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The Epidemiology of Menstrual Pain in a South African University Population

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The Epidemiology of Menstrual Pain in a South African University Population.



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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2023



FACULTY OF HEALTH SCIENCES

DECLARATION

I declare that all the work contained in this thesis is my own, except for data collection. Data collection for this study was completed by miss Chloe Flinn. I performed all data cleaning, data analysis and the write up is entirely my work. It is being submitted for the degree of MSc (Med) in Physiology at the University of the Witwatersrand, Johannesburg. The work herein has not been submitted before for any degree or examination in any other university.

Signed at ……

On the ……30th ……. day of …….July…….…… 2023.

RESEARCH OUTPUT

Local conference presentations

- 4th Annual BFRG Research Day, Johannesburg 2019
  Oral presentation: "The epidemiology of menstrual pain in a South African university population"

ABSTRACT

Dysmenorrhoea, pain associated with menstruation, is a significant public health concern among young women of reproductive age. Identifying associated risk factors for the development of dysmenorrhoea is essential to minimize the impact of monthly menstrual pain on the daily functioning of these women, both in a personal and professional capacity. However, epidemiological data on the prevalence and associated risk factors for dysmenorrhoea in South Africa are scarce. This study aimed to determine the prevalence of dysmenorrhoea and its associated risk factors in a South African university student and staff population. An online survey was distributed to all 26 public universities across South Africa. The final sample comprised data from 7280 participants, and I found a high prevalence [76.7% (95% CI, 75.7-77.6)] of moderate-to-severe dysmenorrhoea among the respondents. Factors significantly associated with increase odds of experiencing moderate to severe dysmenorrhoea included: having heavy (adjusted OR = 2.749, 95% CI 2.208-3.421; $p < 0.001$) menstrual flow, having a positive family history of dysmenorrhoea (adjusted OR = 1.615, 95% CI 1.346-1.938; $p < 0.001$), always experiencing poorer subjective sleep quality ["often" (OR= 1.595, 95% CI 1.16-2.191; p=0.004), "sometimes" (OR= 1.523, 95% CI 1.22-1.902; p=0.0002) and "rarely" (OR=2.046, 95% CI 1.596-2.623; p<0.0001)], and scoring higher on the central sensitisation inventory total score (adjusted OR= 1.033, 95% CI 1.026-1.04; $p < 0.001$). On the other hand, factors significantly associated with decrease odds of experiencing moderate to severe dysmenorrhoea included: older age at the time of the study (adjusted OR= 0.982, 95% CI 0.967-0.998; p= 0.0285), older age at menarche (adjusted OR = 0.938, 95% CI 0.89-0.989; p= 0.0186), having been pregnant (adjusted OR = 0.757, 95% CI 0.605-0.946; p= 0.0145), lower BMI (adjusted OR = 0.986, 95% CI 0.972-1; p = 0.044), being of European ancestry (adjusted OR = 0.698, 95% CI 0.567-0.859; p = 0.007), and having light menstrual flow (adjusted OR= 0.473, 95% CI 0.373-0.6; $p < 0.001$). I also found a significant impact of dysmenorrhoea on daily life, with 51.6% of respondents reporting absenteeism from school or work during menses and 88.4% of the respondents requiring pharmacological treatments, such as contraceptive pills and nonsteroidal anti-inflammatory drugs (NSAIDs), to manage their menstrual pain. The study highlights the need for increased awareness, education, and effective interventions aimed

at reducing the prevalence and impact of dysmenorrhoea on women's lives. The implications of both the increased central sensitisation (CS) and the sleep-pain reciprocal relationship suggest that they could potentially lead to the development of chronic pain conditions. Future research should further explore the interventions and management strategies that could improve sleep quality and prevent the onset of central sensitisation, thus reducing the risk of developing chronic pain conditions. The findings have important implications for the management of dysmenorrhoea that can improve women's quality of life and promote better health outcomes. These findings also point towards the need to educate women about the importance of seeking medical attention for dysmenorrhoea and the potential long-term implications of untreated dysmenorrhoea.

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As I sit down to write this acknowledgement letter for my master dissertation, I cannot help but feel overwhelmed with gratitude. There are so many people who have supported me throughout this journey, and without whom, I could not have achieved this milestone.

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I am also grateful for the opportunity to present my preliminary results at the Brain Function Research Group (BFRG) research day in 2019. The feedback and insights from the BFRG members were invaluable in shaping my research, and I am thankful for their continued support.

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As my mom likes to say, every master dissertation has its ups and downs, its detours, but the most important thing is to learn from all those detours and cross the final line. I am grateful for all the lessons I have learned along the way, and I am excited to see where this journey takes me next.

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List of abbreviations and symbols

BFRG	Brain Function Research Group
BMI	Body Mass Index
CNS	Central Nervous System
COX	Cyclooxygenase
CS	Central Sensitisation
CSI	Central Sensitisation Inventory
CSS	Central Sensitivity Syndromes
FSH	Follicle Stimulating Hormone
HPO axis	Hypothalamic-pituitary-ovarian axis
IUD	Intra-Uterine device
LH	Luteinizing hormone
NSAIDs	Nonsteroidal anti-inflammatory, nonsteroidal anti-inflammatory drug
PCOS	Polycystic ovarian syndrome
PD	Primary dysmenorrhoea
PGF2	Prostaglandin F2
PID	Pelvic inflammatory disease
PMS	Premenstrual symptoms
REM	Rapid eye movement
SD	Secondary dysmenorrhoea
SES	Socioeconomic status
VAS	Visual Analog Scale
WHO	World Health Organization

INTRODUCTION

Dysmenorrhoea refers to painful menstrual periods or cyclic painful cramping in the lower abdomen caused by uterine contractions during menstruation (Mohapatra et al., 2016). Affecting between 51-90% of women of reproductive age (Margaret & Manjubala, 2016), it is considered the most common gynaecological complaint among women of childbearing age (Coco, 1999; Subasinghe et al., 2016). The World Health Organisation (WHO) reports that between 17%-81% of women of reproductive age perceive their menstrual bleeding to be excessive and painful (Latthe, Mignini, et al., 2006). The menstruation-associated pain may radiate to the lower back and/or thighs and is often accompanied by headache, nausea, constipation or diarrhoea, lower back pain, and increased urinary frequency (Burnett et al., 2005). As such, dysmenorrhoea impacts quality of life (Iacovides et al., 2014), at least monthly, and is associated with greater health care costs and significant absenteeism from work and school leading to socioeconomic burden (Karout et al., 2012; Payne et al., 2017; Ramya, 2012; Sewvandi et al., 2013). Dysmenorrhoea is also likely underdiagnosed because women tend to accept the pain as "normal" for a woman to "endure", and hence, women often do not report the pain, nor do they seek medical treatment (Campbell & McGrath, 1997; Coco, 1999; Proctor, 2006; Reddish, 2006). In addition, menstrual pain is also under-treated (Iacovides et al., 2015), which ultimately means that in addition to experiencing substantial pain that impacts their quality of life, the repetitive monthly pain may also put these women at risk of further significant chronically painful clinical conditions, possibly through central sensitisation (Iacovides et al., 2015). In this literature review (Chapter 2), I will review contemporary information relating to the prevalence, severity, and associated risk factors of dysmenorrhoea. In addition, I will focus on the link between dysmenorrhoea, sleep disturbances and central sensitisation.

LITERATURE REVIEW

2.1 A brief overview of dysmenorrhoea

Dysmenorrhoea is categorised as primary or secondary dysmenorrhoea. Primary dysmenorrhoea is defined as recurrent painful menstrual cramps in the absence of a specific pelvic disease or abnormality (Coco, 1999; Dawood, 1990; Iacovides et al., 2015c; Maruf et al., 2013). Primary dysmenorrhoeic pain usually begins within the first year or two of menarche and has a predictable onset; the pain begins just before, or as menstruation starts (day 1 of the menstrual cycle) (Dawood, 2006). The pain is usually most severe during the first or second day of menstruation and typically lasts between 12 to 72 hours (Coco, 1999). Menstrual pain, which can range from mild to severe, is felt in the lower abdomen, and may also be felt in the lower back, or thighs. In addition, pain may be accompanied by other symptoms including nausea, vomiting, fatigue, and diarrhoea (Coco, 1999; Dawood, 2006).

The pathogenesis of primary dysmenorrhoea is not clearly understood; however, the most widely accepted explanation is the overproduction of uterine prostaglandins, particularly prostaglandin F2 alpha (PGF2α) (Dawood, 2006; Iacovides et al., 2013). Prostaglandins trigger uterine muscle contractions, essential for endometrial shedding during menstruation. Hence excess prostaglandin release from arachidonic acid (a common component of cell membrane phospholipids) and other fatty acids results in more frequent and forceful contractions of muscles of the uterus (Dawood, 2006). Prostaglandins also cause constriction of the blood vessels in the uterus. As a result, excess prostaglandin release leads to both ischaemia and hypoxia of the uterine muscle (Dawood, 1990; Willman et al., 1976), and hence pain associated with menstruation. With reduced oxygen supply to the uterine muscle, waste products such as carbon dioxide and lactic acid accumulate, which could also contribute to the discomfort and pain experienced with menstruation (Chan et al., 1981; Dawood, 1990; Willman et al., 1976).

Secondary dysmenorrhoea is diagnosed when menstrual pain can be attributed to a specific underlying pelvic pathology, such as endometriosis, adenomyosis, fibroids, uterine cysts and polycystic ovarian syndrome (PCOS) (Monaghan et al., 2009). In women who develop secondary dysmenorrhoea, menstruation typically becomes suddenly painful after years of pain-free menstrual cycles, i.e. several years after menarche, and in general, secondary dysmenorrhoea is reported in women over the age of twenty years and women in their late thirties or forties (Ju et al., 2014). Unlike primary dysmenorrhoea, pain associated with secondary dysmenorrhoea may have an unpredictable onset, be constant or diffuse, and is not necessarily strictly associated with menstruation (Hofmeyr & Bassin, 1996; Proctor, 2006).

2.2 Prevalence and severity of primary dysmenorrhoea

Primary dysmenorrhoea is the most common gynaecological complaint in women of reproductive age (Iacovides et al., 2013, 2015; Singh et al., 2008). The overall prevalence of primary dysmenorrhoea reported across nations ranges between 51% and 90% among women of reproductive age (Proctor, 2006; Unsal et al., 2010), with the prevalence reported to decrease with increasing age (Dawood, 2006; Ozerdogan et al., 2009; Speroff & Fritz, 2005; Unsal et al., 2010).

The severity of dysmenorrhoea can range from mild to severe. Mild dysmenorrhoea is characterized by cramping pain in the lower abdomen that is usually relieved with over-the-counter pain relievers (Andersch & Milsom, 1982). Severe dysmenorrhoea, on the other hand, can be debilitating and can interfere with daily activities. Approximately 10-25% of women with severe dysmenorrhoea may experience pain that is so severe that it interferes with their daily life (Iacovides et al., 2014, 2015c; Mitsuhashi et al., 2023).

This wide range of prevalence estimates of primary dysmenorrhoea may be due to the lack of a general assessment method and may include women with secondary dysmenorrhoea not yet diagnosed. The various studies in the literature use different questions to assess the presence of menstrual pain, with some also considering the severity of pain and including only “severe pain”, whilst others include the presence of pain regardless of severity (Dawood, 2006; Ozerdogan et al., 2009; Polat et al., 2009; Proctor, 2006).

The lack of agreement on the threshold of pain intensity for designating primary dysmenorrhoea (PD) is a serious issue. Most studies have not consistently quantified the degree of discomfort necessary to classify individuals as having PD, often using visual analog scales (VAS) or numeric rating scales (NRS) (Amodei & Nelson-Gray, 1989; Granot et al., 2001). Additionally, there is inconsistency in the scales (e.g., 0-10 versus 0-100) or criteria (e.g., 4/10 versus 6/10) used to identify women with PD (Arendt-Nielsen et al., 2014; Bajaj et al., 2002; Brinkert et al., 2007; Giamberardino et al., 1997; Iacovides et al., 2013; Ye et al., 2014). Some studies have relied on the Menstrual Symptom Questionnaire scores, categorizing pain as "mild/no menstrual pain" or "moderate/severe menstrual pain" (Aberger et al., 1983; Amodei & Nelson-Gray, 1989; Goolkasian, 1983; Hapidou & De Catanzaro, 1988; Slater et al., 2015). This ambiguity can lead to participants being classified differently in various studies, making it challenging to compare findings accurately. Dysmenorrhoea prevalence is typically described based on individuals experiencing moderate to severe pain that interferes with their daily activities or quality of life (Iacovides et al., 2014, 2015c). The variation in prevalence reports across studies can be attributed to the absence of standardized methods for assessing dysmenorrhea. The literature presents several commonly used definitions of dysmenorrhea, which are listed in Table 2.1 below.

Reports of prevalence estimates vary across studies of women in different countries. Reports include:41% - 97% in a UK population (Zondervan et al., 1998); 52% in Georgia population (Gagua et al., 2012); 33% in Finland population (Suvitie et al., 2016a); 60% in Canadian population (Burnett et al., 2005); 89% in Iran population (Habibi et al., 2015); 45% in Indian population (Shah et al., 2013). These prevalence estimates are most likely underestimations as many women commonly believe the pain to be a normal component of menstruation and do not report severe pain and do not seek help, nor do they seek medical assistance to alleviate the pain (Wong & Khoo, 2010). Also, due to the lack of standardised methods to diagnose primary dysmenorrhoea, these estimates may also include undiagnosed secondary dysmenorrhoea.

Apart from different diagnostic tools being used across studies, attitudes/beliefs toward menstruation also vary across countries and cultures (Iacovides et al., 2015c). Cultural practices, attitudes and beliefs regarding menstruation have a considerable correlation with the reporting of menstrual symptoms including menstrual pain (Chen & Chen, 2005; Stubbs, 2008; Tan et al., 2017). Cultural and ethnic backgrounds determine how pain is communicated (Chen

& Chen, 2005) and how it is treated (Stubbs, 2008; Tan et al., 2017). Women of African and Chinese descent tend not to report issues to do with feminity as they are considered taboo and these young women are taught to expect some "discomfort" from menstruation and therefore perceive menstruation pain as a normal part of their menstrual cycle (Chhabra et al., 2017; Lau et al., 2000).

Menstruation is regarded as a social taboo subject amongst many populations, such as Cherokee Nation of Oklahoma (Sturm, 2002), Indonesia (Hoskins, 2002; Pedersen, 2002), India (Garg & Anand, 2015; Misra et al., 2013), Nepal (Sapkota et al., 2013), Cameroon (Fouedjio et al., 2019), Ethiopia (Belayneh & Mekuriaw, 2019), and Kenya (MacLean et al., 2020) just to name a few. It is not considered as a legitimate or serious health condition by society, but rather as "part of life and part of the menstrual cycle" (Chen et al., 2018). Studies have reported that women who a) express disgust about menstruation, b) view menstruation as a female-only issue, and c) are "traditional" about all issues around menstruation in that they consider menstruation blood and issues to be sacred (a gift or a punishment from god), are less likely to seek treatment (Chen et al., 2018; Tan et al., 2017). Menstruation and its associated discomforts are not only viewed as a normal, but also a positive indication of childbearing potential, and hence, women are often encouraged to be tolerant of menstrual pain without complaining (Chen et al., 2018; Lau et al., 2000). In African rural communities, dysmenorrhoea continues to be masked in shame and secrecy (Chhabra et al., 2017). Collectively, cultural beliefs and lack of education about dysmenorrhoea result in unvoiced grievances related to menstruation and lack of medical assistance, and hence dysmenorrhoea is undertreated, and prevalence estimates are likely underestimated.

Table 0.1: Different definitions of dysmenorrhoea in the literature

Study	Country	Sample size (N)	Definition of Dysmenorrhoea	Prevalence of Dysmenorrhoea
Andersch & Milsom, 1982	Sweden	656	-No pain: "painless menstrual periods." -Mild pain: "sometimes or always experiencing low uncomfortable cramps that never interfered with daily tasks." -Moderate pain: "sometimes or always experiencing very painful menstrual cramps." -Severe pain: "sometimes or always cutting back on activities in addition to experiencing painful menstrual cramps."	72.4% (mild, moderate, and severe)
Tavallaee et al., 2011	Iran	381	-No pain: "painless menstrual periods." -Mild pain: "sometimes or always experiencing low uncomfortable cramps that never interfered with daily tasks." -Moderate pain: "sometimes or always experiencing very painful menstrual cramps." -Severe pain: "sometimes or always cutting back on activities in addition to experiencing painful menstrual cramps."	50.0% (moderate-severe)
Jarrett et al., 1995	United State of America	61	-No pain: "painless menstrual periods." -Mild pain: "sometimes or always experiencing low uncomfortable cramps that never interfered with daily tasks." -Moderate pain: "sometimes or always experiencing very painful menstrual cramps." -Severe pain: "sometimes or always cutting back on activities in addition to experiencing painful menstrual cramps."	44.0% (moderate-severe)
Muluneh et al., 2018	Ethiopia	539	Experiencing one or more of the following symptoms: abdominal pain, groin/pelvic pain, back pain, or thigh pain before and/or during her menstrual periods over the past year.	69.3% (no severity defined)

Study	Country	Sample size (N)	Definition of Dysmenorrhoea	Prevalence of Dysmenorrhoea
Hu et al., 2020	China	4 606	Primary dysmenorrhoea: “Have you experienced one or more of menstrual cramps or abdominal pain during your menstruation for the last one year?” and its severity using VAS. Excluded secondary dysmenorrhoea: “Do you have the following diseases or symptoms?” (i.e.: pelvic inflammation, endometriosis, adenomyosis, hysteromyoma, secondary dysmenorrhoea, and other diseases)	41.7% (mild, moderate, and severe)
Harlow & Park, 1996	United State of America	165	"Have you had menstrual cramps or abdominal pain during your period at least once in the past year?"	71.6% (no severity defined)
El Gilany et al., 2005	Egypt	664	"Having painful menstruation within the preceding three months, and the intensity of the pain was classified as mild, moderate, or severe using VAS."	76.1% (mild, moderate, and severe)
Kazama et al., 2015	Japan	1 167	"Visual Analog Scale (VAS), with moderate (VAS ≥ 4) or severe (VAS ≥ 7)."	46.8% (moderate to severe)
Agarwal & Agarwal, 2010	India	970	“Presence or absence of Dysmenorrhoea [defined as painful menstruation]”, and its severity using VAS	71.96% (mild, moderate, and severe)
Jamieson & Steege, 1996b	United State of America	581	"Do you currently have pain with your menstrual periods?”	90.0% (no severity defined)
Acheampong et al., 2019	Ghana	680	“Have you ever had menstrual pain?”	68.1% (mild, moderate, and severe)
Kural et al., 2015b	India	310	“-Onset of pain within 6–12 hours after onset of menses. -Lower abdominal and pelvic pain associated with onset of menses and lasting for 9–72 hours. -Lower back pain. -Medial or anterior thigh pain.” and its severity using VAS.	84.2% (mild, moderate, and severe)
Grandi et al., 2012	Italy	408	“Menstrual pain associated with a need for medication and inability to function normally”, and its intensity using VAS.	84.1% (mild, moderate, and severe)

2.3 General risk factors associated with dysmenorrhoea

Risk factors for the development of dysmenorrhoea include but are not limited to, nulliparity, obesity, family history of dysmenorrhoea, stress, depression, cigarette smoking, and substance abuse (Akshara et al., 2015). Other reported factors that may increase the risk of dysmenorrhoea include early-onset of menarche (Sundell et al., 1990), higher body mass index (Ju et al., 2014), and prolonged or aberrant menstrual flow (Fatima et al., 2017). In addition, there is evidence supporting a dose-response relationship between exposure to environmental tobacco smoke and increased incidence of dysmenorrhoea (Ballagh & Heyl, 2008). Childbirth, in contrast, may relieve monthly primary dysmenorrhoeic pain (Christiani et al., 1995). Finally poor sleep health, especially self-reported short sleep (i.e.: less than 8 hours) was found to be a risk factor for the development of dysmenorrhoea (Gagua et al., 2012, 2013).

In a review that aimed to ascertain a more accurate worldwide representation of the prevalence, incidence, and risk factors of dysmenorrhoea (primary and secondary dysmenorrhoea), the authors identified 3 longitudinal studies and 12 population-based, cross-sectional studies (Ju et al., 2014). Due to the wide heterogeneity in definitions of dysmenorrhoea, and the different diagnostic tools employed and the different attitudes toward menstruation in various countries (Dawood, 2006; Ozerdogan et al., 2009; Polat et al., 2009; Proctor, 2006), the authors of the review chose a narrative approach rather than a meta-analytic approach (Ju et al., 2014). They found that of the more than 25 risk factors investigated, only family history of dysmenorrhoea (primary and secondary) and higher stress levels had a moderately strong and reliable link with the reporting of painful periods (Ju et al., 2014). In contrast, older age, higher number of live births, and use of birth control dependably revealed a protective effect against the development of dysmenorrhoea (Ju et al., 2014). Ju et al., 2014 argue that it is challenging to identify the precise risk factors for the development and severity of dysmenorrhoea in general because mostly mixed results have been observed for many of the risk factors such as age at menarche, smoking, alcohol consumption, BMI, exercise just to name a few examples. Since, secondary dysmenorrhoea is associated with an underlying and specific pathophysiology, I will focus the rest of my introduction on risk factors for the development of primary dysmenorrhoea.

2.3.1 Genetic predisposition for primary dysmenorrhoea

The strongest risk factor for the development of primary dysmenorrhoea is a family history of dysmenorrhoea. According to numerous reports the prevalence of dysmenorrhoea is considerably higher among adolescent females with positive family history of dysmenorrhoea (Avasarala, Kameswararao & Panchangam, 2008; Ju et al., 2014a; Kumbhar et al., 2011). Thus, evidence indicates that genetic factors are involved in the etiology of primary dysmenorrhoea and family history is a strong predictor for the occurrence of dysmenorrhoea in offspring and siblings (Adeyemi & Adekanle, 2007; Avasarala, Kameswararao & Panchangam, 2008; Ju et al., 2014).

2.3.2 Primary dysmenorrhoea and age at menarche

For most girls, menarche occurs between the ages of 10 and 16 years, however the younger the age of menarche, the higher the risk of dysmenorrhoea (Zegeye et al., 2009). Similarly, Harlow & Park, (1996) reported that earlier age at menarche is associated with a greater likelihood of menstrual pain, as well as greater severity and longer duration of menstrual pain. According to Ameade & Garti (2016) trends show that age of menarche in current times is lower than decades earlier (1980s) in most countries. In Europe, the median age at menarche decreased by 2 to 3 months per decade from 16.5 years in 1840 to about 13.0 years in the 1960s, with a variation of 0.5 years between countries (Gohlke & Wölfle, 2009).

Menarche is considered as a sensitive indicator of various population characteristics including nutritional status, geographical location, environmental conditions, and the magnitude of socioeconomic inequalities in a society (Chumlea, 2003; Swenson & Havens, 2004; & Thomas, *et al.* 2001). Age at menarche is reported to be influenced by socioeconomic-status, with females living in urban areas and part of a higher socio-economic environment, experiencing menarche at an earlier age than those from rural and lower income status (Ameade & Garti, 2016). High body mass index (BMI) was found to be associated with earlier age of menarche, which may be related to hormonal activity in fat tissue, a shared genetic background, or prenatal programming activated by a high maternal BMI (Shrestha et al., 2011). Earlier menarche has also been linked to increased prevalence of obesity, insulin resistance and unhealthy lipid

profiles (Bourguinig, 2004; Shrestha et al., 2011; Tunau et al., 2012). Previous studies have also reported that females with a high energy, high protein and high fat diet tend to have an earlier onset of age at menarche (Abioye-Kuteyi et al., 1997; Kaplowitz, 2006). An American study found that racial status influences the onset of menarche, with females from African and Hispanic ancestries tending to have an earlier onset of menarche than females from European ancestries (Chumlea et al., 2003). This suggests a combination of genetic, environmental, and socioeconomic factors could contribute to an earlier age at menarche in females from African and Hispanic ancestries. It is unclear whether menarche occurring earlier causes dysmenorrhoea directly or if the association is caused by any of the other factors connected to earlier menarche. However, more research is needed to fully understand the complex factors that influence the timing of menarche.

2.3.3 Relationship between dysmenorrhoea and body mass index

According to the research studies, overweight and obesity increase the biosynthesis of prostaglandins; and consequently increase the severity of dysmenorrhoeic pain in both women with primary dysmenorrhoea and with endometriosis (i.e.: secondary dysmenorrhoea) (Benedetto, 1989). However, previous studies on the association between primary dysmenorrhoea and anthropometric indices (including BMI) found no significant association between BMI itself and primary dysmenorrhoea (Haidari et al., 2011; Khodakarami et al., 2015; Raghunath Shinde & Laddad, 2016). However, these studies did report significant associations between severity of dysmenorrhoea and other anthropometric indices, including higher waist-to-hip ratio, higher waist circumference, and greater body fat percentage (Barnard et al., 2000; Haidari et al., 2011; Khodakarami et al., 2015; Raghunath Shinde & Laddad, 2016)

2.3.4 Primary dysmenorrhoea and cigarette smoking

A large study that monitored over 9000 women with dysmenorrhoea (no distinction whether primary or secondary), from a national medical database, over an average duration of 13 years, found that smoking cigarettes was associated with more severe menstrual cramps (Ju et al., 2014b). Also, girls who start smoked from an early age (13 years old) may have the greatest risk of experiencing severe dysmenorrhoea compared to those who start later in life, and

compared with those who quit (Ju et al., 2014b; Parazzini et al., 1994; Sundell et al., 1990). It has been proposed that smoking at an early age may affect the milieu of hormones that are very active during menarche and puberty, which could be one mechanism contributing to the increased menstrual pain reported in smokers who started smoking at a young age (Ju et al., 2014b). Ju et al. (2014b) also incorporated a pilot analysis about the relationship between smoking cessation and dysmenorrhoea: women who gave up smoking were more likely to experience lower or no menstrual pain at all compared to women who continued to smoke (Ju et al., 2014). Pain severity is further reported to be directly related to the number of cigarettes smoked per day (Parazzini et al., 1994; Sundell et al., 1990).

These findings collectively support that women who smoke cigarettes may be at higher risk of dysmenorrhoea (Dorn et al., 2009) in general, and more likely to experience more severe pain, compared to non-smokers with primary dysmenorrhoea (Parazzini et al., 1994) The underlying pathophysiology of the relationship between smoking and menstrual pain may be due to chronic hypoxia (see paragraph 2.1 and 2.4), but this relationship and the underlying mechanisms driving it require further investigation. It is also worth noting that although these studies have represented women of African ancestry, they fail to represent women of African descent living in Africa.

2.3.5 Primary dysmenorrhoea and diet

There is mixed evidence regarding the effect of diet on dysmenorrhoea and its pain intensity. There is a possible association between high sugar (carbohydrate) diet and increased dysmenorrhoea frequency and intensity (Ozerdogan et al., 2009). Lower dysmenorrhoeic pain intensity and duration was observed with a low-fat vegetarian diet (Barnard et al., 2000). This lower pain intensity may be due to the association between low fat diet and lower oestrogen level in women (Prentice et al., 1990). Diet consisting of high fibre intake has also been shown to be associated with lower dysmenorrhoeic pain due to the elevated level of oestrogen elimination through faeces (Aldercreutz, 1990). Fish and fish oil have also been shown to be associated with a decrease in dysmenorrhoea pain intensity and symptoms of dysmenorrhoea (Balbi et al., 2000; Nagata et al., 2005). This association might be due to the fish omega-3 fatty acids content which prevent the biosynthesis of prostaglandins by impeding arachidonic acid

production (Balbi et al., 2000) (see paragraph 2.4). Based on the literature, a low-fat diet may help reduce dysmenorrhoeic pain during menstruation (Prentice et al., 1990).

2.4 Management of primary dysmenorrhoea

There are several approaches to the management of primary dysmenorrhoea including pharmacological, nonpharmacological, and surgical approaches. The most common first line of pharmacological treatment for primary dysmenorrhoea are non-steroidal anti-inflammatory drugs (NSAIDs) (Harel, 2004; Marjoribanks et al., 2015; Zahradnik et al., 2010). This treatment is based on the most widely accepted underlying pathophysiology of primary dysmenorrhoea; abnormally increased secretion of prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) and eicosanoids in the endometrium, which increase uterine contractions (Dawood, 2006). Arachidonic acid, produced from hydrolysis of phospholipids by phospholipase, is used as a precursor for the biosynthesis of prostaglandins and prostanoids through the cyclooxygenase (COX) pathway (Dawood, 2006). NSAIDs inhibit the action of COX (Marjoribanks et al., 2015; Mendiratta & Lentz, 2017), an enzyme responsible for the production of endometrial prostaglandins, consequently alleviating cramps and restoring normal uterine activity. The NSAIDs most commonly prescribed for primary dysmenorrhoea include naproxen, ibuprofen, celecoxib, diclofenac, and mefenamic acid (Iacovides et al., 2015c; Marjoribanks et al., 2015; Oladosu et al., 2018), and, on a global scale, NSAIDs provide effective menstrual pain relief (Ferries-Rowe et al., 2020; Marjoribanks et al., 2015).

Although NSAIDs alleviate pain, they can also cause adverse effects including gastrointestinal and neurological side effects (Marjoribanks et al., 2015). Also, NSAIDS are ineffective in about 20 – 25% of women with primary dysmenorrhoea (Marjoribanks et al., 2015; Oladosu et al., 2018). When NSAIDs are ineffective or are contraindicated, hormonal contraception can be used as a viable and effective second-line therapy for treating primary dysmenorrhoea (Iacovides et al., 2015; Sturpe, 2013). Hormonal contraceptives treat primary dysmenorrhoea by suppressing ovulation and causing regression of the endometrium, shortening the time of endometrial proliferation, and limiting the secretory activity of endometrial glands (Sturpe, 2013). The most studied hormonal contraceptive method for this indication is the combined oral contraceptive pill, but other methods, including the contraceptive patch, contraceptive ring, medroxyprogesterone injection, and levonorgestrel-releasing intrauterine system, are also

recommended because of their similar mechanisms of action (Burnett et al., 2005; Damm et al., 2019).

Some literature supports several dietary, herbal, and alternative medicine methods as emerging dysmenorrhoea therapies (Sturpe, 2013). Even though a variety of herbal and dietary supplements have claimed to help improve dysmenorrhoeic pain (such as vitamin B_1, vitamin B_6, vitamin E, magnesium, and fish oil), systematic reviews have established that the only supplement with any reasonable evidence supporting effectiveness to alleviate pain is vitamin B_1 (Hosseinlou et al., 2014; Proctor et al., 2001; Zhu et al., 2008). It has further been proposed that keeping vitamin D levels high/within normal range can reduce both monthly pain and use of NSAIDs; possibly because higher vitamin D levels have been observed to lead to reductions in prostaglandin synthesis (Lasco et al., 2012). Nevertheless, clinical trials have yet to determine whether Vitamin D or Vit B1 can effectively reduce dysmenorrhoeic pain (Saei Ghare Naz et al., 2020).

Other alternative non-pharmacological approaches include acupuncture. In a recent meta-analysis, the effectiveness of acupuncture in treating primary dysmenorrhoea was investigated. The analysis comprised 42 randomized controlled trials that compared acupuncture or acupressure with sham/placebo groups, medication, no treatment, or alternative treatments. The findings revealed significant reductions in pain scores when compared to NSAIDs (Smith et al., 2016). However, the meta-analysis had some limitations, including the variation in study quality, the lack of comparison to other non-pharmacological treatments, such as heat therapy or massage, and the failure to control for the severity of dysmenorrhoea, making it unclear whether acupuncture is more effective for women with mild dysmenorrhoea than for women with severe dysmenorrhoea. Other non-pharmacological therapeutic approaches include heating pads for cramps, extra bed rest or sleep, physical exercise, meditation, aromatic oils, ginger root tea, salt water, and increased calcium intake (Iacovides et al., 2015c; Marjoribanks et al., 2015). However, the evidence for the effectiveness of these treatments is limited in that many of the studies were small, often did not compare the treatments to a placebo or other active treatments and often did not measure the long-term effects of the treatments. Limited work suggests the possible use of surgical treatment for management of primary dysmenorrhoeic pain in severe cases. Two main surgical treatments that have been utilised in more recent decades due to advances in laparoscopic procedures are uterine nerve ablation

(UNA) and presacral neurectomy (PSN) (Proctor et al., 2005). These procedures interrupt most of the cervical nociceptors (Ramirez & Donnellan, 2017). Observational studies have supported the use of these procedures for primary dysmenorrhoea, however since both operations only partially interrupt the cervical sensory nerve fibres in the pelvic area, these types of surgeries cannot be considered as options for widespread use in clinical practice (Khan et al., 2012). Further, the role of surgical treatment in managing primary dysmenorrhoea is limited due to the associated surgical complications and the recurrence of symptoms (Louden & Skinner, 2001). It is suggested that surgery may be indicated in severe secondary dysmenorrhoea, or in cases where primary dysmenorrhoea is refractory to medical treatment (Talley & O'Connor, 2006).

2.5 Impact of dysmenorrhoea

2.5.1 Quality of life

Monthly dysmenorrhoeic pain affects various aspects of the personal lives of women who experience it. Menstrual pain experienced by some women with dysmenorrhoea can be significantly incapacitating, having been likened to renal colic pain (Ayan et al., 2012; Iacovides et al., 2013). Given that up to 91% of women of reproductive age experience monthly pain, with 2%–29% experiencing severe pain (Ju et al., 2014), these women are frequently absent from university/college and work (Ahuja, 2016; Granot et al., 2001), have reduced physical activities during menstruation each month (Iacovides et al., 2014), and overall, experience a poorer quality of life, compared to women without monthly pain (Okoro et al., 2013, Iacovides, 2013).

Numerous studies performed worldwide in hundreds of women of reproductive age, established that menstrual pain has a negative impact on multiple aspects of their personal lives, including: family relationships, friendships, social and recreational and physical activities, and school/work performance (Iacovides et al., 2013; Ortiz et al., 2009; Wong & Khoo, 2010). A study of 198 female learners, aged 20 years or younger, established that students experienced symptoms severe enough to cause absenteeism from classes and tests, poor academic performance, as well as social withdrawal from friends, gathering, and sports during menses

(Chen & Chen, 2005). These findings are supported by those of others (AuBuchon & Calhoun, 1985; Lau et al., 2000). Similarly, with regards to quality of life, women with dysmenorrhoea have been shown to score significantly lower in the domains of physical and social functioning, physical role functioning, bodily pain, and general health perceptions, compared to women who do not report experiencing dysmenorrhoea (Barnard et al., 2003; Unsal et al., 2010; Vincent et al., 2011).

The impact of monthly dysmenorrhoea extends beyond the personal lives of these women. Primary dysmenorrhoea pain can be described as both chronic (recurring with regular onset) and acute (short period of time)(Baker et al., 1999). The recurrent cyclic pain results in a repeated absenteeism which in turn has significant socioeconomic consequences due to decreased school/work performances (Kansiime et al., 2020). The rate of absenteeism in women who reported having dysmenorrhoea ranges from 34-50% (Andersch & Milsom, 1982; Sundell et al., 1990) with 10-30% losing 1- 2 days of work/school per month (Dawood, 1988; Kansiime et al., 2020) while women not reporting dysmenorrhoea did not lose any day of work/school.

The monthly experience of dysmenorrhoeic pain can further result in an increased risk of experiencing psychological symptoms such as stress and depression. Studies that have tracked changes in mood across the menstrual cycle in women with dysmenorrhoea have found increased agitation and depression symptoms during menses (Baker et al., 1999; Iacovides et al., 2015b; Pakpour et al., 2020). Some studies have investigated psychological symptoms, like depression, in women with recurring primary dysmenorrhoeic pain, with some evidence of a bidirectional association between stress and depression with dysmenorrhoeic pain intensity (Bair et al., 2003; Rhudy et al., 2005; Rhudy & Bartley, 2010; Takahashi et al., 2006; Von Korff & Simon, 1996; Weisenberg et al., 1984, 1998). Another study found a strong association between depression/anxiety and higher number of menstrual symptoms including irritability, agitation, depression, cramps, abdominal pain, lower back pain, pain medicine, breast tenderness (Dorn et al., 2009).

2.5.2 Impaired sleep

Many studies, both epidemiological and experimental, have investigated the relationship between pain and sleep. Pain is reported to be a primary cause of insomnia (Afolalu et al., 2018; Drewes & Arendt-Nielsen, 2001; Stroemel-Scheder et al., 2020), and clinical studies demonstrate significant associations between pain and poor sleep quality in patients with various chronic pain conditions (Afolalu et al., 2018; Drewes & Arendt-Nielsen, 2001; Husak & Bair, 2020; Stroemel-Scheder et al., 2020; Wolfe et al., 2006).

Similarly, dysmenorrhoeic pain is reported to affect sleep composition and quality (Baker et al., 1999). Differences in sleep were reported in women with severe primary dysmenorrhoea during the painful menstruation phase, compared with pain-free healthy controls, and compared with their own pain-free mid-luteal and mid-follicular phase (Baker et al., 1999). Baker's study found that women with primary dysmenorrhoea had higher body temperatures during sleep compared to women without dysmenorrhoea. Additionally, women with dysmenorrhoea had more polysomnographic sleep disturbances, including more awakenings during the night and more time spent awake after initially falling asleep, compared to women without dysmenorrhoea (Baker et al., 1999). Furthermore, women with dysmenorrhoea have reported spending more time in bed before falling asleep and taking more time to wake up, compared with those without dysmenorrhoea (Araujo et al., 2011; Baker et al., 1999; Baker & Driver, 2004; Hachul et al., 2010). Another study reported that women with mild primary dysmenorrhoea reported better sleep quality than women reporting moderate or severe dysmenorrhoea (Woosley & Lichstein, 2014) suggesting that severity of dysmenorrhoea pain influences the extent of sleep disruption.

Pain and sleep disturbances have, in fact, been shown to share a bidirectional relationship, where they both play a role in the maintenance and augmentation of each other (Finan et al., 2013). Accumulating evidence supports that sleep disturbances are actually better predictors of developing chronic pain than chronic pain predicts sleep disturbances (Finan et al., 2013). Thus, more recently studies have shifted their focus to determine the effect of sleep disturbances on pain perception. Using various forms of sleep disruptions, experimental studies have shown that sleep disturbances lead to increased perception of experimentally-induced pain

in healthy participants (Arima et al., 2001; Drewes et al., 1997; Kundermann et al., 2004; Lentz et al., 1999; Moldofsky & Scarisbrick, 1976; Older et al., 1998; Roehrs et al., 2006).

Importantly, longitudinal studies have shown that insomnia is an independent risk factor for the development of chronic pain following acute injury, as well as the spreading of pain from a regional disorder to a more widespread condition (Mikkelsson, 1999; Mikkelsson et al., 1999; Smith et al., 2008).

The mechanisms underlying how sleep disturbances could increase risk for new pain and increase the perception of existing pain appear to be complex and are largely unknown (Boardman et al., 2006; Lyngberg et al., 2005; Mork & Nilsen, 2012; Ødegård et al., 2011). Hypotheses include that sleep disturbances can disrupt neurobiological processes involved in pain processing and regulation, leading to increased pain sensitivity and reduced pain tolerance, making individuals more susceptible to developing chronic pain conditions such as dysmenorrhoea (Christensen et al., 2019; Finan et al., 2013). Specifically, disrupted sleep could lead to alterations in brain regions involved in pain processing and regulation, such as the thalamus and prefrontal cortex, as well as changes in neurotransmitters, including dopamine, serotonin, and GABA, which can modulate sensitivity to nociception (Christensen et al., 2019; Lautenbacher et al., 2006). Sleep deprivation decreases the effectiveness of the noradrenergic and serotonergic systems in descending nociceptive inhibition, leading to reduced pain inhibition and increased spontaneous pain in women (Smith et al., 2007). Additionally, REM sleep deprivation in rats increased the concentrations of glutamate and glutamine in the cerebral cortex, suggesting an increase in excitatory amino acids that may facilitate nociception suggesting that sleep deprivation can lead to decreased pain inhibition via the descending pain-control pathway (Bettendorff et al., 1996). Furthermore, sleep disturbances may lead to inflammation and changes in the immune system, which can contribute to the development and maintenance of chronic pain (Christensen et al., 2019).

In conclusion, it is hypothesized that the repetitive monthly pain in women with primary dysmenorrhoea, and sleep disturbances they experience can contribute to the development and maintenance of central sensitisation. There is evidence to suggest that sleep disturbances can lead to changes in neurotransmitters and hormones involved in pain sensitivity and inflammation, triggering, or exacerbating central sensitisation. Similarly, the recurrent pain

experienced in dysmenorrhoea can contribute to central sensitisation and interfere with sleep, creating a cycle of poor sleep and worsening pain perception suggesting a bidirectional relationship. It is important to consider the bidirectional relationship between sleep disturbances and central sensitisation, as addressing both factors may have reciprocal benefits in managing chronic pain conditions such as dysmenorrhoea.

2.5.3 Risk of central sensitisation

Recurrent menstrual pain may lead to the development of central sensitivity to pain (Yunus, 2007, 2008). Central Sensitisation (CS) is defined as a condition or disorder of the nervous system that is associated with the development and maintenance of chronic pain (Fleming & Volcheck, 2015; Woolf, 2011). Central sensitisation (CS) occurs when the nervous system becomes hypersensitive and overreacts to stimuli, leading to increased pain. The malfunction in CS is due to the amplification and spread of nociceptive signals in the nervous system (caused by chronic pain conditions), causing a persistent state of pain hypersensitivity. This state can result from various factors, such as chronic pain conditions, trauma, inflammation, and sleep disturbances (Fleming & Volcheck, 2015; Woolf, 2011). When central sensitisation occurs, the nervous system undergoes autonomous and sustained facilitation, resulting in the amplification of subsequent responses in nociceptor sensory fibers, even in the absence of ongoing stimulation, after the conditioning stimuli have ceased (Woolf, 2011). This persistent, or regulated, state of reactivity lowers the threshold for what causes pain and subsequently comes to maintain pain (Curatolo et al., 2006; Schwartzman et al., 2001). There is evidence that suggests that recurrent pain, such as monthly menstrual pain, can also be associated with central sensitisation. Hence repetitive dysmenorrhoea pain may also lead to heightened sensitivity to pain, and ultimately, chronic pain (Berkley & McAllister, 2011; Iacovides et al., 2013; Vincent et al., 2011). Primary dysmenorrhoea has indeed been classified as a member of the central sensitivity syndromes (CSS) together with several other clinical conditions including fibromyalgia and tension-type headaches (Yunus, 2007, 2008). The CSS are characterised by pain hypersensitivity in the absence of identifiable tissue injury, inflammation, or a lesion to the nervous system (Iacovides et al., 2013; Woolf, 2011; Yunus, 2007).

Further, the findings of various experimental studies support these claims. Women with primary dysmenorrhoea, compared to those without, have enhanced pain sensitivity to various painful stimuli including, thermal stimuli (Bajaj et al., 2002; Goolkasian, 1983), electrical stimuli (Giamberardino et al., 1997), experimental ischaemic pain (Iacovides et al., 2015b), and experimental musculoskeletal pain (Iacovides et al., 2013). There is therefore increasing experimental evidence to support the hypothesis that primary dysmenorrhoea is associated with increased sensitivity to pain, possibly due to central sensitisation (Giamberardino, 2008; Iacovides et al., 2015b). Studies have also associated secondary dysmenorrhoea, including endometriosis and adenomyosis, with central sensitisation (Stratton & Berkley, 2010).

It is important to highlight that the directionality between central sensitisation and dysmenorrhoea is not yet known. In other words, it is not known whether the repeated experience of dysmenorrhoea leads to heightened sensitivity to pain, or whether these women experience dysmenorrhoea because they have a heightened sensitivity to pain to begin with. The literature simply indicates that women with dysmenorrhoea have increased sensitivity to pain, and central sensitisation is one proposed underlying mechanism for the relationship between dysmenorrhoea and increased pain sensitivity.

2.6 Conclusion

This chapter looked at the prevalence, severity, and some of the associated risks factors of dysmenorrhoea, as well as the effects of primary dysmenorrhoea, specifically with regards to quality of life and sleep disturbances and its potential association with central sensitisation. Dysmenorrhoea is a highly prevalent disorder that periodically disrupts the daily lives of women of childbearing age. I have described and discussed the various risk factors for dysmenorrhoea, including early age at menarche, younger age, nulliparity, heavy or prolonged menstrual flow, smoking, obesity, and positive family history of dysmenorrhoea. In this literature review, I suggest that disrupted sleep, in women with dysmenorrhoea, may contribute to the development and maintenance of central sensitisation, leading to chronic pain conditions. Repeated painful episodes may have far-reaching consequences, including poorer quality of life, strained relationships, social and physical constraints, psychological implications, and sleep disturbances. These consequences may, in turn, predispose women with dysmenorrhoea to chronic pain conditions, either through central sensitisation or disrupted sleep. Therefore,

interventions that address both disrupted sleep and central sensitisation may be important for managing chronic pain conditions such as dysmenorrhoea and improving quality of life for affected women. Although it is not known whether increased sensitivity to pain is the cause- or effect- of dysmenorrhoea, in the context of the literature, I am making a case to include an association between dysmenorrhoea and central sensitisation as potential risk factors.

Similarly, I describe the bidirectional relationship between pain and sleep, and highlight the strong associations between poor sleep and clinical pain. I believe that sleep is often over-looked in clinical pain studies, but that poor sleep should be considered as another potential risk factor for the development of chronic pain. With regards to primary dysmenorrhoea specifically, both central sensitisation and poor sleep have a significant impact on the health of these women, regardless of whether they are the causes- or effects- of dysmenorrhoea, and hence, should both be considered when studying dysmenorrhoea. Lastly, beyond the personal lives of these women, repeated absenteeism from work results in significant socioeconomic burden rendering the condition a significant public health challenge too.

Identifying risk factors associated with dysmenorrhoea can help us design recommendations to manage and/or reduce dysmenorrhoeic pain. Ultimately, this may improve the quality of life in women with dysmenorrhoea but may also help to reduce work or school absenteeism, and hence, socioeconomic burden. To the best of my knowledge, there are no epidemiological data on the prevalence of dysmenorrhoea, and the factors associated with dysmenorrhoea in a South African population, also taking sleep and central sensitisation into account.

2.7 Aims and objectives of the study

Using a large sample of women recruited through university networks across South Africa, the aim of this study is to determine the prevalence and associated factors of dysmenorrhoea (primary and secondary) in a South African university student and staff population.

Specifically, the objectives were to:

i) determine the prevalence of dysmenorrhoea (primary and secondary) in a South African university student and staff population.

ii) describe the demographic and menstrual-related characteristics of women who report no dysmenorrhoea, primary dysmenorrhoea, and secondary dysmenorrhoea.

iii) determine the possible correlates, including sleep quality and central sensitisation, associated with the odds of having moderate-to-severe dysmenorrhoea (whether primary or secondary), over the odds of having no or mild dysmenorrhoea in a South African university student and staff population in univariable and multivariable analysis.

RESEARCH DESIGN AND METHODOLOGY

3.1 Target population

All 26 government-funded universities across South Africa were invited to participate in this study. The target population were the female students and staff, 18 years or older, with access to email. The email inviting participants to take part in the study (Appendix 1) was distributed using each University's email distribution lists. The email contained information that started with an introduction of the research team and was followed by an explanation of the study's aim, and brief methodology. In addition, the email also served as a "subject information sheet", as it explained that participation in the study was completely voluntary, that their information would remain anonymous and confidential (no personal information, such as physical address, telephone number or email address were requested), and that they were free to withdraw from participating at any point before submitting their responses. Lastly, consent was assumed when they proceeded to the next page (Appendix 1) to submit their answers.

Ethical approval was obtained from the Human Research Ethics Committee (clearance certificate number: M170241, Appendix 9), University of the Witwatersrand, before the distribution of the survey. While some universities distributed the survey with the University of the Witwatersrand's ethical clearance certificate, others required that the study be approved by their own research ethic committees before distribution (details in Table 3.1). The map in Figure 3.1 below shows the geographic distribution across South Africa of all the universities that were invited to participate in the study.



Figure 0.1: Map showing the geographical distribution of all public universities in South Africa. All were invited to distribute the survey.

All public universities agreed to participate but only 23 successfully distributed the survey. Table 3.1 displays the list of universities that successfully distributed the survey. It is noteworthy that one university requested not to be identified in the final manuscript and will, therefore, be recorded and labeled as 'Others'.

Table 0.1: Universities that successfully distributed the survey

University	**Distribution and Ethical Requirements**
Cape Peninsula University of Technology	Successfully distributed the survey, following their own ethical approval (CPUT/HW-REC 2017/H35).
Central University of Technology	Successfully distributed the survey, following WITS ethical approval.
Durban University of Technology	Successfully distributed the survey.
Mangosuthu University of Technology	Successfully distributed the survey.
Nelson Mandela Metropolitan University	Successfully distributed the survey, following their own ethical clearance (H17-HEA-NUR-EAP-001).
North-West University	Successfully distributed the survey.
Rhodes University	Successfully distributed the survey.
Sefako Makgatho University	Successfully distributed the survey, with approval from SMUREC (M170241).
Sol Plaatje University	Successfully distributed the survey.
Stellenbosch University	Successfully distributed the survey.
Tshwane University of Technology	Successfully distributed the survey.
University of Cape Town	Successfully distributed the survey, following their own ethical clearance (HREC REF: 300/2017).
University of Fort Hare	Successfully distributed the survey.
University of the Free State	Successfully distributed the survey.
University of KwaZulu-Natal	Successfully distributed the survey.
University of Limpopo	Successfully distributed the survey, following their own ethical approval (TREC/73/2017:IR).
University of Mpumalanga	Successfully distributed the survey.
University of Pretoria	Successfully distributed the survey.
University of South Africa (UNISA)	Successfully distributed the survey, following their own ethical approval (Ref #: 2017_RPSC_041).
University of the Western Cape	Successfully distributed the survey.
University of the Witwatersrand	Successfully distributed the survey.
University of Zululand	Successfully distributed the survey.
Others*	Successfully distributed the survey.

***One university preferred its identity not to be disclosed, hence, it is labelled as "Other".**

3.2 Research instrument

The online survey, constructed by Ms Chloe Flinn, consisted of simple customised, structured questions that were mostly closed ended (i.e., participants had to choose one of several options from drop down menus for a given list of questions on the questionnaire). The survey was written in English and completed on google forms, an online survey (https://www.google.com/forms/about/), which was distributed once to the population electronically through each university's distribution lists/methods. The survey was divided in three sections. The first section gathered socio-demographic data such as gender, menopause status, affiliated university, age, height, weight, ancestry, social class, education, and lifestyle (Appendices 3 - 5). The second section gathered data on menstrual history (Appendices 6 - 8), and the third section gathered data on Central Sensitisation using the validated Central Sensitisation Inventory (CSI) (Mayer et al., 2012; Neblett et al., 2013) (Appendix 8).

3.2.1 Screening section

Respondents were screened for their gender as the study was specifically designed for females in a university population (Appendix 2). If the respondents selected 'male', they were excluded from the survey (and the study), by being redirected to the submission page as they were not allowed to proceed. Respondents were also screening for menopause (Appendix 2). Respondents who selected the "yes" tick box in response to the question "have you gone through or are you going through menopause?" were excluded and redirected to the submission page.

Given that our target population was a university population, respondents needed to belong to one of the 26 South African public universities. To determine which university they belonged to, respondents were asked to select their university from a drop-down option (Appendix 3). This option listed all 26 universities and included a "None" option. Respondents who selected the "None" option were also redirected to the submission page and were excluded from the survey and the study. Thereafter, a multiple-choice question was used to determine whether the respondents were students or staff. They were asked "Are you a full-time or part-time

student, or staff?" and were given four choices: "Full-time student", "Part-Time Student", "Staff" and "None" (Appendix 3). Respondents who selected "none" were redirected to the submission page and excluded from the study. Respondents who fulfilled our study criteria were automatically directed to the sections, which consisted of questions about their sociodemographic details (see section 3.2.2 below) and menstrual cycles (see section 3.2.4 below).

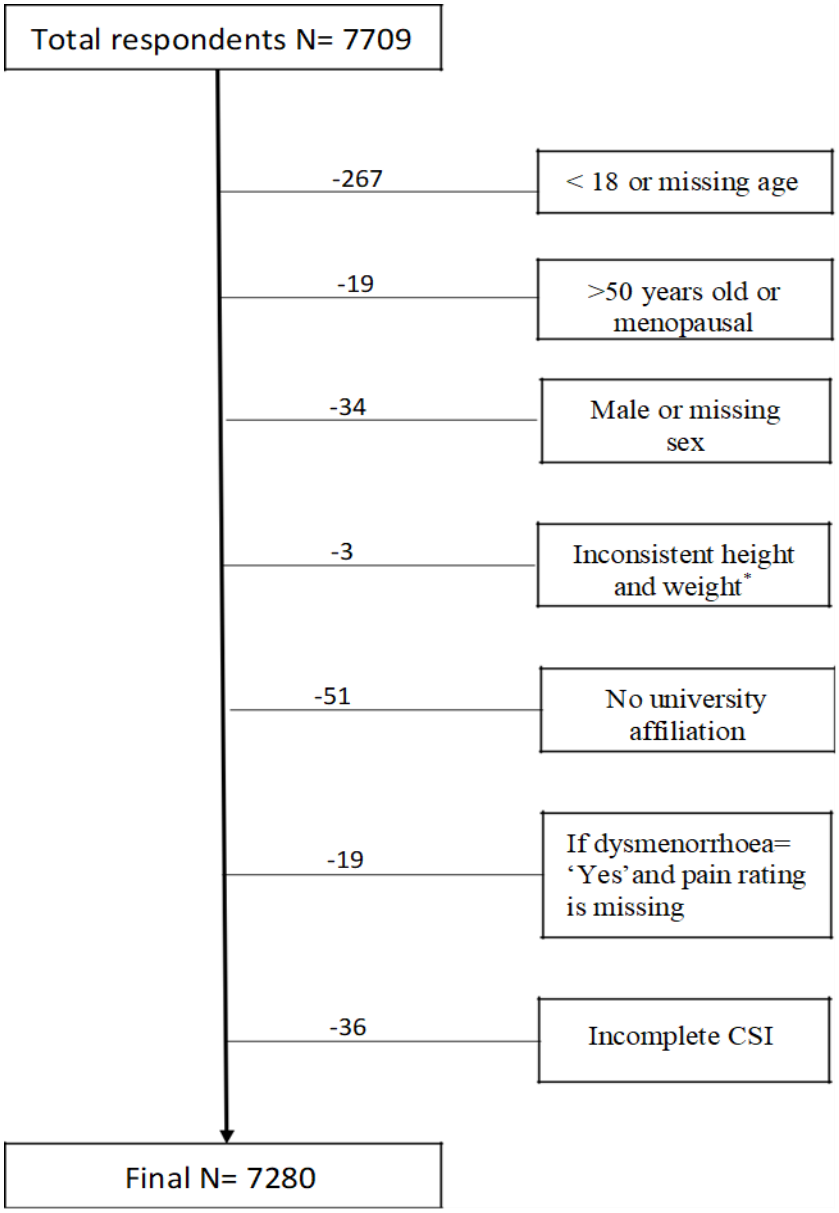
Data cleaning: criteria for manual exclusion

Several parameters were used to decide on the data to be included in the statistical analyses of this study. Those who did not meet the minimum study criteria (as described above) were redirected to a submission page (unable to proceed with the questions), and hence, immediately excluded from the study. Some, however, met the main criteria and were allowed to proceed with the survey, but had missing data. In these cases, I included those who reported their public university population affiliation and manually excluded respondents who did not mention which university they belonged to. Similarly, those who did not mention whether they were staff or student, were considered as not having an affiliation with any public university, and therefore were manually excluded from the study's analysis. Although the survey questions were not mandatory and participants had the option to leave certain questions unanswered, this approach regarding which university our respondents were affiliated with was intentional because my study focused on universities population. In the screening questions (Appendix 2), respondents who left a blank response on the gender variable were manually excluded. The data of respondents younger than 18 years old and older than 50 years old were also manually excluded; as per our ethical obligations and likelihood of menopause, respectively. Those who did not mention their age were also excluded from the statistical analyses.

Also pertinent to the aims of this study was the dysmenorrhoeic status of women, determined by the question "Do you suffer from menstrual (period) pains?" (Appendix 6). In cases where women answered 'yes' to the question but did not give a pain rating in the subsequent section, the data were also excluded since there was no mean to categorise their pain level. This is due

to the fact that the logistic regression model was built based on whether the women reported no pain or mild pain (rating <4) vs. moderate (4 ≥rating ≤6) or severe pain (rating ≥7).

The survey closed with a total of 7709 respondents having completed the survey. Of these, 429 respondents were excluded for various reasons as described above and detailed in Figure 3.2 below, resulting in a total final sample (n) of 7280 participants.



***"Inconsistent height and weight" referred to respondents who had height greater than 1.90m and weighted less than 50kg.**

Figure 0.2: Flow Chart detailing the responses from the screening data and manual cleaning of the data, based on the study criteria (final N= 7280).

3.2.2 Sociodemographic section

The sociodemographic section (Appendix 4) consisted of both free text and multiple-choice questions. Respondents were required to insert their age (in years), their height (in centimeters) and their weight (in kilograms) using text in the provided space. To establish their ancestry, respondents were asked to select one option between "African", "European", "Mixed", "Indian", "Asian' or "Other". If the respondents selected "Other", they had a free text option to write their ancestry. In cases where respondents selected "Other" described mixed ancestries, they were included in the "Mixed" category. The Socioeconomic status (SES) of respondents was determined by having them select their "social standing/ social class" based on their own estimation. They were given three options namely "Lower", "Middle", or "Upper". Level of education was also assessed with the question "What is the highest level of education you have completed?" Answer options were: "No education", "Primary school (Grade 1-7)", "Secondary school (Grade 8-12)", and "Tertiary education". Lastly, this section (Appendix 4) included questions on smoking and exercise as these factors are commonly reported as risk factors for dysmenorrhoea as described in the literature review above. The survey asked: "Do you smoke?" and "Do you exercise?", both with simple "yes" or "no" options. Respondents then proceeded to the "Menstrual cycle" section of the survey (Appendix 5).

3.2.3 Menstrual cycle section

The next section of the survey (Appendix 5) assessed various aspects of the female menstrual cycle. Respondents were first questioned on their menarche with the question "At what age did you have your first menstrual bleeding/menstruation (period)?". Respondents completed this question using a free text space. Answers to the remaining questions in this section were all presented in the form of drop-down menus. To assess regularity of menses, defined as the approximate number of days from one period to another, the question "How regular are your menstrual periods?" was answered by selecting one of the four given choices namely "less than 24 days", "24-35 days", "more than 35 days", and "My cycle occurs randomly (there is no specific number of days from one period to the next)". As shown in appendix 6, also assessed in this section of the survey was, duration of menses (usual length of menstrual periods) and

flow of menses (light, medium or heavy flow). In addition, premenstrual symptoms (e.g., irritability, fatigue, and tearfulness), and premenstrual symptom interference with daily life, were assessed. Other symptoms associated with menstruation were also assessed (e.g., "Fatigue", "Headache", "Back Pain", "Cramps", "Dizziness", "Vomiting", "Diarrhoea", and "Other") which gave them the option of manually entering their answers.

Pertinent to the aims of this study, family history was assessed with the question "Does anyone in your immediate family suffer with menstrual period pains?". Response options for this question were: "No", "My Mother", "My Daughter", "My Sister", "My Aunt", "My Niece", "My Cousin", "My Grandmother", "My Granddaughter", "I don't know". Respondents had the option to choose one or more answers.

Included in this section (Appendix 5) were questions on contraception use and pregnancy history. The use of contraceptives was assessed by asking all the respondents "are you currently using any of the following contraceptives?" The options provided were "IUD, e.g., Copper loop", "Hormonal IUD, e.g., Mirena", "The oral contraceptives pill", "Injections/Patch/Other hormones", "None" or "Other". Respondents could select only one answer. If they selected "Other", they were given the free text option to write what contraceptive measures they were taking. Depending on which contraceptive they were using, our respondents were divided into two groups: those using physical and hormonal contraceptives. Any contraceptives methods that comprised condoms, tube ligation or surgery such as hysterectomy, were considered physical contraceptives. Any other methods such as taking oral contraceptive pill or any form of hormonal implants (e.g.: Mirena, hormonal patches or injection, etc) were considered as hormonal contraceptives. Lastly, questions on pregnancy included: "have you ever been pregnant?", where respondents could answer with a "yes" or "no" option. Followed by the last question: "have you ever had a natural/vaginal birth or C-section?" The three options were provided to answer this question, namely: "I have never given birth", "Natural/vaginal birth" and "C-section" with more than one selection available. Respondents then proceeded to the next section of the survey that asked questions specifically about menstrual pain (Appendices 7 and 8).

3.2.4 Menstrual pain history and diagnosis and management

Presence or absence of menstrual pain

To screen for menstrual pain, respondents were asked, "Do you suffer from menstrual (period) pains?" (Appendix 6). Respondents who answered by selecting "No" skipped the dysmenorrhoea section and were directed to the central sensitisation inventory (Appendix 8). Those who said "Yes" to suffering to menstrual pain continued to the next section with questions specifically related to their menstrual dysmenorrhoeic pain (Appendix 7).

Characteristics of menstrual pain in those who had menstrual pain

As shown in Appendix 7, various questions were asked regarding menstrual pain history including questions on the frequency of menstrual pain ("how often do you experience menstrual pains?"); the severity of menstrual pain; the impact of their menstrual pain on sleep and work/school attendance; whether they had consulted a doctor or a gynaecologist for their menstrual pain; and details regarding their choice of pain treatments (including both pharmacological and non-pharmacological options), and how often treatment is required.

Included in Appendix 7 are questions that were used to make a distinction between primary and secondary dysmenorrhoea. Specifically, the question "Have you ever been diagnosed, by a doctor, with any of the following conditions?" was followed by the list: pelvic inflammatory disease, endometriosis, Adenomyosis, uterine polyps, ovarian cysts, cervical strictures/stenosis, pelvic congestion syndrome, fibroids, other. Respondents who selected one of the given options were classified as having secondary dysmenorrhoea in our study (Origo et al., 2021). Respondents who selected the option "no, I have not been diagnosed with any of the above" were considered as not having secondary dysmenorrhoea. As such, if they reported to have menstrual pain but did not have secondary dysmenorrhoea as defined by a confirmed diagnosis, they were considered as having primary dysmenorrhoea.

Menstrual pain intensity was also assessed in this section (Appendix 7). Pain intensity was rated using a visual analogue scale (VAS) (Coll & Ameen, 2006; Price et al., 1983, 1994; Revill et al., 1976), specifically: "On a scale of 0 – 10 how would you rate the intensity of your menstrual pain over the last 6 months", with 0 being "no pain at all" and 10 indicating "the worst pain I have ever felt". A score of <4 was taken to indicate mild pain, a score greater or equal to 4 and lower than 7 indicated moderate pain and a score greater or equal to 7 was taken to indicate severe pain.

3.2.5 Central sensitisation and Sleep

The final section of the survey was an assessment of central sensitisation using the central sensitisation inventory (CSI) (Appendix 8). The CSI is a validated screening questionnaire used to identify people with central sensitisation (Mayer et al., 2012; Neblett et al., 2013). The questionnaire consists of two parts, i) series of 25 questions with the options "never", "rarely", "sometimes", "often" and "always" and ii) includes 10 disorders associated with central sensitisation (CS), where participants say whether or not (yes or no) they have been diagnosed with each specific disorder; namely: Restless Leg Syndrome, Chronic Fatigue Syndrome, Fibromyalgia, Temporomandibular Joint Disease (TMJ), Migraine or tension headaches, Irritable Bowel Syndrome, Multiple Chemical Sensitivities, Neck Injury (including whiplash), Anxiety or panic attacks and Depression. Those who answered "Yes" to any of the questions in part ii were required to state the year of the diagnosis. A central sensitisation inventory (CSI) total score out of 100 is determined using the answers, where a score of greater than 40 indicates the patient may have central sensitivity syndrome (CSS) (Mayer et al., 2012; Neblett et al., 2013).

3.2.6 Sleep

One of the questions from the CSI was singled out to assess sleep, namely, "I do not sleep well" (variable identified as "I do not sleep well"), to which the possible answers were: "never" (0), "rarely" (1), "sometimes" (2), "often" (3) and "always" (4). I used this variable separately as

an independent variable and a nominal categorical variable; the category 'never' was used as the reference group in univariable and multivariable analyses.

3.3 Data Management and Analysis

The data collected in google forms was imported to a statistical programme (SAS version 9.4).

3.3.1 Descriptive Statistics of the primary, secondary and non-dysmenorrhoeic women

After cleaning the dataset (as described in section 3.2.1.1 above), I first ran descriptive statistics on the whole population, including women with primary dysmenorrhoea, secondary dysmenorrhoea and non-dysmenorrhoeic respondents. Women who answered "yes" to the initial question about having painful menstrual cramps but who then indicated having no pain or only mild pain (pain level estimated at <4 out of 10 on the numerical rating scale, Appendix 7; N= 102) were combined with the group of women who initially responded "no" to having menstrual cramps. This group was defined as no-mild dysmenorrhoea. Women were considered to have dysmenorrhoea (primary or secondary) when they reported pain levels of 4 or above on the numerical rating scale (Appendix 7).

Women were classified to have secondary dysmenorrhoea if they reported having been diagnosed with one of the following pathologies: Pelvic Inflammatory Disease, endometriosis, adenomyosis, uterine polyps, ovarian cysts, cervical strictures/ stenosis, pelvic congestion syndrome and fibroids (Appendix 7).

I chose to present all data using median and interquartile range [25^{th} -75^{th} percentile] (median [IQR]). The variables included: age (years), BMI (kg/m^2), age at menarche (years), central sensitisation inventory (CSI) total score. For the remaining categorical data such as education, socioeconomic status (SES), ancestry, smoking, exercise, menses regularity, length menses, period menses, flow heaviness, premenstrual symptoms, physical and hormonal

contraceptives, ever pregnant, “I do not sleep well”, I present the data as counts and frequencies (n (%)).

To compare characteristics between groups, for categorical variables, I ran an omnibus Cochran-Mantel-Haenszel test comparing the distribution of the different categories amongst the 3 categories of “Dysmenorrhoea” (No-mild, Primary, and Secondary). If the omnibus Cochran-Mantel-Haenszel test was significant, I further ran posthoc tests using Cochran-Mantel-Haenszel analysis, running 2 categories of Dysmenorrhoea at each time (No-mild vs. Primary, No-mild vs. Secondary, Primary vs Secondary) and used a $p<0.0167$ (=0.05/3) as my threshold for significance to adjust for the multiple comparisons.

For continuous parametric variables, I ran a General Linear Model analysis on the main effect of group (No-mild, Primary, and Secondary Dysmenorrhoea) and Tukey posthoc adjustments for multiple comparisons. For continuous non-parametric variables, a Kruskal-Wallis’s test was run as the omnibus test. If significant, it was followed by the Dunn’s posthoc tests.

Once I had done those analyses, a striking feature of the secondary dysmenorrhoeic women was that they were older and had higher SES than the primary dysmenorrhoeic women. Since, the primary dysmenorrhoeic women reported that they had not seen a doctor or gynaecologist for their menstrual pain, it is possible that the phenotype of the group labelled as primary dysmenorrhoea could reflect a mix of primary dysmenorrhoeics as well as secondary dysmenorrhoeics who had not yet been diagnosed because they had not consulted a doctor. Dysmenorrhoea of moderate to severe intensity is likely to have a significant impact on work or school attendance and efficiency, whereas mild or no dysmenorrhoea is not expected to result in such interference (Iacovides et al., 2014, 2015c; Weissman et al., 2004). Therefore, to make the analysis easier to interpret a decision was made to collapse the categories of severity of dysmenorrhoea into two: none/mild and moderate/severe, following a similar approach previously employed in the literature (Jarrett et al., 1995; Kazama et al., 2015; Tavallaee et al., 2011; Weissman et al., 2004). To investigate factors associated with pain severity in dysmenorrhoea, I opted to combine both groups of women with primary or secondary dysmenorrhoea into one group to avoid erroneous findings and conclusions resulting from

misclassification of dysmenorrhoea phenotype; specifically comparing those scoring 4 out of 10 and higher on the pain Likert scale, and those who had no or only mild (scores of 0 - 3) levels of pain. This decision was also based on several studies reporting a bias in discriminating primary vs. secondary dysmenorrhoea (Iacovides et al., 2015c; Nagy & Khan, 2022; Unsal et al., 2010).

3.3.2 Univariable analyses of the association between dysmenorrhoea status (dysmenorrhoeic and non dysmenorrhoeic) and independent variables of interest

I ran univariable and multivariable analyses investigating the association between odds of reporting of dysmenorrhoea (dysmenorrhoea=1, which included the primary and secondary type of dysmenorrhoea, for reasons explained above) and the independent variables of interest. I first ran a univariable analysis to understand associations between variables of interest (listed below) and my outcome variable without confounding or possible collinearity issues. This univariable analysis step also allowed me to further test in the multivariable model if I lost significance in one association because of confounding (i.e., an increase or decrease in the beta estimates of the odds ratios of more than 10%) or because of collinearity between variables (i.e., an increase in the standard error of the estimates of the odds ratios of more than 10%). In case of collinearity, my rule was then that I would select for the model the variable which had been extensively explored and studied in the existing literature.

Table 0.2: Categorization of variables of interest into five categories

Categories	Variables
Sociodemographic characteristics	Age, BMI, ancestry, socioeconomic status, and education
Lifestyle/behaviour characteristics	Smoking, exercise
Menses history and characteristics	Length of menses, flow heaviness, regularity of menses, menses cycle, and age at menarche, family history of dysmenorrhoea
Reproductive history	Ever pregnant, physical, and hormonal contraceptives
Sleep and central sensitisation	Central sensitisation inventory score (CSI total) and just the single question from the CSI about 'not sleeping well'

3.3.3 Multivariable Analysis

Logistic regression analyses were conducted to determine the possible independent variables associated with dysmenorrhoea in a South African university student and staff population.

Our dependent variable of interest was the presence or absence of moderate to severe dysmenorrhoea. The independent variables considered included social and biological independent variables mentioned above (see 3.3.1.2). I focused my analyses on variables which were perceived either as biologically causative relationship (such as hormone-related variables, smoking central sensitisation, sleep quality, exercise,etc), whilst I excluded variables which were singled out as being more of a consequence of dysmenorrhoea (for example, interference of premenstrual symptoms in the participants' quality of life). As explained above in the univariable step, to identify confounding and collinearity, I first tested the association between these independent variables of interest and my dependent variable in univariable analyses, then in multivariable analyses (logistic regression for the outcome 'presence of dysmenorrhoea' using PROC LOGISTIC in SAS 9.4). When I detected confounding (negative or positive, i.e., either a decrease or increase by more than 10% in the absolute value of the raw estimates (the β that leads to the calculation of the $OR=e^{\beta}$) in the multivariable model compared to the

univariable model), this was not considered an issue and thus no further investigation was performed to determine which covariate(s) from the multivariable model contributed to the confounding. However when I detected only collinearity (defined as an inflation by 10% or more in the standard error of the raw β estimate in the multivariable model compared to the univariable model), I had a rule that I would remove one of the covariates involved in the collinearity problem (Kleinbaum et al., 2013).

ANALYSIS AND RESULTS

4.1 Population

My study sample included data from the staff and student populations of 24 of the 26 state universities across all nine provinces in South Africa, and as such, the sample was widely distributed across the country. Table 4.1 below show the distribution (number and percentage of total sample) of the survey population amongst the 24 universities.

In total, data from 7280 participants (of the total number of 7709 respondents) from 23 public universities in South Africa were included in the statistical analyses. Approximately, a quarter of respondents were from the University of Witwatersrand (28.6%), a fifth from UNISA (19.6%), a tenth from the University of Cape Town (11.3%), and a tenth from the University of Western Cape (10.6%). Nelson Mandela Metropolitan University contributed to 6.7% of the respondents. Rhodes University, University of Fort Hare, North-West University, Tshwane University of Technology, and the University of KwaZulu Natal each contributed less than 5% of the total study population. Of the rest of the 13 universities contributed to less than 1% of our total sample.

Table 0.1: Distribution (number of respondents and percentage contribution) of the final study population by university across South Africa (N = 7280)

University	**No. of Respondents**	**%**
Cape Peninsula University of Technology	6	0.08
Central University of Technology	3	0.04
Durban University of Technology	32	0.44
Mangosuthu University of Technology	1	0.01
Nelson Mandela Metropolitan University	617	8.48
North-West University	200	2.75
Rhodes University	384	5.3
Sefako Makgatho University	32	0.44
Sol Plaatje University	4	0.05
Stellenbosch University	24	0.33
Tshwane University of Technology	6	0.08
University of Cape Town	823	11.3
University of Fort Hare	203	2.79
University of KwaZulu-Natal	74	1.02
University of Limpopo	4	0.05
University of Mpumalanga	33	0.45
University of Pretoria	18	0.25
University of South Africa (UNISA)	1424	19.56
University of the Free State	53	0.73
University of the Western Cape	768	10.55
University of the Witwatersrand	2080	28.57
University of Zululand	1	0.01
Other *	490	6.73
Total	7280	100%

***One university preferred its identity not to be disclosed, hence, it is labelled as "Other".**

4.2 Descriptive characteristics of the full sample

4.2.1 Sociodemographic characteristics

Table 4.2 provides the details of the demographic characteristics of the total sample (N=7280) according to whether they reported not experiencing menstrual pain ("no-mild dysmenorrhoea") (n=1698), primary dysmenorrhoea (n=4570) or secondary dysmenorrhoea (n=1012). In total, 5582 [76.7% (95% CI, 75.7-77.6)] reported experiencing dysmenorrhoea. The median age of the entire sample was 22 [20-27] years, with significant differences in age between the three groups (General Linear Model, main effect of group; $p<0.001$); those with secondary dysmenorrhoea were older (25 [21-33] years) than those who had primary dysmenorrhoea (21 [20-25] years).

The median Body Mass Index (BMI) of the population was 23.8 [20.8-27.9] kg/m^2. Women with secondary dysmenorrhoea had the highest BMI (25.2 [21.7-29.9] kg/m^2) compared to those without dysmenorrhoea and compared to the women with primary dysmenorrhoea ($p<0.001$).

Regarding self-reported socioeconomic status, most respondents were middle class (78.7%) with less reporting being in the lower class (14.2%) and in the upper class (7.1%). There were significant differences across groups in terms of socioeconomic status ($p<0.001$). Those who had primary dysmenorrhoea and those reporting no dysmenorrhoea had a higher representation in the lower class (15.1% and 14.1% respectively) compared to those with secondary dysmenorrhoea (10.1%).

There were significant differences across groups in terms of education levels ($p<0.001$). Because the sample consisted of women from universities, many reported having a tertiary education. The categories (no education, primary only, matric) were poorly represented and therefore were all grouped together under a same category: "below than tertiary", which included all respondent who have not yet finished their tertiary education or are not at the

tertiary level but are working at universities in support positions. The population was therefore split between those who had tertiary education (46.4%) and those who did not (53.6%). Respondents who reported experiencing primary dysmenorrhoea were more likely to have below than tertiary (none/primary and/or matric) education (58.4%) compared to those who experienced no-mild dysmenorrhoea (50.0%), or to those reporting secondary dysmenorrhoea (37.6%). Women reporting secondary dysmenorrhoea were the least likely to have less than tertiary education.

There were significant differences across the three groups in terms of ancestry ($p<0.001$). Approximately half of the participants were of African ancestry (53.5%), a quarter were of European ancestry (24.8%), while a few reported Mixed (14.3%) and Indian (7.4%) ancestries. There was a higher frequency of respondents of African ancestry reporting secondary dysmenorrhoea (43.6%) and primary dysmenorrhoea (55.1%) compared to other ancestry groups.

Table 0.2: Sociodemographic characteristics of the respondents

	Full population	No-mild dysmenorrhoea	Primary dysmenorrhoea	Secondary dysmenorrhoea	p-Value
Age, median [IQR]*(years)	n= 7280 22 [20 - 27]	n= 1698 23[a] [20-29]	n= 4570 21[b] [20 - 25]	n= 1012 25[c] [21 - 33]	<.0001
BMI, median [IQR]*(kg/m^2)	n= 5604 23.8 [20.8 - 27.9]	n= 1332 24.0[a] [21.2 - 27.9]	n= 3414 23.3[b] [20.6 - 27.5]	n= 858 25.2[c] [21.7 - 29.9]	<.0001
SES (n (%))	n= 7179	n= 1676	n= 4502	n= 1001	<.0001
Lower class	**1018 (14.2)**	**236[a] (14.1)**	**681[a] (15.1)**	**101[b] (10.1)**	
Middle class	5654 (78.7)	1300 (77.6)	3530 (78.4)	824 (82.3)	
Upper class	507 (7.1)	140 (8.4)	291 (6.5)	76 (7.6)	
Education (n (%))	n= 7242	n= 1683	n= 4551	n= 1008	<.0001
< tertiary (none/primary and/or matric)	**3879 (53.6)**	**843[a] (50.0)**	**2657 [b] (58.4)**	**379[c] (37.6)**	
Tertiary	3363 (46.4)	840 (50.0)	1894 (41.6)	629 (62.4)	
Ancestry (n (%))	n= 7232	n= 1686	n= 4538	n= 1008	<.0001
African	**3866 (53.5)**	**928[a] (55.0)**	**2498[a] (55.1)**	**440[b] (43.6)**	
European	1792 (24.8)	492 (29.2)	986 (21.7)	314 (31.2)	
Mixed	1036 (14.3)	167 (9.9)	705 (15.5)	164 (16.3)	
Indian	538 (7.4)	99 (5.9)	349 (7.7)	90 (8.9)	

The No-mild dysmenorrhoea category included respondents with no and mild (1-3) level of pain. BMI, Body Mass Index; IQR, Inter Quartile Range; SES, Socioeconomic Status; *: this variable was log-transformed for the analysis and the log transformed variable met the criteria for normality. For continuous variables (Log(age) and Log (BMI), I ran a General Linear Model analysis and Tukey posthoc adjustments for multiple comparisons. For categorical variables, I ran a Cochran-Mantel-Haenszel test using the 3 categories of Dysmenorrhoea (No-mild, Primary and Secondary). If this was significant, I further ran posthocs using Cochran-Mantel-Haenszel analysis, running 2 categories of Dysmenorrhoea at each time (No-mild vs. Primary, No-mild vs. Secondary, Primary vs Secondary) and used a p<0.0167 (=0.05/3) as my threshold for significance to adjust for the multiple comparisons. The superscript letters of same value mean no significant differences in the posthoc tests; if they are of different values, there is a significant difference shown in the posthoc tests. For categorical variables, the superscript letters are shown in the category which is associated with higher risk of dysmenorrhoea in subsequent univariable analyses.

4.2.2 Behavioural and lifestyle characteristics

Table 4.3 indicates that approximately 1 in 10 of the respondents reported smoking (11.1%). There were differences across the three groups in terms of smoking ($p<0.001$); those with secondary dysmenorrhoea were more likely to smoke (15.7%), compared to those with primary dysmenorrhoea (10.9%) and compared to those reporting no-mild dysmenorrhoea (8.8%).

Most participants (58.2%) reported exercising, with significant differences across the three groups ($p<0.001$). Respondents reporting no-mild dysmenorrhoea (60.9%), or secondary dysmenorrhoea (62.2%) were more likely to exercise compared to those with primary dysmenorrhoea (56.2%) ($p<0.001$).

Table 0.3: Behavioural and lifestyle characteristics of the respondents

	Full population	**No-mild dysmenorrhoea**	**Primary dysmenorrhoea**	**Secondary dysmenorrhoea**	**p-Value**
Smoke (n (%))	n= 7245	n= 1688	n= 4549	n= 1008	<.0001
No	6444 (88.9)	1539 (91.2)	4055 (89.1)	850 (84.3)	
Yes	801 (11.1)	149[a] (8.8)	494[a] (10.9)	158[b] (15.7)	
Exercise (n (%))	n= 7269	n= 1693	n= 4564	n= 1012	<.0001
No	3044 (41.8)	661 (39.1)	2000 (43.8)	383 (37.8)	
Yes	4225 (58.2)	1032 [a] (60.9)	2564 [b] (56.2)	629 [a] (62.2)	

For categorical variables, I ran a Cochran-Mantel-Haenszel test using the 3 categories of Dysmenorrhoea (No-mild, Primary and Secondary). If this was significant, I further ran posthocs using Cochran-Mantel-Haenszel analysis, running 2 categories of Dysmenorrhoea at each time (No-mild vs. Primary, No-mild vs. Secondary, Primary vs Secondary) and used a p<0.0167 (=0.05/3) as my threshold for significance to adjust for the multiple comparisons. The superscript letters of same value mean no significant differences in the posthoc tests; if they are of different values, there are significant differences in the posthoc tests. For categorical variables, the superscript letters are shown in the category which is associated with higher risk of dysmenorrhoea in subsequent univariate analyses.

4.2.3 Menstrual characteristics and family history of the respondents

Table 4.4 shows the prevalence of menstrual pain severity (a score ≥4 and ≤6 as moderate and a score >=7 as severe), menstrual characteristics, and the severity at which premenstrual syndrome interfered (PMS interference) with quality of life ('Not at all', 'Mild', 'Moderate', and 'Severe') of our respondents.

By design, the non-dysmenorrhoeic women were defined as those with pain ratings <4. By design, the primary and secondary dysmenorrhoeics had pain ratings ≥4 (i.e., moderate, or severe). Here, I only compared the prevalence of moderate/severe pain in the primary vs the secondary dysmenorrhoeics. Of all the respondents, 64.7% of women experiencing primary dysmenorrhoea reported severe menstrual pain, and almost three quarters (72.7%) of women with secondary dysmenorrhoea reported severe menstrual pain (p<.0001).

The age at menarche in our full sample was 13 [12-14] years, with no significant difference between those who had no-mild dysmenorrhoea and both those with primary and secondary dysmenorrhoea. Approximately four out of ten (41.7%) of all respondents had regular menses, over a third (35.7%) sometimes had irregular menses, and a fifth (22.6%) experienced irregular menses. Significant differences existed in the regularity of menses among the three groups (p<0.001). Irregular menses were more likely to be experienced by those with secondary dysmenorrhoea (28.3%), followed by those who did not experience dysmenorrhoea (25.4%).

Most of the total respondents (86.8%) reported that their menses lasts for 3-7 days, with few reporting that their menses lasts for less than 3 days (7.5%) or more than 7 days (5.8%). The length of menses differed significantly across the three groups; women with secondary dysmenorrhoea were more likely to experience menses lasting longer than 7 days (12.2%), compared to those with primary (4.9%) and no (4.3%) dysmenorrhoea (p < 0.001).

Regarding menstrual cycle length (time interval between menses), more than two thirds (67.1%) of the total respondents reported a window of 24-35 days between menstrual cycles, 17.1% reported less than 24 days, and 13.1% reported random intervals between menses. Only

2.7% of respondents reported more than 35 days between menses. The women with secondary dysmenorrhoea were more likely to experience menses at random (18.8%), compared to the women with the no-mild (14.9%) and primary (11.3%) dysmenorrhoea.

With regards to menstrual flow, or bleeding, in our total sample, approximately six out of every ten (60.6%) respondents experienced medium menses flow, approximately three out of ten (29.3%) experienced heavy menstrual flow (29.3%), and a tenth (10.1%) experienced light flow. Heaviness of flow differed significantly across groups ($p<0.001$); those with no-mild dysmenorrhoea were least likely to experience heavy flow (13.5%), and those with secondary dysmenorrhoea were most likely to have heavy flow (41.5%).

Regarding premenstrual symptoms (PMS), 38% of the total respondents reported experiencing moderate PMS, 31.2% of respondents experienced mild PMS, 21.5% reported severe PMS, and 9.2% did not experience PMS at all. There were significant differences across the three groups in terms of PMS ($p<0.001$). Those experiencing secondary dysmenorrhoea were more likely to have severe PMS (34.4%) compared to those with no-mild dysmenorrhoea (6.3%) and compared to those with primary dysmenorrhoea (24.3%). Those who reported experiencing primary dysmenorrhoea also were more likely to have severe PMS than those reporting no-mild dysmenorrhoea. In our total sample, 10.6% of the women reported severe PMS interference, and moderate PMS interference was experienced by almost a third (29.1%) of respondents. Over a third (38.6%) of the women reported mild PMS interference, and about a fifth (21.7%) of the women did not experience PMS interference at all. There were significant differences across the three groups in terms of PMS interference ($p<0.001$). Those with secondary dysmenorrhoea were more likely to experience severe PMS interferences (17.3%) compared to those with primary dysmenorrhoea (11.4%). Respondents reporting no-mild dysmenorrhoea (3.3%) were the least likely to experience severe PMS interference compared to those who had dysmenorrhoea

Approximately 4 out of 5 (79.1%) respondents reported positive family history of dysmenorrhoea. Respondents with a positive family history of dysmenorrhoea were more likely to report experiencing primary (81.9%) and secondary (81.0%) dysmenorrhoea.

Table 0.4: Menstrual characteristics of the total sample and the respondents

	Full sample	No-mild dysmenorrhoea	Primary dysmenorrhoea	Secondary dysmenorrhoea	p-Value
Age at menarche, median [IQR] (years)	n= 6975	n= 1623	n= 4389	n= 963	0.8434
	13 [12 - 14]	13 [12 - 14]	13 [12 - 14]	13 [12 - 14]	
Menses regularity (n (%))	n= 7267	n= 1694	n= 4562	n= 1011	<.0001
Irregular	1642 (22.6)	430[a] (25.4)	926[b] (20.3)	286[c] (28.3)	
Regular	3029 (41.7)	762 (44.9)	1870 (41.0)	397 (39.3)	
Sometimes irregular	2596 (35.7)	502 (29.7)	1766 (38.7)	328 (32.4)	
Length menses (n (%))	n= 7251	n= 1691	n= 4552	n= 1008	<.0001
3 - 7 days	6294 (86.8)	1409 (83.3)	4079 (89.6)	806 (79.9)	
< 3 days	540 (7.5)	210 (12.4)	251 (5.5)	79 (7.9)	
> 7 days	417 (5.7)	72[a] (4.3)	222[a] (4.9)	123[c] (12.2)	
Interval between menses (n (%))	n= 7250	n= 1689	n= 4551	n= 1010	<.0001
24 - 35 days	4867 (67.1)	1125 (66.6)	3117 (68.5)	625 (61.9)	
Random	946 (13.1)	253[a] (14.9)	513[b] (11.3)	180[c] (18.8)	
< 24 days	1242 (17.1)	271 (16.1)	798 (17.5)	173 (17.1)	
>35 days	195 (2.7)	40 (2.4)	123 (2.7)	32 (3.2)	
Flow heaviness (n (%))	n= 7262	n= 1693	n= 4562	n= 1007	<.0001
Light	736 (10.1)	335 (19.8)	317 (6.9)	84 (8.3)	
Medium	4402 (60.6)	1130 (66.7)	2767 (60.7)	505 (50.2)	
Heavy	2124 (29.3)	228[a] (13.5)	1478[b] (32.4)	418[c] (41.5)	
PMS (n (%))	n= 7256	n= 1688	n= 4557	n= 1011	<.0001
Not at all	666 (9.2)	364 (21.6)	253 (5.6)	49 (4.9)	
Mild	2267 (31.2)	835 (49.5)	1223 (26.8)	209 (20.7)	
Moderate	2760 (38.0)	382 (22.6)	1973 (43.3)	405 (40.0)	
Severe	1563 (21.6)	107[a] (6.3)	1108[b] (24.3)	348[c] (34.4)	
PMS interference (n (%))*	N= 6592	n= 1326	n= 4305	n= 961	<.0001
Not at all	1428 (21.7)	571 (43.1)	731 (17.0)	126 (13.1)	
Mild	2542 (38.6)	536 (40.4)	1671 (38.8)	335 (34.9)	
Moderate	1921 (29.1)	175 (13.2)	1412 (32.8.)	334 (34.7)	
Severe	701 (10.6)	44[a] (3.3)	491[b] (11.4)	166[c] (17.3)	
Family history of dysmenorrhoea n (%)	N= 5999	n= 1344	n= 3791	n= 864	<.0001
Yes	4751 (79.2)	948[a] (70.5)	3103[b] (81.9)	700[b] (81.0)	
No	1248 (20.8)	396 (29.5)	688 (18.2)	164 (19.0)	

***PMS interference do not include respondents with No PMS. For continuous variables (Menarche), I ran a General Linear Model analysis and Tukey post-hoc adjustments for multiple comparisons. For categorical variables, I ran a Cochran-Mantel-Haenszel test using the 3 categories of Dysmenorrhoea (No-mild, Primary and Secondary). If this was significant, I further ran post-hoc using Cochran-Mantel-Haenszel analysis, running 2 categories of Dysmenorrhoea at each time (No-mild vs. Primary, No vs. Secondary, Primary vs Secondary) and used a p<0.0167 (=0.05/3) as my threshold for significance to adjust for the multiple comparisons. The superscript letters of same value mean no significant differences in the post-hoc**

tests; if they are of different values, there are significance differences in the post-hoc tests. For categorical variables, the superscript letters are shown in the category which is associated with higher risk of dysmenorrhoea in subsequent univariate analyses.

Contraception and pregnancy.

Table 4.5 details the results for contraception, pregnancy, and parity. About seven out of ten (71.1%) women did not use hormonal contraception, while 28.9% reported using hormonal contraceptives, with significant differences across the groups ($p<0.001$). Those who used hormonal contraceptives were more likely to report secondary dysmenorrhoea (40.2%), compared to those who had primary dysmenorrhoea (24.9%) and those reporting no-mild dysmenorrhoea (33.2%). Most women in our sample did not use physical contraceptives (97.7%), and there were no significant differences across the groups for the use of physical contraceptives.

Almost a quarter of the women reported having been pregnant at some point (24.2%), with significant differences across the groups; women with secondary dysmenorrhoea were more likely to have ever fallen pregnant (32.9%), compared to those reporting primary dysmenorrhoea (20.1%), who were least likely ($p< 0.05$). In addition, those with no-mild dysmenorrhoea were more likely to have been pregnant compared to those with primary dysmenorrhoea (30.1% vs 20.1%, $p<0.0001$).

Table 0.5: Contraception and pregnancy characteristics of the respondents

	Full population	No-mild dysmenorrhoea	Primary dysmenorrhoea	Secondary dysmenorrhoea	p-Value
Hormonal Contraceptives (n (%))	n= 7251	n= 1690	n= 4554	n= 1007	<.0001
No	5153 (71.1)	1129 (68.8)	3422 (75.1)	602 (59.8)	
Yes	2098 (28.9)	561[a] (33.2)	1132[b] (24.9)	405[c] (40.2)	
Physical Contraceptives (n (%))	n= 7243	n= 1687	n= 4549	n= 1007	0.0434
No	7076 (97.7)	1654[a] (98.0)	4449[a] (97.8)	973[a] (96.6)	
Yes	167 (2.3)	33 (2.0)	100 (2.2)	34 (3.4)	
Ever Pregnant (n (%))	n= 7264	n= 1690	n= 4565	n= 1009	<.0001
No	5506 (75.8)	1182 (69.9)	3646 (79.9)	677 (67.1)	
Yes	1758 (24.2)	508 [a] (30.1)	919 [b] (20.1)	332[a] (32.9)	

For categorical variables, I ran a Cochran-Mantel-Haenszel test using the 3 categories of dysmenorrhoea (No, Primary and Secondary). If this was significant, I further ran post-hoc using Cochran-Mantel-Haenszel analysis, running 2 categories of dysmenorrhoea at each time (No-mild vs. Primary, No-mild vs. Secondary, Primary vs Secondary) and used a p<0.0167 (=0.05/3) as my threshold for significance to adjust for the multiple comparisons. The superscript letters of same value mean no significant differences in the post-hoc tests; if they are of different values, there are significance differences in the post-hoc tests. For categorical variables, the superscript letters are shown in the category which is associated with higher risk of dysmenorrhoea in subsequent univariate analyses.

4.2.4 Central sensitisation inventory and poor sleep quality

Table 4.6 provides total score of the central sensitisation inventory (CSI) and poor sleep (using the "I do not sleep well" question of the CSI) characteristics of the total sample (N=7277) according to whether they had no dysmenorrhoea (n=1698), primary dysmenorrhoea (n=4568) or secondary dysmenorrhoea (n=1011).

The median CSI total score of the entire population was 36 [24-48], with significant differences in scores between the three groups (General Linear Model, main effect of group; p<0.001). Respondents reporting no-mild dysmenorrhoea had the lowest median score (28 [17-39]), those with secondary dysmenorrhoea had the highest median score (43[31-56]) and those who had primary dysmenorrhoea (37 [26-49]) had a score that was higher compared to those with no-mild dysmenorrhoea, but lower compared to those with secondary dysmenorrhoea. Most of the

respondents who reported experiencing primary (44.0%) and secondary (57.9%) dysmenorrhoea where most likely to have a CSI total score higher than the cut-off (score >= 40).

Analysis of sleep quality showed that approximately a quarter (25.3%) of our total sample reported they were not sleeping well "often" or "always". Significant differences were seen across the groups (p<0.001); with women with secondary dysmenorrhoea more likely to report that they either "often" or "always" do *not* sleep well (36.4%), compared to those with primary dysmenorrhoea (26.1%) and those with no-mild dysmenorrhoea (16.1%).

Table 0.6: Central sensitisation inventory and sleep quality characteristics of the respondents

	Full population	**No-mild dysmenorrhoea**	**Primary dysmenorrhoea**	**Secondary dysmenorrhoea**	**p-Value**
CSI total score, (median [IQR]) *	n= 7277	n= 1698	n= 4568	n= 1011	<.0001
	36 [24 - 48]	28[a] [17-39]	37[b] [26 - 49]	43[c] [31 - 56]	
CSI Total score >= 40 (n (%))	3009 (41.3)	412 (24.2)	2012 (44.0)	585 (57.9)	<.0001
"I do not sleep well" (n (%))	n= 7223	n= 1687	n= 4531	n= 1005	<.0001
Never	1202 (16.6)	507 (30.1)	605 (13.4)	90 (9.0)	
Rarely	1989 (27.5)	526 (31.2)	1240 (27.4)	223 (22.0)	
Sometimes	2210 (30.6)	382 (22.6)	1502 (33.2)	326 (32.4)	
Often	1190 (16.5)	193 (11.4)	767 (16.9)	230 (22.9)	
Always	632 (8.8)	79[a] (4.7)	417[b] (9.2)	136[c] (13.5)	

CSI =Central Sensitisation Inventory total score; I ran a General Linear Model analysis and Tukey post-hoc adjustments for multiple comparisons. The superscript letters of same value mean no significant differences in the post-hoc tests; if they are of different values, there are significance differences in the post-hoc tests. For categorical variables, the superscript letters are shown in the category which is associated with higher risk of dysmenorrhoea in subsequent univariate analyses.

4.2.5 Medical consultation and treatment of dysmenorrhoea

Table 4.7 shows the data regarding medical consultations and treatment for dysmenorrhoea (from Appendix 7)

Most of the study population had not consulted a doctor or gynaecologist about their menstrual pains, with only 31% reporting that they have ever consulted someone for their menstrual pain. Those with secondary dysmenorrhoea were more likely to have ever consulted anyone about their menstrual pain (75%), compared to those with no-mild dysmenorrhoea (5%) and those with primary dysmenorrhoea (31%).

A small fraction of our population of women with primary dysmenorrhoea did not require any pain medication at all (10%). Even fewer of those with secondary dysmenorrhoea did not require medication (5%). Majority of women with primary (66%) and secondary (75%) dysmenorrhoea required medication, 'often' or 'always'.

Out of the full population who reported experiencing primary and secondary dysmenorrhoea, 88.4% reported using pharmacological treatment for dysmenorrhoea. The highest proportion of those using pharmacological treatment were respondents who reported experiencing secondary dysmenorrhoea (93.0%), followed by those with primary dysmenorrhoea (87.4%). On the other hand, half of our respondents (51.6%) reported using nonpharmacological treatment. The proportion of non-pharmacological treatment users was higher in those who reported secondary dysmenorrhoea (56.8%), followed by those who reported primary dysmenorrhoea (50.4%).

Out of the respondents who experienced moderate to severe dysmenorrhoea, which includes primary and secondary dysmenorrhoea, more than half (51.6%) reported that they had to miss work or school due to menstrual pain during their periods.

Since the variables discussed here are the "consequences" of dysmenorrhoea (and not the cause), I decided not to include them as independent variables in our univariable and multivariable analysis.

Table 0.7: Medical consultation and treatment of dysmenorrhoea of the respondents

	Full population	**No-mild dysmenorrhoea**	**Primary dysmenorrhoea**	**Secondary dysmenorrhoea**	**p-Value**
Ever consult a doctor	N= 7280	n=1698	n= 4570	n= 1012	<.0001
No	5023 (69.0)	1604[a] (95.0)	3165[b] (69.0)	254[c] (25.0)	
Yes	2257 (31.0)	94 (5.0)	1405 (31.0)	758 (75.0)	
Dysmenorrhoea medication frequency	N= 5994	n= 475	n= 4516	n= 1003	<.0001
Not required	656 (11.0)	150 (32.0)	455 (10.0)	51 (5.0)	
Rarely required	1567 (26.0)	254 (53.0)	1114 (25.0)	199 (20.0)	
Often required	1959 (33.0)	42 (9.0)	1562 (35.0)	355 (35.0)	
Always require	1812 (30.0)	29[a] (6.0)	1385[b] (31.0)	398[c] (40.0)	
Pharmacological treatment	N= 5582	-	n= 4570	n= 1012	<.0001
No	649 (11.6)	-	578 (12.7)	71 (7.0)	
Yes	4933 (88.4)	-	3992[a] (87.4)	941[b] (93.0)	
Nonpharmacological treatment	N= 5561	-	n= 4552	n= 1009	<.0001
No	2692 (48.4)	-	2256 (49.6)	436 (43.2)	
Yes	2869 (51.6)	-	2296[a] (50.4)	573[b] (56.8)	
Absenteeism (school/work)	N= 5565	-	n= 4554	n= 1001	<.0001
No	2691 (48.4)	-	2272 (49.9)	419 (41.4)	
Yes	2874 (51.6)	-	2282 (50.1)	592 (58.6)	

For categorical variables, I ran a Cochran-Mantel-Haenszel test using the 3 categories of Dysmenorrhoea (No, Primary and Secondary). If this was significant, I further ran post-hoc using Cochran-Mantel-Haenszel analysis, running 2 categories of Dysmenorrhoea at each time (No vs. Primary, No vs. Secondary, Primary vs Secondary) and used a p<0.0167 (=0.05/3) as my threshold for significance to adjust for the multiple comparisons. The superscript letters of same value mean no significant differences in the post-hoc tests; if they are of different values, there are significance differences in the post-hoc tests. For categorical variables, the superscript letters are shown in the category which is associated with higher risk of dysmenorrhoea in subsequent univariate analyses.

4.3 Univariable logistic regression analysis results of the odds of reporting moderate to severe dysmenorrhoea (primary or secondary dysmenorrhoea)

As mentioned earlier in the methods, a feature of the women with secondary dysmenorrhoea in the initial descriptive analysis that stood out was that they were older and had higher SES than the women with primary dysmenorrhoea. Another striking feature was that those classified as having primary dysmenorrhoea reported that 69% had not seen a doctor for their menstrual pain (vs. 25% in the secondary). As such, it is possible that the phenotype of the group labelled as primary dysmenorrhoea could be a mix of primary dysmenorrhoea and women with undiagnosed secondary dysmenorrhoea. Thus, to avoid false conclusions based on misclassifying the phenotype of dysmenorrhoea, I focused the construction of the univariable and multivariable models on an outcome variable of the odds of having dysmenorrhoea of a severity of at least 4 out of 10 on the pain Likert scale over the odds of having no or only mild (0-3 pain level), regardless of whether the woman reported dysmenorrhoea of primary or secondary origin. I also made this choice based on the reports of several studies highlighting this difficulty at discriminating primary vs. secondary dysmenorrhoea in the absence of medical consultation (Iacovides et al., 2015c; Nagy & Khan, 2022; Unsal et al., 2010).

To better investigate correlates of reporting dysmenorrhoea, in this section, I will focus on univariable logistic regression modelling the odds of reporting dysmenorrhoea, (regardless of whether it is primary or secondary) over the odds of not reporting dysmenorrhoea. In this analysis dysmenorrhoea was defined as menstrual pain intensity rated as 4 or more on the numerical rating scale (appendix 7), while no or mild dysmenorrhoea was considered as menstrual pain intensity rated as less than 4 on the numerical rating scale. The independent variables of interest considered were all variables considered not ‘a consequence’ of dysmenorrhoea from Section 4.2.5 above.

4.3.1 Sociodemographic characteristics

Table 4.8 shows the association of different demographic variables and the odds of reporting dysmenorrhoea (primary or secondary). Older age at the time of the study was significantly associated with lower odds of reporting dysmenorrhoea (OR=0.974, 95% CI 0.966-0.981; p<0.0001). BMI was not associated with dysmenorrhoea (OR=0.997, 95% CI 0.997-1.007; p=0.5305). Education was significantly associated with lower odds reporting dysmenorrhoea (OR=0.834, 95% CI 0.748-930; p=0.0011), with higher level of education having decreased odds of reporting menstrual pain. Self-reported belonging to the upper class was associated with lower odds of reporting dysmenorrhoea (OR=0.783, 95% CI 0.638-0.960; p=0.0187), compared to belonging to the middle class, but not compared to lower class (OR=0.791, 95% CI 0.620-1.009; p=0.0588). Self-reported belonging to the lower class was not associated with higher odds of reporting dysmenorrhoea compared to middle class (OR=0.989, 95% CI 0.845-1.159; p=0.8945). Ancestry was significantly associated with reporting dysmenorrhoea. Compared to women of African ancestry, women of European ancestry had lower odds of reporting dysmenorrhoea (OR=0.835, 95% CI 0.735-0.948; p=0.0054). Women of Mixed (OR=1.644, 95% CI 1.371-1.970; p<0.001) or Indian ancestries (OR=1.401, 95% CI 1.113-1.763; p=0.0041) had higher odds of reporting dysmenorrhoea than those of African ancestry. Women of Indian and Mixed ancestries were not significantly different in their odds of reporting dysmenorrhoea (p>0.05; this result was obtained using Mixed ancestry as the reference group in that analysis).

Table 0.8: Univariable analyses of the association between sociodemographic characteristics and odds of reporting dysmenorrhoea

Variables	N	N_{nd}	N_d	Odds ratio	95% Wald Confidence Limits		Estimate	Standard Error	Wald Chi-Square	Pr>ChiSq
					Lower	Upper				
Age (years)	7280	1698	5582	0.974	0.966	0.981	-0.027	0.004	44.5	<.0001
BMI (kg/m^2)	5604	1332	4272	0.997	0.987	1.007	-0.003	0.005	0.4	0.5305
Education	7242	1683	5559	0.834	0.748	0.93	-0.1815	0.0557	10.6214	0.0011
SES	7179	1676	5503							
SES Lower vs Middle				0.989	0.845	1.159	-0.011	0.081	0	0.8945
SES Upper vs Middle				0.783	0.638	0.96	-0.245	0.104	5.5	0.0187
SES Upper vs Lower				0.791	0.62	1.009	-0.234	0.124	3.6	0.0588
Ancestry	7232	1686	5546							
European vs African				0.835	0.735	0.948	-0.181	0.065	7.7	0.0054
Mixed vs African				1.644	1.371	1.97	0.497	0.093	28.9	<.0001
Indian vs African				1.401	1.113	1.763	0.337	0.118	8.3	0.0041

N= 7280, n_d = number of women who have dysmenorrhoea as defined by menstrual pain at 4 or above, n_{nd}= number of women who have dysmenorrhoea as defined by menstrual pain <4, SES= socioeconomic status, BMI=body mass index.

4.3.2 Lifestyle and odds of reporting dysmenorrhoea

As displayed in Table 4.9 there were significant associations between lifestyle characteristics (exercise and smoking from Appendix 4) and the odds of reporting dysmenorrhoea. Engaging in exercise was associated with lower odds of reporting dysmenorrhoea (OR=0.858, 95% CI 0.758-0.959; p=0.007), whereas smoking was associated with higher odds of reporting dysmenorrhoea (OR=1.373, 95% CI 1.139-1.655; p=0.0009).

Table 0.9: Univariable analyses of the association between lifestyle characteristics and odds of reporting dysmenorrhoea

Variables	N	N_{nd}	N_d	Odds ratio	95% Wald Confidence Limits		Estimate	Standard Error	Wald Chi-Square	Pr>ChiSq
					Lower	Upper				
Exercise	7269	1693	5576	0.858	0.768	0.959	-0.1529	0.0567	7.2722	0.007
Smoke	7245	1688	5557	1.373	1.139	1.655	0.3168	0.0954	11.0332	0.0009

N = 7280, n_d = number of women who have dysmenorrhoea as defined by menstrual pain at 4 or above, n_{nd}= number of women who have dysmenorrhoea as defined by menstrual pain <4

4.3.3 Menstrual characteristics and odds of reporting dysmenorrhoea

The results in Table 4.10 indicates that there are mixed associations between the various menstrual characteristics (Appendix 5) and the likelihood of reporting dysmenorrhoea. Older age at menarche was associated with lower odds of reporting dysmenorrhoea (OR=0.89, 95% CI 0.859-0.922; p<0.001). Severity of PMS was significantly associated with higher odds of reporting dysmenorrhoea. These results show that the higher the severity of PMS, the higher the odds of reporting dysmenorrhoea (p<.0001). Regularity of menses were defined as: regular, sometimes irregular and irregular. Irregular menses showed no statistical association with reporting of dysmenorrhoea relative to those who had regular menses (p=0.4404). Further results suggest that those who experienced 'sometimes' irregular menses were more likely to report having dysmenorrhoea compared to those who had regular menses (OR=1.402, 95% CI 1.230-1.592; p<0.0001). There is evidence of association between the length of menses and the likelihood of reporting dysmenorrhoea. Those who reported menstruating for less than 3 days, compared to 3 to 7 days, had lower odds of reporting dysmenorrhoea (OR=0.453, 95% CI 0.380-0.544; p<0.0001). On the other hand, those who reported menstruating for more than 7 days, compared to 3 to 7 days, had higher odds of reporting dysmenorrhoea (OR= 1.382, 95% CI 1.07-1.794; p=0.015).

There is mixed evidence of associations between periodicity of menses and the likelihood of reporting dysmenorrhoea. Those who reported menstruating at random intervals were less likely to report dysmenorrhoea (OR=0.823, 95% CI 0.7-0.965; p<0.0001), relative to those who experienced their menses with a 24 to 35 days interval. Compared to an interval of 24 to 35 days, experiencing menses with an interval period of less than 24 days (OR=1.077, 95% CI 0.93-1.252; p=0.332) and more than 35 days (OR=1.165, 95% CI 0.82-1.66; p=0.3978) did not modify the odds of reporting dysmenorrhoea. We found strong evidence of an association between flow heaviness and the odds of reporting dysmenorrhoea. Those who experienced heavy flow had higher odds of reporting dysmenorrhoea (OR=2.872, 95% CI 2.46-3.347; p<0.0001), relative to those who experienced medium flow. Those who experienced light flow had lower odds of reporting dysmenorrhoea than those who experienced medium flow (OR=0.413, 95% CI 0.35-0.485; p<0.0001).

When investigating PMS, those who reported experiencing mild PMS were twice more likely to report dysmenorrhoea (OR=2.081, 95% CI 1.753-2.470; p<0.0001), relative to those who did not experience any pain at all ("Not at all"). Those who experienced moderate and severe PMS were 6 times and 10 times, respectively, more likely to report dysmenorrhoea (moderate OR=6.077, 95% CI 5.104-7.235; p<0.0001; severe OR=10.27, 95% CI 8.483-12.433; p<0.0001 respectively), relative to those who did not experience any pain at all ("Not at all"). Family history of dysmenorrhoea was strongly associated with higher odds of reporting dysmenorrhoea (OR=1.865, 95% CI 1.623-2.142; p<0.0001).

Table 0.10: Univariable analyses of the association between menstrual characteristics and reporting dysmenorrhoea

Variables	N	n_{nd}	n_d	Odds ratio	95% Wald Confidence Limits		Estimate	Standard Error	Wald Chi-Square	Pr>ChiSq
					lower	upper				
Age at menarche (year)	**6975**	**1623**	**5352**	0.89	0.859	0.922	-0.117	0.018	41.5	<.0001
Menses regularity	**7267**	**1694**	**5573**							
Irregular vs Regular				0.947	0.83	1.087	-0.054	0.07	0.5953	0.4404
Sometimes irregular vs Regular				1.402	1.23	1.592	0.3379	0.065	27.0368	<.0001
Length menses	**7251**	**1691**	**5560**							
< 3 vs '3 – 7 days'				0.453	0.38	0.544	-0.7913	0.0933	71.9178	<.0001
> 7 days vs '3 – 7 days'				1.382	1.07	1.794	0.3236	0.133	5.9152	0.015
Interval between menses	**7250**	**1689**	**5561**							
Random vs 24 – 35 days				0.823	0.7	0.965	-0.1942	0.0809	5.7573	0.0164
< 24 days vs 24 – 35 days				1.077	0.93	1.252	0.0744	0.0767	0.9413	0.332
> 35 days vs 24 – 35 days				1.165	0.82	1.66	0.1527	0.1806	0.715	0.3978
Flow heaviness	**7262**	**1693**	**5569**							
Heavy vs Medium				2.872	2.46	3.347	1.0548	0.0781	182.306	<.0001
Light vs Medium				0.413	0.35	0.485	-0.8834	0.0817	116.999	<.0001
PMS	**7256**	**1688**	**4557**							
Mild vs Not at all				2.081	1.753	2.47	0.7328	0.0874	70.2246	<.0001
Moderate vs Not at all				6.077	5.104	7.235	1.8045	0.089	411.31	<.0001
Severe vs Not at all				10.27	8.483	12.433	2.3292	0.0975	570.623	<.0001
Family history	**5999**	**1344**	**4655**	1.865	1.623	2.142	0.623	0.0708	77.9711	<.0001

N = 7280, n_d = number of women who have dysmenorrhoea as defined by menstrual pain at 4 or above, n_{nd}= number of women who have dysmenorrhoea as defined by menstrual pain <4; PMS: premenstrual symptoms

Univariable analyses of the association between contraception, and pregnancy characteristics and the odds of reporting dysmenorrhoea

Table 4.11 shows evidence of the association between hormonal contraceptive use and pregnancy, and the likelihood of reporting dysmenorrhoea. Previous pregnancy was significantly associated with lower odds of reporting dysmenorrhoea (OR=0.675, 95% CI 0.598-0.762; p<0.0001). Respondents who reported using hormonal contraceptives were less likely to report dysmenorrhoea (OR=0.769, 95% CI 0.684-0.864; p<0.0001).

Table 0.11: Univariable analyses of the association between contraception and pregnancy characteristics and the odds of reporting dysmenorrhoea

Variables	N	n_{nd}	n_d	Odds ratio	95% Wald Confidence Limits		Estimate	Standard Error	Wald Chi-Square	Pr>ChiSq
					Lower	Upper				
Pregnant	**7264**	**1690**	**5574**	0.675	0.598	0.762	-0.3928	0.062	40.0954	<.0001
Hormonal contraceptives use	**7251**	**1690**	**5561**	0.769	0.684	0.864	-0.2631	0.0597	19.4033	<.0001

N= 7280, n_d = number of women who have dysmenorrhoea as defined by menstrual pain at 4 or above, n_{nd}= number of women who have dysmenorrhoea as defined by menstrual pain <4

4.3.4 Univariable analyses of the association between central sensitisation total scores and individual sleep score and the odds of reporting dysmenorrhoea

Table 4.12 shows the association between central sensitisation inventory's (CSI) scores and the odds of reporting dysmenorrhoea. CSI scores were significantly associated with higher odds of reporting dysmenorrhoea. These results show that the higher the CSI score, the higher the odds of reporting dysmenorrhoea (OR=1.04, 95% CI 1.036-1.044; $p<0.05$).

Compared to those who "never" experienced "not sleeping well", those who selected "always" (OR= 5.106, 95% CI 3.929-6.636; $p<0.0001$), "often" (OR= 3.768, 95% CI 3.11-4.566; $p<0.0001$), "sometimes" (OR= 3.491, 95% CI 2.978-4.092; $p<0.0001$) and "rarely" (OR=2.029, 95% CI 1.743-2.362; $p<0.0001$) to not sleeping well had higher odds of reporting dysmenorrhoea.

Table 0.12: Univariable analyses of the association between central sensitisation inventory total score, and individual sleep score, and the odds of reporting dysmenorrhoea

Variables	N	n_{nd}	n_d	Odds ratio	95% Wald Confidence Limits		Estimate	Standard Error	Wald Chi-Square	Pr>ChiSq
					Lower	Upper				
CSI_total score	**7277**	**1698**	**5579**	1.04	1.036	1.044	0.0391	0.00188	433.895	<.0001
'I do not sleep well'	**7223**	**1687**	**5536**							
Rarely vs Never				2.029	1.743	2.362	0.7075	0.0774	83.4931	<.0001
Sometimes vs Never				3.491	2.978	4.092	1.2502	0.0811	237.663	<.0001
Often vs Never				3.768	3.11	4.566	1.3267	0.098	183.42	<.0001
Always vs Never				5.106	3.929	6.636	1.6305	0.1337	148.705	<.0001

N = 7280, n_d = number of women who have dysmenorrhoea as defined by menstrual pain at 4 or above, n_{nd}= number of women who have dysmenorrhoea as defined by menstrual pain <4. CSI: Central Sensitisation Inventory total score; CSI_notsleepingwell score: Not sleeping well score from CSI

4.4 Multivariable analysis logistic regression analysis results of the odds of reporting dysmenorrhoea (primary or secondary)

To better investigate correlates of reporting dysmenorrhoea, in this section, I use a multivariable logistic regression to model the presence or absence of moderate to severe dysmenorrhoea, (regardless of whether it is primary or secondary) . As done in the univariate analyses, dysmenorrhoea was defined as menstrual pain intensity rated as 4 or more on the numerical rating scale (Appendix 7), while no-mild dysmenorrhoea was considered as reports of menstrual pain intensity of less than 4 on the numerical rating scale. The independent variables of interest considered were all variables considered not 'a consequence' of dysmenorrhoea from Section 4.2.5 above.

In this analysis, only observations with full data were considered in the multivariable model (i.e., no imputation of missing data within those observations were performed as it was beyond the scope of this MSc degree). Thus, from a total of 7280 observations, only 4289 were used for the multivariable analysis. Of this total, 3323 [77.5% (95% CI, 76.2-78.7)] were in the moderate-severe dysmenorrhoea group, while 966 (22.5%) were in the 'no-mild' dysmenorrhoea group.

Table 4.13 shows the adjusted association of different independent variables and the odds of reporting moderate to severe dysmenorrhoea. For our demographics category, as seen in our univariable analysis, older age at the time of the study (adjusted OR=0.982, 95% CI 0.967-0.998; p=0.0285) and older age at menarche (adjusted OR=0.938, 95% CI 0.89-0.989; p=0.0186) was significantly associated with lower odds of reporting dysmenorrhoea. Education was no longer significantly associated with the odds of reporting dysmenorrhoea in the adjusted analysis (p=0.4631). Higher BMI was weakly associated with lower odds of reporting dysmenorrhoea (adjusted OR=0.986, 95% CI 0.972-1; p=0.044) in our multivariable analysis unlike in the unadjusted univariable analysis where BMI showed no significant association.

Self-reported upper socioeconomic status was no longer significantly associated with the odds of reporting dysmenorrhoea (p= 0.7769) in the adjusted analysis. Self-reported lower

socioeconomic status remained not significantly associated with the odds of reporting dysmenorrhoea in the adjusted multivariable analysis (p= 0.2355). Multivariable analysis using women of African ancestry as the reference group, showed that compared to women of African ancestry, women of European ancestry had lower odds of reporting dysmenorrhoea (adjusted OR=0.698, 95% CI 0.567-0.859; p=0.0007), as seen in our univariable analysis. Respondents of Indian ancestry (p=0.4661) and mixed ancestry (p=0.1201) showed no significant association with the odds of reporting dysmenorrhoea compared to women of African ancestry in the multivariate analysis.

The significant associations between lifestyle characteristics and the odds of reporting dysmenorrhoea that we showed in our univariable analysis were lost for the smoking (p=0.3889) and exercise (p=0.5791) variables in the multivariable analysis. We did notice a large negative confounding on both variables when they were introduced in the multivariable model with the absolute value of the estimates decreasing from |0.15| to |0.05| and from |0.31| to |0.12| for exercise and smoking, respectively, which likely explains this loss of significance in the larger model. I did not explore whether this negative confounding was introduced by one or multiple covariates from the multivariable model as my rule was to keep all covariates in the model as long as there were no collinearity issues. As reported in our univariable analysis, we found strong evidence of an association between flow heaviness and the likelihood of reporting dysmenorrhoea; with those who reported experiencing heavy flow having higher odds of reporting dysmenorrhoea (OR=2.749, 95% CI 2.208-3.421; p<0.0001), relative to those who experienced medium flow. Those who experienced light flow had lower odds of reporting dysmenorrhoea than those who experienced medium flow (OR=0.473, 95% CI 0.373-0.6; p<0.0001). Menses regularity was divided between being regular, sometimes irregular, and irregular. In contrast to what we had found in the unadjusted univariable analysis, those who “sometimes” experienced irregular menses had no significant association with the odds of reporting dysmenorrhoea (p=0.1938) in multivariable analysis. Like in our univariable analysis, irregular menses relative to regular menses showed no significant association with the odds of reporting dysmenorrhoea (p=0.844). Length of menses showed mixed evidence of association with reporting dysmenorrhoea unlike in our univariable analysis where they were both significant. Those who menstruated for less than 3 days, compared to 3 to 7 days, had lower odds of reporting dysmenorrhoea (adjusted OR=0.745, 95% CI 0.561-0.99; p=0.0421),

while those who reported menstruating for more than 7 days, compared to 3 to 7 days, showed no significant association with the odds of reporting dysmenorrhoea (p=0.9056).

Unlike in our univariable analysis, there was no evidence of association between the interval between periods and the odds of reporting dysmenorrhoea in adjusted analysis. When compared to those who experienced their menses with an interval of 24 to 35 days, reporting menstruating at random intervals (p=0.2084), within a period interval of less than 24 days (p=0.4353) and more than 35 days (p=0.5664) did not modify the odds of reporting dysmenorrhoea. Family history of dysmenorrhoea remained strongly associated with higher odds of reporting dysmenorrhoea in the multivariate analysis (adjusted OR=1.615, 95% CI 1.346-1.938; p<0.0001).

As in our unadjusted univariable analysis, history of having been pregnant was significantly associated with lower odds of reporting dysmenorrhoea (adjusted OR=0.757, 95% CI 0.605-0.946; p=0.0145) in our adjusted multivariable analysis. Currently taking hormonal contraceptive on the other hand lost its significance (p=0.9447). Again, this loss of significance in the multivariable model was due mainly to negative confounding (with the estimate in the univariable being β=-0.263 while that in the multivariable became β=0.006).

Furthermore, as in our univariable, our multivariable results showed the significant association between evidence of higher central sensitisation (as measured by higher total CSI score) and higher odds of reporting dysmenorrhoea (adjusted OR=1.033, 95% CI 1.026-1.04; p<0.0001).

Lastly, compared to those who never experienced “not sleeping well” those who selected “often” (OR= 1.595, 95% CI 1.16-2.191; p=0.004), “sometimes” (OR= 1.523, 95% CI 1.22-1.902; p=0.0002) and “rarely” (OR=2.046, 95% CI 1.596-2.623; p<0.0001) to the “not sleeping well” question had higher odds of reporting dysmenorrhoea in multivariate analysis, as observed in univariable analysis except for those who selected “always” (p=0.1321) which lost its significance.

Table 4.13: Multivariable analysis of adjusted association of different independent variables and the odds of reporting dysmenorrhoea (primary or secondary)

Variables	Odds ratio	95% Wald Confidence Limits Lower	Upper	Estimate	Standard Error	Wald Chi-Square	Pr>ChiSq
Age (years)	0.982	0.967	0.998	-0.0179	0.00815	4.7981	0.0285
BMI (Kg/m^2)	0.986	0.972	1	-0.0146	0.00723	4.0554	0.044
Education	1.07	0.893	1.283	0.0678	0.0924	0.5383	0.4631
Age at Menarche (years)	0.938	0.89	0.989	-0.0638	0.0271	5.5428	0.0186
SES							
Lower vs Middle	1.166	0.875	1.554	0.1534	0.1466	1.0945	0.2955
Upper vs Middle	0.961	0.727	1.269	-0.0402	0.142	0.0803	0.7769
Ancestry							
European vs African	0.698	0.567	0.859	-0.3596	0.1059	11.5277	0.0007
Mixed vs African	1.227	0.948	1.587	0.2043	0.1314	2.4163	0.1201
Indian vs African	0.889	0.649	1.219	-0.1173	0.1609	0.5313	0.4661
Exercise	0.953	0.805	1.129	-0.0479	0.0864	0.3077	0.5791
Smoke	1.125	0.86	1.473	0.1182	0.1372	0.7425	0.3889
Flow heaviness							
Heavy vs Medium	2.749	2.208	3.421	1.0111	0.1116	82.021	<.0001
Light vs Medium	0.473	0.373	0.6	-0.7487	0.1213	38.0923	<.0001
Menses regularity							
Irregular vs Regular	0.973	0.744	1.273	-0.027	0.137	0.0387	0.844
Sometimes irregular vs Regular	1.131	0.939	1.361	0.1229	0.0946	1.6887	0.1938

Variables	Odds ratio	95% Wald Confidence Limits Lower	Upper	Estimate	Standard Error	Wald Chi-Square	Pr>ChiSq
Length menses							
< 3 vs 3 - 7 days	0.745	0.561	0.99	-0.2939	0.1446	4.1303	0.0421
>7 days vs 3 - 7 days	1.024	0.688	1.526	0.0241	0.2034	0.0141	0.9056
Period menses							
Random vs 24 - 35 days	0.818	0.598	1.119	-0.2012	0.16	1.5827	0.2084
< 24 days vs 24 - 35 days	1.097	0.87	1.383	0.0922	0.1182	0.6086	0.4353
>35 days vs 24 - 35 days	1.166	0.69	1.97	0.1534	0.2676	0.3288	0.5664
Pregnant	0.757	0.605	0.946	-0.2787	0.1139	5.9814	0.0145
Hormonal contraceptives	1.006	0.839	1.207	0.00643	0.0927	0.0048	0.9447
Family history	1.615	1.346	1.938	0.4793	0.0931	26.5021	<.0001
CSI_Total	1.033	1.026	1.04	0.0323	0.00336	92.0162	<.0001
'I do not sleep well'							
Always vs Never	1.39	0.905	2.134	0.3293	0.2187	2.2675	0.1321
Often vs Never	1.595	1.16	2.191	0.4666	0.1621	8.2821	0.004
Sometimes vs Never	1.523	1.22	1.902	0.4206	0.1133	13.7865	0.0002
Rarely vs Never	2.046	1.596	2.623	0.7157	0.1268	31.8687	<.0001

CSI: Central Sensitisation Inventory total score; CSI_notsleepingwell score: Not sleeping well score from CSI.

DISCUSSION

This study was the first to investigate the prevalence, severity, characteristics, and risk factors associated with dysmenorrhoea in a South African population, including a large proportion of women of African ancestry, using a convenience sample from South African universities. In addition, this study examined reported levels of central sensitisation and poor sleep; both as novel factors associated with dysmenorrhoea.

After adjusting for several variables, I found that a range of demographic and menstrual characteristics, as well as family history and central sensitisation inventory total score, were significantly associated with higher odds of reporting moderate to severe dysmenorrhoea. I found that younger age at menarche, being younger at the time of the study, not having been pregnant, having a lower BMI, being of African ancestry vs European ancestry, higher flow heaviness, menstruations lasting 3-7 days vs <3 days, a positive family history of dysmenorrhoea, poorer sleep quality and higher central sensitisation inventory total score were all associated with higher odds of reporting moderate to severe dysmenorrhoea.

These findings contribute to our understanding of dysmenorrhoea by highlighting the multiple factors that are associated with menstrual pain. Additionally, the association between dysmenorrhoea and central sensitisation suggests that dysmenorrhoea should be viewed as a chronic condition that extends beyond just transient pain and discomfort during menses.

5.1 Prevalence of dysmenorrhoea

I found a high prevalence of dysmenorrhoea in my sample, with over three-quarters 76.7% (95% CI, 75.7-77.6) of respondents reporting moderate-severe dysmenorrhoea (pain severity scores of 4 – 10 on a Likert scale). Women reported that their menstrual pain affected their

daily lives, with more than half (51.6%) of them reporting missing school or work due to menstrual pain. My findings are similar to other reports about the prevalence of dysmenorrhoea, including: the 75.2% prevalence reported from a Nigerian high school study (Oluwole et al., 2020), another two high school studies in adolescents in India (71% and 75%) (Chauhan & Kodnani, 2015; Kharaghani & Damghanian, 2017), an Iranian systematic review of 35 studies that found an average prevalence of 73.27% among women between the age of 9 to 45 years old (Samani et al., 2018), and a Turkish study that found a 72.7% prevalence of dysmenorrhoea among women between the age of 17 to 30 years old in a university population (Unsal et al., 2010). The prevalence of dysmenorrhoea, however, was higher in my study than in previous studies in developing countries, including: Iran (14.4%) (Rostami, 2007), Bangladesh (60.9%) (Begum et al., 2009), India (48% and 65%) (Kumbhar et al., 2011; Shah et al., 2013), Canada (60%) (Burnett et al., 2005), Jordan (56%) (Al-Jefout et al., 2015), Saudi Arabia (61%)(Ibrahim et al., 2015), Mexico (48.4%) (Ortiz et al., 2009), and Lebanon, Syria, Pakistan (5% - 70%) (Harlow & Campbell, 2004). The low prevalence of menstrual disorders reported in the developing countries may be due to religious beliefs and practices, cultural taboos and stigma surrounding menstruation, which can prevent women from seeking medical care for their menstrual complaints and probably even preventing them from voicing their menstrual pain in those studies (H.-M. Chen & Chen, 2005; Dawood, 2006; Ozerdogan et al., 2009; Polat et al., 2009; Proctor, 2006; Stubbs, 2008; Tan et al., 2017; Wong & Khoo, 2010). Other factors, such as lack of access to health care, financial difficulties, and limited knowledge about menstrual disorders, may also contribute to the low prevalence of these conditions in these countries. Lastly, the lack of standardized definitions and diagnostic criteria for dysmenorrhoea, as well as differences in the methods used to assess dysmenorrhoea among the various studies, may be contribute to under-reporting of its prevalence.

On the other hand, some others have reported higher prevalence figures than what I found. One study, that used a random sample of Iranian women between the ages of 16 and 56, with the majority being under 30 years of age and without children, revealed the greatest frequency of 91% through self-reporting (Tavallaee et al., 2011). Similarly, prevalence of dysmenorrhoea in Italy (84.1%) (Grandi et al., 2012), Australia (80%) (Hillen et al., 1999), Thailand (84.2%) (Tangchai et al., 2004) and Oman (94%) (Al-kindi & Al-bulushi, 2011), were all higher than what I found. The high prevalence of dysmenorrhoea among adolescent girls in Oman and

Australia may also be due in part to the young age of the population (ranging from 15 to 27 years old). Dysmenorrhoea is more common in young, nulliparous women, and adolescent girls are more likely to experience this condition than older women (Tavallaee et al., 2011). This may be due to the hormonal changes that occur during puberty, which can affect the uterus and cause painful cramps during menstruation (Grandi et al., 2012; Proctor, 2006). These changes include high levels of prostaglandins, which can cause excessive or prolonged uterine contractions (Grandi et al., 2012; Proctor, 2006). They also include hormonal imbalance, such as an excess of oestrogen or a deficiency of progesterone, can also contribute to dysmenorrhoea by causing the endometrium to thicken too much, leading to heavier and more painful periods (Grandi et al., 2012; Proctor, 2006). Additionally, dysmenorrhoea is also more common in women with positive family history of dysmenorrhoea (Avasarala, Kameswararao & Panchangam, 2008; Begum et al., 2009; H.-M. Chen & Chen, 2005; Ibrahim et al., 2015; Ju et al., 2014a; Kumbhar et al., 2011) suggesting that factors such as cultural and genetic factors may influence the relationship between family history and dysmenorrhoea prevalence.

Importantly, it is likely that the wide ranges in the reported prevalence of dysmenorrhoea in the different studies is due to the use of different methods for determining the presence of dysmenorrhoea, and the inconsistent definition of dysmenorrhoea. Pain is subjective, therefore many studies rely on self-reported symptoms and on the ratings of the pain severity (Al-Jefout et al., 2015; Grandi et al., 2012; Ibrahim et al., 2015; Muluneh et al., 2018), while some others use more objective measures such as physical medical exams or diagnostic tests to confirm whether the dysmenorrhoea was secondary (Davis et al., 2005; Dmitrovic et al., 2012; Harel et al., 2005). Disparities in the prevalence estimates of dysmenorrhoea between surveys are likely explained, at least in part, by the fact that the definition of dysmenorrhoea used is not standardized throughout studies and by the categories (i.e.: level of pain intensity) chosen to report. Definitions of dysmenorrhoea vary widely; including but not limited to: menstrual pain associated with “the need for medication or inability to function normally” (Dawood, 1981); any type of pain or discomfort associated with menstrual period (Begum et al., 2009; Tangchai et al., 2004); a painful menstrual cramp of uterine origin (Proctor, 2006); a painful syndrome which occurs at the time of menstrual flow in ovulatory cycles (Rostami, 2007); a pelvic pain associated with onset of menses and lasting for 8-72 hours (Kumbhar et al., 2011); a cramp-like, dull, throbbing pain that usually emanates from the lower abdomen, and that occurs just

before and/or during menstruation (Grandi et al., 2012). Menstrual pain without organic pathology (Shah et al., 2013) may explain the large range in prevalence rates. Thus some include intensity and/or interference in their definition, whilst others do not, and simply rely on a "yes/no" answer to questions such as "have you ever had menstrual pain?" or "do you experience dysmenorrhoea?" (Acheampong et al., 2019; Fernández-Martínez et al., 2018; Gebeyehu et al., 2017).

Furthermore, some researchers chose to define dysmenorrhoea as menstrual pain greater than a specific intensity, while others include women who report pain regardless of the intensity of the pain (Andersch & Milsom, 1982; Tavallaee et al., 2011). Moreover, the assessment of intensity also varies across studies, with some using descriptive tools such as: "mild" pain as "sometimes or consistently experiencing low unpleasant cramps that never interfered with everyday chores", and "moderate" and "severe" discomfort being defined as "sometimes or always feeling very painful menstrual cramps" and "occasionally or always cutting back on activities", respectively (Andersch & Milsom, 1982). In other research, numerical scales, such as the Visual Analog Scale (VAS), are used to determine intensity, e.g. with "moderate" being considered VAS rating of greater or equal to 4, and "severe" was defined as a score of greater or equal to 7 (Agarwal & Agarwal, 2010; Kazama et al., 2015). But the cut-offs between categories may also differ from study to study.

Sometimes participants have been classified as having dysmenorrhoea if they had experienced one or more episode(s) of acute pain or dysmenorrhoea in a defined timeframe. For instance, in one study, an adolescent was deemed to have dysmenorrhoea if she had any of the following symptoms for the previous 12 months: abdominal discomfort, groin/pelvic pain, back pain, or thigh pain (Muluneh et al., 2018). More specifically, this study, which reported a prevalence of 69.3% in a specific town in Ethiopia, asked school girls, "Have you had menstrual cramps or abdominal pain during your period at least once in the past year?" (Muluneh et al., 2018). Another study, reporting a 41.7% prevalence of dysmenorrhoea in a Chinese university population, limited the assessment of dysmenorrhoea to the experience of painful menstruation within the preceding three months (Hu et al., 2020).Thus, across studies investigating the prevalence of menstrual pain, menstrual pain/dysmenorrhoea is defined differently and assessed using different tools, and sometimes intensity is considered (also with varying

definitions). Hence many factors may explain the discrepancies between prevalence rates observed across the studies, and such discrepancies highlight the need for a better and more homogenized definition of dysmenorrhoea across studies.

5.2 Characteristics of women with dysmenorrhoea

5.2.1 Age

Older age at the time of the study was significantly associated with lower odds of reporting dysmenorrhoea in both univariable and multivariable analysis, implying that the older a woman is, the less likely she will report experiencing moderate-to-severe dysmenorrhoea. In line with my findings, several studies have found a significant association between age and moderate to severe dysmenorrhoea whereby the older a woman gets the less likely she is to experience pain related to dysmenorrhoea (Khodakarami et al., 2015; Kural et al., 2015b; Latthe, Mignini, et al., 2006; Patel et al., 2006). The mechanism behind the protective effect of older age against dysmenorrhoea is not entirely clear. Women may develop better pain coping mechanisms as they age and become less sensitive to pain (Ju et al., 2014a), which is one possible explanation. Additionally, older women might have better access to healthcare services or more education and experience in pain management (Chantler et al., 2006; DeVallance et al., 2019; Millen et al., 2014; Munro et al., 2021; Pampel et al., 2010). Another possible explanation is that with age, women may have a decreased sensitivity to prostaglandins, which are hormones that are involved in the development of dysmenorrhoea (Al-Matouq et al., 2019; Blackstone et al., 2017; Martínez et al., 1999; van't Erve et al., 2018).

Contrarily to my findings, some studies have found older age to be associated with higher odds of experiencing dysmenorrhoea (Adeyemi & Adekanle, 2007; Ameade & Garti, 2016; Avasarala, Kameswararao & Panchangam, 2008; Chen & Chen, 2005). These findings suggest that dysmenorrhoea may worsen with age, possibly because dysmenorrhoea is associated with ovulatory menstrual cycles, and ovulatory cycles are more likely to occur in older women (Bourguinig, 2004). Another possible explanation is that older women may have more comorbidities, such as endometriosis or uterine fibroids, that can cause dysmenorrhoea (Chen

et al., 2018). Furthermore, hormonal changes associated with aging, such as changes in oestrogen and progesterone levels, may play a role in the development or worsening of dysmenorrhoea (Chen & Chen, 2005).

Women who reported having secondary dysmenorrhoea were older than those with no-mild dysmenorrhoea, and those who had primary dysmenorrhoea were the youngest amongst the three categories. These findings suggest that primary dysmenorrhoea is more common in younger women whereas secondary dysmenorrhoea is more common in older women of reproductive age, which is consistent with the literature (Harada, 2013; Ju et al., 2014a; Juang et al., 2006; Mendiratta & Lentz, 2017). Possibly because older women may be more knowledgeable and more likely to seek medical care for their pain, which could lead to a diagnosis of conditions associated with secondary dysmenorrhoea. Previous authors have reported that in the cases of secondary dysmenorrhoea, due to pelvic pathology, menstrual pain typically occurs several years after menarche, generally after the twenties (Ju et al., 2014). On the other hand, primary dysmenorrhoea emerges soon (within the first two years) after menarche and is common in younger women (Dawood, 2006; Hofmeyr & Bassin, 1996). Similarly, studies report that older age is associated with an increased risk of secondary dysmenorrhoea, while younger age is associated with an increased risk of primary dysmenorrhoea (Vincent et al., 2011) and that the prevalence of dysmenorrhoea increased with age (Khodakarami et al., 2015; Kural et al., 2015a; Seven et al., 2014). One possible explanation for this association is that as women age, they may be more likely to develop underlying conditions that can contribute to dysmenorrhoea, such as endometriosis or pelvic inflammatory disease (PID) (Latthe, Latthe, et al., 2006; Speroff & Fritz, 2005; Stratton & Berkley, 2010).

5.2.2 Body Mass Index (BMI)

In my univariable analysis, BMI showed no significant association with dysmenorrhoea (sample of combined primary and secondary dysmenorrhoea) whereas, in my multivariate model, controlling for multiple other factors, lower BMI showed a small but significant

association with lower odds of reporting dysmenorrhoea, suggesting that lower BMI might have a protective effect on the odds of reporting dysmenorrhoea.

Previous studies found mixed evidence regarding the association between BMI and dysmenorrhoea. Along the lines of our findings, some showed a positive association between high BMI and dysmenorrhoea (Harlow & Park, 1996; Ju et al., 2014a, 2015; Yan et al., 2015; Zhang et al., 2014). However, others showed no association between BMI and dysmenorrhoea (Fujiwara, 2007; Unsal et al., 2010) or that a very low BMI (below 20 kg/m2) is, in fact, a risk factor for the development of dysmenorrhoea (Latthe, Mignini, et al., 2006), or even that obesity (high BMI) was associated with a lower prevalence of dysmenorrhoea in an adolescent population (Mohamed, 2012). Another study found that both low and high BMI were associated with an increased risk of dysmenorrhoea (Ju et al., 2015). Similarly, a review found that both underweight and overweight women had a higher risk of dysmenorrhoea compared to those with normal BMI (Mendiratta & Lentz, 2017), suggesting that the relationship between BMI and dysmenorrhoea may not be linear.

The reasons for the mixed findings are not fully understood, but it is likely that the relationship between BMI and dysmenorrhoea is complex and likely influenced by multiple factors, including but not limited to hormonal changes, inflammation, and lifestyle behaviors – all of which influence the regulation of the menstrual cycle. For example, others have suggested that a positive association between high BMI and dysmenorrhoea might be mediated by high prostaglandin and/or high oestrogen levels (Martínez et al., 1999; Olson et al., 2006). Adipose tissue produces prostaglandins, which are involved in the pathogenesis of dysmenorrhoea. The levels of prostaglandin E2 (PGE2), a major mediator of menstrual pain, have been found to be positively correlated with BMI (Martínez et al., 1999). Therefore, individuals with a lower BMI may produce less PGE2, which could lead to a lower risk of dysmenorrhoea.

On the other hand, having a lower BMI is associated with less adipose tissue, resulting in decreased levels of leptin, which affects the hypothalamic-pituitary-ovarian (HPO) axis (Seli et al., 2014; Sowińska-Przepiera et al., 2015). The HPO axis regulates the menstrual cycle, and decreased leptin levels can cause decreased pulsatile secretion of gonadotropin-releasing

hormone (GnRH), which in turn results in reduced secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), ultimately leading to decreased production of oestrogen by the ovaries (Seli et al., 2014; Sowińska-Przepiera et al., 2015). This reduction in oestrogen may lead to reduced build-up of the endometrium, resulting in less blood flow (Aladash vili-Chikvaidze et al., 2015; Seli et al., 2014; Sowińska-Przepiera et al., 2015), and potentially less inflammation (Latthe et al., 2006; Mendiratta & Lentz, 2017; Olson et al., 2006; Seli et al., 2014) during menstruation and ultimately less pain. However, possibly, being underweight (very low BMI) may no longer protective due to multiple other health-related factors.

Another important factor to consider is whether BMI may associate differently with primary versus secondary dysmenorrhoea. In simple descriptive analysis, I found that women with secondary dysmenorrhoea had higher BMI than those with no-mild dysmenorrhoea, while women with primary dysmenorrhoea had lower BMI compared to women with secondary and women with no-mild dysmenorrhoea. Similar to my findings, others have reported that a higher BMI is associated with increased risk of secondary dysmenorrhoea (Ju et al., 2014a, 2015; Yan et al., 2015). Similarly, a systematic review found that obesity was associated with an increased risk of secondary dysmenorrhoea (Zhang et al., 2014). Thus, better defining the phenotypes of the women with dysmenorrhoea (e.g., by enrolling in studies only women who have visited a physician for their menstrual pain and excluded causes of secondary dysmenorrhoea) is thus crucial to better understand associations between BMI and dysmenorrhoea.

5.2.3 Socioeconomic status (SES)

In my univariable analyses, women who reported being from the upper socioeconomic class had lower odds of reporting having moderate-severe dysmenorrhoea (sample of combined primary and secondary dysmenorrhoea). However, in the multivariable analysis, controlling for multiple other factors, upper SES was no longer significantly associated with lower odds of reporting moderate-to-severe dysmenorrhoea, suggesting that other factors may drive this association such as age.

Previous studies have reported that dysmenorrhoea was more common among adolescents from low socioeconomic backgrounds compared to those from high socioeconomic backgrounds (Giletew & Bekele, 2019; Juniar, 2015; Unsal et al., 2010; Zurawiecka & Wronka, 2018), whereas one study found that being of the upper socioeconomic status was associated with higher odds of reporting dysmenorrhoea (Klein & Litt, 1981). Others found no association between socioeconomic status and dysmenorrhoea (Akhavanakbari & Ahangar Davoudi, 2010; Hailemeskel et al., 2016; Ohde et al., 2008; Razak et al., 2020)

Additionally, lifestyle behaviors and choices may also play a role, as women with lower SES may be more likely to engage in unhealthy behaviors such as smoking, which is a risk factor for dysmenorrhoea (Pampel et al., 2010). Conversely, women with higher SES may be more likely to engage in healthy behaviors such as exercising and a healthy diet, which may help to prevent or manage dysmenorrhoea (Pampel et al., 2010) whereas those from lower socioeconomic backgrounds may have poorer nutritional intake and physical activity levels, which can lead to an increased risk of dysmenorrhoea (Bavil et al., 2018). Finally, higher SES may be associated with health-seeking behaviors, such as seeking medical help to determine the cause of pain and explore effective analgesic treatments, whereas those with lower SES may be less likely and less willing to seek medical help due to financial barriers (Bavil et al., 2018).

SES may be a proxy for other factors that affect reproductive health, such as stress and psychological well-being, and age (also linked to dysmenorrhoea, as discussed above). Previous studies that have found that lower SES is associated with an increased risk of dysmenorrhoea have suggested that stress and psychological well-being may play a role in this association (Klein & Litt, 1981; Tavallaee et al., 2011). The proposed mechanism by which stress can drive pain include the dysregulation of FKBP51 and glucocorticoid signaling in the spinal cord, which may lead to hyperalgesia and chronic pain (Maiarù et al., 2016). Specifically, the study found that FKBP51 expression was increased in the spinal cords of mice subjected to chronic stress, and that FKBP51 knockdown attenuated the development of chronic pain in these mice (Maiarù et al., 2016). Possible explanations for these different associations between type of dysmenorrhoea and socioeconomic factors (e.g. income), may include but are not limited to access to healthcare (Bavil et al., 2018; Dey & Mahapatra, 2020;

Pampel et al., 2010). For example, women with lower SES may have less access to healthcare, and hence, may not have diagnosis of a pelvic pathology, and hence secondary dysmenorrhoea.

5.2.4 Level of education

In my study, lower odds of reporting dysmenorrhoea were associated with education level below tertiary education in univariable analysis. However, this association was lost in the multivariable analysis. Several studies have investigated the relationship between education level and dysmenorrhoea and did not find a significant association between education level and the prevalence of dysmenorrhoea in young women in various countries, including China (Hu et al., 2020), Iran (Kharaghani & Damghanian, 2017; Samani et al., 2018), Australia (Subasinghe et al., 2016), Spain (Fernández-Martínez et al., 2018), and Ethiopia (Tadese et al., 2021). However, some other studies have reported that higher education level is associated with a lower prevalence of dysmenorrhoea (Derseh et al., 2017; Ju et al., 2014a; Sundell et al., 1990), and argued that higher education may have a protective effect against dysmenorrhoea or that women with higher education may have better knowledge and understanding about dysmenorrhoea, leading to a healthier lifestyle, diet, and access to good healthcare (Chantler et al., 2006; DeVallance et al., 2019; Millen et al., 2014; Munro et al., 2021; Pampel et al., 2010).

Still other studies have found that higher education level is associated with a higher prevalence of dysmenorrhoea among university students compared to non-students, suggesting that higher education may be a risk factor for dysmenorrhoea (Habibi et al., 2015; Sahin et al., 2014; Unsal et al., 2010). As shown with our multivariate analysis, it is important to control for other demographic factors when examining associations between dysmenorrhoea and education level, which not all prior studies did.

In simple descriptive analysis, I found that women with tertiary education were more likely to report no-mild dysmenorrhoea or secondary dysmenorrhoea, while those with lower level of education were more likely to report primary dysmenorrhoea. However, since the women with secondary dysmenorrhoea were older than the other groups, this univariate relationship could be confounded by age.

It is worth noting that the relationship between education and dysmenorrhoea may be complex and may be influenced by a variety of factors, also including age, cultural and economic factors. Since our population was recruited in tertiary education institutions, my analysis of the relationship between education and dysmenorrhoea should be interpreted with caution.

5.2.5 Ancestry

Women of European ancestry had lower odds and women of mixed ancestry had higher odds than those of African ancestry of reporting dysmenorrhoea in my univariable analysis. However, in the multivariable model, only those of European ancestry remained significantly associated with lower odds of moderate-to-severe dysmenorrhoea. My findings suggest that being of European ancestry might have a genetic protective effect against dysmenorrhoea; however, it is also possible that there are other sociocultural protective factors in this group that I did not measure. This finding may reflect possible differences between the groups in education and/or socioeconomic status, or possibly even differences in timing of menarche. Notably, menarche tends to occur at an earlier age in people of African ancestry (Chumlea et al., 2003; Deardorff et al., 2014; Morabia et al., 1998), and since earlier age at menarche predicts dysmenorrhoea in previous reports (Charu et al., 2012; Latthe, Latthe, et al., 2006) and in my multivariable model. The differences I found in prevalence of dysmenorrhoea according to ancestry could also reflect different cultural practices, attitudes and beliefs regarding menstruation, which correlate with reporting of menstrual symptoms (Chen & Chen, 2005; Stubbs, 2008; Tan et al., 2017). In African rural communities, for example, dysmenorrhoea is masked in shame and secrecy (Chhabra et al., 2017), however, my sample was an urban sample with many having a higher than matric level of education. While, to my knowledge, this is the first study to comprehensively examine the prevalence and correlates of dysmenorrhoea in a large South African sample, a prior study of South African students reported that black and mixed students tended to perceive menstruation as more debilitating compared to white students (Padmanabhanunni & Fennie, 2017). On the other hand, black and mixed students were more likely to deny that menstruation caused emotional distress and bothersome cramps (Padmanabhanunni & Fennie, 2017). Given that women of African and mixed ancestry were more likely to report dysmenorrhoea than the other groups, further research is required to

determine contributing factors, and to investigate effectiveness of treatments within these populations specifically.

In my simple descriptive analysis, respondents of African ancestry were less likely to report secondary dysmenorrhoea compared to those of European, Mixed, and Indian ancestry. There was no effect of ancestry on the likelihood of having primary vs. no-mild dysmenorrhoea.

Several studies have investigated the prevalence of dysmenorrhoea among different racial and ethnic groups in other countries. In a study of adolescent girls in the United States, the prevalence of dysmenorrhoea was found to be higher in non-White girls (including African American, Hispanic, and Asian girls) compared to White girls (Klein & Litt, 1981). However, in a study of adult women attending primary care practices, there was no significant difference in the prevalence of dysmenorrhoea between African American and White women (Jamieson & Steege, 1996a). A study of adolescent girls in Malaysia found that Chinese girls were more likely to report dysmenorrhoea than Malay girls (Jaiprakash et al., 2016). Similarly, a cross-sectional study of Chinese university students found that the prevalence of primary dysmenorrhoea was higher among Han Chinese students compared to minority students (Hu et al., 2020). However, a study of adolescent girls in Asia (including girls of Chinese, Malay, and Indian ethnicity) found no significant difference in the prevalence of dysmenorrhoea between different ethnic groups (Wong & Khoo, 2010).

In terms of occupational and lifestyle factors, a study of military personnel found that African American women were more likely to report dysmenorrhoea compared to White women (Gordley et al., 2000). A recent cross-sectional study in Jordan found that lifestyle variables, including exercise and dietary habits, were significantly associated with primary dysmenorrhoea (Al-Husban et al., 2022). One study specifically found that respondents of African ancestry were less likely to report secondary dysmenorrhoea compared to those of European, Mixed, and Indian ancestry, but there was no effect of ancestry on the likelihood of having primary vs. no-mild dysmenorrhoea (Seidman et al., 2018).

This decreased reporting of secondary dysmenorrhoea among women from African ancestry could be explained by confounding effects of socioeconomic status, but as well as cultural and other societal factors. These factors include cultural views that menstrual pain ought to be considered as 'normal' and thus does not warrant a medical visit and/or that menstrual pain is not a topic that should be raised (Padmanabhanunni & Fennie, 2017; Stubbs, 2008). Indeed it is believed that cultural and mythological beliefs in certain areas in the world about menstruation and abnormal uterine bleeding may play a greater role in the prevalence and management of dysmenorrhoea among different ancestry groups than biological factors (Tan et al., 2017). More research is needed to understand the relationship between mixed ancestry and dysmenorrhoea.

5.2.6 Lifestyle factors: smoking and exercise

In univariable analyses, the women who smoked had higher odds of reporting dysmenorrhoea, but this significance was lost in multivariable analyses. Previous studies have shown that females who smoke have more menstrual pain when compared to non-smokers (Harlow, 1996; Sundell, 1990; Parazzini, 1994). In contrast to some previous studies, in our findings smoking was not a risk factor for dysmenorrhoea in adjusted analyses (Ballagh & Heyl, 2008; Dorn et al., 2009; Ju et al., 2014a, 2014b). Previous studies have reported similar results; smoking has been associated with an increased risk of dysmenorrhoea (with no distinction between primary and secondary) among young women in Sweden (Sundell et al., 1990), and in Turkey (Ozerdogan et al., 2009). Previous studies also found that women who smoked had more severe menstrual symptoms (Dorn et al., 2009), worse quality of life associated with chronic pelvic pain (Souza et al., 2011) which increased depending on the number of daily cigarettes smoked (Sundell et al., 1990). On the other hand, some studies found no association between smoking and dysmenorrhoea (Fatima et al., 2017; Kural et al., 2015b; Seven et al., 2014; Singh et al., 2008; Unsal et al., 2010).

Smoking has been shown to reduce endometrial blood flow, by causing vasoconstriction, leading to lower tissue oxygenation and stronger uterine contraction which might lead to an increased period pain and period length (Parazzini et al., 1994). The mechanisms by which

smoking may be associated with dysmenorrhoea are not fully understood, but it is also thought that smoking may affect hormones such as increasing FSH and LH and lower levels of oestradiol and progesterone, two hormones that play a crucial role in the menstrual cycle and reproductive health (Schiller et al., 2012). Smoking has also been found to increase enzymatic lipid peroxidation, primarily mediated by enzymes such as cyclooxygenases (COX), which could contribute to increased prostaglandin synthesis and the development of dysmenorrhoea in women (van't Erve et al., 2018). Additionally, smoking may increase the risk of inflammation and oxidative stress, which may contribute to dysmenorrhoea (Ozguner et al., 2005). Overall, while some studies have found an association between smoking and dysmenorrhoea, others have not.

In our survey, women who reported smoking were more likely to report experiencing secondary dysmenorrhoea, while those who reported that they do not smoke were more likely to report experiencing no-mild dysmenorrhoea or primary dysmenorrhoea. Similarly to my findings, in Italy smoking has been associated with increased risk of primary dysmenorrhoea (Parazzini et al., 1994). My study though, suggests that perhaps that there exist other factors linked to smoking that contribute to the correlation with dysmenorrhoea, and were not accounted for in the univariate analyses. Thus, it is plausible that there may not be a causal and independent relationship between the two variables. This may also explain the discrepancies found in the results of other studies that did not distinguish between secondary and primary dysmenorrhoea.

In my univariable analyses, the women who exercised had lower odds of reporting moderate-severe dysmenorrhoea, but this significance was lost in multivariable analyses. Previous studies have reported mixed evidence regarding the possible association between exercise and dysmenorrhoea. Some studies have reported no significant association between exercise and dysmenorrhoea (Harlow & Park, 1996; Pullon et al., 1988; Sundell et al., 1990) while others found that exercise can decrease the duration and severity of dysmenorrhoea (Dehnavi et al., 2018). Others yet, have suggested that exercise decreases menstrual symptoms (Choi & Salmon, 1995) and pain intensity (Hightower, 1998) by lowering prostaglandin synthesis during menstruation (Martínez et al., 1999). While others suggest that release of beta endorphins as a result of exercise (Bonen, 1984) boosts pelvic blood flow and metabolism

which results in a decrease in menstrual pain intensity (Izzo & Labriola, 1991). In direct contrast, , one study showed that intense exercise resulted in increased menstrual pain (Harlow & Park, 1996). Intensity and type of exercise may thus be important consideration in the relationship between exercise and dysmenorrhoea.

Historically, and based on anecdotal belief, exercise has always been thought to be effective in preventing and treating symptoms of dysmenorrhoea (Daley, 2008). Indeed, limited evidence does support that physical activity, including stretching, isometric and aerobic exercise, can improve primary dysmenorrhoea (Dehnavi et al., 2018; Nasri et al., 2016; Shahrjerdi & Shaych Hosaini, 2010; Shavandi et al., 2010). Somewhat in line with these studies, I found that women with primary dysmenorrhoea were less likely to exercise than those with secondary or no-mild dysmenorrhoea. However, other studies have found no association between exercise, including aerobic exercise (Blakey et al., 2010; Daveneghi et al., 2016; Latthe, Latthe, et al., 2006; Shafaie et al., 2013). Apart from Blakey et al (2010), who looked specifically at primary dysmenorrhoea, the others did not distinguish between primary and secondary dysmenorrhoea. One proposed mechanism that explain how continuous exercise may improve dysmenorrhoea is that exercise may improve physical symptoms by reducing plasma aldosterone levels and increasing plasma estrogen and progesterone concentrations (Armour et al., 2019; Baker et al., 1999; Barcikowska et al., 2020; Ju et al., 2015; Kumar et al., 2014; Moradpour, 2019). Future studies are needed to understand this relationship, and ideally, they should distinguish between primary and secondary dysmenorrhoea.

5.2.7 Menstrual characteristics and family history

Like with older age at the time of the study, older age at menarche was significantly associated with lower odds of reporting dysmenorrhoea in both univariable and multivariable analysis, implying that the older a woman is at the time of her first menstruation, the less likely she will report experiencing moderate-to-severe dysmenorrhoea. In line with my findings, previous studies, have found an association between earlier age at menarche and dysmenorrhoea, with some studies reporting that early age at menarche (age at menarche below 12 years old) is associated with higher odds of severe dysmenorrhoea (Ameade & Garti, 2016; Chumlea et al.,

2003; Harlow & Park, 1996; Rocchini, 2002; Sundell et al., 1990; Zegeye et al., 2009) and others reporting no association between menarche and dysmenorrhoea (Eryilmaz et al., 2010; Ju et al., 2014a; Orhan et al., 2018).

Less continuous exposure to prostaglandins has been used to explain why an older age at menarche may be protective against dysmenorrhoea (Charu et al., 2012). It is believed that women who experience menarche at a later age have a shorter menstrual cycle, and therefore less continuous exposure to prostaglandins, meaning that they may have fewer uterine contractions and less severe dysmenorrhoea (Al-Matouq et al., 2019; Dawood, 2006; Jabbour et al., 2006; Pejčić & Janković, 2016). However, more research is needed, as the mechanisms underlying the possible association between age at menarche and risk of dysmenorrhoea remain largely unknown.

In my simple descriptive analysis, when considering whether age at menarche may associate differently with primary versus secondary dysmenorrhoea, I found that there was no difference between women with no-mild, primary, and secondary dysmenorrhoea. It has been suggested that younger age at menarche is associated with primary dysmenorrhoea (Grandi et al., 2012; Ju et al., 2014a; Wernli et al., 2006; Xu et al., 2004), but one study also found an association between young age at menarche and endometriosis (secondary dysmenorrhoea) (Dossus et al., 2010).

In both univariable and multivariable analysis, irregular menses had no significant association with risk of reporting dysmenorrhoea. On the other hand, “sometimes” irregular menses was found to be associated with higher risks in univariable analysis; a relationship which was lost in multivariable analysis. Similarly to my finding, an older study is in accordance with my results, which suggest that menses regularity is not associated with dysmenorrhoea (Chen, 1984). Unlike my finding, some previous studies have reported that irregular menses is associated with higher risks of reporting dysmenorrhoea (Abu Helwa et al., 2018; Patel et al., 2006; Ryan, 2017; Sahin et al., 2014; Unsal et al., 2010). Previous studies suggest that hormonal imbalances can be caused by stress, anxiety, or depression, which may also be associated with irregular menstrual cycles and dysmenorrhoea (Kaplan & Manuck, 2004). In

addition, early menarche was found to be associated with irregular menstrual cycles, which may lead to dysmenorrhoea, suggesting that puberty-related hormonal changes may also play a role (Avasarala, Kameswararao & Panchangam, 2008). The presence of underlying gynaecological conditions such as endometriosis or uterine fibroids can cause both irregular menstrual cycles and dysmenorrhoea (Barnard et al., 2003). In addition, socioeconomic factors, such as access to healthcare and the use of contraception, may also influence the regularity of the menstrual cycle (Blackstone et al., 2017).

Respondents with regular menses were more likely to report experiencing no-mild dysmenorrhoea, whereas those who reported having irregular menses were more likely to report experiencing secondary dysmenorrhoea and those who reported sometimes irregular menses were more likely to report experiencing primary dysmenorrhoea. My findings are in agreement with several studies reporting that irregular menses are often a sign of specific secondary dysmenorrhoeic conditions, such as polycystic ovary syndrome, fibroids and endometriosis, or underlying hormonal imbalances (Mendiratta & Lentz, 2017; Tavallaee et al., 2011; Tu et al., 2009).

Women who experienced less than 3 days of menstrual bleeding were less likely to report experiencing dysmenorrhoea in both my univariable and multivariable analyses. Whereas those who experienced more than 7 days were at more risk of having/reporting dysmenorrhoea in univariable; an association that was also significant in the multivariable analysis.

Chances of experiencing menses at random intervals were highest among in those moderate-severe dysmenorrhoea, but this association was lost during multivariable analysis. Literature on the association between the menstrual cycle interval length and dysmenorrhoea has generated mixed results. One study reported that women who experience their menstrual cycles at intervals of 35 days or more are at more risk to experience dysmenorrhoea, and those who experience them at random are less at risk (Tavallaee et al., 2011), but others have found no association between menstrual cycle intervals and dysmenorrhoea (Strinić et al., 2003). In our case, we found that those who experienced their menstrual bleeding at random interval were significantly less likely to report dysmenorrhoea only in our univariable analysis.

Related to regularity of menses, and in-line with the traditional definition of primary dysmenorrhoea, I found that women who reported having a 24–35-days interval between menses (considered as a normal menstrual cycle length), and those with menses lasting 3 -7 days were more likely to report experiencing primary dysmenorrhoea. In contrast, those with random menstrual cycle intervals and those with menses lasting less than 3 days were more likely to report no-mild dysmenorrhoea. Finally, those with random menstrual cycle intervals and those with menses lasting longer than 7 days were more likely to have secondary dysmenorrhoea. These results are in line with the definition of secondary dysmenorrhoea and commonly reported complaints that accompany various secondary dysmenorrhoeic conditions, including endometriosis and adenomyosis (Stewart & Deb, 2016; Suvitie et al., 2016b). I presume this may be because there are general differences in menses length between primary and secondary dysmenorrhoea, with secondary dysmenorrhoea associated with longer bleeding and irregular intervals between menses (Stewart & Deb, 2016; Suvitie et al., 2016b). My finding suggests that longer menstrual bleeding and random irregular intervals between menses occur in women with secondary dysmenorrhoea.

Further analysis found that those who experienced heavy flow were at higher risk of having dysmenorrhoea and those with a light flow were least at risk of having dysmenorrhoea. These findings were seen in both my univariable and multivariable analyses, and are in accordance with previous studies in that heavy menstrual flow and irregularity are associated with high risk of having dysmenorrhoea (Harlow & Park, 1996; Sundell et al., 1990). The underlying mechanisms are largely not understood, but it has been proposed that women with heavy menstrual flow experience increased prostaglandin production, leading to stronger uterine contractions and more severe pain during menstruation (Berkley & McAllister, 2011; Ferries-Rowe et al., 2020). Stress and anxiety can also contribute to dysmenorrhoea and irregular menstrual cycles by increasing cortisol levels, which can disrupt the menstrual cycle and exacerbate menstrual pain and lead to muscle tension, which can cause or worsen dysmenorrhoea. (Iacovides et al., 2015a).

In addition, heavy menstrual flow may also lead to anemia, a condition characterized by low levels of iron in the blood, which can cause fatigue and weakness, and may exacerbate symptoms of dysmenorrhoea through lower tissue oxygenation (McLean et al., 2009; Tan et

al., 2017). Further research is needed to better understand the specific mechanisms by which heavy menstrual flow may affect the prevalence and severity of dysmenorrhoea, as well as the potential role of prostaglandins and anemia in this relationship.

In terms of menstrual flow/heaviness of bleeding and the type of dysmenorrhoea (primary and secondary), I found that those reporting light menstrual flow and those with a medium menstrual bleeding flow were more likely to report experiencing no-mild dysmenorrhoea, while the women who reported experiencing heavy menstrual bleeding were more likely to experience primary and secondary dysmenorrhoea. This finding is consistent with previous studies that have found that women with heavy menstrual flow are more likely to report experiencing pain during menstruation (O'Brien et al., 2011). Secondary dysmenorrhoea is commonly accompanied with complaints of abnormal heavy and prolonged menstrual bleeding (menorrhagia) (Stewart & Deb, 2016), in line with my results. Primary dysmenorrhoeic pain is also reported to be associated with heavy menstrual flow (Ferries-Rowe et al., 2020; Iacovides et al., 2015c) .

I also found that women who experience PMS were more likely to report dysmenorrhoea. This finding is in line with previous studies that found a positive association between PMS and dysmenorrhoea (Arafa et al., 2018; Booton & Seideman, 1989; Ilango, 2016; Kitamura et al., 2012; Mitsuhashi et al., 2023; Shiferaw et al., 2014; Zafar et al., 2017). Possible mechanisms behind the association may include hormonal changes during menstrual cycle (Ju et al., 2014a; Kitamura et al., 2012). Another theory suggests that psychological factors, such as stress and anxiety, may play a role in the association between dysmenorrhoea and PMS. Studies have found that women who experience high levels of stress and anxiety are more likely to report symptoms of dysmenorrhoea and PMS (Ju et al., 2014; Fernández-Martínez et al., 2018). However, further research is needed to better understand the relationship between dysmenorrhoea and PMS. Overall, I found that nearly 60% of women reported moderate-to-severe premenstrual syndrome (PMS) and those who reported moderate-to-severe PMS were more likely to report secondary dysmenorrhoea. On the other hand, a higher proportion (71.1%) of women reporting no, or mild PMS were more likely to report no-mild dysmenorrhoea. Regarding PMS interference on the quality of life, overall, about 36% of all respondents reported moderate-to-severe PMS interference, with those reporting severe PMS interference

being more likely to have secondary dysmenorrhoea, and those reporting mild, or no PMS interference were more likely to have no-mild dysmenorrhoea. My findings are in accordance with prior cross-sectional studies which report a reduction in the quality of life of women with dysmenorrhoea, particularly in relation to the often-overlapping symptoms of PMS, such as mood changes (i.e. irritability and depression) and fatigue before and/or during menses (Barnard et al., 2003; Souza et al., 2011; Unsal et al., 2010; Vincent et al., 2011).

Furthermore, I found that women with a positive family history of dysmenorrhoea were at a higher risk of reporting experiencing moderate to severe dysmenorrhoea suggesting that there may be a genetic component to the development of dysmenorrhoea, which is consistent with previous studies (Fernández-Martínez et al., 2018; C.-M. Juang et al., 2006; Latthe, Mignini, et al., 2006; Muluneh et al., 2018; Parveen et al., 2009; Pejčić & Janković, 2016; Sahin et al., 2014).

Family history of dysmenorrhoea was significantly more common among those with primary or secondary dysmenorrhoea compared to those with no-mild dysmenorrhoea. This finding suggests a genetic risk of the development of dysmenorrhoea (regardless of primary or secondary cause), in line with numerous other reports (Avasarala, Kameswararao & Panchangam, 2008; Ju et al., 2014a; Kumbhar et al., 2011; Tavallaee et al., 2011). It may be that genetic variations may play a role by altering the way that hormones and biological factors interact with the reproductive system (Wu et al., 2000).

5.2.8 Contraception and pregnancy

Using hormonal contraceptives was associated with lower risk of dysmenorrhoea in univariable analysis, however, this association has lost its significance in the multivariable model. In my simple descriptive study, more than 70% of our respondents did not use any kind of contraception. Those who reported using contraceptives were more likely to experience no-mild dysmenorrhoea and to have been given a secondary dysmenorrhoea diagnosis, whereas those reporting experiencing primary dysmenorrhoea were the least likely to use contraceptives. The literature indicates that hormonal contraceptives help control

dysmenorrhoea by suppressing ovulation and causing regression of the endometrium, shortening the time of endometrial proliferation, and limiting the secretory activity of endometrial glands (Sturpe, 2013). As a result, hormonal contraceptives are often prescribed for their effects in alleviating dysmenorrhoea (Brant et al., 2017; Davis et al., 2005; Ferries-Rowe et al., 2020; Iacovides et al., 2015a; Kulkarni & Deb, 2019; McKenna & Fogleman, 2021). As seen in the results, contraceptives methods were mostly used by the older age group: those having secondary dysmenorrhoea, implying that older women may be more likely to use contraceptives due to their increased access to information and services, as well as their greater experience and knowledge about reproductive health (Blackstone et al., 2017). Older women may also be more likely to have greater decision-making power and autonomy in their relationships, allowing them to make informed choices about their reproductive health (Blackstone et al., 2017). Therefore, the reason for the low usage rate in our sample may be attributed to the prevalence of young adults who perceive their pain as 'normal' or unworthy to report and therefore do not seek help for it (Berkley & McAllister, 2011; Chhabra et al., 2017; Lau et al., 2000; Metcalfe et al., 2016), to personal choices, cultural, and/or religious beliefs, lack of access to information and services, and misconceptions about contraceptives (Blackstone et al., 2017; Gueye et al., 2015; Ngum Chi Watts et al., 2014) and dysmenorrhoea (Ngum Chi Watts et al., 2014). The low rate can also simply be because the decision to use or not to use contraceptives is multifaceted and influenced by various factors. Women may choose to use contraceptives for a multitude of reasons, such as to prevent unintended pregnancies, regulate menstrual cycles, or manage symptoms associated with menstruation. On the other hand, some women may opt not to use contraceptives due to personal beliefs, cultural or religious reasons, concerns about potential side effects, or lack of access to healthcare (Blackstone et al., 2017; H.-M. Chen & Chen, 2005; Gueye et al., 2015; Ngum Chi Watts et al., 2014; Stubbs, 2008; Tan et al., 2017). Thus, the decision to use or not to use contraceptives is a complex and individualized choice that depends on a range of factors unique to each woman's circumstances.

In both the univariable and multivariate models, having ever been pregnant was a protective factor against moderate-severe dysmenorrhoea, which supports prior work. Previous studies found that women who had given birth experienced a decrease, and even an elimination of period pain, while those who were never pregnant and/or those who had abortion showed no

change in severity of dysmenorrhoea (Kulkarni & Deb, 2019; Metcalfe et al., 2016). In my opinion, the main point here is that although it may not be fully understood how pregnancy reduces pain, my data do support the idea that pregnancy can alleviate or eliminate menstrual pain after childbirth. The specific mechanism behind this effect, whether it is due to hormonal changes in the uterus, the process of giving birth, or some other factor, is still uncertain and requires further investigation.

Most of our respondents (almost three quarters) had never been pregnant at the time of the study. Respondents who reported experiencing primary dysmenorrhoea had the lowest percentage of women who had ever been pregnant compared to those who reported no-mild dysmenorrhoea and secondary dysmenorrhoea, with the proportions being approximately the same in the latter two groups. Our finding supports the notion that pregnancy can have a protective effect on dysmenorrhoea, particularly primary dysmenorrhoea (Juang et al., 2006; Sundell et al., 1990). Juang et al. (2006) proposed that the protective effect of pregnancy may be due to the increased levels of progesterone and the suppression of ovulation which may play a protective role against the development of dysmenorrhoea by decreasing uterine contractility and inflammatory response (Juang et al., 2006). Additionally, pregnancy-induced hormonal levels changes and decrease in prostaglandin levels, leading to a decrease in uterine contractions, may also contribute to the reduction in dysmenorrhoea symptoms (Mendiratta & Lentz, 2017), but the mechanism behind the prolonged protective effect of pregnancy long after giving birth is currently unknown.

On the other hand, the protective effect of pregnancy may not apply to secondary dysmenorrhoea It has been reported that women with secondary dysmenorrhoea were more likely to have ever been pregnant (Patel et al., 2006; Porpora et al., 2010). This may not be due physiological mechanisms but rather the by-product of age, whereby those with secondary dysmenorrhoea tend to be older, and thus were more likely to ever have been pregnant than those with primary dysmenorrhoea.

5.2.9 Poor sleep quality and central sensitisation

Not only do the women with dysmenorrhoea show signs of central sensitisation but they are also likely to not sleep well: my results show that there is a significant association between reporting "not sleeping well" frequency (often/always) and high odds of reporting dysmenorrhoea: the higher the frequency of "not sleeping well", the more likely our participants were to report experiencing moderate-to-severe dysmenorrhoea. These findings remained significant in both the univariable and multivariable analysis. Most of the women who reported that they did not sleep well often or always, were mostly those experiencing primary and secondary dysmenorrhoea. Pain and sleep have a relationship where pain reduces sleep quality and reduced sleep quality increases pain perception (Finan et al., 2013; Gerhart et al., 2017; Krause et al., 2019; Sivertsen et al., 2015). There is evidence that dysmenorrhoeic pain negatively affects objective and subjective sleep quality sleep in women with primary (Baker et al., 1999; Iacovides et al., 2009, 2015c) and secondary dysmenorrhoea (Araujo et al., 2011; Marinho et al., 2018; Nunes et al., 2015). Although we have evidence that dysmenorrhoeic pain negatively affects sleep composition (e.g. a reduction in REM sleep time and sleep efficiency) and sleep quality (Baker et al., 1999; Iacovides et al., 2009; Saei Ghare Naz et al., 2021; Sahin et al., 2014), the implications of my findings extend beyond the effect of pain on sleep. It may be that poor sleep quality in women with dysmenorrhoea is not strictly associated with menstruation, and hence pain, but rather that their sleep quality is "often/always" poor even outside of menstruation. Numerous studies have demonstrated a strong relationship between sleep disturbances and pain, including dysmenorrhoea. Disturbed sleep/insomnia is a risk factor for chronic pain (Edwards et al., 2008; Finan et al., 2013; Saei Ghare Naz et al., 2021; Smith et al., 2000, 2008), as previous studies have shown that individuals with insomnia are more likely to develop chronic pain following an acute injury compared to those without insomnia (Edwards et al., 2008). Additionally, poor sleep quality has been linked to the worsening of pain symptoms in individuals with chronic pain conditions such as fibromyalgia and arthritis (Finan et al., 2013). The suggested mechanism for this relationship is complex and involves multiple factors, including disruptions in the body's natural pain modulation processes, alterations in the immune system and inflammation, and psychological distress (Finan et al., 2013; Smith et al., 2008) which can result in sleep disturbances that can also exacerbate pain, including dysmenorrhoea pain (Sharma et al., 2021).

These findings highlight the importance of addressing both sleep disturbances and pain in the management of chronic pain conditions (Neblett et al., 2013).

I found that high CSI score, a validated subjective measure of central sensitisation, is associated with higher odds of reporting moderate-severe dysmenorrhoea in both univariable and multivariable analysis. I also found that the CSI total score was the highest in respondents with secondary dysmenorrhoea followed by those with primary dysmenorrhoea. Women with no-mild dysmenorrhoea had the lowest CSI total score. Although not consistently (Amodei & Nelson-Gray, 1989), compared to healthy controls, women with primary dysmenorrhoea have been reported to have increased sensitivity to pain both within and outside areas of referred menstrual pain and across the menstrual cycle (Bajaj et al., 2002; Iacovides et al., 2015c). This finding may possibly due to monthly recurring menstrual pain, which may cause central sensitisation (Yunus, 2007, 2008). Central sensitisation, defined as an abnormal increase in nociceptive mechanisms within the central nervous system, leading to increased pain sensitivity to areas outside of the denoted area of the initial pain (Woolf, 2011). Central sensitisation commonly occurs after chronic or repetitive pain (Arendt-Nielsen et al., 2018; Yunus, 2007, 2008). Continued, or repeated (in the case of dysmenorrhoea) input of painful signal/message to the central nervous system (CNS), causes both anatomical changes, metabolic changes, and physiological changes in the CNS, which in can lead to central sensitisation, and hence by increased sensitivity to pain. Furthermore, studies have demonstrated significant differences between the brains of otherwise healthy women who experience moderate-to-severe dysmenorrhoea; including differences in central activity induced by noxious skin stimulation (Vincent et al., 2011), cerebral metabolism (Tu et al., 2009), and cerebral structure (Tu et al., 2010). Menstrual pain may lead to alterations in the CNS and nociceptive pathways, resulting in increased pain sensitivity and the development of chronic pain conditions (Yunus, 2007, 2008). Additionally, a previous study has shown that dysmenorrhoea symptoms are positively correlated with the extent of central sensitisation (Bajaj et al., 2002).

Our findings of increased CSI scores support the notion that women with dysmenorrhoea are more sensitive to pain than women without dysmenorrhoea. Indeed, a total CSI score of 40 and more suggests a possible central sensitivity syndrome (Neblett et al., 2013) and nearly 40% of

our respondents scored 40 or more. This is consistent with studies that have indicated that women with dysmenorrhoea are more sensitive to various forms of pain compared with healthy controls (Bajaj et al., 2003; Giamberardino et al., 2014; Iacovides et al., 2015a). Collectively, these results support that dysmenorrhoea may not merely be a disorder associated with menstruation (Iacovides et al., 2015a). Repeated activation of central sensitisation mechanisms, due to recurring monthly pain, may lead to an increase in pain sensitivity and a lowered pain threshold, predisposing women with primary dysmenorrhoea to other chronic painful conditions (Iacovides et al., 2013, 2015a, 2015c; Neblett et al., 2013). However, it is not yet known whether central sensitisation is the cause-or effect- of experiencing repeated menstrual pain. More longitudinal research needs to be done to establish direction and causality.

The development of central sensitisation can result in a chronic widespread pain condition, such as fibromyalgia, a condition characterized by widespread musculoskeletal pain, fatigue, and sleep disturbances (Yunus, 2007; Woolf, 2011). A study also found that women with dysmenorrhoea may be at an increased risk of developing fibromyalgia due to the development of central sensitisation (Vincent et al., 2011).

It is also possible that chronic pain conditions have been shown to be a major contributor to sleep disturbances, including difficulties falling asleep, frequent awakenings during the night, and poor sleep quality (Finan et al., 2013). In addition, the constant pain signals can disrupt the normal sleep-wake cycle, leading to further sleep disturbances (Chen et al., 2018). For instance, a study by Edwards et al. (2008) found that sleep disturbances predicted increased pain sensitivity and severity in patients with fibromyalgia. Similarly, a study by Finan et al. (2015) reported that sleep disturbances predicted greater pain severity in patients with chronic pain, and pain severity predicted greater sleep disturbances. Chronic pain can start from sleep disturbances or vice versa. In some cases, chronic pain can begin because of sleep disturbances, as chronic sleep deprivation and disrupted sleep patterns can lead to the development of central sensitisation and chronic pain conditions (Finan et al., 2013). On the other hand, chronic pain can also lead to sleep disturbances, as the constant pain signals can disrupt the normal sleep-wake cycle and lead to poor sleep quality (Chen et al., 2018).

5.2.10 Medical consultation and treatment

Despite the large prevalence of dysmenorrhoea in our sample, As discussed above, it is possible that the low medical visit (Dr or gynecologist) rate may be due to different cultural taboos, beliefs, attitudes, and practices which consider menstrual pain as 'normal' part of being a woman and possibly a private matter, that is either not worth seeking assistance for, or possibly even stigmatized (Chen & Chen, 2005; Chhabra et al., 2017; Lau et al., 2000; Stubbs, 2008; Tan et al., 2017).

Most of our respondents used pharmacological (89.0%) and nonpharmacological (50.6%) treatment for dysmenorrhoea with those who reported experiencing primary and secondary dysmenorrhoea (60% - 75%) often or always required dysmenorrhoea pain medication. These findings are in line with the literature where most women with dysmenorrhoea rely on over the counter painkillers (Hadfleld et al., 1996; Hudelist et al., 2012). The medications commonly reported are NSAIDs and include aspirin and a combination medication such as Mybulin, Myprodol, Stilpyn, Betapyn, Ibumol. The high frequency of use of pain medication may be attributed to factors such as education and socioeconomic status. Our population is mainly composed of women in tertiary education suggesting they might have the knowledge and access to over-the-counter pain relief medication (Klein & Litt, 1981).

5.3 Strengths and limitations of my study

Menstrual pain has been shown to be disabling to the affected women and might lead to the development of chronic diseases with time, making it an important public health issue. Our study might be the first one to investigate the prevalence and factors associated with dysmenorrhoea in a South African university population and examine poor sleep as a factor and to also use a valid scale of CSS, to examine its association with dysmenorrhoea. We found that, although dysmenorrhoea is highly prevalent in our population, very few seek medical attention. This study can help start a conversation on how to dismantle the believes behind period pain. Our population distribution spreads across the whole of South Africa and the large number of our respondents, suggesting a good representation of the South African universities'

population. This, however, may also be seen as a study limitation, as our sample may not be a good representation of all women across South Africa. Hence our findings may not be generalized across the entire country, but rather in women associated with tertiary institutions.

It is important to acknowledge certain limitations of our study. Firstly, since this was a cross-sectional study, causal relationships cannot be established. Secondly, we found that many of the participants did not consult a doctor for their menstrual pain, which made it difficult to accurately distinguish between primary and secondary dysmenorrhoea. However, we did use certain characteristics such as having been diagnosed of gynecological condition associated with secondary dysmenorrhoea such as PCOS, PID, endometriosis, and regular pain onset associated with menstruation and predictable menstrual cycles to help differentiate between the two types of dysmenorrhoea.

I recognize that selecting variables based on their importance in the literature may introduce a confirmation bias. This means that there is a possibility of favoring variables that align with my preconceived ideas or desired outcomes, which could impact the objectivity and reliability of the research findings.

To address these limitations, future longitudinal studies are needed to track the natural occurrence and history of dysmenorrhoea in women over time to better understand the factors that contribute to or prevent menstrual pain. Additionally, it is possible that reporting bias may have influenced our results, as women with dysmenorrhoea may have been more likely to participate in the study, which could potentially overestimate the overall prevalence rates in the general population.

CONCLUSION

In conclusion, my study aimed to investigate the prevalence and risk factors associated with dysmenorrhoea in a population of South African universities. I found a high prevalence of moderate-to-severe dysmenorrhoea of almost 77% in women surveyed across South African universities. Differences were observed between primary and secondary dysmenorrhoea, with secondary dysmenorrhoeics tending to be older, have higher socioeconomic status, and were more likely to be employed. Factors associated with increased odds of moderate-to-severe dysmenorrhoea in adjusted analyses included younger age at the time of the study, younger age at menarche, non-European ancestry, heavy menstrual flow, longer menses, nulliparity, high CSI total score, and poor sleep.

My data show that the impact of dysmenorrhoea on daily life is substantial, with 76% of our respondents reporting being absent from school or work during menses. Furthermore, 89% of the population reported needing pharmacological treatments such as contraceptive pills and nonsteroidal anti-inflammatory drugs (NSAIDs) to manage their menstrual pain. The implications of both the increased CS and the sleep-pain reciprocal relationship suggest that they could potentially lead to the development of chronic pain conditions. These findings highlight the urgent need for interventions to reduce the burden of dysmenorrhoea on women's lives.

My study highlights that dysmenorrhoea is a prevalent problem among women in South African universities. The findings emphasize the need for increased awareness, education, and effective interventions aimed at reducing the prevalence and impact of dysmenorrhoea on women's lives. Addressing CSS and other underlying causes of dysmenorrhoea is crucial to reduce the impact of dysmenorrhoea on women's lives and prevent the development of chronic conditions later in life.

Future research should further explore the prevalence and risk factors associated with dysmenorrhoea and address the limitations of this study. The findings of this study have important implications for the management of dysmenorrhoea to reduce the impact of menstrual pain on women's lives and the economy. By addressing this issue, we can improve women's quality of life, promote better health outcomes, and contribute to a healthier and more productive society.

A critical part of better management of dysmenorrhoea includes educating women about the importance of seeking medical attention for their menstrual pain and the potential long-term implications of untreated dysmenorrhoea.

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APPENDICES

Appendix 1: The information on the email that was distributed by the universities across South Africa.

The Epidemiology of Menstrual Pain in a South African University Population

Hello, I (Dr Stella Iacovides) and my co-investigators (Dr Fiona Baker and Chloe Flinn) are currently conducting research in the field of sleep and pain, specific to women with dysmenorrhoea. Dysmenorrhoea is simply painful menstruation (period pains). Our current investigation aims to determine the prevalence and severity of dysmenorrhoea in a South African student and staff population, as well as the factors involved.
In order to achieve this we are inviting you (the participant) to fill out the attached survey which contains questions regarding demographics, your menstrual cycle and the Central Sensitization Inventory (CSI). The CSI is a validated questionnaire which will allow us to determine the percentage of women that have, or are prone to having, Central Sensitivity Syndrome (CSS). Please note that this is not a diagnostic tool, and any concerns raised by the questionnaire may be followed up with your doctor.

Please ensure you answer all the questions and click 'submit' at the end.
By submitting the completed questionnaire your agreement to participate in the research is assumed. Your participation is completely voluntary, if you exit the questionnaire before completion we will assume this to be your withdrawal from the study and all previous answers will not be saved. Participating in, or withdrawing from, the survey will serve no benefit or loss to you.

This survey is meant for FEMALES ONLY (There is no need to answer the survey if you have gone, or are going, through menopause), who study/work at a Government funded University.
Universities included in this study (alphabetical order):

1. Cape Peninsula University of Technology
2. Central University of Technology
3. Durban University of Technology
4. Mangosuthu University of Technology
5. Nelson Mandela Metropolitan University
6. North-West University
7. Rhodes University, Tshwane University of Technology
8. Sefako Makgatho University
9. Sol Plaatje University.
10. Stellenbosch University
11. Tshwane University of Technology
12. University of Cape Town
13. University of Fort Hare
14. University of the Free State
15. University of Johannesburg
16. University of KwaZulu-Natal
17. University of Limpopo
18. University of Mpumalanga
19. University of Pretoria
20. University of South Africa (UNISA)
21. University of Venda
22. University of the Western Cape
23. University of the Witwatersrand
24. University of Zululand
25. Vaal University of Technology
26. Walter Sisulu University

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Appendix 2: Screening questions : Gender and menopause



The Epidemiology of Menstrual Pain in a South African University Population

*Required

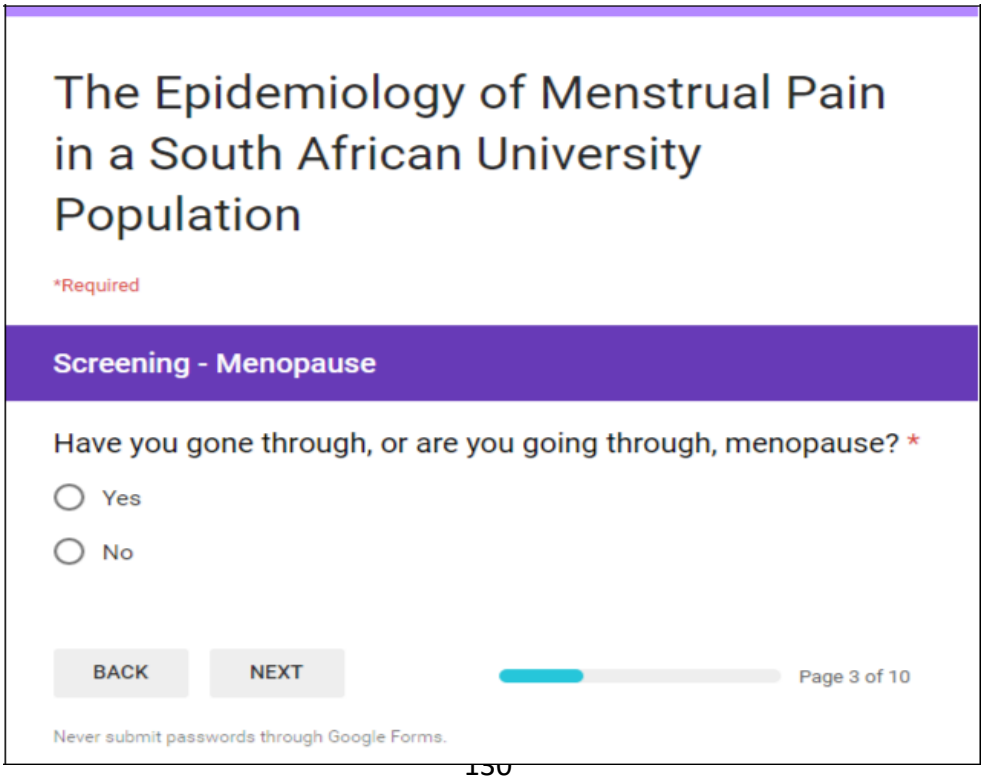
Screening - Gender

Gender *

- Female
- Male

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The Epidemiology of Menstrual Pain in a South African University Population

*Required

Screening - Menopause

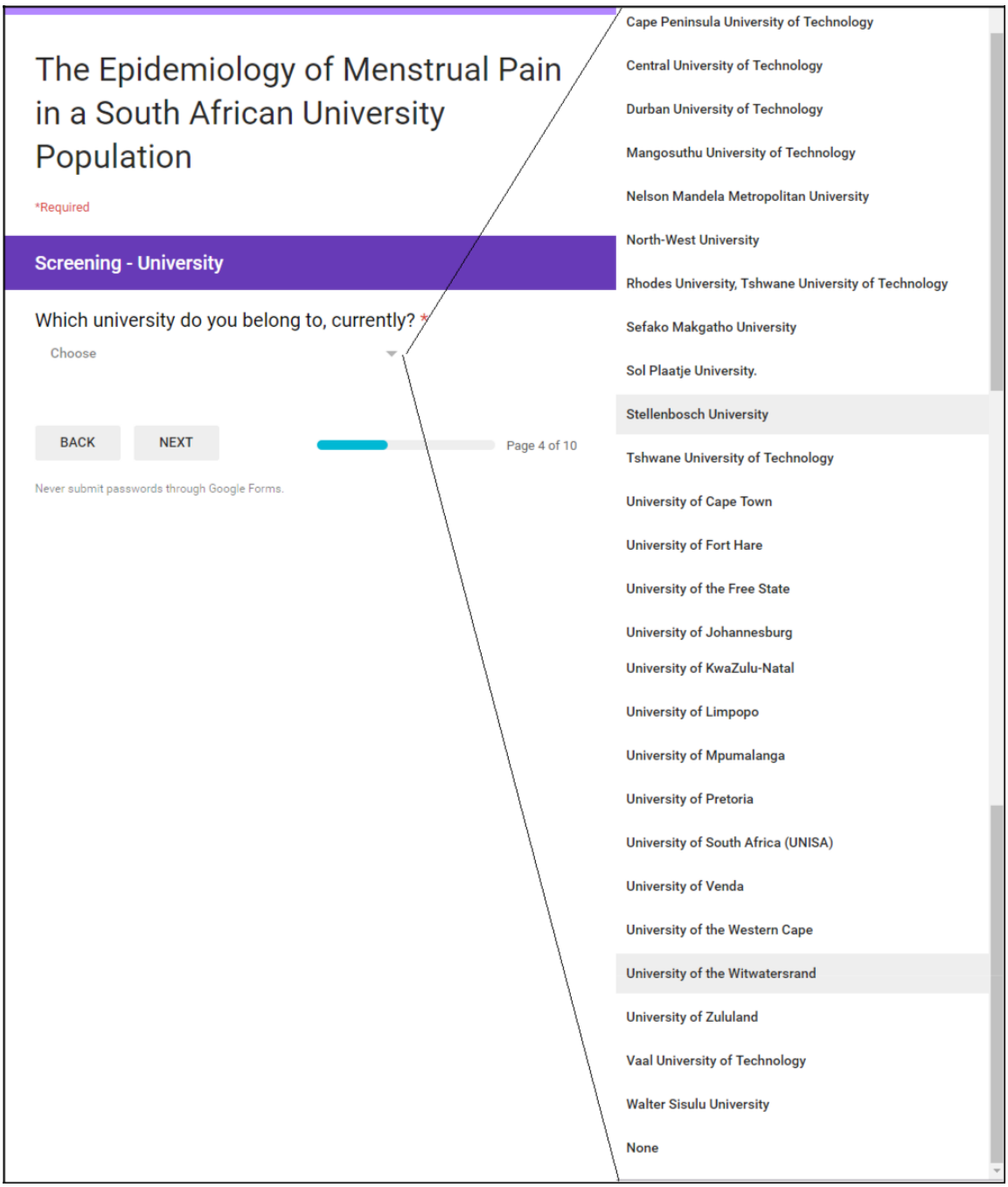
Have you gone through, or are you going through, menopause? *

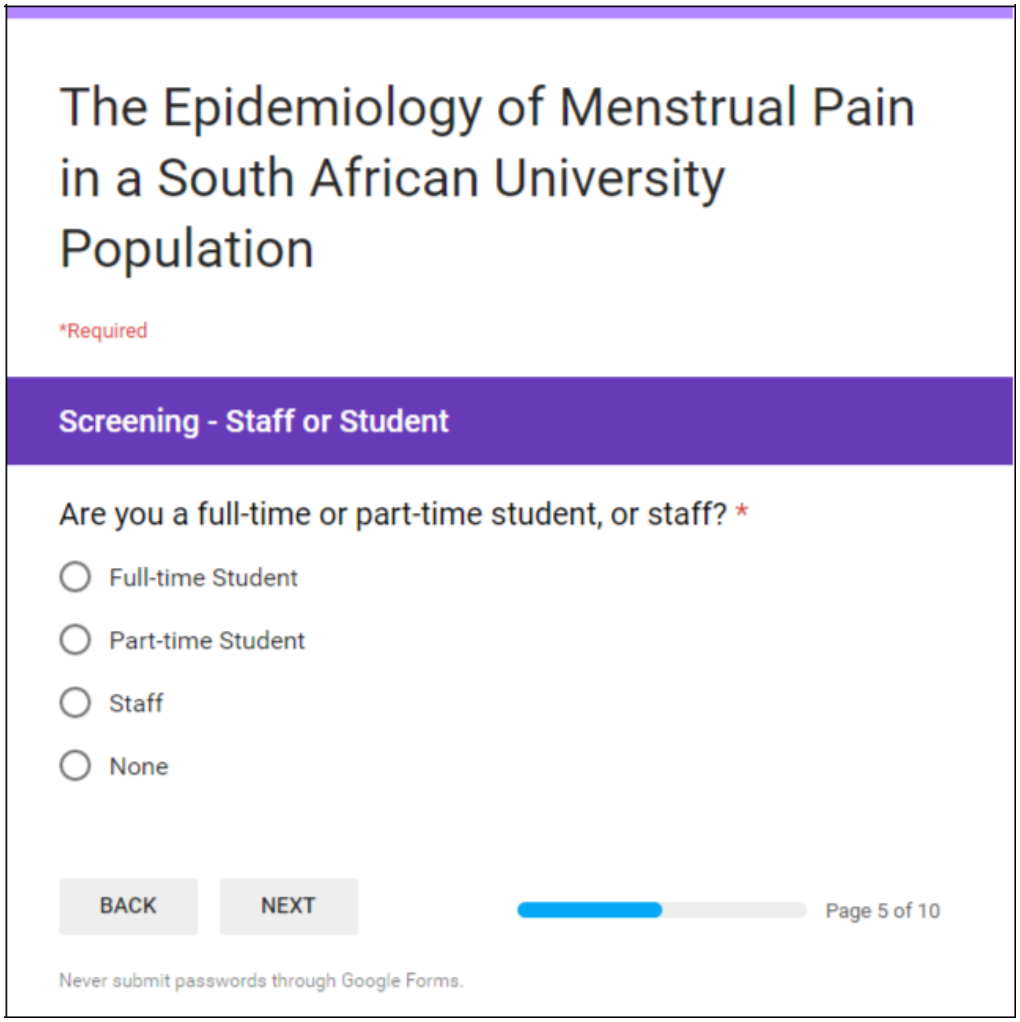
- Yes
- No

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Appendix 3 : Screening : University





The Epidemiology of Menstrual Pain in a South African University Population

*Required

Screening - Staff or Student

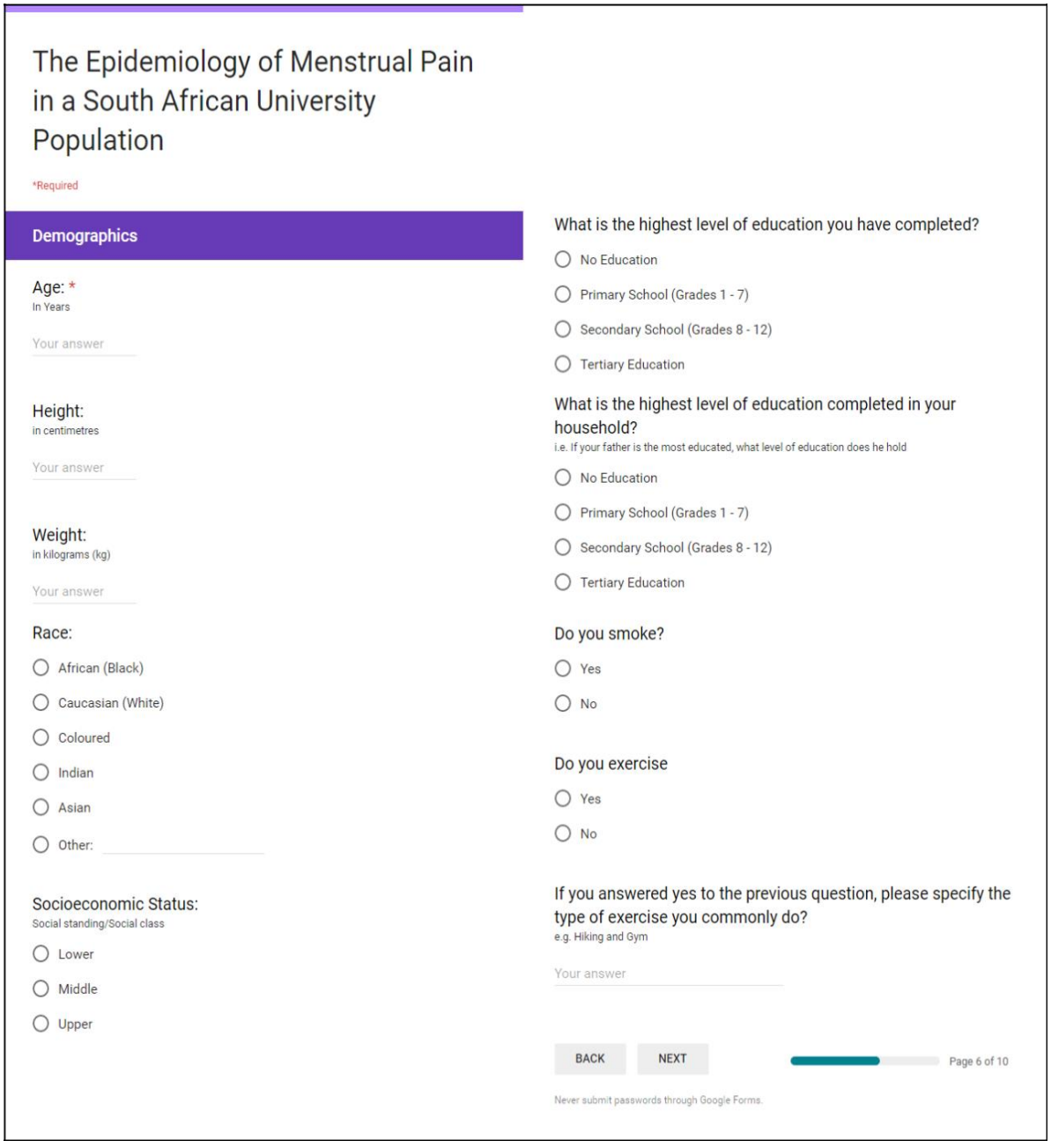
Are you a full-time or part-time student, or staff? *

- ○ Full-time Student
- ○ Part-time Student
- ○ Staff
- ○ None

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Appendix 4 : Sociodemographic questions



The Epidemiology of Menstrual Pain in a South African University Population

*Required

Demographics

Age: *
In Years

Your answer

Height:
in centimetres

Your answer

Weight:
in kilograms (kg)

Your answer

Race:

- African (Black)
- Caucasian (White)
- Coloured
- Indian
- Asian
- Other:

Socioeconomic Status:
Social standing/Social class

- Lower
- Middle
- Upper

What is the highest level of education you have completed?

- No Education
- Primary School (Grades 1 - 7)
- Secondary School (Grades 8 - 12)
- Tertiary Education

What is the highest level of education completed in your household?
i.e. If your father is the most educated, what level of education does he hold

- No Education
- Primary School (Grades 1 - 7)
- Secondary School (Grades 8 - 12)
- Tertiary Education

Do you smoke?

- Yes
- No

Do you exercise

- Yes
- No

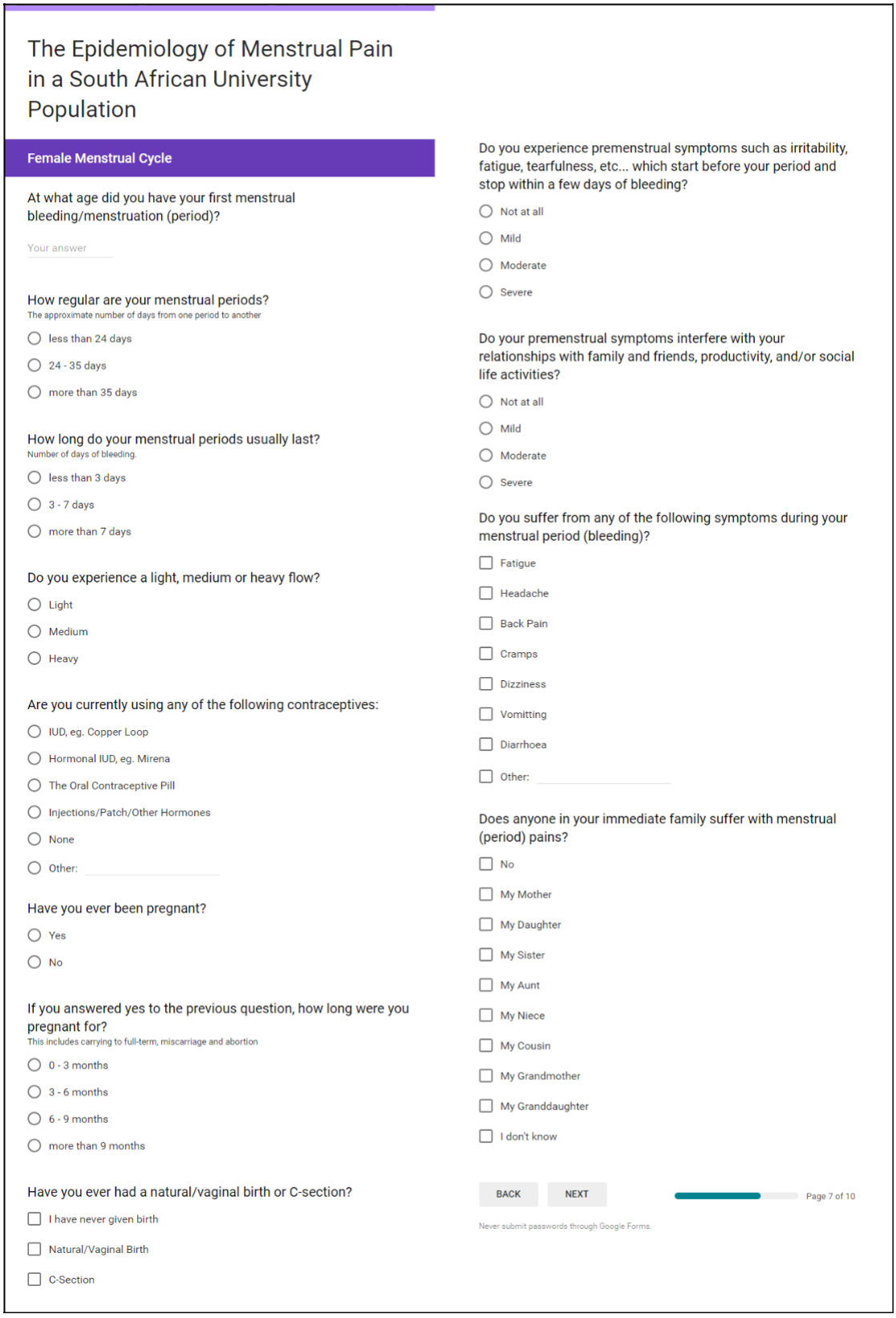
If you answered yes to the previous question, please specify the type of exercise you commonly do?
e.g. Hiking and Gym

Your answer

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Appendix 5: Menstrual cycle questions



The Epidemiology of Menstrual Pain in a South African University Population

Female Menstrual Cycle

At what age did you have your first menstrual bleeding/menstruation (period)?

Your answer

How regular are your menstrual periods?
The approximate number of days from one period to another

- less than 24 days
- 24 - 35 days
- more than 35 days

How long do your menstrual periods usually last?
Number of days of bleeding.

- less than 3 days
- 3 - 7 days
- more than 7 days

Do you experience a light, medium or heavy flow?

- Light
- Medium
- Heavy

Are you currently using any of the following contraceptives:

- IUD, eg. Copper Loop
- Hormonal IUD, eg. Mirena
- The Oral Contraceptive Pill
- Injections/Patch/Other Hormones
- None
- Other:

Have you ever been pregnant?

- Yes
- No

If you answered yes to the previous question, how long were you pregnant for?
This includes carrying to full-term, miscarriage and abortion

- 0 - 3 months
- 3 - 6 months
- 6 - 9 months
- more than 9 months

Have you ever had a natural/vaginal birth or C-section?

- I have never given birth
- Natural/Vaginal Birth
- C-Section

Do you experience premenstrual symptoms such as irritability, fatigue, tearfulness, etc... which start before your period and stop within a few days of bleeding?

- Not at all
- Mild
- Moderate
- Severe

Do your premenstrual symptoms interfere with your relationships with family and friends, productivity, and/or social life activities?

- Not at all
- Mild
- Moderate
- Severe

Do you suffer from any of the following symptoms during your menstrual period (bleeding)?

- Fatigue
- Headache
- Back Pain
- Cramps
- Dizziness
- Vomitting
- Diarrhoea
- Other:

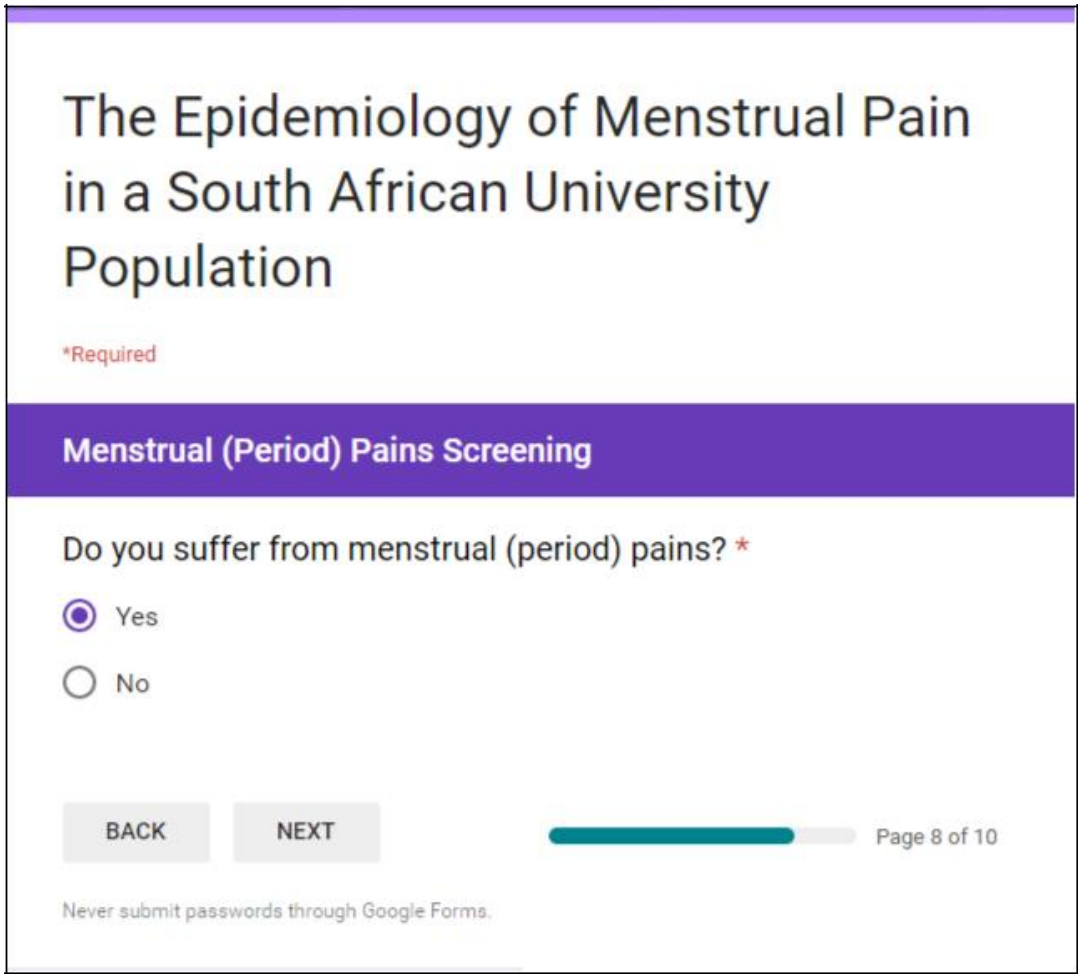
Does anyone in your immediate family suffer with menstrual (period) pains?

- No
- My Mother
- My Daughter
- My Sister
- My Aunt
- My Niece
- My Cousin
- My Grandmother
- My Granddaughter
- I don't know

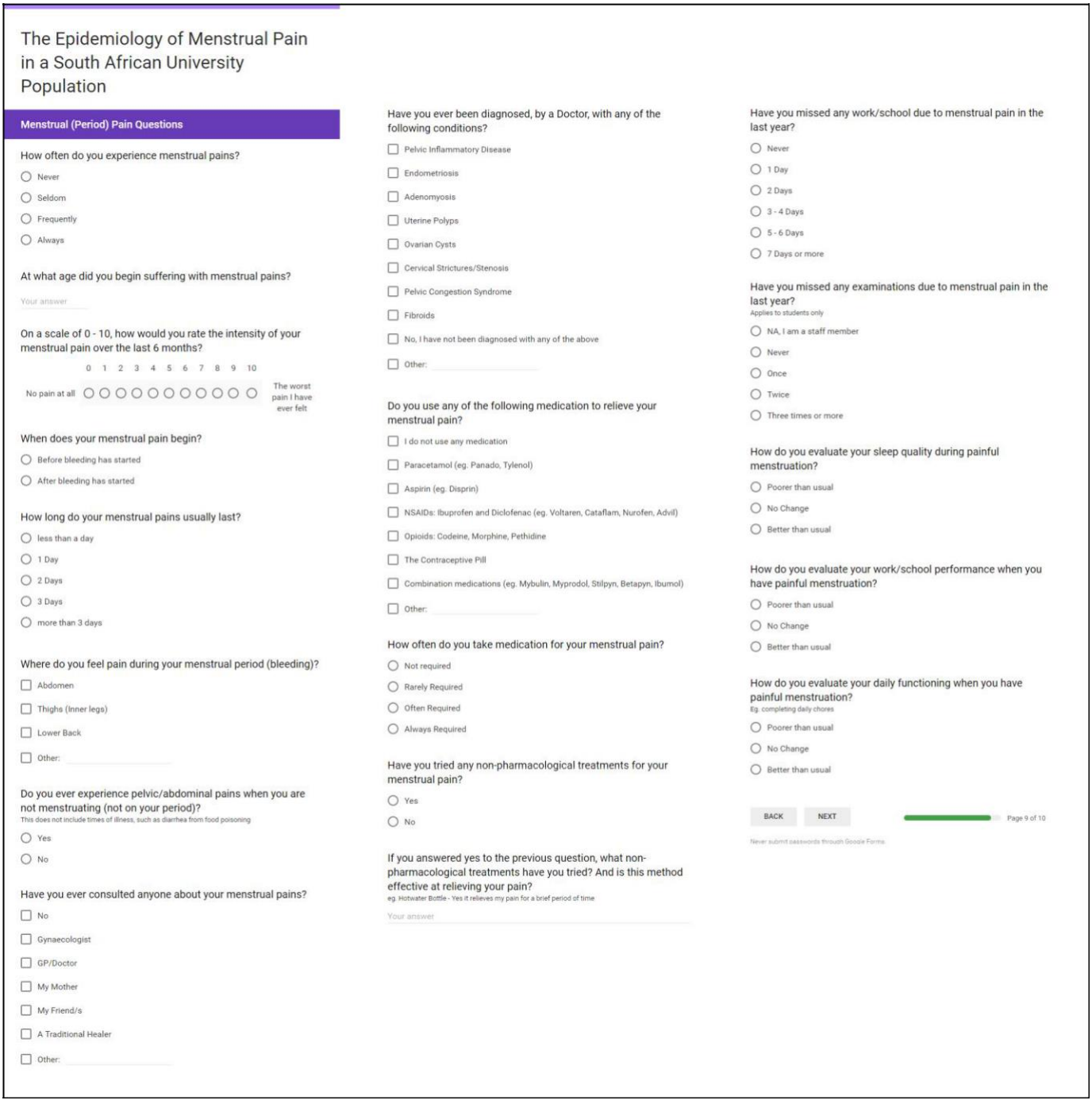
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Appendix 6 : Presence or absence of menstrual pain



Appendix 7 : Menstrual dysmenorrhoeic pain



The Epidemiology of Menstrual Pain in a South African University Population

Menstrual (Period) Pain Questions

How often do you experience menstrual pains?
- Never
- Seldom
- Frequently
- Always

At what age did you begin suffering with menstrual pains?

Your answer

On a scale of 0 - 10, how would you rate the intensity of your menstrual pain over the last 6 months?

0 1 2 3 4 5 6 7 8 9 10

No pain at all ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ The worst pain I have ever felt

When does your menstrual pain begin?
- Before bleeding has started
- After bleeding has started

How long do your menstrual pains usually last?
- less than a day
- 1 Day
- 2 Days
- 3 Days
- more than 3 days

Where do you feel pain during your menstrual period (bleeding)?
- Abdomen
- Thighs (Inner legs)
- Lower Back
- Other:

Do you ever experience pelvic/abdominal pains when you are not menstruating (not on your period)?
This does not include times of illness, such as diarrhea from food poisoning
- Yes
- No

Have you ever consulted anyone about your menstrual pains?
- No
- Gynaecologist
- GP/Doctor
- My Mother
- My Friend/s
- A Traditional Healer
- Other:

Have you ever been diagnosed, by a Doctor, with any of the following conditions?
- Pelvic Inflammatory Disease
- Endometriosis
- Adenomyosis
- Uterine Polyps
- Ovarian Cysts
- Cervical Strictures/Stenosis
- Pelvic Congestion Syndrome
- Fibroids
- No, I have not been diagnosed with any of the above
- Other:

Do you use any of the following medication to relieve your menstrual pain?
- I do not use any medication
- Paracetamol (eg. Panado, Tylenol)
- Aspirin (eg. Disprin)
- NSAIDs: Ibuprofen and Diclofenac (eg. Voltaren, Cataflam, Nurofen, Advil)
- Opioids: Codeine, Morphine, Pethidine
- The Contraceptive Pill
- Combination medications (eg. Mybulin, Myprodol, Stilpyn, Betapyn, Ibumol)
- Other:

How often do you take medication for your menstrual pain?
- Not required
- Rarely Required
- Often Required
- Always Required

Have you tried any non-pharmacological treatments for your menstrual pain?
- Yes
- No

If you answered yes to the previous question, what non-pharmacological treatments have you tried? And is this method effective at relieving your pain?
eg. Hotwater Bottle - Yes it relieves my pain for a brief period of time

Your answer

Have you missed any work/school due to menstrual pain in the last year?
- Never
- 1 Day
- 2 Days
- 3 - 4 Days
- 5 - 6 Days
- 7 Days or more

Have you missed any examinations due to menstrual pain in the last year?
Applies to students only
- NA, I am a staff member
- Never
- Once
- Twice
- Three times or more

How do you evaluate your sleep quality during painful menstruation?
- Poorer than usual
- No Change
- Better than usual

How do you evaluate your work/school performance when you have painful menstruation?
- Poorer than usual
- No Change
- Better than usual

How do you evaluate your daily functioning when you have painful menstruation?
Eg. completing daily chores
- Poorer than usual
- No Change
- Better than usual

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Appendix 8 : Central sensitisation inventory (CSI)

The Epidemiology of Menstrual Pain in a South African University Population

Central Sensitization Inventory (CSI)

Please select the best response for each statement

	never	rarely	sometimes	often	always
I feel unrefreshed when I wake up in the morning	○	○	○	○	○
My muscles feel stiff and achy	○	○	○	○	○
I have anxiety attacks	○	○	○	○	○
I grind or clench my teeth	○	○	○	○	○
I have problems with diarrhea and/or constipation	○	○	○	○	○
I need help in performing my daily activities	○	○	○	○	○
I am sensitive to bright lights	○	○	○	○	○
I get tired very easily when I am physically active	○	○	○	○	○
I feel pain all over my body	○	○	○	○	○
I have headaches	○	○	○	○	○
I feel discomfort in my bladder and/or burning when I urinate	○	○	○	○	○
I do not sleep well	○	○	○	○	○
I have difficulty concentrating	○	○	○	○	○
I have skin problems such as dryness, itchiness or rashes	○	○	○	○	○
Stress makes my physical symptoms get worse	○	○	○	○	○
I feel sad or depressed	○	○	○	○	○
I have low energy	○	○	○	○	○
I have muscle tension in my neck and shoulders	○	○	○	○	○
I have pain in my jaw	○	○	○	○	○
Certain smells, such as perfumes, make me feel dizzy and nauseated	○	○	○	○	○
I have to urinate frequently	○	○	○	○	○
My legs feel uncomfortable and restless when I am trying to go to sleep at night	○	○	○	○	○
I have difficulty remembering things	○	○	○	○	○
I suffered trauma as a child	○	○	○	○	○
I have pain in my pelvic area	○	○	○	○	○

Have you ever been diagnosed by a doctor with any of the following disorders?

	Yes	No
Restless Leg Syndrome	○	○
Chronic Fatigue Syndrome	○	○
Fibromyalgia	○	○
Temperomandibular Joint Disease (TMJ)	○	○
Migraine or tension headaches	○	○
Irritable Bowel Syndrome	○	○
Multiple Chemical Sensitivities	○	○
Neck Injury (including whiplash)	○	○
Anxiety or panic attacks	○	○
Depression	○	○

If you answered yes to any of the above questions, please state what year you were diagnosed:
Eg. Irritable Bowel Syndrom - 1998

Your answer

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Appendix 9 : Ethical clearance certificate

R14/49 Dr Stella Iacovides et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170241

NAME: (Principal Investigator)	Dr Stella Iacovides et al
DEPARTMENT:	Physiology
PROJECT TITLE:	The Epidemiology of Menstrual Pain in a South African University Population
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	17/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month of