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An Investigation of Menstruation Symptoms Across Consecutive Menstrual Cycles and the Association With Iron Deficiency or Self-Reported Heavy Menstrual Fluid Loss

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Alexa Irving

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Abstract

Background: Menstrual cycle (MC) symptoms can vary by type and severity among women, and can affect their physical, emotional, and mental health (Schoep et al., 2019). However, few studies have prospectively examined symptoms during menstruation in healthy women. Menstrual bleeding increases iron requirements, and iron deficiency (ID) is common among menstruating women (WHO, 2023). The primary objective of this study was to describe the menstruation-related symptoms experienced by naturally menstruating women. A secondary aim was to examine whether iron status or self-reported menstrual flow contributed to differences in menstruation-related symptoms between women.

Methods: Naturally menstruating women (n = 97) aged 18-40 residing in Aotearoa/New Zealand participated in a longitudinal prospective cohort study across up to five MCs. Daily surveys during menstruation captured symptom type and severity using a five-point scale, along with perceived bleeding heaviness. Iron status was assessed via venous blood samples collected at baseline and at the end of the study (mid-luteal phase of the last cycle of data collection). Iron deficiency was defined as serum ferritin (SF) <30 µg/L and Hb ≥120 g/L. Group differences in symptom severity were analysed using Wilcoxon rank-sum tests and multiple linear regression to predict associations with symptom severity.

Results: Menstruation-related symptoms were generally mild, with most rated as "none" and "a little." The most frequently reported symptoms included abdominal cramps, fatigue, mood changes, sleep disturbances, headaches, and reduced concentration. Compared with non-heavy bleeders, women with self-reported heavy menstrual bleeding (HMB) had higher severity for fatigue, abdominal cramps, and reduced concentration ($p < 0.05$). Women with ID reported significantly higher severity for fatigue, dizziness, joint pain/muscle cramps, and lower back pain ($p < 0.05$). In the multilinear regression, iron status did not predict symptom severity; only bleeding heaviness contributed to the overall symptom severity score.

Conclusion: Perceived HMB was associated with greater menstruation-related symptom severity and independently predicted overall symptom severity. Women who reported HMB experienced higher severity of specific symptoms, including fatigue, abdominal cramps, and reduced concentration. In contrast, ID did not independently predict symptom severity. These results suggest that perceived bleeding heaviness may explain some of the inter-individual variability in menstruation symptom experience.

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Abbreviations

Abbreviation	Meaning
BIA	Bioelectrical impedance analysis
E2	Oestradiol
GABA	Gamma-aminobutyric acid receptors
Hb	Haemoglobin
HMB	Heavy menstrual bleeding
ID	Iron deficiency (without anaemia)
IDA	Iron deficiency anaemia
MC	Menstrual cycle
PD	Primary dysmenorrhoea
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
QoL	Quality of life
SF	Serum ferritin

Terminology disclaimer:

To avoid misinterpretation, the terms 'psychological changes' and 'emotional changes' are used interchangeably as umbrella terms to describe a range of self-reported symptoms, including low mood/depression, anxiety, and stress, rather than clinically diagnosed mental health conditions. These terms are not intended to reflect formal psychological disorders, but rather the emotional and psychological symptoms women experience and associate with their menstrual cycle. Where clinically diagnosed mental health conditions are referenced, this will be explicitly stated.

Chapter 1 Purpose

1.1 Introduction

The menstrual cycle (MC) is a biological process within the female reproductive system, often impacting physical, mental and emotional well-being (Critchley et al., 2020). Generally lasting between 21 and 35 days (Mihm et al., 2011), the MC is characterised by fluctuations of the sex steroid hormones, oestradiol (E2, the primary form of oestrogen) and progesterone, and broadly can be divided into two phases: the follicular phase (lasting from menstruation to ovulation) and the luteal phase (lasting from ovulation to menstruation) (Handy et al., 2022). The early follicular phase is characterised by menstrual bleeding and low levels of sex steroid hormones (Thiyagarajan et al., 2022). During this phase, a dominant follicle will be selected and, during its maturation, will secrete E2. As the follicle reaches peak maturation, occurring just before ovulation, there is a corresponding exponential rise in E2 levels that trigger ovulation. Ovulation, the release of the ovum from the mature follicle in the ovary, marks the transition between the follicular and luteal phases, and is initiated by a luteinising hormone (LH) surge after the E2 peak at the end of the follicular phase. Following ovulation, progesterone and E2 are secreted by the corpus luteum in the ovaries during the luteal phase, causing a progressive rise in their concentrations throughout the second half of the cycle. As a result, there is a peak in progesterone and a secondary peak in E2 during the mid-luteal phase (Thiyagarajan et al., 2022). If fertilisation of the ovum does not occur, the corpus luteum breaks down, and progesterone and oestrogen levels decline. The decrease in progesterone and E2 then leads to the shedding of the uterine lining, marking the end of one MC and the beginning of the next cycle (Handy et al., 2022; Thiyagarajan et al., 2022).

Common symptoms of the MC include abdominal or menstrual cramps (dysmenorrhoea), fatigue, heavy menstrual bleeding (HMB), and emotional changes (Schoep et al., 2019). While research has investigated the aetiology of menstruation-related symptoms, there is limited research on what other health and biological factors may worsen the severity of menstruation-related symptoms, particularly in otherwise healthy females. One health outcome that may be considered is iron deficiency (ID). However, the association between iron status and the self-reported severity and frequency of these menstruation-related symptoms remains underexplored.

Iron is an essential mineral in many foods and plays several critical physiological roles in the human body. Iron is part of haemoglobin (Hb), the protein found in red blood cells, which facilitates the transport of oxygen from the lungs to tissues, as well as in myoglobin, which aids in delivering oxygen to muscle tissues (Abbaspour et al., 2014). Iron deficiency is the most common nutrient

deficiency, estimated to affect a third of women aged 15-49 years globally (WHO, 2023). For this thesis, ID refers to iron deficiency without anaemia, defined as serum ferritin (SF) concentrations below 30 μg/L, with Hb levels ≥120 g/L. This definition is consistent with contemporary clinical characterisations of non-anaemic ID (Clénin, 2017) and aligns with the WHO guidelines that distinguish ID from iron-deficiency anaemia (IDA) (WHO, 2023). Although New Zealand clinical reference ranges commonly use an SF threshold of <15 μg/L to diagnose ID (Ngan, 2005), this serum ferritin threshold primarily reflects more advanced iron depletion and may underestimate ID in menstruating women. Evidence indicates that depleted iron stores and ID-related symptoms such as fatigue can occur at SF concentrations below 30 μg/L (Greig et al., 2013; Sawada et al., 2014). Therefore, the <30 μg/L threshold was selected to improve sensitivity and better capture early or functional ID relevant to symptom expression in this population.

Fatigue is the persistent feeling of exhaustion and reduced energy levels and has been associated with HMB and ID (Wang et al., 2013). Fatigue is a commonly reported symptom during the MC, with research reporting that fatigue levels tend to be their highest in the luteal and menstrual phases and lowest in the follicular phase (Pallavi et al., 2017). It is proposed that fluctuating levels of sex steroid hormones, E2 and progesterone, may influence the severity of fatigue that menstruating women may experience throughout their MC (Li, Lloyd, & Graham, 2020). However, limited research has investigated whether fatigue worsens during menstruation in otherwise healthy, naturally menstruating women and whether ID exacerbates women's self-perceived severity of fatigue.

Dysmenorrhoea refers to spasmodic and painful cramps in the lower abdomen that begin shortly after the onset of menses, and is classified as either primary or secondary dysmenorrhoea (PD or SD, respectively) (Itani et al., 2022; Wang et al., 2022). Primary dysmenorrhoea is recurring lower abdominal pain experienced during the MC without any medical condition or underlying pathology. Secondary dysmenorrhoea is abdominal pain that is associated with an underlying or suspected medical condition, such as endometriosis, adenomyosis, uterine fibroids, or pelvic inflammatory disease (Nagy et al., 2023). Considerable research has been conducted on PD, particularly regarding its impact on quality of life (QoL), with previous research reporting that this pain can affect academic performance, reduce concentration, productivity, and daily functioning (Armour et al., 2019; MacGregor et al., 2023; Quick et al., 2019). Research has shown that PD can affect 45-90% of pre-menopausal women (Karout et al., 2021; MacGregor et al., 2023). However, the association between the severity of PD and iron status has not yet been adequately examined.

Many women may experience emotional changes throughout their MC, including depression, anxiety and stress, which remain poorly understood in otherwise healthy menstruating women (Schoep et al., 2019). Emotional changes are also reported by women who experience premenstrual syndrome and premenstrual dysphoric disorder (PMS & PMDD, respectively) (Liguori et al., 2023). The presentation of PMS and PMDD has been proposed to result from varying sensitivity of gamma-aminobutyric acid receptors (GABA) to allopregnanolone, which may result in the emotional symptoms associated with luteal-phase progesterone fluctuations (Bäckström et al., 2003; Tiranini & Nappi, 2022). While this proposed mechanism requires further research, particularly in otherwise healthy women, it is possible that low levels of sex steroid hormones may also influence emotional changes that women report during menstruation. In addition to the potential physiological influence that sex steroid hormones may have on emotional symptoms, ID may also affect the severity of these emotional changes (Kim & Wessling-Resnick, 2014). Despite much of the available research on ID focusing on women with preexisting psychiatric disorders, some studies suggest there is an association between ID/IDA and higher psychological stress in non-clinical populations (Hidese et al., 2018; Lee et al., 2020).

Research has investigated the prevalence and severity of ID and MC-related symptoms independently. However, there is limited research that has explored the relationship between iron status and menstruation-related symptoms, including whether ID can influence menstruation-related symptom severity. Therefore, this study aims to examine the relationship between iron status and menstruation-related symptoms, focusing on how differences in iron status may influence self-reported menstruation-related symptom severity and frequency in naturally menstruating women. In addition, with HMB considered a risk factor for ID, the study will investigate the association between perceived menstrual fluid loss and self-reported menstruation-related symptom severity and frequency.

1.2 Research aims and objectives

Aims

The primary aim of this study was to describe the menstrual cycle symptoms during menstrual bleeding in naturally menstruating women. The secondary aim was to examine differences in self-reported menstruation-related symptoms between iron deficient and iron-sufficient women and self-reported heavy menstrual bleeders and non-heavy menstrual bleeders.

Objectives

1. Describe the type and self-perceived severity of menstruation-related symptoms in women during menstrual bleeding.
2. Describe the type and self-perceived severity of menstruation-related symptoms in women who are iron sufficient and iron deficient during menstrual bleeding.
3. Describe the type and self-perceived severity of menstruation-related symptoms in women who self-rate themselves as heavy or not heavy menstrual bleeders.

Hypotheses

1. Heavy menstrual bleeders will experience higher self-reported severity of physical symptoms (dysmenorrhoea and fatigue) and emotional changes compared to women who perceive their menstrual bleeding to be regular or light.
2. Women who are iron deficient will report higher severity of physical symptoms (fatigue and dysmenorrhoea) and emotional changes during their menstrual bleed compared to women who are iron sufficient.

1.3 Structure of Thesis

This thesis will begin with an introductory chapter that outlines the study's purpose and significance. The reader will be introduced to the potential consequences of ID and common menstruation-related symptoms before exploring their possible association and addressing existing research gaps. Following the introduction, a literature review will examine the available literature regarding iron status and menstruation-related symptoms. Chapter 3 is the manuscript of the study, providing the reader with details on the methods, results, and a discussion of the findings. Future research recommendations, study strengths, and limitations will be presented in the final chapter of this thesis, establishing a foundation for continued investigation.

1.4 Researchers' Contributions

Table 1.1 *Researcher's contributions to the study*

Researcher	Contribution to thesis
Alexa Irving **MSc (Nutrition and Dietetics) Student**	Primary author of thesis Thesis editor Managing of the statistical analysis
Dr Maria Casale **Primary supervisor** Lecturer Nutrition and Dietetics, Massey University	Provided guidance and feedback on elements of the thesis Thesis editor
Dr Claire Badenhorst **Co-Supervisor** Associate Professor - Director of Research, Edith Cowan University	Conceptualised the study, applied for funding, applied for ethics, recruited participants, completed data collection Provided guidance and feedback on elements of the thesis Thesis editor
Karen Mumme **Statistics and analytical advisor** Research Assistant, Massey University	Supported development and execution of data and statistical analysis Advised on statistical methodology and analytical decisions
Dr Beatrix Jones **Statistics and analytical advisor** Associate Professor of Statistics, University of Auckland	Supported development and execution of data and statistical analysis

Chapter 2 Literature Review

2.1 Introduction

For clarity, throughout this thesis, the menstrual cycle (MC) is often referred to in broad terms as comprising two main phases: the follicular phase, which spans menstruation through ovulation, and the luteal phase, which extends from ovulation to the onset of the next menstrual bleed. Where relevant, particularly within the literature review, a more detailed framework is used that distinguishes between the ovarian cycle (follicular, ovulatory, and luteal) and the endometrial cycle (menstrual, proliferative, and secretory phases). The term “premenstrual” is used to describe the late luteal phase immediately preceding menstruation.

Menstruation is a defining and essential part of life for women, marking a key biological transition from adolescence into womanhood (Azurah et al., 2013). Yet, significant gaps remain in understanding the association between bleeding patterns, symptoms, and iron status. Frequent or severe menstrual symptoms such as abdominal cramps (primary dysmenorrhea [PD]), heavy menstrual bleeding (HMB), fatigue, and emotional changes, including depression, stress and anxiety, can interfere with women’s quality of life (QoL) (Schoep et al., 2019). Moreover, HMB is also well recognised as a significant contributor to iron deficiency (ID) (Peuranpää et al., 2014). Women who are diagnosed with ID may experience symptoms such as fatigue, irritability, muscle weakness, shortness of breath, dizziness, poor concentration, hair loss, and restless leg syndrome (Percy et al., 2017). To date, few studies have examined whether there is a relationship between self-reported menstruation-related symptom severity and iron status. A more comprehensive understanding of these relationships is crucial for improving women’s health outcomes (Zia et al., 2022).

This literature review will examine existing research on the prevalence and frequency of symptoms experienced during menstruation and their association with ID. It will provide commentary on these studies' strengths and limitations while identifying key areas for further research. Relevant studies will be included when they involve otherwise healthy women who do not use any forms of birth control and iron supplements to better capture natural MC variations and symptoms, and the potential interaction with iron status.

Review methods

To evaluate a) the prevalence of ID in menstruating women, b) menstruation-related symptoms experienced by both ID and non-ID women, and c) the relationship between ID and these symptoms, a literature search of relevant articles was conducted. This review included papers predominantly

published from 1990 onwards. Relevant studies were identified through a literature search of PubMed and Google Scholar. The search strategy included the following terms:

- “Premenopausal women” OR “healthy women” OR “healthy females” OR “women and girls of reproductive age”
- “Menstruation” OR “menstrual cycle” OR “period” OR “menstruation-related symptoms”
- “Iron status” OR “iron deficiency” OR “iron deficiency anaemia”
- “Heavy menstrual bleeding” OR “menorrhagia”
- “Dysmenorrhoea” OR “cramps” OR “menstrual pain”
- “Psychological changes” OR “emotional changes” OR “anxiety” OR “depression” OR “stress”

Abstracts from the literature search were reviewed for topic relevance. Studies were included if they included premenopausal women with one or more of the following: assessed iron status and/or biomarkers (haemoglobin [Hb], serum ferritin [SF]), evaluated menstrual bleeding patterns or HMB, and/or examined associated symptoms such as PD, fatigue, depression, anxiety, or stress.

2.2 An Overview of the Menstrual Cycle

The menstrual cycle is a physiological process, including the ovarian and endometrial cycles, is characterised by hormonal fluctuations and typically lasts between 21 and 35 days (Thiyagarajan et al., 2022). During the ovarian cycle, three main phases occur: the follicular, ovulatory, and luteal phases. The endometrial cycle consists of the menstrual, proliferative, and secretory phases. The follicular phase of the ovarian cycle begins with menstruation and progresses to the proliferative phase of the endometrial cycle. The luteal phase of the ovarian cycle corresponds with the secretory phase of the endometrial cycle (Thiyagarajan et al., 2022). Events in the ovarian cycle drive fluctuations in oestradiol (E2) and progesterone. Physiological changes in the body and the reproductive system occur in response to changes in these female sex steroid hormones (Thiyagarajan et al., 2022). The length of MCs and ovulatory function can differ significantly among women. Many women may have regular ovulatory cycles, but it is not uncommon for subclinical ovulatory disturbances, such as anovulation (absence of ovulation and flow for ≥3-6 months) and short luteal phase (insufficient ovulation duration or insufficient progesterone), to occur in women with “normal” cycle lengths (Prior, 2022). These MC presentations or subclinical ovulatory disturbances are proposed to be the initial functional hypothalamic (FH) suppression that occurs in response to stress, energy deficit or illness. With more severe stress, FH suppression may result in

severe MC disruptions, including oligomenorrhoea (cycle lasting >35 days) and FH amenorrhoea (Prior, 2022).

2.2.1 Menstrual Cycle Symptoms

Research has shown that women will likely experience one or more symptoms during their MC, typically during their luteal phase (Gudipally & Sharma, 2020). Common symptoms include PD, HMB, headaches, nausea, painful defecation, breast tenderness, back pain, and psychological changes (Schoep et al., 2019). These symptoms can affect daily life, impacting both physical and emotional well-being (Schoep et al., 2019). The following sections will discuss psychological symptoms, then physical symptoms during the menstrual phase, followed by risk factors that influence the severity of these symptoms in healthy women.

Given the breadth of symptoms reported across the MC, this literature review focuses on fatigue, PD, and psychological symptoms during menstruation, as these are commonly reported menstruation-related symptoms and are frequently associated with reduced QoL in premenopausal women (Armour et al., 2019; Schoep et al., 2019). In addition, these symptoms were prioritised due to their frequent co-occurrence with HMB, and overlap with symptoms commonly reported with ID (Greig et al., 2013; Munro et al., 2023). Other menstruation-related symptoms were not explored in depth as evidence linking them directly to iron status is limited, or they were more strongly associated with hormonal fluctuations through the MC and not menstruation itself (Handy et al., 2022; Schoep et al., 2019).

2.2.2 Psychological Symptoms

Psychological symptoms, including stress, anxiety and depression, have been found in previous research to vary during a woman's MC (Farage et al., 2008). These symptoms reportedly rise during the late luteal phase and remain elevated into the early menstrual phase, and have been found to negatively affect women's QoL (Meaden et al., 2005; Schoep et al., 2019). The available literature consistently illustrates a cyclical relationship between emotional changes and menstruation (Rapkin & Winer, 2009). Additionally, previous research has indicated that psychological and neuroendocrine changes (e.g., mood changes related to hormonal fluctuations) may increase the severity of these symptoms (Handy et al., 2022). However, much of this research has focused on premenstrual disorders such as premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), which involve a cluster of physical, cognitive, and affective symptoms occurring during the luteal phase (Delara et al., 2012).

Female sex steroid hormone fluctuations across the MC have been associated with increased feelings of anxiety, depression and emotional irregularities (Farage et al., 2008). These emotional

changes may increase premenstrually when oestrogen and progesterone levels start to decline (Farage et al., 2008). Conversely, when progesterone levels are high (mid-luteal phase), the hormone is metabolised quickly into pregnenolone and allopregnanolone, and research has suggested that this may modulate gamma-aminobutyric acid type A (GABA-A) receptor activity, and exert anxiolytic, anti-stress, and antidepressant effects (Kimball et al., 2020; Stefaniak et al., 2023). However, individual variation in progesterone levels between women may contribute to differing emotional responses, particularly during the late-luteal phase when progesterone levels decline (Farage et al., 2008). Cortical GABA levels also appear to decrease from the follicular to the luteal phase in healthy women (Epperson et al., 2002). This decline may reduce inhibitory neurotransmission and increase emotional changes during the late luteal phase, when progesterone levels decline (Farage et al., 2008). Oestradiol is suggested to influence mood via serotonergic pathways by increasing tryptophan, upregulating serotonin receptors, and inhibiting monoamine oxidase, which breaks down serotonin (Bendis et al., 2024). When E2 levels decline, during the late luteal phase, serotonin availability may decline, contributing to psychological symptoms of anxiety, depression and stress (Bendis et al., 2024; Halbreich & Kahn, 2001). However, much of this evidence stems from animal models or women with PMDD or PMS (Bendis et al., 2024; Hantsoo & Epperson, 2020; Yen et al., 2018), and there are limited studies about how these mechanisms operate in healthy women. Nonetheless, these serotonergic changes may help provide a basic mechanistic rationale for why psychological symptoms still occur in healthy women throughout their MC.

The most common psychological changes reportedly experienced during the premenstrual phase include anxiety, depressed or unstable emotions, and stress (Gonda et al., 2008). In an observational cross-sectional study from Abbas et al. (2020), it was reported that 34.6% of the 338 women surveyed experienced anxiety during the premenstrual phase of the MC. Interestingly, in previous cross-sectional research by Dorn et al. (2009), women with pre-existing depressive and/or anxious symptoms were more likely to experience intense psychological menstrual symptoms across their MC. Similarly, in a prospective cohort study by Nolan and Hughes (2022), data on symptoms at multiple MC cycle phases (premenstrual, perimenstrual, and luteal) were collected, with results reporting emotional symptom exacerbation during the premenstrual phase, particularly among women with pre-existing depression. These findings suggest that inter-individual variability in emotional changes may be influenced by baseline psychological status. However, the presence of pre-existing psychological conditions in these studies may limit the generalisability of these findings to the broader population.

Previous research has reported that women with higher-than-average progesterone levels (above the sample mean of 44.8 pg/mL; (Reynolds et al., 2018)) may exhibit greater general anxiety and attachment anxiety across the MC. In a study by Reynolds et al. (2018) with 100 women, individuals with above-average salivary progesterone levels reported greater general and attachment anxiety. Whilst those with lower salivary progesterone levels did not show a significant association with anxiety. Within this previous research, the between-person differences were significant, suggesting that women with higher progesterone may experience greater general and attachment anxiety. Based on these results, the authors suggested that attachment anxiety may increase with progesterone levels throughout the MC. However, limitations of this research include reliance on salivary progesterone over serum (Petsos, 1986), inconsistent confirmation of ovulation via LH surge, and a small sample size that may limit the precision and applicability of these results to the wider population of women.

Building on the association between progesterone and anxiety, some studies suggest that the relationship may work in the opposite direction, where stress can influence progesterone levels. Progesterone may rise in response to stressors during the follicular phase, when baseline levels are typically low (Herrera et al., 2016). In a controlled experimental study with 27 naturally menstruating women, Herrera et al. (2016) examined the effects of exposure to a physical stressor (cold pressor test) during the follicular phase. Those exposed showed increased salivary progesterone and cortisol, while E2 levels remained unchanged. Baseline progesterone was positively correlated with cortisol, and changes in progesterone across the session, suggesting an association between the stress response and the two hormones. However, as progesterone was measured in saliva, the accuracy of absolute concentrations may not be as accurate as with serum or plasma assays (Petsos, 1986; Schiffer et al., 2019).

Research into depressive symptoms across the MC shows subtle but consistent changes in symptom severity among healthy women (Gonda et al., 2008). For example, daily symptom tracking over three cycles in 63 individuals showed a significant increase in depression from the late follicular to late luteal phases, despite overall symptom changes being small in magnitude (Gonda et al., 2008). Similarly, Guevarra et al. (2023) examined whether women experienced increased affective symptoms in the mid-luteal phase. Ninety-six women completed daily questionnaires assessing anhedonic depression and stress for 35 consecutive days. Saliva samples were collected to track hormone fluctuations and precisely determine MC phases, though salivary assays can be less precise than serum measures for progesterone, which is often near the lower limit of detection (Petsos,

1986; Schiffer et al., 2019). The study tested the "*window of vulnerability"* model, which proposes that mid-luteal increases in progesterone heighten sensitivity to affective symptoms. Results showed a modest but significant increase in anhedonic depression during the mid-luteal phase, providing partial support for a recurring, phase-specific risk factor in women. Collectively, this research would suggest that from the mid-late luteal phase, depressive symptoms may intensify for women.

Much research on psychological symptoms during the MC has focused on clinical populations, such as those with PMS, PMDD, and formal psychological diagnoses. There remains a critical need to explore psychological changes in otherwise healthy women and the interaction of these changes with other possible lifestyle risk factors, such as ID. Most research on psychological changes across the MC has focused on the premenstrual phase, with comparatively little attention given to symptoms during menstruation itself. Therefore, further research is needed on the psychological and emotional changes that occur during menstruation.

2.2.3 Physical Symptoms

The MC is commonly associated with a range of physical symptoms, including PD, fatigue, breast tenderness, bloating, and headaches (Schoep et al., 2019). In this section, the primary focus will be on PD and fatigue.

Dysmenorrhoea refers to the pain women experience in their lower abdomen during menstruation and is classified as either PD or secondary dysmenorrhoea (SD) (Itani et al., 2022). Primary dysmenorrhoea affects between 45-90% of pre-menopausal women and is thought to be due to the increased secretion of prostaglandins, which causes stronger uterine contractions (Karout et al., 2021; MacGregor et al., 2023). Secondary dysmenorrhoea is caused by underlying medical conditions or pelvic pathology such as endometriosis, ovarian cysts, fibroids, adenomyosis, or pelvic inflammatory disease (Clemenza et al., 2021). As this research focuses on healthy, pre-menopausal women, the following discussion will be focused on PD.

A meta-analysis from Wang et al. (2022), which included 96 studies with a combined sample of 78,068 students, reported an overall pooled prevalence of PD at 66.1%. Although the specific timing of PD was not reported in the study, it most commonly occurs premenstrually or during menstruation (Wang et al., 2022). Other studies have found variability in PD prevalence rates, ranging from as low as 16%, to as high as 95% (Armour et al., 2019; Itani et al., 2022; Vincenzo De Sanctis et al., 2015). However, this variability in PD prevalence rates may be due to differences in study designs and methodologies, such as population samples, diagnostic criteria, and symptom

assessment methods. For example, Vincenzo De Sanctis et al. (2015) summarised prevalence rates from multiple studies with different definitions of PD and populations (school-aged adolescents), Armour et al. (2019) pooled data from 38 heterogeneous studies (examining prevalence and academic impact of PD) in a meta-analysis and Itani et al. (2022) estimated PD prevalence using secondary data from the global severity of disease analysis. In studies that have employed more structured sampling approaches, for example Olubunmi et al. (2016), used age-stratified sampling and structured questionnaires, severe menstrual pain was reported in 54.7% of women aged 13-20 years, 53.7% of women aged 21-30 years, and 57.3% of women aged 31-44 years. However, across this literature, PD symptom reporting has frequently been generalised across the MC rather than anchored to or prospectively collected during the menstruation phase.

Current evidence on factors influencing pain severity in PD remains limited, though emerging research points to a complex interplay of hormonal regulation and prostaglandin activity (Abu Helwa et al., 2018; Sundari et al., 2020; Zhou et al., 2018). For example, hormonal dysregulation has been proposed by researchers to have a role in PD pathophysiology. Previously, Liedman et al. (2008) reported that women with PD exhibited elevated oxytocin and FSH levels, altered vasopressin during ovulation, and increased E2 concentrations in the late follicular phase. However, within the research on PD, the concentration of prostaglandins before or during menstruation remains a key focus in understanding PD pain. Prostaglandins are hormones synthesised from fatty acids, primarily arachidonic acid, and are released from phospholipids in cell membranes when progesterone levels drop before menstruation (Kulkarni & Deb, 2019). Previous research has noted that the overproduction of prostaglandins can lead to uterine ischemia, hypoxia, and increased nerve sensitivity (Barcikowska et al., 2020). A review from Zhou et al. (2018) reported that prostaglandin F2α levels were significantly higher in women with PD, and this was positively correlated with the degree of pain they experienced. Dietary composition may also influence prostaglandin synthesis, particularly through increased intake of saturated and trans fats and additives, which could increase arachidonic acid availability, leading to greater prostaglandin production and thus more intense uterine contractions (Sundari et al., 2020). However, this evidence is limited, as the study was observational and relied on self-reported dietary habits, making it difficult to establish a clear causal relationship between diet and cramps. Although prostaglandin activity is a central physiological mechanism for PD, it does not fully account for the variability in severity experienced by menstruating individuals.

In addition to the biological mechanisms, lifestyle and behavioural factors such as dietary behaviours have been associated with PD severity. In a study investigating dietary behaviours, low intake of fruits and vegetables and frequent consumption of fast food were associated with increased severity of PD (Bajalan et al., 2019). Similar results were reported by Sundari et al. (2020) who found that 92.4% of participants (n = 262 adolescents) experienced PD, and 96.4% of these individuals had a poor diet. Further evidence from a cross-sectional study by Abu Helwa et al. (2018), in 956 women surveyed, reported that 85.1% experienced PD. Among those with PD, 80.3% reported moderate-to-severe PD. The study identified behavioural factors, specifically stress and skipping breakfast, as being associated with increased pain severity. However, these findings contrast with a systematic review of 77 studies, which reported no association between skipping breakfast and PD severity (Mitsuhashi et al. (2022). While similar results exist across these various studies, most rely on self-reported measures of diet history and PD severity, which may introduce recall bias and limit the ability to infer causality (Kim, 2024). Despite this, researchers have reported that intake of vitamins D and B12, vitamins that have roles in anti-inflammatory pathways (Fenercioglu, 2024; Simonenko et al., 2024) and prostaglandin regulation, provides a plausible pathway through which diet may modulate PD symptoms. For example, in a cross-sectional study of 321 women, Naraoka et al. (2023) investigated how lifestyle factors and nutrient intake were associated with the severity of PD and HMB. Nutrient intake was assessed using a brief self-administered diet history questionnaire (BDHQ). Lifestyle factors, including exercise, sleep and breakfast consumption, were captured through a research-developed questionnaire. Women with severe pain had significantly lower intake of animal proteins, vitamin D, and vitamin B12, along with reduced frequency of breakfast. However, in this study, dietary intake was self-reported using the BDHQ, without serum verification of nutrient status. This is a particular limitation, particularly for vitamin D, as dietary sources from intake alone are unreliable unless supplementation is considered, which was not accounted for in this study.

Fatigue is a disabling symptom, commonly reported by women throughout their MC, alongside PD (Abu Helwa et al., 2018; Li, Denson, & Graham, 2020). Women report greater fatigue prevalence compared to men, with evidence suggesting that mental fatigue tends to increase during the luteal phase (Li, Lloyd, & Graham, 2020). It is proposed that hormonal fluctuations in E2 and progesterone may influence fatigue, but the exact mechanisms remain unclear and require further investigation. Regardless, in previous longitudinal research in four randomised testing sessions across the MC phases, Peltonen et al. (2022) reported that neuromuscular fatigue varied across the MC. Specifically, they reported that women experienced greater fatiguability and reduced muscle

activation in the mid-luteal phase compared with the ovulatory and menstruation phases. Similarly, a prospective study of 100 healthy young women with regular MCs reported improved fatigue resistance and peak muscle strength during the follicular phase compared to both the luteal and menstrual phases (Pallavi et al., 2017). Conversely, Janse de Jonge et al. (2001) in their study of muscle function throughout the MC found no significant changes in fatigability across MC phases. In addition, no correlations between muscle fatigability and hormone concentrations were reported throughout the MC. It is noted that these studies focused predominantly on athletic performance in young women and did not generalise to broader populations or capture the subjective experience of fatigue outside of sports contexts (Janse de Jonge et al., 2001; Pallavi et al., 2017; Peltonen et al., 2022). Therefore, future research is needed on fatigue across the MC in broader populations, including non-athletic women, to better understand how menstruation can influence both perceived and performance-based fatigue.

The underlying factors driving the prevalence and severity of physical symptoms experienced during menstruation are still not well understood. Much of the existing research has approached symptoms across the MC, not in isolation during the menstrual phase. As a result, it remains unclear how symptoms such as PD and fatigue are specifically experienced during menstruation. In addition, the interaction of lifestyle factors such as ID and how these may impact the severity of physical symptoms women experience during menstruation requires further research.

2.2.4 Risk Factors That Impact the Severity of Menstrual Cycle Symptoms in Healthy Women

Within the literature, HMB is a well-recognised variation in menstrual bleeding. It is defined within research as excessive menstrual blood loss of ≥ 80 mL per cycle (Davies & Kadir, 2017), which can interfere with an individual's physical, emotional, social, and/or material QoL (Thiyagarajan et al., 2022). There is growing recognition that HMB may contribute to the severity of common menstruation-related symptoms, including dysmenorrhoea, fatigue, and psychological changes (Kocaoz et al., 2019; Pouraliroudbaneh et al., 2024; Vannuccini et al., 2023). In a cross-sectional study where women self-reported their symptoms, higher scores of fatigue severity were associated with heavier bleeding (Kennedy et al. (2022). Research by Kocaoz et al. (2019) found similar results, identifying that fatigue was common among women with HMB, with a prevalence rate of ~38%. These results also align with Wang et al. (2013) who in a cross-sectional study of 48 adolescents with HMB and 102 healthy controls, found that fatigue severity scores were significantly higher in those with HMB. However, within this previous research, specific prevalence rates for fatigue were not consistently reported, with the authors instead relying on fatigue severity scores. Despite this,

collectively these findings demonstrate an association between HMB and fatigue; however, contributing lifestyle factors (e.g., dietary intake or ID) and mechanisms linking menstrual volume and symptom severity remain underexplored.

Body weight may be a possible factor that affects menstruation-related symptom severity, particularly in relation to PD. Previously, Mitsuhashi et al. (2022) reported that low body mass index (BMI) (<18.5 kg/m^2) was associated with increased prevalence and severity of PD, possibly due to disrupted energy availability affecting reproductive hormone regulation. However, findings remain inconsistent. Conversely, Naraoka et al. (2023) found no significant correlation between BMI and PD severity, suggesting that BMI alone may be an insufficient marker for understanding symptom severity. Recent studies have explored fat and lean mass as potential contributors to menstrual symptoms. In a narrative review, Syeda Farha et al. (2023) noted that emerging evidence suggests an association between higher body fat percentage and increased severity of PMS, with adipose tissue acting as an endocrine organ that produces inflammatory mediators and hormones such as leptin. Here, it was proposed that leptin may influence gonadotropin regulation, potentially exacerbating menstrual symptoms. It should be noted that this previous research focuses on PMS and the physiological mechanisms of PMS, such as inflammation and hormone regulation. However, these mechanisms may be relevant to PD during the premenstrual phase. Interestingly, Tembhurne and Mitra (2016) demonstrated a statistically significant association between both BMI and body fat percentage with PD severity through their cross-sectional observational study. Ninety women were assessed using a body composition scanner and a verbal dysmenorrhoea scale, with findings indicating that higher adiposity was linked to more severe PD. However, the study's small, single-centre sample, reliance on subjective symptom ratings, and lack of control for confounding factors, such as physical activity and menstrual regularity, limit the validity and broader applicability of these findings. In contrast Singh et al. (2015) conducted a comparative cross-sectional study of 60 women (30 with PD, and 30 eumenorrheic controls), assessing body composition across menstrual phases using bioelectrical impedance analysis (BIA). Although the PD group had higher body fat and lower lean mass, no statistically significant differences were reported. Beyond menstrual symptoms, body composition has also been linked to broader physiological outcomes such as self-perceived fatigue. Higher fat mass and lower physical performance were associated with greater self-reported fatigue in a cross-sectional study of 452 adolescents, measured using the Multidimensional Fatigue Inventory (MFI-20 (Vantieghem et al., 2018). While the findings suggest a link between adiposity and fatigue, the use of a school-based sample and a fatigue tool not validated in obese adolescents limits generalisability (Vantieghem et al., 2018). The study nonetheless offers preliminary evidence for a

potential relationship between body composition and fatigue. Some researchers have suggested that low BMI could influence reproductive hormone regulation via energy availability, though this remains a hypothesis (Mitsuhashi et al., 2022). Overall, body composition may be relevant to menstrual symptom severity, but current evidence is limited and inconsistent, suggesting the need for further research to clarify potential associations.

There has been limited research regarding the severity of psychological symptoms during the MC. Despite this, HMB has been associated with higher rates of depression and anxiety (McGrath et al., 2021). In a retrospective record review, Sarkar et al. (2021) reported a bidirectional relationship over two years. Specifically, 65.3% of adolescents with HMB also experienced moderate to severe depression, and 42.8% of adolescents with moderate to severe depression experienced HMB. Similarly, in Kennedy et al. (2022) cross-sectional study, using validated surveys (PHQ-9 for depression and the Perceived Stress Scale, PSS), each point scored on the PSS or PHQ-9, was associated with a 3% increased likelihood of also experiencing HMB. Moreover, in a retrospective cohort study, Weyand et al. (2022) collected medical records over 23 months and reported that 50.9% of the adolescents with HMB also experienced depression, compared to 24.2% of those without HMB. In Vannuccini et al. (2020) cross-sectional observation study of elite female athletes, it was observed that HMB was associated with more severe psychological symptoms, such as poorer mental health and higher stress. However, the specific population measured in this study limits the broader applications of these results to women in the general population. Additionally, Naraoka et al. (2023) conducted a cross-sectional study with 321 women, and found that higher stress levels were associated with increased severity of PD and HMB. Cumulatively, these findings would suggest an increased risk of psychological symptoms when HMB is self-reported; however, prospective studies are needed to help understand whether women experience increased psychological or physical symptom severity when menstrual bleeding is present.

Symptoms such as HMB, psychological changes, cramps, and fatigue are common during the MC. The extent to which menstruation symptoms are influenced by objectively measured nutrient status remains unclear and under-investigated. While iron's role, particularly in relation to HMB, is well established (Munro et al., 2023), less is known about how iron status may affect the prevalence and severity of menstruation-related symptoms in otherwise healthy women. Although some studies have explored associations between dietary intake and symptom severity (Sundari et al., 2020), dietary intake alone does not reliably indicate nutrient deficiency unless supplementation or serum biomarkers are considered.

2.3 Iron Deficiency in Premenopausal Women

Iron deficiency is the most common micronutrient deficiency worldwide, and the leading cause of anaemia in developed and developing countries (Fernandez-Jimenez et al., 2020). The population groups most at risk of ID include women of reproductive age and postpartum women, due to increased iron demands, regular menstrual blood loss, and lactation (WHO, 2023). Iron deficiency is the depletion of the body's iron stores, particularly within the macrophage and hepatocyte stores, and can occur despite Hb levels remaining within the normal range (Camaschella, 2019). Because most of the body's iron is used for red blood cell production, untreated ID will often lead to iron deficiency anaemia (IDA) (Percy et al., 2017). Iron deficiency anaemia is a more advanced stage of ID, defined by the reduced number or size of erythrocytes and/or low Hb concentrations, which is typically accompanied by changes in red blood cell structure (Percy et al., 2017). Haemoglobin is required to carry oxygen, and if there is not enough, abnormal red blood cells, or insufficient Hb, the blood's capacity to transport oxygen to the body's tissues decreases (Kumar et al., 2022). Globally, IDA is estimated to affect around half a billion women aged 15-49 years. In 2019, an estimated 30% (539 million) of non-pregnant women and 37% (32 million) of pregnant women aged 15-49 years were affected by IDA (WHO, 2023).

Menstruation can contribute to iron depletion in women, as each millilitre of peripheral blood lost contains approximately 0.5 mg of iron (Percy et al., 2017). Common symptoms of ID include fatigue, behavioural changes, cognitive difficulties, dizziness, muscular weakness, insomnia, restless leg syndrome, pica, and alopecia (Munro et al., 2023). Once IDA becomes apparent, symptoms can manifest as persistent fatigue, dyspnoea, tachycardia, skin pallor, cold extremities, and delayed capillary refill (Clark, 2009).

Many of these symptoms are also experienced by individuals with HMB, as elevated peripheral blood loss with menstruation can significantly contribute to the development and worsening of ID/IDA (Percy et al., 2017). Research has focused primarily on the association between ID/IDA and HMB. However, there is limited research on how iron status might influence the self-reported frequency and severity of menstruation-related symptoms.

2.3.1 Symptoms of Iron Deficiency

Even in the absence of IDA, ID in otherwise healthy women can cause a range of symptoms that may be overlooked or mistaken for normal fluctuations in energy or emotions (Sawada et al., 2014). Several of these symptoms, particularly fatigue and emotional changes, are also frequently

reported during the MC, as discussed earlier. The commonality in symptoms could complicate the identification of ID in menstruating women.

Fatigue is one of the most commonly reported symptoms experienced by healthy women with ID, even without anaemia (Sawada et al., 2014). In a large-scale cross-sectional study by Patterson et al. (2000), data from over 28,000 Australian women demonstrated that those reporting a history of low iron consistently scored lower on physical, mental, and vitality scales, with young women showing a higher prevalence of constant tiredness (67%) compared to their non-ID peers (45%). However, the study's reliance on self-reported iron status may have led to recall bias within the data, while the cross-sectional design limits causal inference. Moreover, the term "low iron" was not clinically defined, raising uncertainty around the severity of deficiency required to manifest fatigue (Patterson et al., 2000).

Additional research has demonstrated an association between ID and fatigue in otherwise healthy women (Greig et al., 2013). A review of studies that used validated QoL instruments, including the General Health Questionnaire and Piper Fatigue Scale, consistently reported higher fatigue levels in women with ID compared to non-ID controls (Greig et al., 2013). These findings reinforce that ID, even without anaemia, can lead to an increase in women's self-reporting fatigue (Sawada et al., 2014). Whilst fatigue as a symptom of ID and the impacts of this symptom have been investigated, there is no research on whether fatigue in ID women is greater during menstruation compared to non-ID menstruating women.

Several studies have examined the relationship between ID and emotional changes in women, but findings remain mixed. A review by Greig et al. (2013) identified five studies assessing mental health outcomes, three of which reported poorer emotional well-being in ID participants compared to iron-sufficient controls. However, the quality of the evidence varied, as some studies did not use validated tools. Only one study from Patterson et al. (2001) used validated assessment tools (Piper Fatigue Scale and the SF-36) in a randomised control trial involving 66 women, including 44 who were ID. The ID participants showed significantly lower mental health and vitality scores and higher fatigue compared to the iron-replete controls. Moreover, in a study by Ballin et al. (1992), who conducted a double-blind placebo-controlled trial in 59 adolescent girls (aged 16-17), with 29 receiving iron supplementation and 30 receiving a placebo, subjective improvements in mood, concentration and energy amongst those receiving iron supplements were reported. However, within this study, the outcomes were based on subjective self-reports of the participants. Similarly,

Månsson et al. (2005) studied a cohort of upper secondary school students, of which 12% were diagnosed with ID. Using a 30-item symptoms checklist, the study reported reductions in dizziness, irritability, and low mood following iron supplementation for three months. While all three studies suggest emotional symptoms may improve with restored iron status, the majority of this research has collected self-reported emotional symptom data and not used validated surveys or tools to quantify the change in emotions (Ballin et al., 1992; Månsson et al., 2005). Despite some evidence linking ID to emotional symptoms, existing research has primarily focused on symptoms directly associated with the nutrient deficiency itself. The extent to which menstruation-related symptoms differ among individuals based on their iron status, and whether ID influences the self-reported frequency or severity of these symptoms, remains unexplored.

Table 2.1 *Studies Exploring the Relationship Between HMB, ID, and menstruation-related Symptom Severity*

Author	*Population*	*Design*	*Methodology*	*Results*
(Bernardi et al., 2016), USA	44 pre-menopausal females, mean age 37.9 years ± 9. 4	Quantitative cross-sectional pilot study	• A 44-item survey assessed menstrual flow, IDA symptoms. • Blood was collected for iron studies. • IDA was defined as Hb as <11.6 g/dL • ID defined as SF <41 ng/mL.	• 35% of HMB were anaemic • Women with HMB had significantly lower Hb and SF levels
(Bruinvels et al., 2016), UK	1862 pre-menopausal females, aged ≥18 years	Cross-sectional survey	• Online + in-person surveys using a 12-item 'Female Health Questionnaire' assessed HMB & self-reported IDA.	• 54% reported HMB • IDA self-reported by 32.4% of participants • Self-reported IDA in 40.7% of HMB participants ○ 26% of non-HMB had self-reported IDA

(MacLean et al., 2025), Australia & UK	1937 non-pregnant females, aged 18-50	Cross-sectional survey	• Data was combined from five studies. Participants completed a 'Female Health Questionnaire' assessing iron risk factors.
			• Four-item questionnaire used to assess HMB. Two or more HMB symptoms = HMB.
			  1. Needing frequent changes of sanitary products (every 2 h or less)
			  2. Passing large clots
			  3. Needing double sanitary protection
			  4. Flooding through clothes or bedding
			• IDA was defined as Hb <120g/L via finger-prick (Haemocue BioRad 801)
				• 33.7% reported HMB
				• IDA was present in 13% of participants
				• Mean Hb concentration was 133.5 ± 12.3 g/L
				• Participants with HMB had higher rates of IDA

(Pita-Rodríguez et al., 2023), Cuba	742 reproductive-aged females, aged 18-40	Cross-sectional survey	• Participants completed 'Survey of Symptoms during Your Monthly Period' questionnaire. Included: - Bleeding amount	• 19.8% self-reported HMB • 7.4% reported non-HMB (acute bleeding) • 21.4% of participants had IDA • Anaemia was present in 55.4% of HMB

Author	*Population*	*Design*	*Methodology*	*Results*
			- Bleeding frequency - Duration of bleeding - Regularity of MC • Blood drawn by antecubital puncture before questionnaire administered • IDA defined as Hb < 120 g/L • ID defined as SF concentration < 15 µg/L.	• IDA was associated with HMB
(Toheed et al., 2017), Pakistan	317 pre-menopausal females, aged 10-19	Observational cross-sectional study	• Convenience sampling used over a six-month period. • Menarche and menstruation-related symptoms details were collected. • IDA was defined as haemoglobin <12 g/dL.	• 15.8% reported 'irregular' heavy bleeding • 3.5% reported heavy 'regular' bleeding • 50.6% participants had IDA • HMB (regular or irregular) was significantly associated with IDA • PD was present in 57.9% IDA participants o IDA was seen in 52% of women with PD
(Bano, 2012), Saudi Arabia	700 pre-menopausal females, aged 10-15	Cross-sectional survey	• Participants completed a pre-tested questionnaire in a classroom. Questions included: - Menarche age - Severity of PD - Use of analgesics - Medical attention • A 24-hour dietary recall to estimate daily iron intake • Blood sample and clinical pallor assessment conducted by medical professional	• 33.7% of participants had IDA • A positive correlation between IDA and PD was found o IDA increased with PD severity o 61/143 participants with PD had moderate to severe IDA, compared to 3/15 participants with no PD

Author	*Population*	*Design*	*Methodology*	*Results*
			• IDA was classified by Hb concentration and severity of pallor.	
(Janapriya et al., 2024), Indonesia	103 pre-menopausal females, ages 16-18	Correlational, descriptive, cross-sectional study	• WaLLID Score questionnaire used to measure PD • DASS-21 questionnaire was used to measure depression and anxiety • Hb levels were measured using a digital Hb metre	• 44.7% of participants had PD • 47.5% had IDA • Very strong relationship between Hb levels and incidence of PD ○ Lower Hb level, the higher intensity of pain felt for PD
(Hasnia et al., 2024), Indonesia	132 pre-menopausal females, aged 15-18	Observational analytic, cross-sectional research study	• WaLIDD score questionnaire was used to measure PD participants, • Easy Touch GCHb haemoglobin test kit was used to test for Hb • Hb for IDA was <12 gr/dL.	• 34% had participants had IDA • 91.7% participants had PD ○ 100% of IDA participants experienced PD (n = 45) • Significant association between IDA and PD

(Hidese et al., 2018), Japan	5185 females, mean age,
	45.1 ± 13.6 years, with no history of depression
		Cross-sectional survey	• Participants' entered Health Data Lab database based on questionnaires provided by Genequest Inc.
			• Depression, ID, and other illness were identified based on participants' self-report to "have you ever had that illness?"
				• IDA prevalence:
				  ○ Women with depression: 33.4%
				  ○ Women in control group: 25.8%
				• K6 scores were positively associated with self-reported history of IDA
				• Self-reported history of IDA is associated with higher psychological distress

Note. DASS = Depression Anxiety Stress Scales; GCHb = Glycated Haemoglobin test; Hb = Haemoglobin; HMB = Heavy menstrual bleeding; ID = Iron deficiency; IDA = Iron deficiency anaemia; K6 = Kessler Psychological Distress Scale; MC = Menstrual cycle; PD = Primary dysmenorrhoea; WaLLID = Weighted analgesia Level Index for Dysmenorrhoea.

2.3.2 Association Between Iron Status and Menstrual Cycle Symptoms.

Although pain, fatigue, and psychological changes are common during the MC and in ID/IDA, research into these symptoms has typically examined them in isolation rather than in combination. This has resulted in a substantial research gap, with limited evidence exploring how iron status may influence the prevalence and self-reported severity of menstruation-related symptoms. Given the overlapping of symptom profiles, further research is needed to investigate the interactions between ID and the self-reported severity and frequency of menstruation-related symptoms. The following section will discuss the limited research available that provides some initial insights on the degree of overlap in symptoms between the MC and ID, drawing on studies summarised in Table 2.1.

As menstrual blood loss increases, SF levels decline, often falling below diagnostic thresholds of <30 µg/L for ID (Mansour et al., 2021). Although an SF threshold of <15 µg/L is standard in New Zealand healthcare, this lower cutoff may underestimate the ID in menstruating individuals, prompting the use of <30 µg/L in this study (Ngan, 2005). Studies consistently report an association between HMB and ID/IDA (Bruinvels et al., 2016; MacLean et al., 2025; Pita-Rodríguez et al., 2023), with reports indicating that up to 80% of women who have HMB may be affected by ID. However, much of this evidence is derived from cross-sectional studies, many of which rely on self-reported bleeding severity and anaemia status, limiting the reliability of these studies due to the potential influence of recall bias on the results (Bernardi et al., 2016; Toheed et al., 2017). Additionally, Bruinvels et al. (2016) recruited convenience samples, such as online respondents and elite athletes, and subsequently, their results may not be fully representative of the general population. Despite these limitations, the association between HMB and ID/IDA is consistent across studies, as demonstrated in Table 2.1. Given that a third of menstrual bleeders may report experiencing or have had a previous diagnosis of ID (Bernardi et al., 2016), further research is needed to explore the impact of ID on the self-reporting of other symptoms, such as fatigue, emotional changes, and PD, which may be commonly self-reported by women within the menstrual phase of the MC.

Several studies have found a strong association between IDA and increased PD prevalence and severity, with PD reported in 44.7% to 91.7% of premenopausal females (Bano, 2012; Hasnia et al., 2024; Janapriya et al., 2024; Toheed et al., 2017). In research by Hasnia et al. (2024), all anaemic participants were reported to experience PD. Similarly, Toheed et al. (2017) found that over half of the anaemic female adolescents within their study reported suffering from PD. However, it should be noted that Hasnia et al. (2024) did not report when this testing was completed within the MC (e.g., which phase of the cycle), or whether IDA was diagnosed using Hb alone. Regardless of these previous study limitations, Bano (2012) also reported that lower iron intake was associated with

more severe PD. It has been proposed that in IDA, impaired oxygen delivery may exacerbate ischaemia and hypoxia in uterine tissues during menstruation, lowering pain thresholds and intensifying menstrual cramps (Janapriya et al., 2024). While this proposal provides a possible explanation for the interaction between IDA and PD self-reported severity, the exact causal mechanisms remain unclear and are still subject to further investigation. In addition to PD, it is also important to consider broader experiences of pelvic pain during menstruation. While this thesis focuses on PD, the author recognises that further research is needed to determine whether pelvic pain or PD severity differs between those with and without IDA.

Fatigue is a common symptom experienced in both ID and throughout the MC (Li, Lloyd, & Graham, 2020), making it difficult to determine its primary cause. However, few studies have explored whether there is an association between fatigue related to ID/IDA and fatigue associated with the MC. A meta-analysis from Yokoi and Konomi (2017) found inconsistent evidence between ID and fatigue. The association between ID and fatigue remains unclear, as shown by Sawada et al. (2014), whose cross-sectional analysis reported inconsistent findings and offered no definitive insight into whether an ID diagnosis exacerbates feelings of fatigue in menstruating women. Therefore, whether fatigue associated with ID/IDA is consistent throughout the MC or predominantly occurs during specific phases, such as the luteal phase and menstruation, remains unclear and requires further study.

A limited number of studies have examined how ID may influence the severity of menstruation-related symptoms. Most existing research treats ID solely as an outcome of HMB, rather than as a possible contributing factor to the severity of symptoms experienced during the MC. Consequently, there is a need for further research to determine whether differences in iron status are associated with differences in MC and menstruation-related symptom frequency and self-reported severity. Additionally, many studies do not explicitly distinguish whether participants experience heavy or light bleeding, nor do they analyse menstruation-related symptoms based on bleeding severity. This lack of differentiation limits understanding of how menstrual bleeding patterns may influence menstruation-related symptoms. Finally, menstruation-related symptoms can vary between women. Much of the available research has focused on menstruation-related symptom severity prior to (premenstrual) and not during menstruation, or considered how iron status could influence self-reported symptoms frequency and severity that women report while menstrual bleeding is present. As such, this remains an area in need of future research.

2.4 Summary

This review has highlighted the variability in symptom frequency and self-reported severity experienced by women throughout their MC, including the premenstrual phase. Symptoms such as PD, HMB, fatigue, and emotional/psychological symptoms such as anxiety, depression, and stress are commonly reported (Schoep et al., 2019). The review also discussed the high prevalence of ID and IDA among premenopausal women. However, to the best of the authors' knowledge, few studies have evaluated whether iron status influences the self-reported severity of menstruation-related symptoms.

Although symptoms such as fatigue, PD, and psychological changes are commonly reported by menstruating women (Maheshwari et al., 2023), there are limited studies into whether menstruation-related symptom severity and frequency differ between women with heavy versus light menstrual bleeding. Future research should aim to assess iron status in conjunction with menstruation-related symptoms (e.g., fatigue, PD, emotional changes) to better understand the influence of ID on self-reported symptom frequency and severity. This may inform more targeted education, prevention, and support strategies for those affected by ID and menstruation-related symptoms. Given the complex interplay between iron status and menstrual health, further exploration is crucial to enhance women's understanding of their bodies and improve symptom management during menstruation.

Chapter 3 Research Study Manuscript

3.1 Abstract

Objectives: Iron deficiency (ID) and heavy menstrual bleeding (HMB) may exacerbate menstrual cycle symptom severity during menstruation. However, few studies have prospectively examined these relationships. This study aimed to describe menstruation-related symptoms and evaluate whether iron status and self-reported bleeding heaviness influenced symptom severity.

Methods: Ninety-seven naturally menstruating women aged 18-40 residing in Aotearoa/New Zealand completed daily symptom surveys and self-reported bleeding heaviness during menstruation for up to five cycles. Symptom severity was rated on a five-point Likert scale, and daily menstrual bleeding was rated as scant, moderate or heavy. Venous blood samples were collected at baseline and at the end of the study (mid-luteal phase of the last cycle of data collection) and were analysed for haemoglobin (Hb), C-reactive protein (CRP) and serum ferritin (SF). Iron deficiency was defined as SF <30 μg/L and Hb ≥120 g/L. Body composition was measured using bioelectrical impedance analysis (BIA) at baseline and at the end of the study. Group differences in symptom severity were analysed using Wilcoxon rank-sum tests. A multiple linear regression was completed to determine associations of overall symptom severity with iron status and self-reported bleeding heaviness.

Results: Overall symptom severity during menstruation in this cohort of women was low. Fatigue/tiredness (median 1.78 [1.43-2.33], $p = 0.003$), abdominal cramps (1.21 [0.57-1.69], $p = 0.013$), and reduced concentration (median 0.77 [0.28-0.91], $p = 0.006$) were higher in self-perceived HMB compared to self-perceived non-heavy bleeders. Iron deficient participants reported higher severity for fatigue (median 1.50 [1.11-2.33], $p = 0.001$), musculoskeletal pain (joint pain [0.43 (0.13-0.99)], and lower back pain [0.66 (0.42-0.95], both $p = 0.002$), and dizziness (median 0.61 [0.28-1.13], $p = 0.003$). Results from the regression analyses found that self-perceived HMB ($B = 6.181$, $p = 0.002$) independently predicted overall symptom severity.

Conclusion: Women who perceived themselves to have HMB reported higher symptom severity, as bleeding heaviness independently predicted menstruation-related symptom severity. Iron deficiency did not significantly predict overall symptom severity during menstruation. Integrating an assessment of bleeding patterns into menstrual health assessments may improve the identification and management of women who may be at risk of severe menstruation-symptoms.

3.2 Introduction

The menstrual cycle (MC) involves cyclical hormonal and physiological changes, where fluctuations in oestradiol (E2) and progesterone can initiate ovulation and prepare the body for potential pregnancy (Thiyagarajan et al., 2022). Menstruation marks the beginning of the MC and is characterised by menstrual fluid loss and low levels of steroid hormones, oestrogen and progesterone (Thiyagarajan et al., 2022). Commonly reported MC symptoms include abdominal pain, mood/emotional changes, and fatigue, the severity of which is highly individual between women (Schoep et al., 2019). Despite the high prevalence of these symptoms reported by women throughout their MC, much of the existing literature focuses on the premenstrual phase, describing the symptom profiles of women with premenstrual syndrome (PMS) or premenstrual dysmorphic disorder (PMDD) (Delara et al., 2012; Rapkin & Winer, 2009). Consequently, the symptoms experienced and their self-reported severity during menstruation in otherwise healthy women remain unexplored (Delara et al., 2012).

Menstrual cycle symptoms have been shown to adversely influence quality of life (QoL), and have been reported to negatively impact physical, emotional, and social wellbeing (Bitzer et al., 2013; Iacovides et al., 2014; Lukes et al., 2012; Schoep et al., 2019). Primary dysmenorrhoea (PD), defined as lower abdominal pain without underlying pelvic pathology, for example, has been associated with reduced academic performance, concentration difficulties, and absenteeism (Armour et al., 2019; Hashim et al., 2020). Similarly, women experiencing HMB often report elevated stress, fatigue and poorer QoL (Kocaoz et al., 2019). While symptom variability among women is well documented, the underlying contributors to these differences remain poorly understood. Factors such as menstruation flow rates (e.g., scant or heavy) and iron status may influence symptom perception and overall wellbeing, yet these relationships have not been comprehensively investigated in healthy regularly menstruating women.

Menstruation contributes to increased iron requirements in women of reproductive age (Tang et al., 2025). Menstrual fluid loss can vary both between individuals and across cycles (Habiba & Benagiano, 2023). The causes of abnormal uterine bleeding (AUB) in non-pregnant women can be classified using the PALM-COEIN system, which categorises AUB aetiologies into structural (polyps, adenomyosis, leiomyomas, malignancy) and non-structural (coagulopathy, ovulatory disorders, endometrial, iatrogenic, not otherwise classified) factors, providing a standardised framework for clinical assessment and research (Munro et al., 2018). A key subtype of AUB is HMB, defined as menstrual blood loss exceeding 80 mL per cycle (Hapangama & Bulmer, 2016). It is estimated that HMB may affect up to 50% of women making it one of the most common gynaecological complaints

(Munro et al., 2023). Due to the regular and large volumes of blood lost with HMB, its occurrence is strongly associated with ID. Previous research has suggested HMB may contribute to up to 80% of ID cases in regularly menstruating women (Bruinvels et al., 2016; MacLean et al., 2025; Pita-Rodríguez et al., 2023). Although associations between ID and HMB are well established (Munro et al., 2023; Wang et al., 2013), no studies to date have examined how iron status or HMB contribute to self-reported menstruation-related symptom severity among menstruating women.

While limited evidence directly explores the relationship between ID, HMB, and menstruation-related symptom severity, existing research has described MC symptoms experienced by women with ID or HMB separately. For example, studies investigating the prevalence of PD in ID women have reported conflicting findings. Hasnia et al. (2024) reported that all participants with iron deficiency anaemia (IDA) experienced PD (n = 45), whereas Toheed et al. (2017) observed IDA in only 52% of their cohort who also reported PD. In the general premenopausal population, reported prevalence rates of PD range between 44.7% and 91.7% (Bano, 2012; Hasnia et al., 2024; Janapriya et al., 2024; Toheed et al., 2017). Although these prevalence rates of PD are comparable between women with and without ID/IDA, it remains unclear whether the presence of ID exacerbates the severity of dysmenorrhoeic symptoms for menstruating women.

Fatigue is a commonly reported symptom among women with HMB, with approximately 38% of women also reporting fatigue (Kocaoz et al., 2019; Wang et al., 2013). A similar pattern has been observed in women with ID. However, standardised prevalence rates among reproductive-aged women with an ID diagnosis are limited; one study observed fatigue in 22.5% of reproductive-aged women with ID (Akkad et al., 2015). In addition to fatigue, emerging evidence suggests that ID is associated with a higher risk of psychiatric disorders (Lee et al., 2020) and psychological symptoms such as anxiety, depression, and stress, which have been reported across the MC (Gonda et al., 2008). Women with ID have also been reported to exhibit higher depressive symptoms compared with non-ID women (Ciulei et al., 2023). Interestingly, mood changes are also frequently reported among women with HMB (Han et al., 2025; Weyand et al., 2022). Such results would align with previous research that has reported psychological symptoms such as anxiety, depression, and stress are common across the MC (Gonda et al., 2008). Despite these parallels across various cohorts of menstruating women and studies within the literature, the combined influence of ID and HMB on self-reported menstruation symptom severity has yet to be elucidated.

Most studies in this field have employed cross-sectional designs, relying on retrospective symptom reporting, which limits the ability to assess temporal variation across the MC or associations between iron status and menstrual fluid loss. Longitudinal data capturing prospective symptom reporting is needed to better understand these relationships. Therefore, the primary aim of this study was to describe the type and self-reported severity of menstruation-related symptoms experienced by naturally menstruating women. A secondary aim was to examine whether iron status and self-reported menstrual flow contributed to differences in self-reported symptom severity between women. It was hypothesised that women with HMB would report a greater severity of menstruation-related symptoms compared to women who reported lighter menstrual bleeds. It was also hypothesised that women with ID, independent of bleeding heaviness, would report a greater severity of menstruation-related symptoms compared to women who were iron sufficient.

3.3 Methods

This was a longitudinal, prospective cohort study of naturally menstruating women residing in Aotearoa/New Zealand. Data collection occurred for up to five consecutive menstrual cycles. Data was collected between July 2023 and March 2025. The study received ethics approval from the Massey University Human Ethics Committee (22/56). Informed consent was obtained from all individual participants included in the study.

3.3.1 Participants and Recruitment

A convenient, snowball sampling strategy was used to recruit women for this study. This was achieved through advertising flyers placed around the Massey University (Albany) campus, student emails, social media posts on the research teams' personal profiles and community group pages, as well as via word of mouth. Prior to participation, individuals who were interested reviewed the study information sheet and completed an online screening questionnaire to ensure they met the study inclusion criteria. Priority ethnicity was assigned according to standard New Zealand reporting conventions, where participants who selected more than one ethnicity were categorised according to the ethnicity order used in national health datasets (e.g., Māori > Pacific Peoples > Asian > Middle Eastern/Latin American/African > European). Individuals were eligible if they were, naturally menstruating, aged 18-40 years, not currently using hormonal contraception or had used within the past six months, not pregnant, breastfeeding, or had been pregnant or breastfeeding within the previous 12 months, had not smoked, or taken iron supplements in the past two months, and did not have a pre-existing medical condition known to affect iron metabolism or menstrual function. Individuals who had undergone surgery that could affect the normal functioning of their reproductive system and hormones, or who anticipated changes to reproductive structure or

function (e.g., pregnancy, hormonal contraception use, other hormonal medication, medically diagnosed polycystic ovary syndrome) during the study period were also excluded. Following screening, eligible participants provided contact details, which were used by the research team to share study information and schedule the initial familiarisation testing session. A total of 694 women were screened, and 385 were deemed eligible for study participation. A total of 115 participants enrolled in the study. From this, 18 withdrew, resulting in a final sample of 97 participants included in the analysis. Reasons for withdrawal included medical issues (n = 6), pregnancy (n = 2), and other lifestyle factors (n = 10). The withdrawal rate for this study was 15.7% and the compliance rate was 84.3%.

The sample size was calculated using the formula $n = Z^2 \cdot p \cdot (1-p) / d^2$. Based on an estimated prevalence of ID of 30% in the population of reproductive age (Fernández-Gaxiola & De-Regil, 2019; WHO, 2023), a 10% margin of error, and a 95% confidence level (Z = 1.96), a minimum of 81 participants was determined to be adequate.

3.3.2 Study Procedures and Data Collection

Participants attended a familiarisation session, during which they were provided with detailed information about the study and were given the opportunity to ask questions. Once all participant questions were answered, written informed consent was obtained from each individual. Participants completed a baseline questionnaire capturing demographic information and MC history. Body composition was then measured using bioelectrical impedance analysis (BIA). A resting venous blood sample was then collected for baseline iron status, including haemoglobin (Hb), serum ferritin (SF), and C-reactive protein (CRP), to assess iron status and inflammation.

Following the familiarisation session, the research officer was notified at the onset of the participant's next menstrual bleed. This bleed marked the commencement of the MC data collection for the study. A link to the online daily survey was sent to the participant via email or text message on days when menstrual fluid loss was visibly present. The participants were asked to complete this daily survey each night. This survey collected information on the participants' self-reported bleeding heaviness, physical and emotional symptoms, and the self-reported severity of these symptoms. This daily data on days of visible menstruation was collected for up to five consecutive MCs. Full details of surveys used can be found in Appendix A.

For this study, the final session was conducted in the mid-luteal phase of their last cycle of data collection. Which for the majority of participants (85.6%) was the fifth consecutive cycle of data

collection. The mid-luteal phase for data collection was scheduled seven days following a positive urinary luteinising hormone (LH) test or approximately five days before the onset of the next menstrual bleed. During this session, participants underwent a second body composition assessment and provided a resting venous blood sample.

3.3.2.1 Anthropometry and Body Composition

Height was measured to the nearest centimetre using a stadiometer. Body composition was determined using a BIA (InBody 230, Seoul, South Korea) following a 2-hour food and water fast. The measurements of interest included weight, muscle mass, per cent body fat, fat-free mass, and total body water. Body mass index (BMI) was calculated by dividing the participant's weight (kg) by their height squared (m^2). For the analysis of body composition in this study, baseline body composition was used and served as the reference for the analysis between iron status and menstrual bleeding groups.

3.3.2.2 Survey Instrument

To assess daily menstruation symptoms and perceptions of menstrual fluid loss, participants completed a custom online questionnaire hosted on the Massey University Qualtrics account. The survey captured whether bleeding was present, participants' self-rated menstrual blood flow (scant, moderate, or heavy), and their perception of whether blood loss was normal. Previously, this form of data collection, specifically self-reported menstrual flow rates, has been shown to be a valid measure of menstrual blood loss in research settings (Russo et al., 2024). The daily survey also included a comprehensive MC symptom list, including physical and emotional symptoms, such as cramps, fatigue, mood changes, and bloating. The severity of the symptoms experienced was rated on a five-point Likert scale, ranging from "none at all" to "a great deal." The symptom survey used in this study was adapted from previous research by Bruinvels et al. (2021), as no validated tool currently exists to capture daily menstruation-related symptoms and their self-reported severity.

3.3.2.3 Blood Sample Collection and Analysis

Venous blood samples were collected during the familiarisation session and the participant's final visit. Blood samples were collected from participants at rest from the antecubital vein by a trained phlebotomist. Samples were collected using a 23-gauge butterfly needle into two plasma separator tubes (PST) and immediately inverted slowly eight times to ensure clotting did not occur prior to anticoagulation. Haemoglobin was measured on site at Massey University (Albany) from whole blood using the HemoCue® Hb 201+ System. The blood samples were centrifuged within 30

minutes of collection at 4°C at 2000 RCF for 10 minutes. Plasma supernatant was divided into 1-2 ml aliquots and stored at -80°C until analysis.

Batches of 100 plasma samples were periodically sent to a commercial lab (Auckland LabPlus) for analysis. Serum iron was analysed using an *in vitro* quantitative assay on COBAS C and COBAS INTEGRA systems, CRP was analysed by immunoturbidimetric assay, and SF was analysed using validated automated electrochemiluminescence immunoassays (ECLIA) on a Roche COBAS analyser (Elecsys Ferritin assay, Roche diagnostics). Manufacturer-reported intra- and inter-assay coefficients of variation were ≤1.5 and ≤2.3% for serum iron, ≤3.0 and ≤4.5% for CRP, and ≤6%, ≤4.7% and ≤4.4% for SF, respectively. Total iron binding capacity (TIBC) was determined as part of routine iron studies. Transferrin saturation (TSAT) was calculated as serum iron divided by TIBC and expressed as a percentage. All assays were performed as single analytical measurements in accordance with manufacturer instructions and accredited laboratory procedures. For this study, ID was defined as iron deficiency without anaemia, characterised by SF <30 µg/L and Hb ≥120 g/L, and iron sufficiency as SF ≥30 µg/L and Hb ≥120 g/L (Clénin, 2017).

3.3.4 Data Handling and Statistical Analysis

Statistical analysis was completed on IBM SPSS Statistics version 29 (IBM Corp, 2023). Data was tested for normality using the Shapiro-Wilk test, and homogeneity of variance was assessed using Levene's test. Variables that met the assumptions for normality were summarised as mean ± standard deviation, while non-normal data were presented as median and interquartile range (25% and 75% percentiles). Categorical data is reported as the number of participants and percentages.

To address objective 1, a principal component analysis (PCA) with varimax rotation was conducted on 17 menstruation symptoms. Data was suitable for PCA, with Bartlett's test of sphericity indicating sufficient correlations among variables ($p < 0.001$), and the Kaiser-Meyer-Olkin (KMO) measure exceeding the recommended threshold of 0.6. Based on the eigenvalue > 1 criterion, a single component (PC1) was retained, describing 38% of the variation in menstrual symptoms. The average symptom scores were highly correlated with PC1 ($r = 1.00$, $p < 0.001$); therefore, for ease of interpretation, subsequent analyses used the average scores to represent the overall symptom severity for participants across cycles.

To address objective 2 and objective 3, group comparisons were performed between self-perceived heavy and non-heavy bleeders, and between iron-sufficient and ID participants. For analysis, light/scanty and moderate bleeders were grouped as non-heavy bleeders (n = 85), and

heavy bleeders were classified as heavy (n = 12). For this analysis, menstruation-related symptom severity scores were compared across self-perceived bleeding and iron status groups using the Wilcoxon-rank sum test. Variables compared included baseline characteristics, body composition, iron status, and symptom severity scores. A total symptom severity score was calculated by summing responses to 17 symptoms, each rated on a 5-point Likert scale from 0 (none at all) to 4 (a great deal), resulting in a possible total score range of 0-68, with higher scores indicating greater symptom severity. Independent sample t-tests were used to compare normal continuous variables, and the Wilcoxon rank-sum test was used to compare non-normal data. Categorical data was compared using Pearson's Chi-squared test. Statistical significance was defined as $p < 0.05$.

A multiple linear regression was performed to identify associations of overall menstruation-related symptom severity with SF and self-reported bleeding heaviness. The dependent variable was the total symptom severity score. Independent variables were selected a priori for their physiological relevance and included self-reported bleeding heaviness, SF, Hb, CRP, and body fat percentage. These variables were selected as potential confounders given existing evidence suggesting iron status, inflammation, oxygen transport, and adiposity may be associated with menstruation-related symptom severity (Abbaspour et al., 2014; Greig et al., 2013; Munro et al., 2023; Tembhurne & Mitra, 2016; Zhou et al., 2018). All possible symptom associations were entered simultaneously. Assumptions of linearity, homoscedasticity, normality of residuals, independence of errors, and multicollinearity were checked and met. Model performance was evaluated using R^2, adjusted R^2, and associated significance values. Individual associations were interpreted using unstandardised coefficients (β), standard errors, 95% confidence intervals, and p-values. Although the full five-variable model was tested, the inclusion of Hb, CRP, and body fat percentage did not meaningfully improve the explanation of symptom severity, resulting in minimal increases in R^2 and adjusted R^2. Consequently, a reduced model including only the bleed score and SF was identified as a more parsimonious representation of the relationship between iron status and self-reported menstrual fluid loss and symptom severity and was therefore selected as the final analytical model.

3.4 Results

3.4.1 Participant Characteristics

Table 3.1 summarises the baseline characteristics of the 97 participants included in this study. Most of the participants identified as European (n = 70; 72%) and had an average menstrual bleed of five days. The mean age of participants was 31 years, and most (89%) had completed tertiary education.

Table 3.1 *Summary of Baseline Participant Characteristics (n = 97)*

Characteristic	Overall (N = 97)	Heavy Bleeders n = 12 (12.4%)	Non-Heavy Bleeders n = 85 (87.6%)	*p*-value[1]	Iron Sufficient [†] n = 69 (71.9%)	Iron Deficient [‡] n = 27 (28.1%)	*p*-value[1]
Ethnicity[§]							
European	70 (72.0%)	10 (83.3)	60 (71.0%)	>0.900	51 (73.9)	18 (66.7)	0.412
Māori	7 (7.2%)	0 (0.0%)	7 (8.2%)		6 (8.7)	1 (3.7)	
Pasifika	1 (1.0%)	0 (0.0%)	1 (1.2%)		1 (1.4)	-	
Asian	18 (19.0%)	2 (17.0%)	16 (19.0%)		10 (14.5)	8 (29.6)	
MEELA	1 (1.0%)	0 (0.0%)	1 (1.2%)		1 (1.4)	-	
Education[§]							
School Yr12/13	8 (8.2%)	2 (17.0%)	6 (7.1%)	0.500	5 (7.2)	3 (11.1)	0.804
Polytech	3 (3.1%)	0 (0.0%)	3 (3.5%)		2 (2.9)	1 (3.7)	
University	86 (89.0%)	10 (83.0%)	76 (89.0%)		62 (89.9)	23 (85.2)	
Age of menarche (years)[††]	12.7 ± 1.5	11.9 ± 1.4	12.8 ± 1.5	0.110	12.7 ± 1.5	12.4 ± 1.7	0.507
Missing	*1*	*0*	*1*		*0*	*1*	
Age (years)[¶]	31.0 (25.5, 35.0)	30.5 (25.0, 37.0)	31.0 (26.0, 35.0)	0.930	31.0 (25.5, 35.0)	30.0 (24.0, 38.0)	0.639
Height (cm)[††]	166.8 ± 6.4	169.9 ± 4.7	166.4 ± 6.5	0.335	167.4 ± 6.5	165.0 ± 6.0	0.401
Missing	*14*	*3*	*11*		*7*	*7*	
Weight (kg)[¶]	68.4 (60.3, 75.6)	69 (65.8, 82.4)	68.1 (59.8, 74.9)	0.334	68.9 (62.2, 74.9)	63.9 (55.9, 77.7)	0.323
Missing	*14*	*3*	*11*		*7*	*7*	
BMI (kg/m^2)[¶]	24.4 (22.0, 26.3)	24.7 (22.2, 27.9)	24.3 (22.0, 26.3)	0.692	24.5 (22.4, 26.2)	24.4 (21.1, 28.7)	0.678
Missing	*14*	*3*	*11*		*7*	*7*	

Characteristic	Overall (N = 97)	Heavy Bleeders n = 12 (12.4%)	Non-Heavy Bleeders n = 85 (87.6%)	*p*-value[1]	Iron Sufficient † n = 69 (71.9%)	Iron Deficient ‡ n = 27 (28.1%)	*p*-value[1]
Muscle mass (kg)¶	26.1 (24.0, 28.9)	28.7 (25.2, 30.3)	26 (24.0, 28.6)	0.352	26.7 (24.5, 29.6)	25.1 (21.9, 26.5)	**0.006**
Missing	*14*	*3*	*11*		*7*	*7*	
Body fat mass (kg)¶	20.0 (14.5, 24.1)	21.4 (15.1, 31.6)	19.7 (14.5, 24.0)	0.524	19.8 (14.5, 24.0)	20.6 (15.2, 32.3)	0.674
Missing	*14*	*3*	*11*		*7*	*7*	
Percent of body fat††	19.5 ± 8.7	31.5 ± 12.2	29.3 ± 8.2	0.529	28.8 ± 7.9	32.2 ± 10.7	0.214
Missing	*14*	*3*	*11*		*7*	*7*	
Free fat mass (kg)¶	47.3 (43.5, 51.7)	51.6 (42.6, 56.6)	47.3 (43.5, 51.6)	0.316	47.3 (43.4, 52.7)	47.4 (44.5, 51.1)	0.604
Missing	*14*	*3*	*11*		*7*	*7*	
Total body water (%)¶	34.6 (31.9, 37.9)	37.8 (31.2, 41.4)	34.6 (31.9, 37.8)	0.316	34.6 (31.7, 38.6)	34.7 (32.7, 37.4)	0.601
Missing	*14*	*3*	*11*		*7*	*7*	
Waist to hip ratio¶	0.9 (0.8, 0.9)	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	1.000	0.9 (0.8, 0.9)	0.9 (0.8, 0.9)	0.447
Missing	*14*	*3*	*11*		*7*	*7*	
Haemoglobin (g/L)¶	133.0 (125.0, 141.0)	126.0 (117.0, 136.0)	134.0 (127.0, 142.0)	**0.032**	135.5 (125.0, 141.0)	132.0 (126.0, 139.0)	0.374
Missing	*3*	*1*	*2*		*3*	*0*	
Serum ferritin (µg/L)¶	41.0 (27.0, 57.5)	26.5 (22.5, 46.5)	44.5 (30.5, 61.0)	0.066	51 (39.0, 75.0)	19 (13.0, 26.0)	**< 0.001**
Missing	*1*	*0*	*1*				
C-reactive protein (mg/L)¶	0.6 (0.6, 1.7)	1.1 (0.7, 2.7)	0.6 (0.6, 1.6)	**0.025**	0.6 (0.6, 1.2)	1.0 (0.6, 2.4)	0.226

Characteristic	Overall (N = 97)	Heavy Bleeders n = 12 (12.4%)	Non-Heavy Bleeders n = 85 (87.6%)	*p*-value[1]	Iron Sufficient † n = 69 (71.9%)	Iron Deficient ‡ n = 27 (28.1%)	*p*-value[1]
Missing	*2*	*0*	*2*		*0*	*1*	
Total iron binding capacity (TIBC)¶	58.0 (52.0, 63.5)	65.5 (55.0, 71.5)	57 (52.0, 62.0)	**0.035**	55.0 (51.0, 59.0)	66 (61.0, 71.0)	**< 0.001**
Missing	*1*	*0*	*1*				
Iron saturation¶	0.3 (0.2, 0.3)	0.2 (0.2, 0.3)	0.3 (0.2, 0.3)	0.282	0.3 (0.2, 0.4)	0.2 (0.1, 0.3)	**< 0.001**
Missing	*1*	*0*	*1*				

Note. MELAA = Middle Eastern, Latin American and African.

[1] Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test; Shapiro–Wilk test.

†Serum ferritin ≥30 μg/L and Hb ≥120 g/L

‡Serum ferritin <30 μg/L and Hb ≥120 g/L

††Mean ± standard deviation

§ Number and % of participants

¶ Median and 25th, 75th centiles

3.4.2 Menstruation-related Symptoms

The prevalence and severity of each symptom are shown in Figure 3.1. Across the 17 assessed symptoms, the majority (76.29%) of responses were reported as “A little.” Fatigue was the most common symptom, reported as “A little” by 63.9%, “Moderate” by 30%, and “A lot” by 5.2%. Abdominal cramps, headache, mood changes, and sleep difficulty showed a similar pattern, with more than 80% of participants reporting mild severity and fewer than 10% reporting moderate severity. Appetite changes and bloating had the highest proportion of moderate responses after fatigue (each at 12.4%). Other symptoms with at least one moderate response included water retention (8.2%), joint/muscle pain (5.2%), concentration difficulties (1.0%), dizziness (1.0%), constipation (2.1%), breast tenderness (1.0%), lower back pain (4.1%), and breathing difficulties (1.0%). Several symptoms had at least one “A lot” response, including fatigue (5.2%), bloating (2.1%), dizziness (1.0%), concentration difficulties (1.0%), and water retention (1.0%). No symptom was rated as “A great deal.” In addition to the symptoms reported at mild or moderate levels, a notable proportion (16.86%) of participants indicated that they did not experience certain symptoms at all (“None at all”). The highest proportion of “None at all” responses was observed for breathing difficulties (56%), constipation (39%), nausea (28%), and joint/muscle pain (25%).

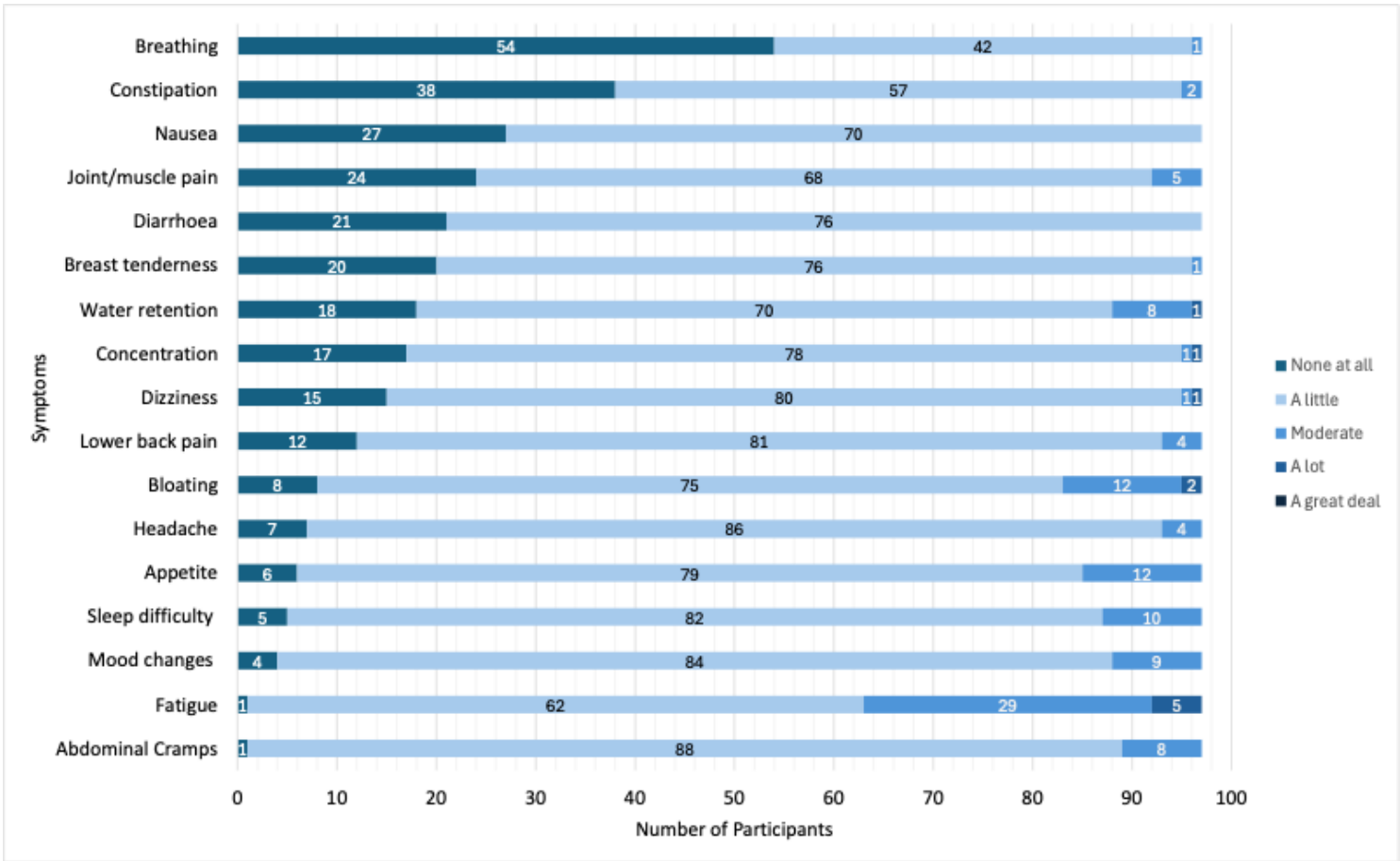

Figure 3.1 *Stacked Bar Chart of the Average Distribution of Menstrual Symptom Severity Ratings over at least Five Cycles.*

A principal component analysis identified a single component (PC1) based on the eigenvalue > 1 criterion, accounting for 38% of the variance in menstruation-related symptoms. The average menstruation-related symptom scores were highly correlated with PC1 (r = 1.00, p < 0.001); therefore, subsequent analyses used the average scores to represent the overall symptom severity across participants. Table 3.2 presents the loadings of each symptom on PC1 (i.e., the correlation of each symptom with PC1). All but one symptom (breathing difficulty) loaded positively onto this component. Symptoms such as abdominal cramps, mood changes, and appetite showed the strongest associations with PC1, whereas dizziness and concentration demonstrated weaker associations.

Table 3.2 *Factor Loadings Showing the Correlation of Each Symptom with the First Principal Component (PC1)*

Symptom	PC1 loading
Abdominal cramps	0.79
Mood changes	0.78
Appetite	0.69
Headache	0.58
Bloating	0.58
Joint/muscle pain	0.51
Fatigue	0.51
Lower back pain	0.48
Constipation	0.45
Nausea	0.43
Sleep difficulty	0.43
Diarrhoea	0.41
Breast tenderness	0.41
Water retention	0.35
Dizziness	0.25
Concentration	0.15
Breathing	-0.22

3.4.3 Menstruation-related Symptom Severity by Self-Perceived Bleeding Heaviness

Table 3.3 presents the median severity scores and interquartile ranges (IQR) for 17 menstruation symptoms between the self-perceived non-heavy (n = 85) and heavy (n = 12) menstrual bleeding groups. Participants who self-perceived HMB experienced higher severity for

several symptoms. Significant differences were observed for fatigue/tiredness (p = 0.003), reduced concentration (p = 0.006), abdominal cramps (p = 0.013), disrupted sleep (p = 0.031), dizziness/light-headedness (p = 0.026), and joint pain/muscle cramps (p = 0.034), with higher median scores among self-perceived HMB. No significant differences were observed between groups for the remaining symptoms.

Table 3.3 *Comparison of Symptom Severity (Median and IQR) Between Non-Heavy and Heavy Menstrual Bleeders*

Symptom	Overall (N = 97)[1]	Non-heavy bleeders[2] n = 85 (87.6%)	Heavy bleeders[2] n = 12 (12.4 %)	p-value[3]
Abdominal cramps	96 (99%)	0.69 (0.37-0.87)	1.21 (0.57-1.69)	**0.013**
Bloating	89 (91.8%)	0.83 (0.23-1.18)	1.23 (0.48-1.71)	0.080
Breast pain/tenderness	77 (79.4%)	0.19 (0.04-0.40)	0.34 (0.05-0.88)	0.355
Constipation	59 (60.8%)	0.13 (0.00-0.33)	0.04 (0.00-0.69)	0.964
Cravings/increased appetite	91 (93.8%)	0.63 (0.27-1.00)	1.20 (0.57-1.58)	0.062
Diarrhoea	76 (78.4%)	0.15 (0.03-0.26)	0.34 (0.54-0.97)	0.101
Difficulty breathing	43 (44.3%)	0.00 (0.0-0.07)	0.02 (0.00-0.14)	0.656
Disrupted sleep	92 (94.8%)	0.51 (0.20-0.97)	0.98 (0.52-1.35)	**0.031**
Dizziness/light headedness	82 (84.5%)	0.29 (0.07-0.70)	0.74 (0.34-1.12)	**0.026**
Fatigue/tiredness	96 (99%)	1.08 (0.66-1.59)	1.78 (1.43-2.33)	**0.003**
Headache	90 (92.8%)	0.38 (0.17-0.64)	0.52 (0.37-1.03)	0.159
Joint pain/muscle cramps	73 (75.3%)	0.17 (0.00-0.44)	0.37 (0.12-1.52)	**0.034**
Lower back pain	85 (87.6%)	0.38 (0.18-0.70)	0.46 (0.13-1.08)	0.561
Mood	93(95.9%)	0.65 (0.28-1.13)	0.99 (0.58-1.39)	0.124
Nausea/sickness/vomiting	70 (72.2%)	0.10 (0.00-0.31)	0.41 (0.02-0.69)	0.128
Reduced concentration	80 (82.5%)	0.27 (0.05-0.58)	0.77 (0.28-0.91)	**0.006**
Water retention	79 (81.4%)	0.28 (0.05-0.81)	0.69 (0.21-1.46)	0.103
Total symptom score[2]	8.21 (5.38–12.10)	7.74 (5.15–11.31)	14.01 (8.49–19.10)	**0.014**

Note. Classification of heavy and non-heavy menstrual bleeding was based on participants' self-reported bleeding status; no objective measure of menstrual blood loss was used.

[1] n (%)

[2] Median (IQR)

[3] Wilcoxon rank sum test

3.4.4 Iron Status and Menstruation-related Symptom Severity

Table 3.4 presents the median severity scores for 17 menstruation symptoms between participants who were iron-sufficient (n = 69) and ID (n = 27). Several symptoms were reported with significantly higher severity among participants with ID, including fatigue/tiredness (p = 0.001), dizziness/light-headedness (p = 0.003), joint pain/muscle cramps (p = 0.002), lower back pain (p = 0.002), nausea/sickness/vomiting (p = 0.030), disrupted sleep (p = 0.043), headache (p = 0.008), and mood changes (p = 0.042). No other symptoms differed significantly between groups.

Table 3.4 *Comparison of Symptom Severity (Median and IQR) Between Iron-Sufficient and Iron Deficient Participants*

Symptom	Iron sufficient†[1] n = 69 (71.9%)	Iron deficient‡[1] n = 27 (28.1%)	p-value[2]
Abdominal cramps	0.68 (0.39-0.90)	0.78 (0.43-1.40)	0.059
Bloating	0.77 (0.20-1.19)	1.09 (0.35-1.44)	0.077
Breast pain/tenderness	0.19 (0.04-0.40)	0.24 (0.06-0.59)	0.528
Constipation	0.05 (0.00-0.33)	0.18 (0.00-0.77)	0.229
Cravings/increased appetite	0.69 (0.25-0.96)	0.95 (0.45-1.44)	0.149
Diarrhoea	0.15 (0.03-0.30)	0.17 (0.04-0.51)	0.510
Difficulty breathing	0.00 (0.00-0.05)	0.05 (0.00-0.25)	0.060
Disrupted sleep	0.46 (0.17-0.98)	0.77 (0.47-1.10)	**0.043**
Dizziness/light headedness	0.25 (0.03-0.69)	0.61 (0.28-1.13)	**0.003**
Fatigue/tiredness	0.98 (0.50-1.59)	1.50 (1.11-2.33)	**0.001**
Headache	0.31 (0.12-0.56)	0.46 (0.34-1.13)	**0.008**
Joint pain/muscle cramps	0.13 (0.00-0.38)	0.43 (0.13-0.99)	**0.002**
Lower back pain	0.31 (0.15-0.62)	0.66 (0.42-0.95)	**0.002**
Mood	0.63 (0.28-1.11)	1.04 (0.56-1.38)	**0.042**
Nausea/sickness/vomiting	0.10 (0.00-0.30)	0.24 (0.07-0.58)	**0.030**
Reduced concentration	0.21 (0.04-0.62)	0.41 (0.15-0.77)	0.055
Water retention	0.28 (0.03-0.83)	0.51 (0.16-0.96)	0.160
Total symptom score	7.35 (4.93, 10.75)	10.07 (6.86, 17.81)	0.003

[1]Median (IQR)

[2] Wilcoxon rank sum test

†Serum ferritin ≥30 µg/L and Hb ≥120 g/L; ‡Serum ferritin <30 µg/L and Hb ≥120 g/L

3.4.5 Variables Associated with Symptom Severity

A multiple linear regression was conducted to explore whether menstruation-related symptom severity was associated with self-reported bleeding heaviness and iron status-related variables. The initial model included bleed score, SF, CRP, Hb, and body fat percentage (Table 3.5). In this full model, none of the variables reached statistical significance (all $p > 0.05$), and the model explained only a small proportion of variance in symptom severity (adjusted $R^2 = 0.073$). Although the bleed score approached significance ($p = 0.067$), the inclusion of the additional physiological variables did not meaningfully improve model performance.

Table 3.5 *Associations of Menstruation Symptom Severity from Confounders and Bleed Score Using Multiple Linear Regression*

Variable	*β*	Standard Error	95% CI	*p*-value
Bleed score	4.12	2.21	-0.29, 8.53	0.067
Serum ferritin (µg/L)	-0.02	0.02	0.05, 0.02	0.343
Haemoglobin (g/L)	-0.03	0.04	-0.10, 0.04	0.401
C-reactive protein (mg/L)	-0.06	0.11	-0.27, 0.16	0.606
Body fat Percentage	0.09	0.06	-0.04, 0.21	0.178

Note. $R^2 = 0.133$, Adjusted $R^2 = 0.073$, $p < .001$. $p < .05$ indicates statistical significance. n = 78

A reduced model containing only the bleed score and SF was examined (Table 3.6). The bleed score was observed to be significantly associated with symptom severity ($\beta = 6.18$, $p = 0.0018$), whereas the association between symptom severity and SF was not statistically significant ($p = 0.2130$). The two-variable model (n = 96) yielded an adjusted R^2 of 0.113. Overall, self-perceived bleeding heaviness was the only variable associated with menstruation-related symptom severity in this cohort. In the final model, each one-unit increase in bleed score was associated with a 6.18 point increase in total menstruation-related symptom severity (95% confidence interval: 2.37 to 9.99).

Table 3.6 *Associations of Menstrual Symptom Severity from Serum Ferritin and Bleed Score Using Multiple Linear Regression*

Variable	*β*	Standard Error	95% CI	*p*-value
Bleed score	6.18	1.92	2.37, 9.99	**0.0018**
Serum ferritin (µg/L)	-0.02	0.01	-0.05, 0.01	0.213

Note. $R^2 = 0.132$, Adjusted $R^2 = .113$, $p < .001$. $p < .05$ indicates statistical significance. n = 96

3.5 Discussion

The main findings in this study were that overall menstruation-related symptom severity in this cohort was low, with an overall mean severity of 0.53 on a 0-4 scale (0 = none at all; 4 = a great deal), indicating generally mild symptom severity on days with visible menstrual fluid loss. No participants reported scores of 3 or higher, indicating an absence of high symptom severity during menstruation in this cohort. Despite low overall severity, self-perceived HMB was found to result in greater symptom severity ratings for abdominal cramps, fatigue, dizziness, and reduced concentration compared to self-perceived non-heavy bleeders. In contrast, SF levels were not found to be significantly associated with overall symptom severity, and no additional covariates, including CRP, Hb, and body fat percentage, contributed to symptom severity ratings when self-perceived bleeding heaviness was included. Across all analyses, self-perceived bleeding heaviness consistently emerged as the only factor that independently explained variation in symptom severity during menstruation in this cohort of healthy, regularly menstruating women. These results would suggest that perceived menstrual blood loss, not iron status or other physiological markers, was a primary determinant of symptom severity during menstruation in this cohort.

3.5.1 Overall Symptom Severity During Menstruation

The overall severity of menstruation symptoms was low in this cohort. This contrasts with existing studies reporting greater symptom severity within the late-luteal and premenstrual phase of the MC. For example, Farage et al. (2008) reported that psychological symptoms such as anxiety and irritability peaked during the late luteal phase, while Guevarra et al. (2023) observed a significant increase in anhedonic depression during the mid-luteal phase in a cohort of 96 women. Similarly Nolan and Hughes (2022) found that emotional symptoms were exacerbated in the premenstrual phase of the MC. These findings are biologically plausible, as the late luteal and mid-luteal phases are characterised by declining levels of steroid hormones, which have previously been associated with heighten MC symptom sensitivity (Farage et al., 2008; Hantsoo & Epperson, 2020). In contrast, the current study collected prospective daily symptom data exclusively during menstruation and the early follicular phase, a period characterised by more stable, low oestradiol (E2) and progesterone levels (Handy et al., 2022; Thiyagarajan et al., 2022). The lower symptom severity observed here is therefore consistent with a phase of the cycle where steroid hormonal variability is minimal. A second factor that likely contributed to these lower severity scores is the study design. Much of the existing research has relied on retrospective, cross-sectional surveys, which are susceptible to recall bias, and participants may overestimate the severity of their symptoms when asked to reflect on their experiences after the fact (Bitzer et al., 2013; Schoep et al., 2019). This study employed daily prospective tracking, allowing participants to report symptoms in real time. This approach likely

enables more accurate symptom reporting and may have contributed to the lower symptom severity observed.

3.5.2 Iron Deficiency Symptoms

The results of this study suggest that common symptoms of ID, including fatigue, dizziness, disrupted sleep, joint pain/muscle cramps, and lower back pain, were experienced during menstruation. In this cohort, median severity scores for fatigue, nausea, dizziness, disrupted sleep, joint pain/muscle cramps, and lower back pain were significantly higher among ID participants compared to iron sufficient participants. However, contrary to hypothesis 2, PD severity did not differ significantly between ID and iron sufficient participants; therefore, this component of the hypothesis was not supported. These findings align with previous cross-sectional studies that have reported ID to be associated with higher fatigue and poorer vitality. For example, Patterson et al. (2000) identified fatigue and dizziness as common complaints among young women with low iron stores. Within the same study, lower physical, mental, and vitality scores in women with a history of ID were reported. Similarly, Sawada et al. (2014) found that young women with ID experienced greater anger and fatigue than their iron-replete counterparts. In addition, higher psychological distress was a commonly reported symptom among women with self-reported IDA (Hidese et al., 2018). In alignment with the results of the present study, previous research has also reported an association between ID and sleep disturbances, which may result from restless legs (Leung et al., 2020) as well as neuromuscular complaints (Munro et al., 2023). It is worth noting that despite the similarities in the results between this study and previous research, much of the previous research has relied on retrospective self-reporting of symptoms or focused on more severe presentations of ID (e.g., anaemia). Previous research, such as Patterson et al. (2000) relied on self-reported iron history and their study lacked biochemical verification of iron status and hence ID. In contrast, the current study prospectively collected symptom data during menstruation and biochemically verified iron status for all participants. Because this study collected symptoms prospectively and verified iron status biochemically, it reduced recall bias and misclassification, strengthening the validity and reliability of the findings reported. Within this study, the SF cutoff used (< 30 µg/L) does not reflect severe ID, and interestingly, SF was not significantly associated with symptom severity during menstruation. This would suggest that, despite the higher symptom severity observed among ID participants, the severity of symptoms reported by women during menstruation cannot be attributed to iron status or ID diagnosis alone and that other individual factors may contribute to the high interindividual variability in symptoms experienced by women during menstruation. Future research is therefore still needed to investigate co-occurring factors, such as volume of menstrual flow, total energy intake and or psychosocial factors (e.g., stress, wellbeing, sleep quality and

duration, exercise) and their association with self-report symptom severity during menstruation in ID and iron-sufficient women.

3.5.3 Heavy Menstrual Bleeders

Participants who self-perceived their menstruation to be heavy (HMB) reported greater severity of abdominal cramps, fatigue, dizziness, disrupted sleep, and reduced concentration than non-heavy bleeders. Although emotional changes were included in hypothesis 1, no significant differences in emotional symptom severity were observed between HMB and non-heavy bleeders; therefore, this part of the hypothesis was not supported. This pattern is consistent with previous cross-sectional studies, associating HMB with poorer well-being and functional impairment. For example, Bruinvels et al. (2016) reported that 54% of exercising women self-reported as having HMB, and also reported reduced well-being. Building on that, Kocaoz et al. (2019) found that approximately 38% of women with HMB experienced clinically relevant fatigue. Similarly, Lukes et al. (2012) observed poorer QoL among women with greater daily menstrual blood loss, further reinforcing the association between HMB and symptom severity. Interestingly, and complementary to our results, research in women who have ID and HMB has shown elevated reports of fatigue, cognitive difficulty, and reduced mental clarity (Munro et al., 2023). While fatigue is commonly attributed to depleted iron stores, the results from this study demonstrated increased fatigue severity in participants who self-perceived their flow as heavy, irrespective of iron status. Previous literature has also reported on associations between cognitive disturbances with ID (Munro et al., 2023). Although previous research highlights the contribution of ID to severe cognitive symptoms, the findings from this study indicate that women with self-perceived HMB may report reduced concentration even when iron is sufficient. Taken together, these findings suggest that HMB may contribute to greater fatigue and reduced concentration during menstruation in the absence of ID. Overall, these results position HMB as an independent contributor to symptom severity during menstruation for regularly menstruating women, underscoring the need for further investigation into mechanisms driving these effects.

3.5.4 Iron Deficient Heavy Bleeders

Although the co-occurrence of HMB and ID is well established in literature (Bernardi et al., 2016; Munro et al., 2023), relatively few studies have examined how these two conditions jointly influence menstruation-related symptom severity. Cross-sectional studies have reported that women with HMB often present with lower iron indices; Bernardi et al. (2016) reported significantly lower Hb and SF in women with HMB, and Pita-Rodríguez et al. (2023) found that IDA was present in 55% of women with HMB. Systematic reviews further note that up to 80% of women with HMB may

have ID or IDA (Mansour et al., 2021). Building on that context, the present study found that HMB, but not ID, was associated with more severe symptoms during menstruation. Neither SF nor Hb was independently associated with menstruation symptom severity. It should be noted though that the small number of participants with HMB (n = 12) may limit the ability to examine whether HMB and ID interact to influence presence or severity of menstruation symptoms. Despite this, the physiological associations between iron depletion and HMB still provide important context for interpreting the descriptive patterns observed in this cohort. Participants with self-perceived HMB had lower Hb, higher total iron-binding capacity, and higher CRP compared with non-heavy bleeders, suggesting increased iron requirements and inflammatory strain, despite only modest differences in SF. This pattern is consistent with previous research that has suggested that common menstruation-related symptoms, including fatigue, dizziness, headache, and reduced concentration, may arise through overlapping mechanisms such as increased blood loss, reduced oxygen-carrying capacity, increased iron need and inflammatory activation (Hasnia et al., 2024; Kusumawardani, 2018; Muñoz et al., 2009). These findings may suggest that HMB may contribute to menstruation-related symptom severity via increased iron utilisation and inflammation, changes that may occur before a decline in SF. While the small number of participants with HMB limited the ability to assess the combined effects of HMB and ID, the observed haematological and inflammatory differences indicate that symptom burden may reflect physiological strain not fully represented by iron stores alone. Interpreted in this context, the results highlight the importance of considering menstrual blood loss alongside iron parameters when evaluating menstruation-related symptoms, rather than viewing symptoms or iron status in isolation (Mansour et al., 2021; Munro et al., 2023).

3.6 Conclusion

To the best of our knowledge, this is the first study to examine menstruation-related symptom severity and the relation to both self-perceived menstruation heaviness and iron status. The findings from this study suggest that perception of menstruation heaviness was the only independent factor associated with menstruation-related symptom severity. Although descriptive comparisons suggested that symptoms such as fatigue, dizziness, disrupted sleep, and musculoskeletal discomfort were more severe in ID participants, iron status itself was not significantly associated with symptom severity. In contrast, self-perceived HMB consistently increased the severity of symptoms such as abdominal cramps, fatigue, and reduced concentration. As such it may be suggested, that menstruation-related symptom support should consider multiple individual health factors, in particular perception or self-reported menstruation flow rate, as this could influence symptom severity and subsequently overall well-being in regularly menstruating women.

Chapter 4 Conclusion and Recommendations

4.1 Overview and Achievement of Aims and Objectives

The aim of this study was to describe menstruation-related symptoms in naturally menstruating women. A secondary aim was to examine differences in menstruation-related symptoms between ID and iron-sufficient naturally menstruating women, and self-perceived heavy and non-heavy menstrual bleeders. To address these aims, a previously published survey was used to collect data on menstruation symptoms and perceptions of blood loss (Bruinvels et al., 2021). Iron status was assessed using serum ferritin (SF) and haemoglobin (Hb). Data from 97 women was included in the analysis.

For the first objective, our results suggest that across this cohort of women, symptoms were commonly reported but generally mild, with median severity scores ranging from 1 to 2 on a five-point Likert scale. No symptom was rated as “a lot” or “a great deal”. The most frequently reported symptoms were abdominal cramps, fatigue, mood changes, sleep difficulty, appetite changes and headaches. These findings suggest that, among healthy women without diagnosed reproductive conditions, symptom severity during menstruation is relatively modest compared to that in the premenstrual phase described in previous literature (Farage et al., 2008; Meaden et al., 2005).

In this study, women with ID appeared to experience greater symptom severity than their iron sufficient counterparts, particularly for fatigue, dizziness, disrupted sleep, nausea, and musculoskeletal discomfort. These differences were evident in the descriptive analyses; however, iron status (SF and Hb) was not significantly associated with overall symptom severity in the regression model. Participants who self-perceived themselves as heavy menstrual bleeders (HMB) reported higher severity for symptoms such as abdominal cramps, fatigue, dizziness, sleep disturbances, and reduced concentration compared to non-heavy bleeders. Interestingly, self-perceived bleeding heaviness was the only factor associated with overall symptom severity in the regression model. A result that would reinforce previous research results that have reported on the association between HMB and increased physical and cognitive symptom burden in menstruating women.

Overall, the study provides evidence that self-reported menstruation symptom severity during menstruation is influenced by the individual’s perception of their bleeding heaviness. Nevertheless, the descriptive association between ID and increased symptom severity highlights the potential value of monitoring iron status, particularly in women who report HMB. These findings

advance understanding of how bleeding patterns and ID may interact with individual menstrual cycle and symptom experiences.

4.2 Strengths

To the best of our knowledge, this is the first study to prospectively examine menstruation symptoms across multiple cycles in naturally menstruating women, while also accounting for iron status and self-perceived menstrual bleeding severity. A strength of this study is its longitudinal design, which enabled the tracking of menstruation symptoms across five consecutive menstrual cycles (MCs). This extended timeframe provided a unique opportunity to observe how symptoms varied or remained consistent within individuals, offering a richer and more reliable picture of menstruation for each participant. By capturing repeated measurements, the study was able to identify patterns that might otherwise be missed, particularly in relation to self-perceived bleeding heaviness. Another strength of this study was the prospective data collection, which allowed participants to report symptoms in real time rather than relying on recall. By recording symptoms in real time, the study minimised recall and reporting bias and strengthened the accuracy of symptom severity ratings and results. This allowed for a more precise and authentic representation of participants' menstruation experiences. Finally, the use of a previously published survey, originally applied in research by Bruinvels et al. (2021) added further strength to this study. Its established structure allowed for consistent reporting of menstruation symptoms in a format consistent with existing literature. This allowed for a comparison between results obtained in this cohort and those reported in previous research and contributed to the external validity of this study.

4.3 Limitations

A limitation of this study is the timing of symptom data collection, which was restricted to during menstruation and did not include the premenstrual phase. This decision was made to reduce participant burden during prospective longitudinal data collection. However, it may have limited the ability to capture a full spectrum of MC symptom experiences, particularly symptoms that may occur more readily in the days preceding menstruation (e.g., mood changes, breast tenderness, and bloating), and which have been reported to be more severe during the late luteal phase compared to menstruation (Handy et al., 2022; Schoep et al., 2019). Future research should consider daily prospective symptom tracking across the whole MC, including the premenstrual phase and menstruation, to provide a more comprehensive understanding of symptom patterns throughout the MC. Another limitation of this study was the absence of an objective measurement of menstrual fluid loss. Perceived menstrual bleeding heaviness was self-reported, which may introduce some degree of subjective bias and misclassification; however, perceived menstrual flow has been shown

to reasonably reflect menstrual blood loss and is widely used in menstrual health research when objective measurement is not feasible (Magnay et al., 2018). While this method was appropriate for minimising participant burden in a longitudinal study, it does limit the precision of HMB classification. Clinically, HMB is defined as ≥ 80 mL of blood loss per cycle (Davies & Kadir, 2017); however, objective quantification of this threshold requires the alkaline hematin method, which is largely confined to research settings due to its low clinical feasibility. As such, accurate classification based on absolute blood loss was not possible in the present study (Wheeler & Hemingway, 2024). These approaches, while effective in research settings, are often impractical for routine clinical use or everyday settings. Future research should consider utilising other ecologically valid approaches that allow for alternative and possibly more accurate measurement of menstrual fluid loss while simultaneously capturing symptom data across the MC. A further limitation of this study was the small number of participants within the subgroups, particularly those who self-reported as HMB. Only 12 participants identified as HMB. The small subgroup sizes reduced statistical power and limited the ability to detect subtle interaction effects between perceived bleeding heaviness and iron status. Future research with study designs that prioritise HMB and ID as key inclusion criteria may allow for more robust evaluation of potential combined or interactive effects of these two factors on MC symptoms. A final limitation of the study that is worth noting is the limited diversity of age within the participants. While the sample had a strong representation of individuals in early adulthood, with a mean age of 30.5 years, older menstruating individuals, particularly those experiencing perimenopause, were underrepresented. This is a result of the upper age limit for inclusion in this study being 40 years. The absence of participants in their forties limits the ability to explore how MC and menstruation symptoms and bleeding perceptions may evolve as women enter perimenopause. It would be valuable for future research to include a wider range of participants to explore how menstruation experiences and iron status might shift throughout a woman's reproductive lifespan.

4.4 Findings in Relation to Hypotheses

Hypothesis 1: *Heavy menstrual bleeders will experience higher self-reported severity of physical symptoms (dysmenorrhoea and fatigue) and emotional changes compared to women who perceive their menstrual bleeding to be regular or light.*

Supported: Women who self-identified as HMB reported significantly higher severity of fatigue and abdominal cramps across cycles (Table 3.3), consistent with the predicted increase in physical symptoms.

Not Supported: Emotional changes, including mood symptoms, did not differ significantly between heavy and non-heavy bleeders (p = 0.124; Table 3.3), indicating only partial support for this hypothesis.

Hypothesis 2: *Women who are iron deficient will report higher severity of physical symptoms (fatigue and dysmenorrhoea) and emotional changes during their menstrual bleed compared to women who are iron sufficient.*

Supported: Iron deficient participants reported significantly higher fatigue, joint/muscle pain, lower-back pain, dizziness, and abdominal cramps severity (Table 3.4), supporting the predicted association between ID and greater physical symptom severity.

Partially Supported / Not Fully Supported**:** Although mood severity was significantly higher among ID participants (p = 0.042; Table 3.4), iron status did not independently predict overall symptom severity in the multiple linear regression model. This indicates limited support for the emotional-symptom component of the hypothesis and suggests that bleeding heaviness, rather than iron status, was the primary contributor to overall symptom severity.

4.5 Research recommendations and future implications

This study provides new insights into how ID and HMB relate to menstruation symptom severity. Based on the findings and acknowledged limitations of the study, several recommendations for research and clinical practice are presented here:

Recommendations for clinical practise

- Since this study reported an association between perceived HMB and severe menstrual symptoms, practitioners in women's health and primary care should encourage systemic tracking of MC symptoms and menstrual fluid loss to identify patterns and detect changes over time. Consistent monitoring could support early intervention to reduce symptom burden and improve QoL.
- Women presenting to primary care with severe or debilitating menstruation symptoms that impact daily functioning should receive a detailed evaluation of their MC, flow patterns, and symptom history. Where indicated, referral to an appropriate women's health specialist to assess iron status, nutrition and lifestyle factors may be considered before initiating hormonal interventions, such as birth control.
- For women who have concerns about their MC health, menstruation symptoms, and flow patterns should be systemically documented in electronic health records. This would allow

clinicians to monitor trends over time, identify at-risk individuals, and implement targeted interventions (e.g., support for ID).

- Women who present with HMB and/or persistent fatigue should be considered for an iron status blood test. This will allow clinicians to determine whether further investigation or management is required, including dietary or supplemental support where ID is identified.

Future research directions

- Since this study only collected data during menstruation, future studies should consider tracking daily symptoms across the entire MC, or at least during the premenstrual phase, as well as menstruation. This would provide a more comprehensive dataset of MC symptoms, their severity and association with self-perceived HMB and iron status.
- Objective measurement of menstrual fluid loss could be incorporated in future studies investigating the association between menstrual fluid loss and symptom severity. Future studies may consider the following tools: PBAC scoring, menstrual cups, or weighing sanitary products, depending on study resources.
- Future studies may consider including perimenopausal women, as changes to menstrual fluid loss as a result of steroid hormone changes with perimenopausal may increase susceptibility to ID and IDA, and self-reported severity of symptoms during menstruation.
- Intervention studies may be considered to determine whether dietary, supplemental, or combined strategies reduce the rating of severity of menstruation symptoms in women with HMB and/or ID.

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Appendix A

Menstrual cycle and symptoms questions

Link to results To help us with our data collection and ensure that we are linking your response to your data. Please enter your <u>Surname</u> in the textbox below

_____

Q11 To help us with our data collection and ensure that we are linking your response to your data. Please enter your <u>Surname</u> in the textbox below

_____

Menstrual cycle Is menstrual bleeding present?

- ○ Yes
- ○ No

Menstrual cycle How would you rate the menstrual blood flow in the last 24 hours?

- ○ Minimal, Light, Scant
- ○ Moderate
- ○ Heavy

Menstrual cycle Is the amount of menstrual blood lost normal for you?

- ○ No
- ○ Yes

Have you experienced any of these symptoms today? Select all that apply and how much they have impacted your sport and everyday activities.

	None at all	A little	A moderate amount	A lot	A great deal
Stomach cramps	☐	☐	☐	☐	☐
Headache/migraine	☐	☐	☐	☐	☐
Lower back pain	☐	☐	☐	☐	☐
Joint pain and or muscle cramps	☐	☐	☐	☐	☐
Nausea/sickness/vomitting	☐	☐	☐	☐	☐
Diarrhoea	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐
Increased tiredness/fatigue	☐	☐	☐	☐	☐
Dizziness/light headness/reducted concentration	☐	☐	☐	☐	☐
Disrupted sleep	☐	☐	☐	☐	☐
Water retention	☐	☐	☐	☐	☐
Changes in mood/increased irritability	☐	☐	☐	☐	☐
Cravings/increased appetite	☐	☐	☐	☐	☐
Poor concentration and memory problems	☐	☐	☐	☐	☐
Bloating/ Increased gas	☐	☐	☐	☐	☐

Changes to/difficulties breathing	☐	☐	☐	☐	☐
Breast tenderness/pain	☐	☐	☐	☐	☐
Other (please specify)	☐	☐	☐	☐	☐