uninterrupted; intensity may last up to 30 min	Intensity that generally cannot be sustained for more than 10 min

Note. METS = Metabolic Equivalents, VO_2max = maximal oxygen consumption, HR_{max} = maximum heart rate, HRR = heart rate reserve, RPE = rate of perceived exertion.

Duration: the duration includes the length of time in which the PA is performed.

Type: the type of PA can be summarized by physiologically determined categories such as aerobic or anaerobic or the features of the behavior itself (Smith & Biddle, 2008). More descriptive classifications may reference the major bio-motor abilities, including endurance, strength, speed, flexibility, and coordination activities (Bompa & Buzzichelli, 2019).

Domain: The domain refers to the context or setting in which the PA is performed, such as leisure time, occupational, transport, or school (Smith & Biddle, 2008).

Many measurement techniques are used to assess PA, which depends on the specific outcome of interest and may vary across the subdisciplines of PA sciences (Smith & Biddle, 2008). As criterion measures, indirect calorimetry, double-labeled water techniques, and direct observations are rated (Smith & Biddle, 2008). Further, PA can be measured objectively by device-based pedometers, accelerometers, heart rate monitors, and multichannel activity monitors (Burchartz et al., 2020, Smith & Biddle, 2008) and by subjective measures, including self-report questionnaires, interviews, and diaries (Nigg et al., 2020).

However, the terms exercise and sports need to be distinguished from PA. PA includes all bodily movements and PA in daily life (Caspersen et al., 1985), as noted previously, and can be classified into different categories, such as leisure-time PA, active transport, occupation (Smith & Biddle, 2008). Even though PA and exercise are often used as synonyms in everyday language, exercise describes a subset of PA. Exercise is a planned, structured, and repetitive bodily movement with a final or intermediate objective, such as improving or maintaining one or more components of physical fitness (Caspersen et al., 1985; Montoye, 1996). Different definitions exist for physical fitness, but physical fitness commonly describes a set of attributes or characteristics of individuals that relate to their ability to perform PA and daily life activities. Usually, physical fitness characteristics are separated into health and skill-related components (Caspersen et al., 1985; Corbin, 1977). Health-related components of physical fitness include cardiorespiratory endurance, body composition, muscular strength, muscular endurance, and flexibility. The skill-related components of physical fitness incorporate agility, coordination, balance, power, reaction time, and speed (Caspersen et al., 1985; Corbin, 1977).

2.2.2. Physical Activity recommendations and health benefits

The vital role of PA as a health-protective behavior has become even more explicit in recent years (Bull et al., 2020; Katzmarzyk & Mason, 2009). Individuals who are unable to attain sufficient levels of PA display an increased risk for several chronic degenerative diseases, such as hypertension, obesity, or some forms of cancers, as well as premature all-cause mortality (Knight, 2012; Lee et al., 2012). Further, evidence supports the positive effects of PA in the treatment of chronic diseases such as cardiovascular, metabolic, and psychiatric diseases (Pedersen & Saltin, 2015).

For adults, according to the World Health Organization, at least 150-300 minutes of moderate aerobic PA per week, or at least 75-150 minutes for vigorous aerobic PA or an equivalent combination, is recommended to achieve substantial health benefits and mitigate health risks (Haskell et al., 2009; World Health Organization, 2020). However, an inverse dose-response relationship exists between the volume of PA and all-cause mortality rates (Lee & Skerrett, 2001).

Even though the beneficial effects of PA are wide-known, women are overall less active than men in all regions of the world, apart from east and southeast Asia (Guthold et al., 2018). According to Guthold et al. (2018), the world-wide differences in levels of insufficient activity between women and men can be up to 10 percentage points or more. However, a trend of equal PA levels between women and men can be observed in Europe (Marques et al., 2015). In Switzerland, females are as active as their male counterparts, and 74% are considered sufficiently active (Lamprecht & Stamm, 2000).

2.2.3. Determinants of physical activity

As briefly summarized in the last section, PA is a major public concern due to its association with overall health (Warburton et al., 2006; Warburton & Bredin, 2017). Many females are physically inactive despite the well-known beneficial effects (Guthold et al., 2018). However, human behavior is determined by multiple factors (Hagger et al., 2020). To explain and conceptualize the multiple factors that determine behavior, different frameworks exist, such as the self-determination theory (Ryan & Deci, 2000), the theory of planned behavior (Ajzen, 1991), the self-efficacy theory (Bandura, 1977), the transtheoretical model of behavior change (Prochaska & DiClemente, 1982) or the social-ecological models (Sallis & Owen, 1998). To provide guidance for designing effective PA programs, models in behavioral science must be predictive of behavior and indicate procedures that promote long-term behavior change (Baranowski et al., 1998). Even though various frameworks exist, traditional theory-based PA promotion interventions demonstrate limited success in long-term maintenance (Dishman & Buckworth, 1996; Marcus & Forsyth, 1999). According to correlational research, current theories and models focusing on individual dispositions in PA behavior explain, at best, 20–40% of the overall PA variance (Baranowski et al., 1998; Spence et al., 2000).

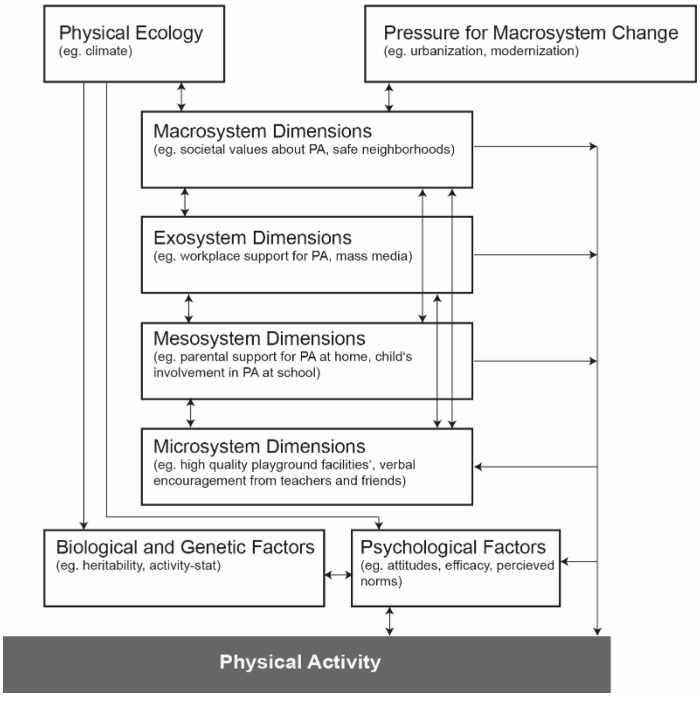

Figure 3. The ecological model of physical activity. Adapted from Spence & Lee (2003, p.15).

Therefore, broader, multilevel, and ecological approaches are requested for effective PA interventions (Spence & Lee, 2003), which also integrate biological processes (Bouchard et al., 1994). Especially in females, the MC and phases in the reproductive life, such as puberty or menopause, might expand sociological or cultural explanations for PA behavior (Garcia et al., 1995). Therefore, biological processes should be integrated into the PA behavior models (Spence & Lee, 2003). Spence & Lee (2003) propose a model that portrays PA as being influenced by a complex interplay of environmental settings and biological and psychological factors (s. Fig. 3).

2.2.4. Exercise training and endurance training

Next to long-term maintenance of PA, specific stimuli are necessary to achieve health-related benefits of PA and prevent injuries or overload (Kraemer et al., 2002). Therefore, exercise training, as a planned and targeted stress-strain process to improve bio-psycho-social ability (Güllich & Krüger, 2023), must follow specific principles and strategies to promote good health (Ketelhut & Ketelhut, 2020). As endurance training is of particular importance in this dissertation, it is the only bio-motor ability examined in the following sections, and other abilities such as strength, speed, flexibility, and coordination (Bompa & Buzzichelli, 2019) are deliberately neglected.

Endurance exercise training is a broad term, however, it has been suggested to include all sports events or PA that rely predominantly on the oxidative metabolism for energy supply (Jones & Poole, 2008). The physiological basis of aerobic endurance is not fully understood yet (François Péronnet & Thibault, 1989). Nonetheless, a highly developed aerobic endurance, such as the capacity to sustain a very high fraction of maximal oxygen uptake (VO_2max) for a given time, can be associated with a combination of several factors (Bosquet et al., 2002). Those additional factors include a high percentage of type I muscle fibers, the large storage capacity of muscle and/or liver glycogen, spare carbohydrate use by increased use of fatty acids as main energy substrates, and efficient heat management (Foster et al., 1978; Péronnet et al., 1987). VO_2max is generally considered a key physiological factor for aerobic endurance (Bassett & Howley, 2000). Further, aerobic endurance training facilitates in general numerous chronic positive changes, such as myocardial (Blomqvist & Saltin, 1983; Ekblom et al., 1968; Ekblom & Hermansen, 1968; Levy et al., 1993; Pluim et al., 2000; Scharhag et al., 2002), circulatory adaptations (Convertino, 1991; Gillen et al., 1991) or adaptations in the pulmonary and skeletal muscular system (Davies et al., 1981; Davis et al., 1979; Holloszy & Coyle, 1984). Those adaptations contribute significantly to improvements in aerobic fitness (DiMenna & Jones, 2016).

To improve aerobic endurance, different variables and training methods should be considered. The main training variables are training type, intensity, duration, and volume (Liguori & Medicine, 2020). A broad variety of training methods combining different training variables can be applied to improve aerobic capacity. Common training methods are high-volume with low to moderate-intensity training, tempo training, extensive and intensive interval training, and high-intensity interval training (Buchheit & Laursen, 2013; Faude et al., 2009; Ketelhut & Ketelhut, 2020; Reuter & Dawes, 2016). Another widely used training method to improve aerobic capacity is polarized training, a combination of high-volume, low-intensity training, tempo training, and high-intensity interval training (Stöggl & Sperlich, 2014). In polarized training, elevated percentages of time or distances are spent in both high-intensity and low-intensity exercise, and only a minor proportion of training is spent in tempo training (Treff et al., 2019). The effectiveness of the different training methods is discussed extensively in the literature (Meyer et al., 2007; Stöggl & Sperlich, 2014; Wahl et al., 2010). However, polarized training seems to have an overall positive impact on aerobic endurance in a broad range of participants (Filipas et al., 2022; Hydren & Cohen, 2015; Muñoz et al., 2014; Stöggl & Sperlich, 2014; Zapata-Lamana et al., 2018).

2.2.5. Summary

PA can generally positively affect health (Bull et al., 2020). Sufficient amounts of PA reduce the risk for several chronic degenerative diseases, such as hypertension, obesity, or some forms of cancers, as well as premature all-cause mortality (Knight, 2012; Lee et al., 2012) and positively impact chronic diseases such as cardiovascular, metabolic, and psychiatric diseases (Pedersen & Saltin, 2015). The term exercise must be differentiated from PA and is defined as a specific category of PA (Güllich & Krüger, 2023), which is a planned, structured, and repetitive bodily movement with a final or intermediate objective (Caspersen et al., 1985). The term exercise also includes aerobic endurance exercise (Corbin, 1977), which can result in positive adaptations, mainly in the cardiovascular system (DiMenna & Jones, 2016). However, when aerobic endurance is targeted in the training, training variables need to be considered to achieve improvements in the aerobic capacity. To increase aerobic capacity, different training methods are applicable (Ketelhut & Ketelhut, 2020; Meyer et al., 2007; Stöggl & Sperlich, 2014; Wahl et al., 2010), such as polarized training, which combines high-intensity, low-intensity, and tempo training (Treff et al., 2019).

2.3. Physical activity and the menstrual cycle – a bidirectional interaction

PA and the MC are mutually influential, displaying a bidirectional interaction. This bidirectional relationship is based on various mechanisms and will be discussed in the upcoming chapters. According to the evolutionary framework by Caldwell & Hooper (2023), stress, such as exceeding amounts of PA, impacts reproductive function and can limit reproduction. The limitation occurs because reproduction, from pregnancy until lactation, is highly energy-demanding (Williams et al., 2001), and energy-saving measures are implemented for safety under high-stress conditions (Caldwell & Hooper, 2023). Otherwise, if the reproductive function is maintained, the reproductive hormones can also affect other tissues within the female body as well as the metabolism (Hackney, 2017; Janse De Jonge, 2003). Therefore, the hormonal fluctuations over the MC might also impact PA and exercise (Hackney, 2017). As many females of reproductive age are physically active (Lamprecht & Stamm, 2000), it is crucial to understand the bidirectional relationship between PA and the MC (Ahrens et al., 2014).

2.3.1. Effects of physical activity on the menstrual cycle

Depending on the females' characteristics and the type of PA, PA can have a divergent effect on the MC, leading to positive or negative effects on the MC characteristics or disorders.

In overweight or obese females or females with reduced insulin sensitivity, PA increases insulin sensitivity (Moran et al., 2003), promotes non-insulin-dependent glucose uptake, and substantially improves peripheral insulin resistance (Ryder et al., 2001). Insulin resistance appears to be linked to menstrual irregularities and disorders (Ezeh et al., 2021; Fernandes et al., 2005). Additionally, improvements in insulin resistance positively impact MC characteristics, such as the prevalence of ovulation (Redman, 2006). However, the specific neuroendocrine mechanism mediating the influence of PA on the reproductive axis has yet to be identified (Redman, 2006). Currently discussed mechanisms are alterations affecting adiponectin, such as leptin, and hyperandrogenism due to insulin resistance or reduced sensitivity (Tsilchorozidou et al., 2004). Thus it seems that PA can support the functional capacity of the MC due to a positive influence on hormonal regulation processes (Redman, 2006).

In females who experience PMS, PA and exercise can reduce PMS symptoms (Pearce et al., 2020). The interaction between PA and PMS seems multifaceted, and different mechanisms are discussed in the literature. For example, exercise might modify PMS symptoms by causing a general increase in endorphin levels (Steinberg & Sykes, 1985). Further, PA has been shown to influence the regulation of estrogen and progesterone synthesis (Cano Sokoloff et al., 2016), potentially resulting in a positive impact on females with an increased sensitivity leading to PMS (Gnanasambanthan & Datta, 2019). Additionally, PA contributes to the production of anti-inflammatory chemicals (Flynn et al., 2007) and a reduction in feelings of depression (Dunn et al., 2001). These effects may potentially have a beneficial impact on PMS and thus improve MC regulation.

On the other hand, PA and exercise can also harm MC characteristics (Dawson & Reilly, 2009), especially among females with high levels of PA or females at risk for low-energy availability (Redman & Loucks, 2005; Witkoś & Wróbel, 2019). Negative consequences caused by PA include an increased risk for delayed menarche, secondary amenorrhea or oligomenorrhea, or reduced ovulating ability, which have been associated with more hours of intense PA (Gordon et al., 2017).

Previous studies have found that high-intensity activity is associated with amenorrhea, oligomenorrhea, luteal phase deficiency, and anovulation, likely through disturbances of the hypothalamic-pituitary-adrenal axis (Ahrens et al., 2014). Like the positive effects, the adverse effects are based on various impact mechanisms. As a study by Warren & Perlroth (2001) emphasizes, leptin may be a critical factor in the interaction between low energy availability and the reproductive axis. In the hypothalamic neurons, leptin receptors are present, which are able to modulate and control the GnRH pulse generator. High amounts of PA seem to alter leptin concentrations (Ahrens et al., 2014; Welt et al., 2005). Further, PA impacts the hypothalamic–pituitary–adrenal axis, resulting in increased levels of androgens, which could impair follicular development (Warren & Perlroth, 2001; Welt et al., 2005).

Additional, stressors, such as psychosocial, social, or PA-related stressors (Berga et al., 1997; Coyle, 2000), can mediate the central suppression of the reproductive axis by inhibiting GnRH release (Berga et al., 1997). The occurrence of stress alters cortisol concentrations, and increased cortisol concentrations reflect the activation of the hypothalamic-pituitary-adrenal axis (Widmer et al., 2005). However, increased cortisol concentrations stimulate corticotrophin-releasing hormone secretion, inhibiting GnRH release (Keizer & Rogol, 1990). Also, the hypothalamic-pituitary-thyroidal axis may independently impair gonadal function due to specific thyroid hormone receptors at the ovarian level (Berga et al., 1997; Doufas & Mastorakos, 2000). Overall, excessive amounts of PA or high-intensity activity, particularly when coupled with low-energy availability, may have detrimental effects on the MC, increasing the risk of MC disorders.

2.3.2. Effects of the menstrual cycle on physical activity

Current research suggests that many hormonal and mechanical changes within the female body are related to the hormonal fluctuations over the MC. The MC could theoretically affect exercise performance by inducing thermoregulatory, respiratory, and renal changes (Janse De

Jonge, 2003). However, these hypothetical links are not necessarily backed up by research, and current evidence on the relationship between MCs and exercise performance is still contradictory (Oosthuyse & Bosch, 2010), which could reflect high heterogeneity in study design and quality (McNulty et al., 2020). The current state of research focusing on the main trends are briefly summarized in the next sections.

2.3.2.1. The effects of the menstrual cycle on the female physiology

Substrate metabolism

Substrate metabolism is a large contributor to aerobic endurance performance, and the ability to optimize fat metabolism is deemed preferable during moderate- and high-intensity exercise (Hicks et al., 2023). In the energy metabolism, both estrogen and progesterone might impact glycogen uptake and storage (Hackney, 1990). During phases with high estrogen concentration, an increased glycogen repletion rate can be monitored after intensive exercise (Nicklas et al., 1989). Further, an increased reliance on fat metabolism was observed during phases of high progesterone concentrations (Jurkowski et al., 1981; McCracken et al., 1994; Nicklas et al., 1989), with a greater shift from follicular to luteal phase in females with a smaller increase in progesterone/estrogen ratio (Hackney et al., 2022). However, the impact of progesterone on fat metabolism is still controversially discussed in the literature, as it might be dependent on exercise intensity, previous carbohydrate loading, and the ratio between estrogen and progesterone concentrations (Bailey et al., 2000; De Souza et al., 1990; dos Santos et al., 2021; Hackney et al., 2022; Hessemer & Bruck, 1985; Kanaley et al., 1992; McLay et al., 2007; Smekal et al., 2007).

Respiration

Research on the effect of estrogen and progesterone on respiration during rest and exercise remains inconclusive, and effects might be strongly dependent on exercise intensity, resulting in high ambiguity and limited comparability of the previous studies (Hicks et al., 2023). Overall, the ventilatory rate has been demonstrated to be greater at rest in the luteal phase (MacNutt et al., 2012). Furthermore, progesterone might modify respiratory patterns, potentially resulting in an increased minute ventilation and respiratory drive (Dombovy et al., 1987; Dutton et al., 1989; Slatkovska et al., 2006; Smekal et al., 2007). This, in turn, could positively influence the muscle strength of the thoracic pump during the luteal phase (Da Silva et al., 2006).

Cardiovascular function

In addition to respiration, estrogen and progesterone might also affect cardiovascular function. Progesterone is expected to influence overall plasma volume, as increased plasma volume has been detected from ovulation until the mid-luteal phase (Fortney et al., 1988). Further, peripheral hemodynamics and renal function are altered by the MC (Van Beek et al., 1996), with lower skin flow in the luteal phase, which might be related to the higher core temperature of 0.3–0.5°C. Also, decreased estrogen levels increase peripheral resistance and decrease exercising muscle blood flow (Collins, 1996, 2001).

Thermoregulation

The higher initial core body temperature due to high progesterone concentrations may increase the risk for heat accumulation (Pivarnik et al., 1992) and heat stress (Hessemer & Bruck, 1985; Hessemer & Bruck, 1985). However, those effects highly depend on individual heat acclimation, training status, and duration length of performance (Kuwahara et al., 2005; Walters et al., 2000).

Central nervous system

Estrogen and progesterone are classified as neuro-steroids with contrasting effects. According to Smith et al. (1999), estrogen increases, and progesterone enhances cortical excitability (Smith et al., 1999). The cortical excitability is linked to voluntary activation, with a peak maximal voluntary contraction around ovulation and a decrease in the luteal phase (Ansdell et al., 2019). Further, estrogen and progesterone seem to modulate motor unit firing rates, which might impact maximal strength (Tenan et al., 2013, 2016).

Muscle physiology

The influence of estrogen on contractile proteins during active muscle contractions is suggested to promote a stronger binding of the myosin head to actin, thus enhancing force production (Lowe et al., 2010). However, potential effects might be fiber-type dependent (Qaisar et al., 2013).

In general, the hormones estrogen and progesterone exert influences on a range of functions in the female body, spanning the nervous and cardiovascular systems to muscle metabolism and physiology (Ansdell et al., 2019; Collins, 1996, 2001; Hackney et al., 2022; Qaisar et al., 2013). These alterations are hypothesized to impact various aspects of PA and exercise, including readiness, exercise effectiveness, adaptation responses, and recovery. Consequently, considering these hormonal alterations in the exercise planning process could prove advantageous (Kissow et al., 2022).

2.3.2.2. The effects of the menstrual cycle on peak performance

Peak performance is highly relevant, especially for competitive athletes. However, current research indicates that the fluctuating hormonal concentrations of estrogen and progesterone have, at most, a minor to non-existent significant impact on maximum performance.

Overall, no alterations were identified for anaerobic maximum performance, lasting 15 seconds up to 3 minutes (Julian et al., 2017; Lara et al., 2020; Sunderland & Nevill, 2003; Tsampoukos et al., 2010), or maximal sprinting or repeated jump tasks (Julian et al., 2017; Sunderland & Nevill, 2003; Tsampoukos et al., 2010). Also, even though maximal voluntary contraction, isokinetic peak torque, and force production show a higher ambiguity among current studies, with some studies indicating altered strength levels over the MC phases (Rodrigues et al., 2019), others do not report any changes (Romero-Moraleda et al., 2019). According to a current review by Blagrove et al. (2020), strength-related variables, such as maximum voluntary contraction, isokinetic peak torque, explosive strength, or rate of force development, are only minimally affected by changes in the reproductive hormones, and the effects seem negligible.

Regarding peak aerobic performance, peak oxygen uptake seems to be unaltered by the MC (Carmichael et al., 2021; Schumpf et al., 2023; Vaiksaar et al., 2011) as well as prolonged continuous aerobic performance (Greenhall et al., 2021). However, intermittent aerobic exercise might be affected, favoring the follicular phase (Graja et al., 2022; Julian et al., 2017) compared to the luteal phase.

A somewhat clearer picture emerges from studies addressing the subjective perception of performance. According to Paludo et al. (2020), some perceptual responses are affected by the MC, with a “favorable” subjective response in athletes during higher concentrations of estrogen and progesterone, compared to the low hormone phases (Paludo et al., 2022). However, females' perceptual responses seem to be highly individual (Findlay et al., 2020).

Concluding, when overall performance levels are compared, there might be only a trivial performance reduction during the early follicular phase of the MC compared to all other MC phases (McNulty et al., 2020). Alterations of peak performance might be highly individual due to the inter-individual differences in the MC and related absolute hormonal concentrations and hormonal shifts over the MC (Hackney et al., 2022). Further, as peak performance does not only rely on physiological but also psychological processes, differences in perceptual responses over the MC might explain the different performance perception of female athletes, which is not reflected in the physiological results (Carmichael et al., 2021; McNulty et al., 2020; Paludo et al., 2022)

2.3.2.3. The effects of menstrual cycle adapted training

Even though peak performance seems mainly unaltered by the MC (Carmichael et al., 2021), there is evidence that the reproductive hormones estrogen and progesterone alter specific processes within the body, which might modulate the readiness, the effectiveness of and response to exercise (Ansdell et al., 2019; Collins, 1996, 2001; Hackney et al., 2022; Qaisar et al., 2013). Therefore, the efficiency of MC-adapted training, or phased-based training in resistance and endurance training, is discussed in the literature.

Resistance training

A review by Thompson et al. (2020) identified four studies that analyzed the effects of phase-based resistance training (Reis et al., 1995; Sakamaki-Sunaga et al., 2016; Sung et al., 2014; Wikström-Frisén et al., 2017). The studies mainly compared follicular phase-based training with a higher training volume load in the follicular phase and luteal phase-based training with a higher training volume in the luteal phase. Three of the four studies suggest that performing a higher volume of training in the follicular phase is superior to regular training or luteal phase-based training (Reis et al., 1995; Sung et al., 2014; Wikström-Frisén et al., 2017), whereas one study was not able to identify an effect of phase-based training on muscular strength (Sakamaki-Sunaga et al., 2016). However, Thompson et al. (2020) noted a lack of MC verification in some of the studies, as well as the combination of participants with a natural MC and hormonal contraceptive use, which limits the generalizability of the results. Since the review in 2020, only one more study was published by Vargas-Molina et al. (2022), partly favoring phase-based training with greater increases in maximum benchpress strength and improvements in countermovement performance compared to regular load-matched resistance training. However, the authors highlight the limitation due to a small sample size (Vargas-Molina et al., 2022). Overall, to date, only a few studies have investigated the effect of phase-based resistance training, but they indicate that follicular phase-based resistance training enhances leg muscle strength gains compared to luteal phase-based training or regular training (Kissow et al., 2022; O’Loughlin et al., 2023).

Endurance training

Research on the effect of MC phase-adapted endurance training is sparse. To our knowledge, only Han (2012) investigated the effect of follicular vs. luteal phase-based endurance training in his dissertation. In this study, thirteen untrained females underwent one-leg endurance training on a cycle ergometer for three MCs. The training involved focusing on one leg during the first half of the MC (follicular phase training) and the other leg during the second half (luteal phase training). While both groups exhibited an increase in VO_2peak, no discernible difference existed between the follicular and luteal phase training. Notably, the maximum workload during pre and post incremental tests significantly increased in both legs, with a more pronounced increase after follicular phase training than luteal phase training. However, these significant increases in maximum workload from follicular to luteal phase training were only evident after the third MC training phase (weeks 8-12). In summary, follicular phase-based training led to a significantly higher increase of maximum power output on a bicycle ergometer without any different effect of VO_2peak or muscle diameter (Han, 2012).

According to Kissow et al. (2022), the impact of phase-based aerobic training is mainly unknown. However, given the possible alterations of the aerobic energy systems and metabolic perturbations due to hormonal changes, it might be speculated that a greater training response may occur with follicular phase-based endurance training, but more research is necessary (Kissow et al., 2022).

2.3.3. Summary

To summarize, a bidirectional connection between MC and PA exists (s. Fig. 4). PA can positively impact hormone production, reducing PMS symptoms or the risk for MC-related disorders (Moran et al., 2003; Pearce et al., 2020). Controversially, PA can also harm the MC, depending on participants' and specific PA characteristics, such as volume and intensity, increasing the risk for MC-related disorders (Dawson & Reilly, 2009; Gordon et al., 2017). This shows the relevance of optimizing the dosage of PA in order to benefit from its positive aspects while avoiding possible negative consequences for the MC.

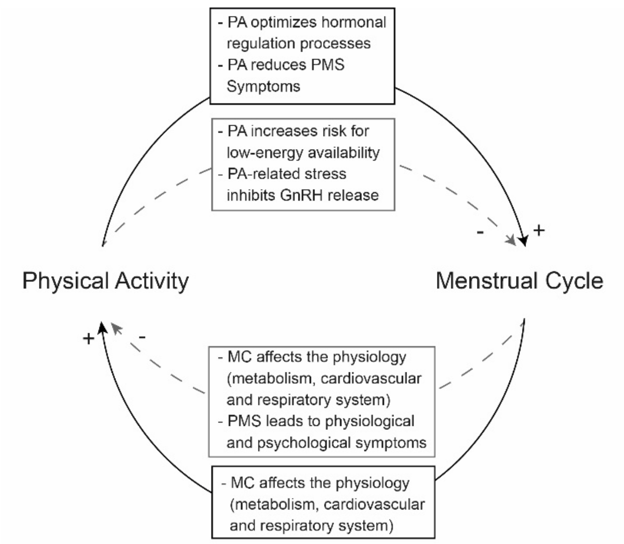

Figure 4. Possible bi-directional interaction between physical acitivity and the menstrual cycle. Based on the the Chapter 2.3.

On the other hand, emphasizing the bidirectional connection between MC and PA, the MC can also impact PA by altering readiness and response to PA due to changes in the thermoregulatory, respiratory, and renal systems related to the estrogen and progesterone concentrations (Janse De Jonge, 2003). Therefore, it is speculated that MC phase-adapted training, which takes into account the phase-specific physiological changes, lead to gratear training responses (Kissow et al., 2022). Previous research on MC phase-adapted training in resistance training indicates a positive effect (Kissow et al., 2022), but less is known about the effectiveness of MC phase-adapted endurance training (Han, 2012; Kissow et al., 2022). Exploring the effects of MC phase-adapted endurance training would be relevant, as many females are engaged in endurance sports (Pauline, 2014). Further, endurance activities are often promoted due to their health-enhancing effects (DiMenna & Jones, 2016), but optimal load control is also relevant for MC health, to benefit from the positive aspects but avoid negative consequences (Redman, 2006). Overall exercise load control is regulated through intensity and volume, but an optimal load-recovery distribution also contributes to overall load, which can be influenced by proper exercise periodization (Gabbett, 2023). Therefore, MC phase-adapted exercise might also impact the load-recovery distribution.

3. Research questions

Current research highlights the interaction of the MC and PA in females' reproductive lives. Firstly, the PA can affect the MC, both negatively as well as positively, depending on participants and PA characteristics. While there is a considerable body of research concerning the relationship between PA and MC in athletes, there is a scarcity of studies focusing on recreationally active females (Ahrens et al., 2014). Not only do the recreationally active females represent the larger proportion of the population compared to athletes, but they might also show a high level of vulnerability due to less support in the sports context, e.g., from coaches or the medical team.

Secondly, according to the literature, MC phase-adapted resistance training might improve performance and well-being, but less is known about MC phase-adapted endurance training (Kissow et al., 2022). Endurance training is a common activity among recreationally active females (Pauline, 2014), which is usually linked to health benefits (DiMenna & Jones, 2016). However, if endurance training is not adequately load-controlled, it might serve as a risk factor for MC-related disorders. Therefore, it is necessary to shed light on MC-phase adapted endurance training.

Study I:

Current research indicates that in addition to the positive effects of PA on the MC, PA might lead to MC alterations or disorders with increased PA volume and intensity. However, many studies focus on athletes, and less is known about the recreationally active females, who represent a large part of society. Therefore, the research question for the first manuscript is:

(1) *Are MC-related symptoms and disorders related to PA intensity and training volume in recreationally active females in Switzerland?*

Manuscripts II + III:

Reproductive hormones alter functions within the female body (Janse De Jonge, 2003), and resistance training indicates increased effectiveness of MC phase-adapted training

(Thompson, 2014). However, less is known about MC phase-adapted endurance training. Therefore, the second and third manuscripts are focusing on:

(2) *The effectiveness of an MC phase-adapted endurance training compared to traditional block-periodized endurance training on performance, cardiovascular parameters and well-being*

(3) *The effectiveness of an MC phase-adapted endurance training compared to a contrary-adapted MC phase-based endurance training on performance and cardiovascular parameters.*

4. Summary

The manuscripts I-III, intending to answer the research questions, are summarised below. The complete manuscripts can be found in Appendix I.

4.1. Manuscript I

Title: Self-reported physical activity intensity and training volume are related to menstrual health among recreationally active Swiss females.

Summary: The impact of MC disorders on health is substantial, contributing to heightened risks for cardiovascular diseases, reduced bone mass, osteoporosis, depression, anxiety disorders, and infertility (Shufelt et al., 2017). Even though the MC plays a vital role for health (Popat et al., 2008), MC-related symptoms and disorders are widespread among females in the general population (Bachmann & Kemmann, 1982; Direkvand-Moghadam et al., 2014). This prevalence further increases among athletes with high levels of PA and exercise. The prevalence of MC-related symptoms and disorders increases in athletes engaging in high levels of PA and exercise (Gimunová et al., 2022; Ravi et al., 2021). However, information about MC-related issues in recreationally active females is limited, prompting the exploration of prevalence rates and potential links with PA. This study investigates the association between PA intensity, overall training volume, and menstrual health patterns in Swiss recreationally active females of reproductive age.

Between May and June 2023, a cross-sectional online survey was conducted among females (≥18 years) within their reproductive age who were neither currently pregnant nor using hormonal contraceptives. The survey gathered data on demographics, engagement in PA, PA intensity distribution and exercise, and menstrual health, including menstrual history, symptoms and disorders, and contraception. The analysis focused on the association between PA intensity, overall training volume, and MC health, considering PMS, oligomenorrhea, and secondary amenorrhea. Binary logistic regressions, adjusted for BMI and age, were employed for analysis.

In total, 2376 participants initiated the survey, with 54.5% (1294 participants) completing it. Of the completed responses, 860 were included in the analysis (mean age=29.5±8.3 years, BMI=22.5±3.1, 361±295 min/week of moderate to vigorous PA, mean training volume=4.8±4.1 h/week, and average MC length=29.2±8.4 days).

The results revealed a 17% prevalence of PMS, 18% oligomenorrhea, and 2.9% secondary amenorrhea. No relationship was found between PMS and PA intensity or overall training volume. Higher levels of light PA were linked to a higher prevalence of oligomenorrhea (Odds-

Ratio = 1.019, 95% Confidence Interval; 1.000-1.039). Higher levels of moderate PA (Odds-Ratio = 1.048, 95% Confidence Interval, 1.009–1.088) and increased overall training volume (Odds-Ratio = 1.028, 95% Confidence Interval, 1.024–1.143) were associated with a higher prevalence of secondary amenorrhea. These relationships persisted after adjustments for Body-Mass Index and age ($p < 0.05$).

In conclusion, this study emphasizes the prevalence of MC disturbances and disorders among recreationally active females in Switzerland. Given the potential long-term health implications, it underscores the critical need to address menstrual health in this population. While marginal associations were observed between light and moderate PA, total training volume, and MC disorders, no significant relationship was found regarding premenstrual symptoms. Further exploration through prospective studies is warranted to comprehend possible causal links and derive meaningful interventions for reducing potential health risks in recreationally active females.

4.2. Manuscript II

Title: Effects of a training intervention tailored to the menstrual cycle on endurance performance and hemodynamics.

Summary: The recognition of MC phases as influential factors in developing endurance performance, training response, and recovery in women with regular menstruation is gaining prominence. It is suggested that adapting training programs to the MC could mitigate risk factors associated with MC-related symptoms and diseases and improve performance (McNulty et al., 2020; Oosthuye & Bosch, 2010; Ihalainen et al., 2021). This conceptual framework is grounded in the fluctuations of steroid hormone concentrations, primarily estrogen and progesterone, and their intricate interactions during the MC (Pitchers & Elliott-Sale, 2019). Current findings in research on resistance training support the assumption that responses to follicular phase-based training are superior to luteal phase-based or traditional approaches (Thompson et al., 2020), such as polarized training (Kenneally et al., 2018). Aligning a training program to the individual MC phases holds promise in influencing training response, adaptation, and recovery in females (Ihalainen et al., 2021). Despite this, a notable gap exists in the literature, as no study, besides the dissertation project from Han (2012), has delved into the impact of MC phase-adapted polarized training intervention on performance. Therefore, we aimed to assess the effect of MC phase-adapted endurance training on performance, cardiovascular parameters, and well-being.

Fourteen naturally menstruating, moderately active women (age: 24 ± 3 years; BMI: 22.3 ± 2.7) were randomized into an intervention (INT) and a control (CON) group. Throughout an 8-week intervention period, both groups participated in a polarized running training program. In the INT, the training sessions were MC phase-adapted with higher training loads within the mid and late follicular phase (Fig. 4). Prior to and after the intervention, maximal oxygen consumption (VO_2max), velocity and heart rate at ventilatory thresholds one and two, systolic and diastolic blood pressure , heartrate variability indices (root mean square of successive RR interval differences (RMSSD), standard deviation of NN intervals (SDNN)) and pulse wave velocity were assessed. To determine recovery, well-being, and PMS, the premenstrual assessment form and the Short Recovery and Stress Questionnaire with the two subscales short recovery scale and short stress scale were also assessed at three time points: before the intervention, after four weeks, and at the end of the intervention.

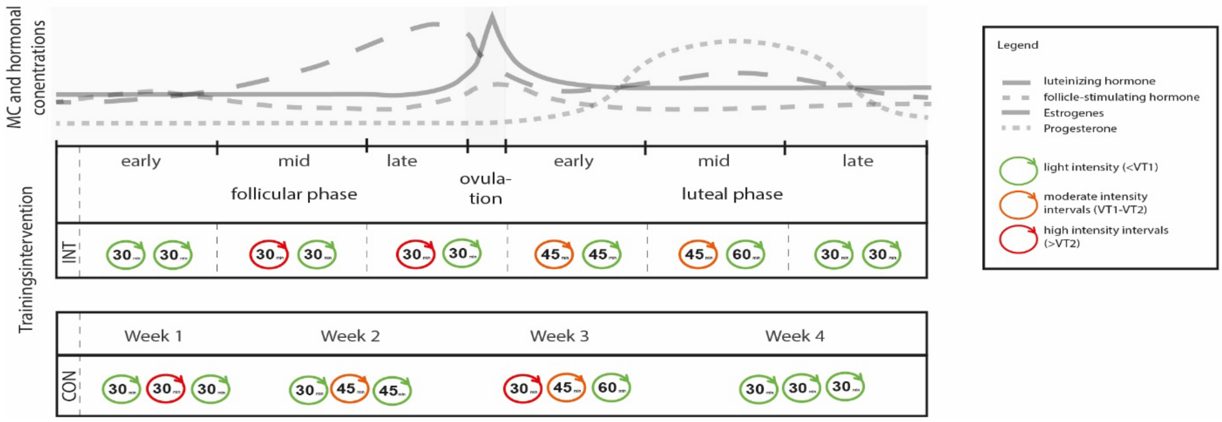

Figure 5. Exemplary four-week training plan for the intervention group (INT, menstrual cycle phase-adapted training) and control group (CON, block-periodized training).

Seven females were assigned to the INT (age: 22.4±1.2; Body-Mass Index: 22.7±2.9 kg/cm2; VO_2max: 41.1±4.4 ml/min/kg;) and to the CON (age: 24.1±3.0; BMI: 21.8±2.1 kg/cm2; VO_2max: 43.6±6.1 ml/min/kg). No significant group differences were discovered in the baseline assessment for anthropometrics, physiological and psychological parameters ($p<.05$).

A significant time effect was found for VO_2max ($F(1,6) = 17.93$ $p=.005$ partial $\eta^2 = .75$), but not for the other physiological or psychological parameters ($p<.05$). Also, no group effect was found for any of the parameters ($p<.05$). No significant time × group interaction effects were found in all physiological (VO_2max: $p = .890$; vVT1: $p = 1.000$; heartrate at ventilatory threshold 1: $p = .464$; velocity at ventilatory threshold 2: $p = .356$; heart rate at ventilatory threshold 2: $p = .762$; systolic blood pressure: $p = .948$; diastolic blood pressure: $p = .203$; RMSSD: $p=.257$; SDNN: $p=.241$; pulse wave velocity: $p = .818$), and psychological parameters (Premenstrual Assessment Form: $p = .745$, Short Recovery Scale = .637, Short Stress Scale = 1.000).

An 8-week polarized running training, block-periodized or MC phase-adapted, improves VO_2max in naturally menstruating females. These results align with previous positive findings on the effects of endurance training on VO_2max (Muñoz et al., 2014; Stöggl et al., 2014). MC phase-adapted running training seems to impact performance to the same extent as traditional block-periodized training in an 8-week training intervention. The results do not indicate any additional benefit of an MC phase-adapted training on recovery and premenstrual symptoms in recreationally active females. However, a post-hoc analysis brought to light that in 57% of participants in the CON group, the recovery phases in the traditional block-periodized training protocol coincidentally aligned with current training recommendations for MC phase-adapted training (Pitchers & Elliott-Sale, 2019). Consequently, the structure of the training protocols might have exhibited a too low variance between the INT and CON groups. Moreover, the less dependable calendar-based determination of the MC (Thompson & Han, 2019) hinders the generalization of the results and comparability of the INT and CON.

4.3. Manuscript III

Title: Polarized running training adapted to versus contrary to the menstrual cycle phases has similar effects on endurance performance and cardiovascular parameters.

Summary: Previous investigations into the efficacy of MC phase-adapted resistance training have demonstrated enhanced performance outcomes (Thompson et al., 2020). The influence of reproductive hormones on metabolic changes raises the possibility that endurance performance is also subject to variations across the MC (Willett et al., 2021). Recognizing this, MC phase-adapted endurance training has been proposed as a potentially advantageous approach (Kissow et al., 2022). However, the singular existing study in this realm failed to identify significant differences in performance, cardiovascular parameters, and well-being between MC phase-adapted endurance training and traditional block-periodized training (Kubica et al., 2023). Nonetheless, the limited small sample size and only minor differences in the training interventions impede the clarity of the results. Therefore, the present study seeks to address these gaps by comparing the effects of polarized running training adapted to the MC phases versus polarized training adapted in opposition to the MC in a larger sample size.

Thirty-three naturally menstruating, moderately trained females (age: 26 ± 4 years; Body-Mass Index: 22.3 ± 3.2 kg/m2; VO_2max: 40.35 ± 4.61 ml/min/kg) were randomly assigned to a control (CON) and an intervention (INT) group. Both groups engaged in a load-matched 8-week running training intervention consisting of three weekly training sessions. In the INT, the training sessions were adapted to the MC with high-intensity sessions during the mid and late follicular phase, low-intensity sessions during the early and mid-luteal phase, and recovery during the late luteal and early follicular phase. In the CON, training sessions were adapted contrary to the MC (Fig. 5).

Endurance performance and cardiovascular parameters were assessed at baseline and after the intervention. To explore interactions between time and group for the outcomes, repeated measures analysis of variance (ANOVA) was employed. Post-hoc analyses with Bonferroni's correction were conducted where necessary. To determine the reliability of the variables, intraclass correlation coefficients and their 95% confidence intervals were calculated based on a mean rating, consistent, two-way mixed effects model (Koo & Li, 2016; Weir, 2005). Furthermore, standard error of measurement and minimum difference to be considered real were calculated (Weir, 2005)

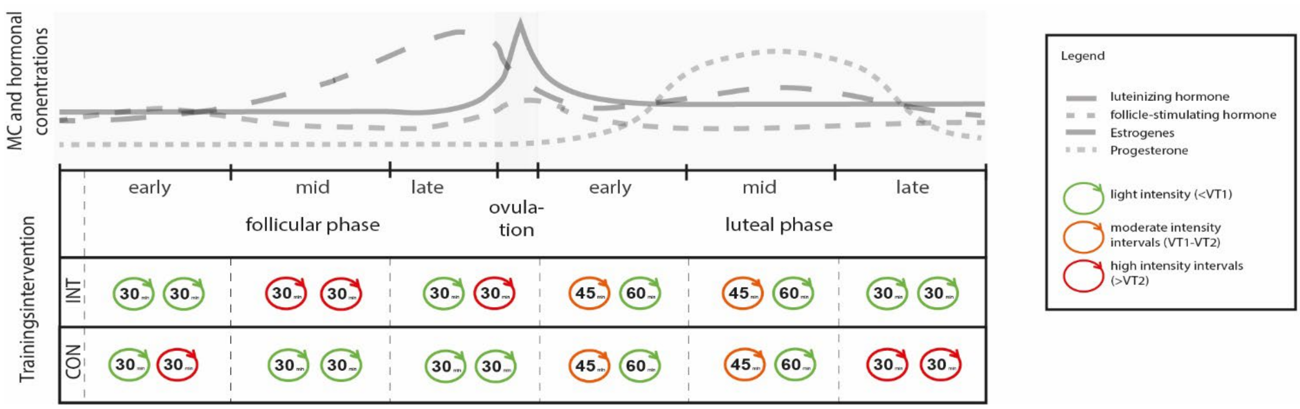

Figure 6. Exemplary four-week training plan for the intervention group, following a menstrual cycle phase-adapted training, and control group, following a contrary to the menstrual cycle phase-adapted training.

A total of twenty-six females completed the intervention. Utilizing repeated measures ANOVA, no significant time × group interaction effect was observed for any parameter. A significant time effect was found for VO_2max ($F(1,12) = 18.753$, $p = .005$, $\eta p^2 = .630$), the velocity at the ventilatory threshold one ($F(1,12) = 10.704$, $p = .007$, $\eta p^2 = .493$) and two ($F(1,12) = 7.746$, p

= .018, ηp^2 = .413). However, the proportion of participants with changes in VO_2max exceeding the minimal difference to be considered real was larger in the INT compared to the CON.

Both intervention groups exhibited improved endurance performance, suggesting the efficacy of the training interventions. Notably, there was no discernible additional benefit from employing the MC phase-adapted polarized training approach. Results based on the minimal differences required to be considered real indicate substantial individual variability in the training response within the MC phase-adapted training group. The observed high variability in individual training responses emphasizes the need for replications with extended intervention periods, larger sample sizes, and enhanced accuracy in MC determination, guiding the refinement of training strategies for female populations.

5. Discussion

The three studies integrated into this cumulative dissertation aimed to address two primary objectives. The first objective was to investigate the relation between MC symptoms and disorders among recreationally active females with PA intensity and exercise volume. The second objective was to assess the effects of MC phase-adapted endurance training on various parameters, including endurance performance, cardiovascular health, and overall well-being.

PA intensity, exercise volume, and MC symptoms and disorders

In the initial study (Manuscript I), we identified a 17% prevalence of PMS, 18% oligomenorrhea, and 2.9% secondary amenorrhea among recreationally active females. These prevalence rates align closely with prior studies' findings encompassing recreationally active females and the general population (Bachmann & Kemmann, 1982; Baranauskas et al., 2023; Tschudin et al., 2010). As previous research indicates, prevalence rates among recreationally active females are lower compared to the prevalence rates among high-performance athletes in other publications, where prevalence rates can be up to 28% % for amenorrhea and 25% for oligomenorrhea (Baumgartner et al., 2023; Dadgostar et al., 2009; Gibbs et al., 2013; Joubert et al., 2022; Torstveit & Sundgot-Borgen, 2005). Notably, the participants in the two intervention studies (Manuscript II and III) revealed a higher prevalence of PMS, with 43% (Manuscript II) and 50% (Manuscript III) of participants classified as experiencing PMS compared to 17% in the broader cross-sectional analysis. It is important to note that “oligomenorrhic” and “secondary amenorrheic” participants were deliberately excluded from the intervention studies, limiting information on these specific conditions in comparison to the cross-sectional analysis. The differences in PMS prevalence in the second and third study compared to the first might indicate a specific participants group in our randomized-controlled trials. PMS can lead to performance decreases and a reduction of physical capacities (Meignié et al., 2021) and its possible effect on training response remains unclear, which might have impacted our results.

Surprisingly, in our first study, we were not able to detect an alteration in the odds-ratios for PMS depending on self-reported PA intensity or overall training volume. This finding diverges from recent literature, where intervention studies imply a positive impact of moderate to vigorous intensity training on PMS (Vishnupriya & Rajarajeswaram, 2011). However, when comparing participants with and without PMS, those with PMS exhibited lower levels of PA than those without PMS. This cross-sectional observation raises questions about the directional relationship between PMS and PA. On the one side, PMS might lead to reduced PA, for example because of PA avoidance due to premenstrual symptoms, such as backpain, fatigue or depressed mood (Kolić et al., 2021). Alternatively, increased PA might affect PMS by reducing premenstrual symptoms. For example, moderate PA is suggested to improve several symptoms of PMS, such as mood disturbance, fatigue, or cognitive dysfunction (Daley, 2009). Further, repetitive muscle contractions help venous blood return and prevent or reduce back pain and discomfort in the pelvis and abdomen, symptoms of PMS, by decreasing the local concentration of prostaglandins and other inflammatory substances (Rostami et al., 2023). However, in the second study, no effect was found for either MC phase-adapted training or traditional periodized polarized training on PMS. Though, the participants in our second and third manuscripts were already physically active, and during the intervention period around 120 minutes of PA per week were added to their regular PA behaviour, which might have resulted in exceeding levels of PA, and limt the positive influence on PMS. According to Morino et al. (2016), low as well as high amounts of PA are related to PMS. This might explain why the relationship due to its possible U-shape is not reflected in the odds-ratio in the first manuscript. Linear regressions, which were used to assess the relationship between PA and MC, assume a linear relationship between the independent variables and the dependent variable. A U-shaped connection, also known as a quadratic relationship, involves a curved pattern. Unfortunately, comparing PA levels between our study participants and Morino et al. (2016) is difficult, as Morino et al. (2016) reports PA levels in kilocalories. Therefore, it remains unclear whether our participants might have reached the category of too high amounts of PA. Furthermore, a recent meta-analysis from Pearce et al. (2020) highlighted, even though there might be a positive associations between PMS and PA, there exists still an uncertainty surrounding the efficacy of exercise for alleviating PMS, regarding the specific modalities of PA, such as intensity, type, or volume to beneficially alter PMS (Pearce et al., 2020).

Notably, higher levels of light PA were linked to an elevated risk of oligomenorrhea, whereas moderate and vigorous intensity PA showed no significant relation in our first study. Secondary amenorrhea was related to higher levels of moderate PA and overall training volume. Previous research indicates no clear trend, with studies reporting higher levels of oligomenorrhea among less active with lower amounts of light PA (Gudmundsdottir et al., 2014), no relationship (Mena et al., 2021), or when combined with secondary amenorrhea with increased light, moderate and vigorous exercise intensity (Baranauskas et al., 2023). As mentioned in Chapter 2.1.3. the mechanisms behind oligomenorrhea and secondary amenorrhea are multifaceted (Koltun et al., 2020; Seshadri et al., 1994); therefore, depending on the underlying cause, PA might have different effects on the MC disorder. For example, in females with MC disorders caused by hypothalamic inhibition, there might be an energy deficiency underlying, which could be negatively affected by increased amounts of PA due to the additional energy demand (Baranauskas et al., 2023; Koltun et al., 2020; Slater et al., 2016). This fits into the suggestions from Baranauska et al. (2023), that excessive volumes of light or moderate intensity training may represent non-specific exercise sessions, such as "junk miles" or cross-training sessions, aimed at augmenting energy expenditure rather than fostering sport-specific skill development. This practice could potentially render females more susceptible to the development of hypothalamic inhibition due to low energy availability. However, Baranauska et al. (2023) assessed light exercise compared to light PA in our study, with light PA being characterized as walking, golf, or yoga. Therefore, in our study, only high amounts of moderate PA could indicate possible “junk miles”. On the other hand, in females with hyperandrogenism as a possible cause of MC disorders, PA might have a positive impact by altering hormonal profiles (Mario et al., 2017; Rickenlund et al., 2003; Samadi et al., 2019).

When interpreting the results, the following methodological considerations should be considered. We conducted a cross-sectional survey, which enabled us to include a broad range of participants. However, cross-sectional data provides no information about a causal relationship between MC, PA intensity, and exercise volume. Further, even though we used standardized questionnaires to assess PA (Nigg et al., 2021), self-report PA data is prone to overestimation (Olds et al., 2019), which may lead to deviations in our results. Also, we have only recorded PMS retrospectively. As mentioned in Chapter 2.1.3. the retrospective assessments of PMS we have used in our study are remarkably prone to bias of false positive reports and the influence of individual beliefs about the PMS (Schmalenberger et al., 2021). Daily assessments provide a more reliable statement on PMS. However, we targeted a representative sample size, which would have been restricted by a prospective study design including daily assessments. Additionally, prevalence rates for oligomenorrhea and secondary amenorrhea were determined based on personal recall of MC patterns. Even though this is a common approach used by multiple studies (Baranauskas et al., 2023; Joubert et al., 2022), there may still be a risk of misclassification.

Further, the survey was distributed via social media and e-mail. Therefore details about recipients and responders are lacking, and there might be a risk of selection bias (Wang & Cheng, 2020). However, the percentage of participants with PMS is comparable to a population-based study among Swiss females (Tschudin et al., 2010). Finally, to analyze the relationship between MC symptoms and disorders and PA, odds ratios were calculated. This is a common approach in epidemiology, as odds ratios are less sensitive to variations in the incidence of the outcome in the population, making them useful in scenarios where the incidence rates are not constant. However, depending on the sample size and prevalence of the outcome, odds ratios might overestimate the risk (Nemes et al., 2009), and the repeated calculations of odds-ratios in our analysis increase the risk of a type-I error (Finner & Roters, 2002).

Even though there are some limitations and considerations that need to be taken into account, the results show the importance of MC in recreationally active females, with many females suffering from PMS, oligomenorrhea, and secondary amenorrhea. However, the relationship between PA and MC is not clarified yet, even though we see light alterations with high amounts of light, moderate PA, and overall training volume.

MC phase-adapted endurance training

The second manuscript, comparing MC phase-adapted endurance training to block-periodized training, revealed no significant advantages of the MC phase-adapted training on endurance performance, cardiovascular parameters, or alleviation of PMS. Both groups exhibited improvements in velocity at the ventilatory thresholds and relative VO_2max after 8 weeks of training. Interestingly, the training plan in the control group coincidentally aligned with that of the MC group, with 57% of participants' recovery periods matching the late luteal and early follicular phases of their MC.

Given the findings in the second manuscript, the third manuscript took a distinct approach by comparing the effects of MC phase-adapted endurance training with a training regimen contrary to the MC phases. Although both training programs significantly improved aerobic capacity and running velocity at the ventilatory thresholds, the results showed no significant differences between the two approaches. To summarize, both of our training interventions had a noteworthy impact on endurance performance yet failed to demonstrate significant effects on cardiovascular parameters or PMS. Furthermore, no significant distinctions emerged between traditional training periodization, MC phase-adapted training, or training contrary to the MC phases.

Studies examining the effects of MC phase-adapted endurance training are notably scarce. The only comparable research comes from Han (2012), who analyzed the impact of MC phase-adapted endurance training in his dissertation project. The training involved focusing on one leg during the first half of the MC (follicular phase training) and the other leg during the second half (luteal phase training). No difference was found between to follicular phase training and the luteal phase training on VO_2peak. Notably, the maximum workload during pre and post incremental tests significantly increased in both legs, with a more pronounced increase after follicular phase training than luteal phase training. However, these significant increases in maximum workload from follicular to luteal phase training were only evident after the third MC training phase (weeks 8-12). In our study, no evident disparity between the MC phase-adapted interventions and traditional training or contrary MC phase-adapted training emerged on VO_2max after 8 weeks, aligning with the findings from Han (2012) on the VO_2peak. However, compared to Han (2012), our study included already active subjects in a running-based endurance training program and covered a shorter intervention period, which limits the comparability of the results. Also, our outcome contrasts with results from prior studies on MC phase-adapted resistance training (Thompson et al. 2020). Notably, these studies primarily focused on alterations in training volume between the follicular and luteal phases, whereas our approach mainly modified training intensity, with minor adjustments to training volume. By modifying the training intensity, we aimed to avoid overuse issues, which runners are prone to when high training volume alterations are made, particularly when weekly running distance varies over 30% (Winter et al., 2020). This divergence in methodology might account for the conflicting results observed in our study compared to previous research on MC phase-adapted resistance training.

Our training intervention was based on current recommendations for MC phase-based training (Elliott-Sale & Pitchers, 2019), resting upon the possible alterations in the physiological processes by estrogen and progesterone, as summarized in the chapter 2.3.2.1. These alterations are hypothesized to impact various aspects of PA and exercise, including readiness, exercise effectiveness, adaptation responses, and recovery. Therefore, considering these hormonal alterations in the exercise planning process could prove advantageous (Kissow et al., 2022), which could not be confirmed by our training intervention. However, alterations such as in the metabolism depend on many other factors, such as nutrition and exercise intensity and hormonal shifts (Hackney et al., 2022), and therefore, these alterations could have been superimposed.

Usually, aerobic training is linked to various positive health outcomes, especially in the cardiovascular system (see chapter 2.2.4.). However, in both of our intervention studies, we were not able to detect alterations in the cardiovascular parameters, including resting heart rate, heart rate variability, systolic and diastolic blood pressure, as well as pulse wave velocity. Unfortunately, no previous study has assessed the effects of MC-based training on hemodynamic parameters. Though, the missing time effects in both studies contrast with previous studies showing positive effects of general aerobic endurance training on cardiovascular parameters. (Cornelissen & Smart, 2013; Esmailiyan et al., 2021; Reimers et al., 2018). Divergent effects might be explained by our healthy participant characteristics, as the reductions seem to be more pronounced in participants with previous hypertension (Pescatello et al., 2015) or higher initial heartrate (Reimers et al., 2018). Further, the duration of the intervention also seems to impact adaptations in the cardiovascular system, with longer interventions leading to a substantial effect on the outcomes (Reimers et al., 2018)

Additionally, some methodological considerations for the manuscripts II and III should be taken into account. First, we decided to focus on polarized training, which was adapted to the MC phases, to prevent an increased injury risk by high alterations in training volume (Winter et al., 2020) and to use a training approach that is common and effective for improving aerobic capacity (Stöggl & Sperlich, 2014). However, it might be suggested that this led to only minor changes between the intervention and control groups in both studies. Further, the training intervention was, besides single visits during the intervention period mainly based on a "home-based" training. Previous studies indicate that exercise intensity might be reduced in "home-based" training compared to supervised training (Cittanti, 2019; Fennell, 2016). Even though we monitored the number of training sessions, the average heart rate, and training duration in both groups, we could not verify the respective training times in the specific intensity zones. Alterations in the time spent in the training intensity zones might have reduced training adaptations.

Moreover, data on the individual training sessions would have improved the insights and verification of training intensity and adherence. Also, even though we used standardized, reliable, and valid tests to assess endurance performance and cardiovascular parameters, day-to-day variability can play a significant role. For example, the day-to-day variability of VO_2max fluctuates within a range of 2.8% (Zinner et al., 2023). The fluctuations emphasize the relevance of verifying whether the changes detected are physiological or only due to day-to-day variability. Therefore, we calculated the minimal differences to be considered real for each parameter in the third manuscript. Those results hint at the superiority of the MC-phase adapted training on VO_2max and blood pressure. However, these results were only reported descriptively, and no statistical verification was carried out.

Additionally, some methodological challenges occurred during the interventions. Even though we explicitly included participants with a regular MC, the MC shows a high intra-individual variability (Alliende, 2002). During the intervention, we tried to adapt the training plans to any changes in the MC in constant dialogue with the participants. However, there still exists a chance that not all training plans were adapted flawlessly to the MC, leading to minor deviations between the intended and actual training plans.

Overall, the generalization and transferability of our results in the randomized controlled trials is limited. We only included a specific group of participants, with already active females, with a regular MC, and not using hormonal contraceptives. We conclude that periodized training adapted to the MC might not alter performance, cardiovascular health, or PMS to any extent other than traditional training in that specific population.

5.1. Limitations

Some limitations, next to the methodological considerations mentioned in the discussion section, need to be considered when interpreting the results. First, the restricted quality of evidence in the three studies should be considered, with a cross-sectional study and two randomized control trials with small sample sizes (Goldet & Howick, 2013). Secondly, when we conducted the research, financial resources were limited. Therefore, the MC was only verified by the calendar-based counting method (Manuscript II), which limits the informative value due to the restricted participants' characterization, MC determination, and MC phase verification (Schmalenberger et al., 2021). In the third manuscript, we were able to additionally include basal body temperature and LH-measurements. However, participants with luteal phase deficiency or variations in estrogen/progesterone concentrations might not be detected an influence the results, as a luteal phase deficiency negatively impact performance and health (Schliep et al., 2014; Schmalenberger et al., 2021)

Third, some confounding variables might have influenced our results. As main confounding variables, we did not consider nutrition and the risk of low-energy availability. This limits the interpretability of the cross-sectional analysis as low-energy availability might have a superior effect on MC and cover the effects of PA (De Souza & Williams, 2004; Torstveit & Sundgot-Borgen, 2005). Also, as previous studies implicate that alterations in the metabolism over the MC are affected by nutrition, nutritional aspects might have influenced the results of our randomized-controlled trials (Smekal et al., 2007). Nutritional behavior related to training, such as pre-exercise fueling, was recommended but not controlled.

Further, the two randomized controlled trials intervention studies might have been influenced by factors for which we did not control. Susceptible factors are alterations in regular PA, sleep, or additional stressors (Watson, 2017). Especially during the first randomized controlled trial (Manuscript II), COVID-19 was highly prevalent, with many participants being excluded due to extended infection periods. However, other participants might have been affected during the intervention or had an infection prior to the intervention start, with unclear effects on performance and cardiovascular parameters (Śliż et al., 2022).

5.2. Future directions

For future research, we identified several possible avenues for further research and exploration, which are summarized in Fig. 6. Especially in our randomized-controlled trials, we focused on healthy participants without any diseases and a regular MC. However, it would be interesting to investigate potential variations in training responses among populations deemed "at risk", particularly those with alterations in the MC, such as oligomenorrhea or secondary amenorrhea, or populations with comorbidities such as diabetes or cardiovascular diseases. Additionally, it would be of interest to explore if endurance training adapted to those minor changes in the physiological processes by estrogen and progesterone might have a relevant effect on high-performance athletes. Given the heightened relevance for elite athletes for even minor performance changes, understanding how MC-tailored training can affect their performance outcomes is of importance. Also, larger sample sizes should be prioritized to enhance the statistical power and generalizability of findings.

Expanding the repertoire of endurance training investigations, we advocate for in-depth examinations of prolonged interventions exceeding eight weeks. The integration of other training methods, such as high-intensity training or high-volume with low-intensity training, warrants scrutiny for potential synergistic effects.

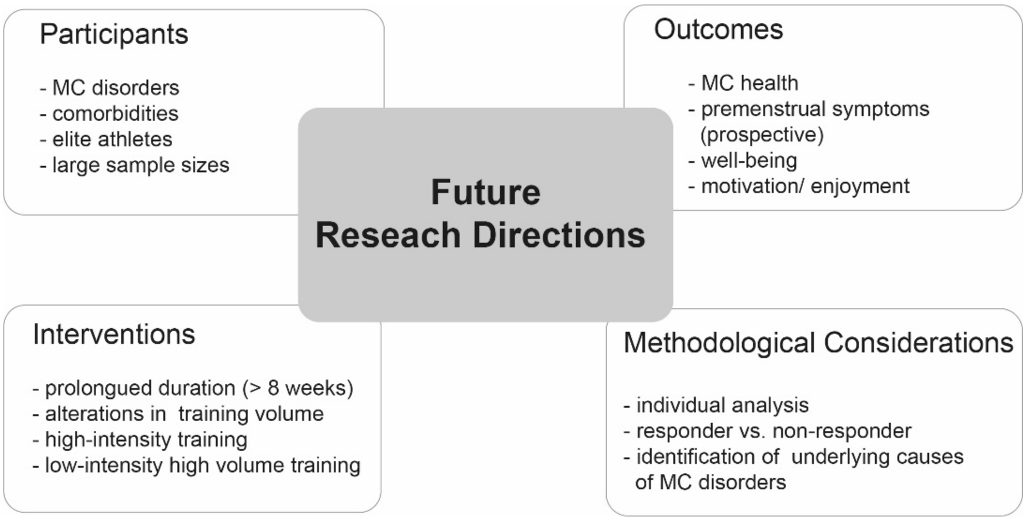

Figure 7. Possible future research directions on menstrual cycle, physical activity and exercise.

To accommodate the inherent variability in individual responses, we propose the implementation of individualized assessments. These assessments should consider individual hormonal concentrations and incorporate subjective perceptions and experiences throughout the MC. Acknowledging the individualized nature of MCs and exploring the concept of responders and non-responders to MC phase-adapted training can offer nuanced insights.

In scrutinizing the relationship between PA and MC disorders, a more in-depth analysis of possible causal relationships is warranted. Investigating links between hyperandrogenism and hypothalamic inhibition can elucidate underlying mechanisms and inform targeted preventive strategies. These research directions aim to advance our understanding of the intricate interplay between PA, MC health, and individual characteristics, paving the way for more tailored and effective interventions.

Additionally, diversifying outcome assessments beyond performance and cardiovascular health is imperative. Attention should be directed towards evaluating MC health outcomes, prospective assessments of PMS, well-being, enjoyment, and PA motivations, as these factors can significantly influence long-term adherence.

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