CHEMICAL EXPOSURE AND MENSTRUAL REGULATION

by

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ABSTRACT

It is estimated that individuals are exposed to hundreds of harmful chemicals at any given time, where it is nearly impossible to find unexposed populations anywhere in the world. Exposure routes include eating, drinking, breathing, and dermal absorption. After chemicals enter the body, their impact depends on their properties, whether they are excreted or stored, and their rates of entry and excretion. Endocrine disrupting chemicals (EDCs) are of particular concern, as they may impact metabolism and interfere with homeostatic feedback regulation of various endocrine organs by interfering with hormone production. In women, this may increase the risk of negative reproductive health outcomes, such as during the menstrual cycle. Despite the inevitable exposure to EDCs, there is limited research that examines exposure routes and assesses which may have the greatest impact on female reproductive health. Therefore, the purpose of this study is to see if different levels of chemical exposure can cause menstrual irregularities and if additional factors modulate these effects.

Using an online survey, we collected information about lifestyle, nutrition, health status, and chemical exposure in women aged 18-35 who experience a menstrual cycle. The survey included questions regarding reproductive health, product use, general health, mental health, work, and additional factors that are known to impact reproductive health. The survey data was analyzed using a regression analysis to see which exposure routes, health statuses, or additional factors may contribute to menstrual irregularities, and which may not.

A correlation was found between increase in age and a decrease in the risk of experiencing dysmenorrhea from 56% to 45% ($p=0.016$, $OR=0.907$). A correlation was found between high chemical exposure and a decrease in the risk of experiencing dysmenorrhea from 56% to 14% ($p=0.015$, $OR=0.274$). A correlation was found between menstruation that lasts eight or more days and an increase in the risk of both dysmenorrhea and menorrhagia from 56% to over 100% ($p=0.014$, $OR=3.969$) and 20% to over 100% ($p<0.001$, $OR=17.943$), respectively. A correlation was found between moderate alcohol consumption and a decrease in the risk of experiencing menorrhagia from 20% to 2% ($p=0.001$, $OR=0.106$). A correlation was found between moderate to heavy drug use and a decrease in the risk of experiencing menorrhagia from 20% to 4% ($p=0.010$, $OR=0.210$), and a correlation was found between moderate stress and a decrease in the risk of experiencing menorrhagia from 20% to 4% ($p=0.016$, $OR=0.220$).

Our study aims to encourage future research in the field of women's health, where research in this area is often limited, especially regarding research looking at women's health under a more holistic lens.

Keywords: Chemical exposure, Endocrine Disrupting Chemicals (EDCs), Lifestyle, Dysmenorrhea, Menorrhagia, Female reproductive cycle.

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Chapter 1: Introduction

1 Endocrine Disrupting Chemicals

Individuals are constantly exposed to potentially harmful chemicals in almost every aspect of daily life at home, in the workplace, and at school.[1,2] It is estimated that individuals are exposed to hundreds of harmful chemicals at any given time, where it is nearly impossible to find unexposed populations anywhere in the world.[3] Chemical contaminants are found in indoor and outdoor air, soil, water, food, dust, and many consumer products.[1] Exposure routes include eating, drinking, breathing, and dermal absorption.[1]

One such group of chemicals that individuals are exposed to on a regular basis are endocrine disruptors, or endocrine disrupting chemicals (EDCs). EDCs affect the endocrine system, which includes the adrenal glands, the thyroid gland, the pituitary gland, the hypothalamus, and the male and female gonads.[1] and is responsible for regulating growth, sexual development, reproduction, and metabolism.[4] The organs of the endocrine system secrete hormones that travel to various parts of the body through the blood within the cardiovascular system.[1] EDCs specifically interfere with these hormones[5,6] by affecting their production and release, transport throughout the body, metabolism, and elimination, among other mechanisms of action.[1,7,8] Many EDCs can mimic estrogen and bind to estrogen receptors, having either estrogenic or anti-estrogenic effects.[8,9] EDCs are often found in plastics, pesticides, and industrial chemicals,[2,10] as well as in foods through processing and storage[5]. Exposure to hormone disrupting chemicals may increase the risk of women experiencing negative reproductive health outcomes through their direct or indirect affects on the reproductive system.[1,10]

Unfortunately, for many chemicals a safe exposure threshold is not known.[1] Many chemicals do not go through rigorous scientific testing, meaning that many are lacking information regarding their possible negative effects, including to the reproductive system.[2,3,5,11] In fact, most commercially used chemicals have not been tested for endocrine disrupting effects, so there are still many unknown sources of EDC exposure.[3] For a chemical to be considered dangerous according to toxicological standards, the chemical must cause adverse health effects that are proportional to an increasing dose, though EDCs do not follow this trend.[5] EDCs follow a nonlinear U-shaped dose response curve due to the many different means through which they can

disrupt the endocrine system,[3] meaning that they can have differing effects at various doses.[1] For example, organochlorine pesticides such as methoxychlor and chlorpyrifos have been found to enhanced gonadotropin releasing hormone (GnRH) gene expression at low doses and inhibition of this same gene at high doses.[12] Specifically, some EDCs only cause adverse health effects at low doses and not at high doses by affecting the endocrine system's ability to respond through high-dose inhibition.[5,6] Even low doses of a harmful chemical can affect an individual[6] depending on how many other chemicals they are exposed to and in what doses, as well as whether the individual has any underlying health issues.[2] For example, the effects caused by phthalate exposure may be cumulative.[13] EDCs may also have different impacts during different parts of the life cycle depending on when in the life cycle the exposure occurs[10] and for how long[6]. In some circumstances, low doses of EDCs may be more harmful than high doses[4,10] and the effect of exposure to several EDCs at once may be more pronounced than the effect of each EDC individually[3,14]. For this reason, even small additions, or subtractions of EDC exposure at low doses can have significant impacts on reproductive health as compared to high doses.[6] This also means that current safe exposure levels may not reflect true safe exposure levels for low dose exposures, as a threshold exposure level may not exist.[6]

There may also be a difference in absorption of chemicals based on sex, where researchers McCormick and Abdel-Rahman found that absorption of certain chemicals through the skin were twice as great in female rats as opposed to male rats, as sex hormones can affect absorption and transport of chemicals.[15] It is impossible to avoid all exposure to harmful chemicals, but an individual can minimize their exposure so that enough of these chemicals do not enter the body or disrupt normal function.[1] After harmful chemicals enter the body, their impact is dependent upon their individual chemical properties and whether they are excreted from the body or stored, as well as how much of the chemical entered the body over a particular time period.[1] The amount of a chemical that remains inside the body is known as the body burden.[1] There are many chemicals that can begin to accumulate in the body that increase body burden, such as lipophilic chemicals that accumulate in adipose tissue.[1] An example of a lipophilic chemical is di(2-ethylhexyl) phthalate (DEHP), which is an endocrine disruptor that has been found in sanitary pads.[16] DEHP is part of a class of chemicals called phthalates, which are commonly found in plastics and various

personal care products.[1] They are also commonly found within the environment in water, soil, air, and dust and can enter the body through absorption, ingestion, and inhalation.[1] Organochlorine pesticides and dioxins or dioxin-like compounds are other such chemicals that are readily stored in adipose tissue, where they remain for extended periods of time.[1] Both organochlorine pesticides and dioxins are considered persistent organic pollutants (POPs), which persist within the body for extended periods of time[1] and more easily accumulate over time as a result.

In addition, individuals vary in their capability to absorb, metabolize, and excrete chemicals, meaning that some individuals are more susceptible to the effects of harmful chemicals, such as those with nutrient deficiencies or pre-existing illnesses.[1] If a chemical that enters the body is not stored, it can be metabolized or may simply be excreted right away.[1] Excretory pathways include exhalation; tears; shedding of dead skin, nails, and hair; saliva; sweat; urine, feces, and breast milk.[1] The half-life of a harmful chemical will also impact the body burden, where the longer the half-life of a chemical, the longer it remains in the body. For example, polychlorinated bisphenols (PCBs), which are lipophilic, can have a half-life of several years in humans.[17]

Exposure to any harmful chemical can come from more than one source, so it is important to consider all possible exposure routes.[1] For example, some endocrine disruptors are found in both menstrual products and food, so both diet and consumer products should be considered to reduce exposure to endocrine disruptors. This will be discussed in later sections. In addition, the timing of exposure can have a huge impact on reproductive function.[10] For example, exposures during development have been seen to cause long term health effects, even as a zygote.[1] Chemicals can enter the placenta and fetus from the pregnant mother and cause adverse health effects in her offspring.[2] Woodruff *et al*. found that pregnant women in the United States between 2003 and 2004 were exposed to a minimum of 43 harmful chemicals while pregnant, where these chemicals may have even greater effects on the fetus than the mother if these chemicals accumulate within the fetus.[18] A more recent study in 2011 by Sutton *et al.* had similar findings, where researchers found that almost all pregnant women in the United States had several types of harmful chemicals in their body that included phthalates, pesticides, PCBs, and bisphenol A (BPA), among others; some of these chemicals, such as phthalates, were found in high enough levels to be associated with adverse health effects in humans.[11] In a meta-analysis done by Mendola *et al.*, researchers

found that exposure to certain pesticides after birth can lead to reproductive developmental issues in females that can impact puberty and menopause, ovulation and fertility, and menstruation.[19]

Due to the inevitable exposure to EDCs and previous research that indicates negative impacts on reproductive health, our research aims to see which areas of exposure may contribute the most to these issues by looking at the pain and bleeding women experience during menstruation and comparing their experiences with chemical exposure routes and additional factors that may increase or decrease chemical exposure and/or pain and bleeding during menstruation.

1.1 Pain and the Menstrual Cycle

Painful menstruation, also known as dysmenorrhea, is extremely common in reproductive aged women and has been reported to affect anywhere from 16 to 95% of these women.[20–28] The World Health Organization (WHO) considers dysmenorrhea as the number one source of chronic pelvic pain in women.[20] This pain occurs during menstruation, though it can start before and is characterized by a throbbing pain in the lower abdomen and pelvis.[22] It is often the most severe on the first day of menstruation[24] when the menstrual flow is at its heaviest. Nieczuia-Dwojacka *et al.* found that that women with primary dysmenorrhea often have more days between periods and a longer period of bleeding.[29]

Dysmenorrhea can be classified into two categories: primary dysmenorrhea and secondary dysmenorrhea.[20,21] Primary dysmenorrhea refers to menstrual pain that does not have an underlying cause and originates in the uterus.[23,30] Pain caused by primary dysmenorrhea typically lasts for 2-3 days after the onset of the menstrual cycle.[21,24] This type of dysmenorrhea often appears soon after the onset on menarche and usually improves after a woman has experienced 30 years of menstruation[28] or has given birth to children[30]. Dysmenorrhea is most common in women in their early twenties.[21]

Primary dysmenorrhea is thought to be caused by a decrease in blood flow to the uterus[23,26,31] and an increase in spastic uterine contractions,[23,26] both of which may be caused by an overproduction of prostaglandins[27] (specifically prostaglandins E_2 (PGE_2) and F_2 (PGF_2)[21]). Increased levels of prostaglandins can also increase pain sensitivity,[21,24,26] which is thought to be

caused by myometrial and endometrial innervation in the uterus.[23] In a study by Proctor and Farquhar, they found that women with severe dysmenorrhea have higher concentrations of prostaglandins than women with lesser or no dysmenorrhea, with the first two days of menstruation having the highest concentrations of prostaglandins found in the menstrual flow.[28] Other research shows the overproduction of prostaglandins by the endometrium is a cause of primary dysmenorrhea,[21,24,32] as well as some of the other associated symptoms.[33] Concentrations of both $PGF_{2\alpha}$[34] and PGE_2 are higher in women who suffer from dysmenorrhea than in women who do not,[35] and pain intensity increased proportionally to $PGF_{2\alpha}$ increase,[36] $PGF_{2\alpha}$ and PGE_2 have also been linked to reduced blood flow to the endometrium of the uterus, increased myometrial contractions, and decreased oxygen to the uterus, all of which can cause pain.[37]

Although the main cause of primary dysmenorrhea is uterine inflammation, the sensitization of the peripheral and central nervous systems is thought to play an important role.[38] Extended periods of pain in the peripheral nervous system that travels to the central nervous system can alter the structure and function of the nervous system, which results in sensitization.[38] Together, the peripheral and central nervous systems may then cause hyperalgesia, allodynia, and spontaneous, ongoing pain.[38]

Secondary dysmenorrhea refers to menstrual pain that results from an identified cause, such as endometriosis or ovarian cysts, and may appear long after menarche.[21,23] Secondary dysmenorrhea is less common in younger girls as compared to older women, as these causative conditions typically occur later in life.[30] The pain caused by secondary dysmenorrhea can start as much as two weeks before menstruation and can continue several days afterwards.[21] The pain experienced in primary and secondary dysmenorrhea, however, are very similar.[21]

Dysmenorrhea has a serious impact on the quality of life of women that have this condition.[21,24,27,28] Dysmenorrhea is a frequent cause of missed school and work, where Tu, Bettendorf, and Shay found that up to one-half of women with dysmenorrhea in their study had absenteeism due to their pain.[21] Even when women suffering from dysmenorrhea choose to go to work or school, the pain experienced may cause difficulty concentrating.[32] In another study, 32-40% of women with dysmenorrhea experienced absences and trouble functioning socially due to

their pain.[22] Dysmenorrhea can also impact sleep, where women are often unable to get adequate rest due to pain.[32]

When pain becomes chronic, the changes made to the nervous system may cause pain to occur independently from the stimulus or even in its complete absence.[38] Women who experience dysmenorrhea experience an increase in visceral and muscular sensitivity, as well as increased pain sensitivity, outside of the uterus even when dysmenorrhea is absent and a woman is not menstruating.[23,39] These changes to the nervous system are perhaps why suffers of chronic pain typically also suffer from mental health issues or are more likely to suffer from additional chronic pain conditions.[38] In fact, the changes seen in the brains of women with dysmenorrhea are consistent with other chronic pain conditions.[23]

Risk factors for developing dysmenorrhea include early menarche,[13,14,23] late menarche,[22] younger age,[13,23] irregular or prolonged menstrual flow,[21–25,30] smoking,[21–23,30] low body mass index (BMI),[21–23,30] high BMI;[23] pelvic infections,[21] previous abortions,[21,22] somatic complaints around the time of menstruation,[21] psychological disturbances,[21,30] a history of sexual assault,[21,23,30] nulliparity,[30] inadequate exercise,[22,32] stress,[22,32] mental illness,[22,23,32] genetics,[22,23] and low socioeconomic status.[22] However, there are also many protective factors that may reduce the risk of developing dysmenorrhea or lessening pain, some of which will be discussed in future sections. These protective factors include exercise, oral contraceptives, higher equality, a stable relationship, and certain dietary choices.[21] Many of these risk factors were taken into consideration for our research and data collection.

1.2 Bleeding and the Menstrual Cycle

Heavy menstrual bleeding, or menorrhagia, is another common menstrual issue that as many as 50% of the female population suffers from.[40] Typical blood loss during menstruation is 30 mL on average but may range anywhere from 13-80 mL.[41,42] Menorrhagia is classified as either a menstrual flow of more than 80mL per cycle[43] or a heavy menstrual flow lasting for more than seven days[44].

Symptoms that often accompany menorrhagia aside from iron deficiency or anemia include pain in the abdomen, breasts, and back; headaches; pressure and weakness in the pelvis; and distension of the abdomen.[45] Menorrhagia may be caused primarily, where the underlying cause is not known, or secondarily because of another disorder.[40] For example, women with congenital bleeding disorders or platelet disorders[42] may have a heavy menstrual flow as a symptom of their disorder. Such disorders include hemophilia A and B, Von Willebrand disease, Bernard-Soulier syndrome, and Glanzmann's thrombastenia.[40]

Fifty to eighty percent of menorrhagia cases have no underlying pathology[46] and may instead be caused by abnormally high levels of prostaglandins[40] and increased fibrinolysis[47] in the endometrium[48], though the mechanism of menorrhagia is not well understood. Excessive uterine blood loss may be a result of increased levels of PGE_2 and decreased levels of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)[49] and increased levels of prostacyclin, which is a vasodilator and platelet aggregation inhibitor.[50]

The endometrium may also become inflamed, which is caused by leukocytes, macrophages, and natural killer cells. These cells breakdown the endometrial epithelium and cause vasodilation of capillaries in the endometrial epithelium, which increases bleeding.[51] This heavy level of bleeding may not only impact the health of the individual, but also impacts quality of life and interrupts routine activities.

1.3 The Female Body and Reproductive Health

1.3.1 Early Life and Menstrual Irregularities

As mentioned previously, prenatal exposure to chemicals can have an affect on health later in life. The human reproductive system is especially vulnerable to chemicals during infancy, childhood, and adolescence due to the many developmental changes that occur during this time.[11] For example, exposure to certain harmful chemicals during fetal development may increase the risk of childhood cancers, while postnatal exposure to certain pesticides during development may interfere with developmental stages of reproductive function in women[8] such as puberty, menstruation, and menopause, and can also affect fertility.[2] Exposure to EDCs during fetal

development or infancy may also lead to the development of disease later in life[1–3], where the lag time between exposure and disease onset can be years or decades.[10]

Females may also be reaching puberty much earlier than previously documented, where the average age of menarche has been shown to be decreasing by about 3 months per decade since 1977.[52] At the same time, there has also been an increase in reproductive system diseases.[53] Females who experience menarche before they are 12 years old may have an increased chance of experiencing breakthrough bleeding between periods as well as shorter, more frequent periods, while those who experience menarche when they are 15 years or older may be more likely to experience longer and irregular cycles.[54] The change in the average age of menarche may be associated with chemical exposure, as exposure to EDCs may impact the starting time of puberty.[55]

1.3.2 *Female Anatomy, Hormones, and the Menstrual Cycle*

Both the uterus and the ovaries play a major role in the ovarian and uterine cycles associated with menstruation. The uterus is supplied with blood by the uterine arteries and contains many blood vessels, lymphatic vessels, and parasympathetic and sympathetic autonomic nerve fibres.[56] The shedding of the endometrium results in large, exposed areas of wounds on the uterine walls, which may act as a pathway for chemicals from women's sanitary products[57] or other sources to enter the bloodstream and the circulatory system.

For most women, the average menstrual cycle is about 28 days,[58] where the first day of the cycle is the first day of menstruation.[33,41,42,56] Menstruation typically lasts from one to seven days[56] and generates anywhere from 5-80 mL of blood per cycle, with an average blood loss of 30 mL per cycle.[41] The menstrual cycle typically starts in pubertal females between the ages of 11 and 12 (but can range from 9-16) and continues until menopause is reached between 45-55 years of age.[42] The menstrual cycle is the most irregular during adolescence and just prior to menopause.[58] Since menstrual cycle characteristics, such as cycle length, are associated with fertility and reproductive health, the menstrual cycle can be used to determine a woman's reproductive and endocrine system health.[59]

The menstrual cycle consists of three uterine phases and two ovarian phases.[33,56] The uterine menstrual phase and the proliferative phase occur during the follicular phase in the ovaries, while the secretory phase in the uterus corresponds with the luteal phase in the ovaries.[33,56] To understand the menstrual cycle, both the ovarian and uterine phases must be considered, as, although the uterus is where menstruation occurs, the uterine events leading up to menstruation are caused by changes in the secretion of hormones in the ovaries, which is in turn influenced by the ovary's interactions with the hypothalamus and the anterior pituitary gland, often referred to as the hypothalamic-pituitary-ovarian axis.[33,41,56] If the uterine and ovarian cycles are not synchronized or hormonal communication is disrupted, reproductive functions may be compromised.[56,60]

1.3.2.1 The Ovarian Cycle

Ovarian function is controlled by a cascade of hormones that starts in the hypothalamus, where gonadotropin-releasing hormone (GnRH) is released[41] into surrounding blood vessels in pulsating secretions that change in frequency and amplitude over the menstrual cycle[33,56,58,70], which begins for the first time at puberty[42].

The ovaries are responsible for ejecting a single oocyte that travels to the uterus during each menstrual cycle[60], as well as the secretion of estrogen and progesterone, the female sex hormones, and inhibin[35] and activin, which inhibit and stimulate the anterior pituitary gland to release follicle stimulating hormone (FSH), respectively.[42] These inhibitory and stimulatory actions are achieved by down or upregulating the anterior pituitary gland's GnRH receptors,[42] where estrogen increases, and progesterone decreases pulsatile secretions of GnRH.[56] GnRH travels through the blood to the anterior pituitary gland and binds to receptors; initiating the pulsatile secretion of FSH and luteinizing hormone (LH)[41,42,58,60] into surrounding blood vessels, though the anterior pituitary gland's response to GnRH also varies over the course of the menstrual cycle.[33,56] For example, depending on the pulse frequency of GnRH secretions, the anterior pituitary gland may only primarily release FSH at one frequency, and LH at another frequency.[56] When GnRH pulsatile secretions are low, FSH is released from the anterior pituitary gland,

whereas when GnRH pulsatile secretions are high, LH is released from the anterior pituitary gland.[60] Additionally, if GnRH were constantly released without pulses, no FSH or LH would be secreted from the anterior pituitary gland, just as if no GnRH were being produced at all.[56] Regardless, FSH and LH both travel through the bloodstream to the ovaries, whose response to FSH and LH also change throughout the menstrual cycle.[33,56]

When FSH and LH reach the ovaries, they bind to receptors in the granulosa cells of ovarian follicles, which contain the oocytes.[41,60] These granulosa cells secrete estrogen and inhibin during the follicular phase,[60] as well as small amounts of progesterone[33,56] just before ovulation.[42] As the follicles mature, the granulosa cells differentiate into theca, which also synthesizes estrogen.[33,56,58] Between 3-30 follicles mature during each cycle, and usually only one of these follicles will continue to develop[41] after the first week of the cycle.[33,56,58] Between days five to seven of the cycle, one follicle becomes the dominant follicle, and by day eight it begins to stimulate its own growth while supressing the growth of the other follicles.[58] This follicle will continue to mature, as well as the oocyte, until eventually the wall of the follicle breaks and releases the oocyte, which travels to the fallopian tube; this results in ovulation[41] at around day 14 of the menstrual cycle.[33,60] The granulosa cells of the leftover follicle then grow to create the corpus luteum structure, which secretes estrogen, progesterone,[60] and inhibin. This structure continues to develop for another ten days, at which time it begins to degrade unless fertilization occurs.[33] If fertilization does not occur and degeneration continues, it will result in menstruation and the start of the next menstrual cycle.[33,60] Therefore, the follicular phase that occurs in the ovaries consists of the development of follicles up until the oocyte is released into the fallopian tubes at ovulation, and the luteal phase occurs when the leftover follicle becomes the corpus luteum after ovulation until its degeneration and the start of menstruation.[33,56,60] The follicular phase and the luteal phase each last about 14 days,[56,60], though the follicular phase has more variation in length[38,41,58] and can affect the length of the menstrual cycle.[42]

The disruption of ovarian function can lead to many reproductive issues, such as infertility, anovulation, and abnormal secretion of estrogen.[61] For example, exposure to DEHP may affect the ovaries, likely through mono-(2-ethyl-5-hexyl) phthalate (MEHP), by reducing estrogen levels and

thus slowing follicle growth.[61] DEHP may also cause oxidative stress, which further inhibits follicular growth and may also lead to follicular death.[61]

1.3.2.2 The Menstrual Cycle

The first phase of the menstrual cycle is the menstrual phase. During this phase, menstruation occurs and typically lasts for three to five days. Menstruation is a result of the shedding of the functional layer of the endometrium as it degenerates,[33,41,42,62] which occurs in patches.[56]

After the functional layer of the endometrium is shed during the menstrual phase, it must be restored; this occurs during the proliferative phase[56] in response to estrogen[38,42] and is marked by the regeneration and thickening of the functional layer of the endometrium from the basal layer.[33,41,56] There is an increase in estrogen levels during the proliferative phase, whose hormonal actions sustain this phase and causes the endometrium to grow,[41,42,56] along with the myometrium, leading to progesterone receptor synthesis in endometrial cells.[33] The full function of the endometrium is restored after the restoration of the vasculature[41] and uterine glands.[42,56] The proliferative phase lasts for roughly ten days and ends with ovulation, after which the secretory phase begins.[33]

During the secretory phase after ovulation, progesterone begins to bind to the progesterone receptors of the endometrial cells, changing the endometrium into a secreting tissue.[33] This causes the glands of the endometrial epithelium to dilate and produce mucus.[33] Enzymes also begin to accumulate in the connective tissue before angiogenesis occurs.[33] This is to provide a hospitable environment for a potential embryo if fertilization occurs.[33] The uterine environment is further made hospitable to a possible fetus through the inhibitory action of progesterone, which works against estrogen[58] and prostaglandins, so contractions of the myometrium do not occur, allowing implantation of a fertilized egg in the uterus.[33]

Secretions from uterine glands are highest around 12 days after ovulation, where the secretory phase typically lasts 14 days.[56] If fertilization does not occur and the corpus luteum

begins to degenerate, decreases in estrogen and progesterone cause the endometrium to synthesize prostaglandins.[33] These prostaglandins build up in the endometrial tissue[32] and cause vasoconstriction (so the blood and oxygen supply to the endometrium is reduced and it begins to degenerate)[41,58,62], rhythmic myometrial contractions[28,33,58], inflammation[63], and lowered pain thresholds[21]. Specifically, PGE_2 inhibits platelet aggregation and acts as a vasodilator, while $PGF_{2\alpha}$ causes smooth muscle contractions, leading to pain; both cause inflammation.[63] The reduction in blood flow to the endometrium causes a reduction in oxygen and nutrients to the tissue and a buildup of wastes, resulting in degeneration.[56,58] All but a very thin, underlying layer of the endometrium, the basal layer, will degenerate.[33,41,56,62] The basal layer does not degenerate because it is still richly supplied with blood from the straight arteries, which do not undergo vasoconstriction[56] by prostaglandins. The basal layer will regenerate the endometrium again for the following cycle.[33,41,56,62]

Soon after the vasoconstriction caused by prostaglandins occurs in the endometrium, vasodilation of these arteries follows and the weakened capillaries hemorrhage. This blood, along with the sloughed endometrium, makes up the menstrual flow.[33,41,57] The immune system also plays a role in menstruation and regulates the inflammatory response, tissue breakdown, and pain experienced during menstruation, as well as the repair of the functional layer of the endothelium.[23]

Within the first two days of the new menstrual cycle, new follicles within the ovaries begin to secrete estrogen, which leads to vasoconstriction within the uterus and clot formation on the basal layer of the endometrium, allowing the functional layer of the endometrium to regenerate.[58]

1.4 The Role of Lifestyle, Nutrition, Socioeconomic Status, and Medical Conditions on Reproductive Health

Menstrual irregularities may be attributed not only to EDCs, but also to additional factors such as diet and exercise. It is important to understand the many ways in which the menstrual cycle may be affected, as this helps to reduce variables when studying the effects of EDCs on the menstrual cycle. For this reason, the following sections will discuss how consumer product use, diet, ethnicity, socioeconomic status, exercise, smoking, alcohol consumption, sleep, the

workplace, mental health, and other medical conditions may have an impact on the menstrual cycle. Outside of these topics, there are still many areas of study that may impact the menstrual cycle, both positively and negatively.

1.4.1 Consumer Product Use and Reproductive Health

Many consumer products, including personal care products and cosmetics, contain a variety of chemicals, including EDCs. Some of the most common EDCs found in these products include phthalates, parabens, dioxins, volatile organic compounds (VOCs), and pesticides. Women are exposed to these products daily and exposure can come from multiple sources. For example, phthalates are found in many fragrances[13,57,64], deodorants[13,57], skin and hair products[13,57], nail polish[13,57], and cosmetics[13,57] in various concentrations, which add to total exposure levels. They are also used during food processing[7,13], which can introduce these chemicals into food. These chemicals are often ingested, inhaled, and absorbed through the skin on dermal contact;[7,13,61,65–67] these routes are considered major exposure pathways for phthalates.[65] In fact, phthalates can enhance skin penetration and have been found in personal care products and women's sanitary products.[16] Phthalates are also used in industrial processes and are found in many common products,[64–66,68] such as medical devices and various personal care products.[7,13,61,69] Other products include lubricants, food, pharmaceuticals, resins, and products containing polyvinyl chloride (PVC).[16] Phthalates, such as DEHP, are used in the plastic industry to make plastics more flexible[14,61,68] and soft[14,57,65], such as in food packaging[64] and sanitary pad production. Phthalates have been shown to cause fertility problems along with other reproductive health issues.[54,57,66,67] For example, Liu *et al*. found that phthalates were the cause of multiple reproductive health issues in rats, including spontaneous abortion, follicular development disorders, hormone imbalances, ovarian issues, vaginal bleeding issues, and cancer, to name a few.[54] Phthalates have been found in personal care products in several countries, including Canada[16], the United States[16], and China[57]. Because DEHP is not covalently bonded to the plastics it is found in, DEHP can leach from these products through the heating, cleaning, and general use of plastic products.[61] For this reason, DEHP and other phthalates can also migrate from these products to soil, sediment, water, dust, and

air so that exposure may not only be by dermal absorption, but inhalation and ingestion.[13] The French Agency for Food, Environmental, and Occupational Health and Safety also found phthalates in feminine hygiene products.[74,84]

Parabens have also been found in women's sanitary products, food, and other personal care products within the United States.[16,31] These chemicals are typically used as antimicrobial preservatives in such products.[31] Bisphenols, a type of paraben, have been found in women's sanitary products, where bisphenol F (BPF) was found in many tested brands of pads and panty liners and BPA was found in pads, tampons, and panty liners.[16] These bisphenols likely come from the plastics sanitary products as made from in the form of impurities or additives.[16] BPA has also been found in food, consumer products, and packaging, where exposure can occur through ingestion, absorption, or inhalation.[7] Examples of these include food containers, cellphones, laptops, hospital equipment, and water pipes.[70] BPA, a very well-known EDC and estrogen mimetic, causes nervous system issues[71] and reproductive issues as well as other adverse health effects[4] even at extremely low doses that are below regulatory safety standards in the United States.[70] These adverse effects include endometriosis[85] and ovarian cysts.[86]

A safe BPA dose has yet to be determined, as BPA may have different adverse effects depending on the organ or organ system exposed to it.[71] Parabens are generally excreted from the body quite quickly, yet these chemicals are found in most of the United States population.[31] A study by Smith *et al*. found more than 92% of individuals had parabens in their urine, suggesting exposure to parabens is continuous and chronic.[31] As of 2013, there have been no studies looking at paraben concentrations found in urine and their association with female reproductive health, as parabens are also endocrine disruptors.[31]

Dioxins are known endocrine disruptors that can affect reproductive function, among its many other effects on various body systems.[87] In a study by De Vito and Schecter, they tested tampons from 1997 and found dioxins and furans present in low concentrations.[73] However, the materials used in the production of sanitary pads and tampons may have changed greatly since 1997, making it unclear of dioxin and furan levels are lower or higher than those found in this study, as Woo *et al*. in a more recent 2019 study still found dioxins present in sanitary products.[74]

These chemicals, along with furans, are produced through the bleaching process, where the highest level of dioxins produced comes from elemental chlorine bleaching.[73] It is likely that dioxin levels have decreased in sanitary products, as many manufacturers have changed their bleaching processes to safer alternatives.[75] The dioxins, dioxin-like compounds, and furans that have been found in sanitary products include polychlorinated dibenzodioxins (PCDDs), PCBs, and polychlorinated dibenzofurans (PCDFs).[74] Triclocarban (TCC), a source of dioxins and other harmful substances,[76] has also been found in pads, tampons, panty liners, cleansing lotions, bar soaps, and feminine wipes and bactericidal creams.[16] Regardless of this, the major contributor to dioxin exposure is likely through the consumption of animal products and dairy, where bioaccumulation of dioxins is high.[73]

Volatile organic compounds (VOCs) have been found in a variety of consumer products, such as feminine hygiene products, including women's sanitary products; vaginal washes, sprays, powders, wipes, and moisturizers.[77] VOCs within these products typically act as binders, fragrances, adhesives, moisture barriers, or adsorbents.[77] These chemicals are easily absorbed by the skin, though other exposure pathways include ingestion and inhalation.[78]

There are several VOCs that have been identified to be endocrine disruptors including toluene, xylene, and methylene chloride, all of which have been identified in at least some sanitary pad brands from Finland, Japan, Greece, France, Korea, and the United States.[67] Another report by Women's Voices for the Earth identified styrene, chloroform, and chloromethane in well-known Procter & Gamble's Always sanitary pads through an independent product test done by Paradigm Environmental Services.[79] Unsurprisingly, Lin *et al*. found that scented sanitary pads and tampons contained higher amounts of terpenes and aromatic compounds (such as ethylbenzene, toluene, xylene, styrene, and benzene) than unscented products.[77] What was surprising, however, was that store brands often had lower levels of VOCs than non-store brands and organic disposable sanitary pads and tampons did not have a significant difference in VOCs levels as compared to non-organic disposable products (the same was found for products with "sensitive skin" and "natural" labels).[77] Regarding "organic" labels, this may be due to the lack of controls placed on manufacturers, as this term lacks regulation or definition outside of the production of organic food by the United States Department of Agriculture (USDA).[77] Differences in store and non-store brand VOC levels

may be due to differences in manufacturing practices and sourcing of materials.[77] In addition, the concentrations and types of VOCs present in sanitary products can vary by country due to different VOC use standards.[74] Many of the chemicals found in disposable sanitary pads and tampons are also found in other feminine hygiene products.[77]

Organic farming practices, including the farming of not only food and livestock, but also cotton and other plant and animal products not regularly consumed, prohibits the use of synthetic pesticides, fertilizers, and growth hormones, as well as antibiotic use, aside from when necessary.[80] Regarding plants specifically, they are not allowed to contain chemical food additives, be irradiated, or be grown from genetically modified organisms (GMOs).[80]

Synthetic pesticides, such as the organophosphates malathion[81] and chlorpyrifos[81], are often used in food and plant production (such as non-organic cotton).[1] Organophosphates do not persist in the environment, but their residues on the products that they are used on contribute to exposure in individuals.[1] In fact, Lu *et al*. found that organophosphates were present in soil, food, and indoor air and dust in both agricultural and non-agricultural communities, while these chemicals were also found on toys and on children's hands in agricultural communities.[83] Pesticide exposure may come not only from the use of pesticides, but also through the diet by consuming contaminated animal products, rice, fruits, and vegetables.[8] For example, DEHP has been found in meat and dairy products at extremely high concentrations.[61] These products may contain over 300 μg/kg of DEHP, where 50 μg/kg/day of DEHP can cause endocrine disruption, specifically testicular toxicity, according to the European Food Safety Authority.[61]

A surprising place that pesticides may be found are within women's sanitary products. A report by Women's Voices for the Earth suggests that third-party testing they had done found several pesticides in a specific brand of tampon,[83] including malathion, methidathion, malaoxon, mecarbam, fensulfothion, pyrethrum, and procymidone, where exposure to these chemicals through the vagina has not yet been studied.[75] However, it is unclear what sort of quality control was used in the lab.[83] The French Agency for Food, Environmental, and Occupational Health and Safety also found glyphosate, hexachlorobenzene, lindane, and quintozene in some sanitary products.[74,84] Interestingly, quintozene and lindane have been prohibited in the European Union

since 2000, and hexachlorobenzene has been prohibited since 2004, yet the products tested in 2016 still contained these pesticides.[84] This may be dependent on where the manufacturers of these products source their cotton, as these pesticides may not be banned in other countries.

Unfortunately, most studies on the risks of pesticide exposure have not considered exposure to more than one pesticide at a time or the presence of pesticide by-products.[8] This is concerning, since some pesticide by-products are more harmful than the parent compound, including aldicarb-sulfoxide and oxons of chlorpyrifos, methyl-parathion, and diazinon, while the combination of some pesticides has greater toxic effects than all of them used separately.[8] These pesticides may be ingested or inhaled and cause various female reproductive issues.[88] Research suggests that postnatal exposure to certain pesticides can also cause issues with developmental stages (puberty[84], menstruation[89,90], ovulation[91,92], menopause[93], etc.) in adult females regarding reproductive function.

Nearly seven years of a female's life is spent menstruating when the average length of a period (five days)[42] and female reproduction (40 years)[94] are considered. Typically, the average woman will experience 450 menstruation events in her lifetime.[43] A typical sanitary product, such as a pad or tampon, absorbs between 5-15 mL of blood when saturated, where normal blood loss can range anywhere from 13-80 mL of blood per cycle.[43] It has been estimated that the average woman may use upwards of 10,000 sanitary pads or tampons during her menstruating years.[77,83] Therefore, over their lifetime, women have chronic exposure to sanitary products. This is concerning, as many chemicals have been found in women's sanitary products that cause adverse health effects including dioxins,[73,83,94] plasticizing chemicals,[94] phthalates,[83,94] and VOCs.[94] These sanitary products contact the sensitive skin and vaginal mucosa, which is highly permeable with high absorption capabilities.[77]

Women's sanitary products, such as menstrual pads, tampons, and panty liners, may expose women to several plasticizers.[16] The manufacturing practices used to create these products has the potential to leave chemicals within the product, such as through the bleaching process or the use of non-organic cotton that may contain pesticide residues. In addition, these products are largely made of plastics, such as polypropylene (PP) and polyethylene (PE), which are themselves made

of chemicals and may also contain plasticizers, such as phthalates.[16] In 2019 Woo *et al*. found that residual organic solvents from the manufacturing process present in sanitary pads can increase health risks, including reproductive harm through their toxic effects.[74]

In a recent 2020 study by Gao and Kannan, they tested various women's sanitary products from the United States from both popular and generic brands and found that all products tested contained the phthalates Dess-Martin periodinane (DMP), diethyl phthalate (DEP), dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), DEHP, and the parabens 2-C-Methylerithritol 4-phosphate (MeP), and ethylparaben (EtP).[16] Tampons were found to contain the highest DEHP levels, while panty liners had the highest levels of DMP, DBP, DIBP, and DEP.[16] Phthalates, parabens, and many other such chemicals are EDCs that are used as plasticizers and antimicrobial agents and have been found not only in women's sanitary products, but other personal care products and even food.[16] DEHP specifically has been known to cause uterine bleeding, among other things.[53] The high levels of phthalates found in these sanitary products likely came from the plastics they were made of, the plasticizing process, and the hot-melt adhesive process.[16,57] The hot-melt adhesive process serves to glue all the various layers of sanitary products together, though the high temperatures required may cause leaking of chemicals into other layers of the product as well, even if those layers are not made of plastics themselves.[16,57] For example, Gao *et al*. found that the concentration of phthalates present in sanitary pads that had a top layer of cotton still had just as many phthalates present in the top layer as those found in other non-cotton top layer materials. This was likely caused by the absorption of phthalates into the cotton layer during the production process from plastics and the hot-melt adhesive process.[57] They also found that 98% of sanitary pads tested in China contained phthalates, where DEP, DBP, and DEHP accounted for more than 60% of phthalates tested, while sanitary pads with fragrance also had greater amounts of DIBP than in pads without fragrance.[57] Park *et al*. also found that sanitary pads had significantly higher phthalate levels than did other commercial plastic products and found DBP, DEHP, and DEP in the sanitary pads tested.[67]

Gao and Kannan found that phthalate levels in women's sanitary products were much higher than any other chemicals analyzed in their study.[16] The study estimated that dermal absorption from the use of women's sanitary products accounted for anywhere from 3-15% of an

individual's total phthalate exposure, though transfer rates of the chemicals tested in this study are unknown for women's sanitary products and the absorption rate of phthalates varies greatly in human skin.[16] Gao *et al.* estimated that sanitary products account for around 8% of phthalate exposure doses in women.[57] However, the vulvar absorption rate of phthalates is not yet known and an absorption rate of two times that of the epidermis was arbitrarily used and the study did not consider menstrual blood being used to transfer phthalates into the bloodstream.[57] In addition, this study did not look at vagina absorption rates of phthalates from tampons, which are in much closer proximity to the mucosa than sanitary pads are, increasing phthalate transfer risks.[57] As such, further research is required to determine if these calculations are an under- or over-estimation.

Many of the chemicals found in sanitary products are known for their adverse health effects, including the promotion of inflammation and endometriosis[95] and menstrual irregularities.[96] To avoid most of these harmful chemicals, the use of reusable pads made of 100% organic, unbleached cotton may be a preferred option, though testing on these products has not been done to confirm they do not contain EDCs or other harmful substances.

1.4.2 Diet and Reproductive Health

Chemical exposure may also occur through the diet and likely plays a larger role than the chemical exposure that occurs through sanitary product use. This topic is considered in the following section.

1.4.2.1 Dietary Intake and Chemicals

Aside from chemicals found in personal care products, there may be many other avenues of exposure to chemicals that impact reproductive health. Diet may also impact the chemicals an individual is exposed to, as well as an individual's use of personal hygiene products and medications. Lu *et al*. in 2006, found that organic diets significantly reduced the intake of organophosphorus pesticides like malathion and chlorpyrifos (which are regularly used in agricultural production and are known for their neurologic effects) to undetectable levels in

children.[97] These pesticides may be found in fruits and vegetables, and products made with them, as well as wheat and corn products, such as pasta and cereal.[97] A meta-analysis by Smith-Spangler *et al*. in 2012 further supported these findings, as they found that eating organic foods (animal and plant products) not only reduces exposure to pesticide residues, but it also reduces exposure to antibiotic-resistant bacteria.[80]

Diet may also be a main source of exposure to phthalates and BPA, which are known EDCs.[64,68] Aside from diet, these EDCs have also been found in water and consumer products as well as in the air and dust.[64,68] They are most likely introduced into foods that individuals consume through the use of plastics in the manufacturing process, including through processing, storing, and transporting these foods, as well as through an individual's use of plastic containers, cutlery, dinnerware and consumption of canned foods.[68] In fact, Sathyanarayana *et al*. showed that consumption of fresh, un-canned food that was not exposed to plastic packaging or prepared in plastic containers led to a significant decrease in phthalate and BPA concentrations found in urine.[68] In another study, Rudel *et al*. found the consumption of fresh food as opposed to foods exposed to plastics (canned foods, frozen foods, foods microwaved in plastic, food covered in plastic films, food from restaurants, and drinks from cans or polycarbonate bottles) led to a significant decrease in DEHP and BPA metabolites found in urine.[64] DEHP, BPA, and other EDC may also be introduced to foods such as milk through the use of PVC tubing when milking cows and have even been found in whole eggs in Asia.[64] Exposure to dioxins may also come primarily from the diet, where consumption of animal meat and dairy products may account for up to 95% of dioxin exposure in humans.[73]

It may not only matter what individuals eat, but where their food is grown. Zhang *et al*. found that vegetables grown in plastic greenhouses was a major source of phthalate exposure for people in China, where phthalate exposures were higher in individuals from urban areas as compared to individuals from rural areas.[98] Of these phthalates, DEHP made up 55% of total phthalate concentrations found in these vegetables, followed by di-n-butyl phthalate (DnBP) and DiBP.[98]

Diet may not only be a major source of chemical exposure, but it may also have a positive impact on reproductive health. Ji *et al*. found that antibiotic and phthalate exposure were lower in individuals on vegetarian diets than on unrestricted diets.[66] Specifically, of the phthalates tested, there was a significant correlation between the concentration of MEHP metabolites in the urine and the consumption of dairy products.[66] MEP, mono-n-butyl phthalate (MnBP), and mono-isobutyl phthalate (MiBP) also all significantly decreased in individuals on a vegetarian diet.[66]

1.4.2.2 Effect of Diet on Menstrual Irregularities

There is some evidence that an individual's nutrition and metabolism may have a large impact on the menstrual issues women experience. A set of studies by Barnard *et al*. in 2000 found that a vegan diet (consisting of grains, vegetables, legumes, and fruits), with an approximate fat intake of 10% and a protein intake between 10-15% of an individual's daily caloric intake, decreased participants cramps and weight and improved sleep, digestion, and perceived energy.[99] They also found low-fat, vegetarian diets improved glycemic management, blood pressure, and serum lipids.[99] In a follow-up study, Barnard *et al*. also found that the duration of menstrual pain (dysmenorrhea) and intensity were significantly lower in women on a vegan diet as opposed to an unrestricted diet, as were some premenstrual symptoms.[100] The researchers suggest their results might be caused by dietary effects on estrogen activity, where an increase in sex-hormone binding globulin or a decrease in serum estrogen may reduce estrogenic stimulation of the endometrium to limit tissue proliferation that produces prostaglandins.[99] Vegetables, fruits, and legumes also have a profound effect on omega-3 and omega-6 fatty acid ratios, which can affect what type of prostaglandins are formed from these precursor molecules.[100] These animal-product-free foods have a low-fat content but are often rich in omega-3 fatty acids in relation to other types of fat, whereas diets containing cooking oils and animal fats have a greater proportion of omega-6 fatty acids.[100] This is an important distinction, as 3-series prostaglandins are formed from omega-3 fatty acids and have anti-inflammatory properties, while the 2-series prostaglandins PGE_2 and $PGE_{2\alpha}$ are formed from omega-6[100] and PGE_2 is involved in inflammation, swelling, and pain.[101] Barnard *et al*. found that a higher intake of omega-3 or a higher omega-3 intake as compared to omega-6 was associated with a decrease in pain from menstruation in women[100] In a recent meta-analysis

conducted by Isaza, they also found omega-3 could improve dysmenorrhea,[102] though nausea and an increase in acne were associated with omega-3 intake.[21] These findings were also confirmed in other studies, but more research is still needed.[28]

1.4.2.3 Disordered Eating and Reproductive Health

Disordered eating and eating disorders may have an impact on the menstrual cycle. According to the American Psychiatric Association, these chronic illnesses typically start around adolescence and young adulthood and are common in young women.[103] If the body does not receive enough energy and nutrients, it can impact the onset of puberty and menarche, as well as regular menstruation after menarche.[104] It is also typical to see comorbid conditions in individuals with disordered eating, some of which include reproductive issues and decreased bone health.[104] Disordered eating that leads to low weight, along with excessive exercise and high stress levels, may result in hypothalamic amenorrhea, where menses stops or does not start in the first place.[104] Hypothalamic amenorrhea results from a decrease in GnRH secretion, which ultimately causes a decrease in estrogen secretion.[105] In addition to causing amenorrhea, a decrease in estrogen secretion also leads to decreased bone mineral density, infertility, painful intercourse, and vaginal and breast atrophy.[104] GnRH secretion may also be impacted by stress, as increasing cortisol levels inhibit this secretion.[104]

As low weight may lead to a later onset of menarche, girls with a high BMI that are considered obese may have a earlier onset of menarche.[106] Being overweight may also lead to irregular and infrequent periods.[55,106] Interestingly, exposure to the DEHP metabolite MEHP may be associated with a higher BMI and waist circumference.[61] Also, women who experience menstrual irregularities are more likely to have a larger waist circumference and higher BMI than those who do not experience menstrual irregularities.[106] This may be related to the higher insulin and testosterone levels and the lower sex hormone-binding globulin (SHBG) found in obese women, which leads to hormonal changes that may cause menstrual irregularities.[107] In addition, stress plays a role in obesity by altering the bodies ratio of androgens to estrogens, which in turn can cause abdominal obesity in women.[38] Stress causes increased levels of cortisol in the body,

inhibiting lipid mobilization in adipose tissue, especially in visceral adipose tissue, which has a high number of cortisol receptors.[38]

Adipose tissue is important for various physiological functions, one of which is the function of the endocrine system.[108] Adipocytes can secrete endocrine factors that regulate inflammation and produce substances that can influence vascular function, immune function, and hormonal status.[108] In addition, adipose tissue is responsible for the storage of substrates in the body, but it is also capable of storing chemicals[108] such as persistent EDCs due to their high lipid solubility.[10] This suggests that individuals who have more fat tissue may have greater body burdens of various chemicals, such as persistent organic pollutants (POPs).[109]

POPs, most of which are endocrine disruptors and are resistant to metabolism, have a high affinity for lipids and can be stored in adipose tissue,[109] which in the short term can protect various other tissues and organs in the body from being exposed to these chemicals.[108] Some of these POPs include some organochlorine pesticides[17,108], polychlorinated biphenyls (PCBs)[108,109], dioxins[108,109], and furans[108,109]. DEHP, DBP, and other phthalates may also accumulate in adipose tissue to a lesser extent, though they are generally non-persistent[109] due to their half-life of around five hours and their ability to be metabolized into more easily excretable substances.[13] Despite their short half-lives, phthalate exposure is detected in most populations worldwide likely due to chronic exposure, but it may also be due to bioaccumulation.[13] However, differences in body composition and metabolism can affect the half-life, persistence, and degradation of EDCs in tissues and bodily fluids.[10]

Other lipophilic xenobiotics are also capable of accumulating in adipose tissue and other tissues with high lipid content.[110] However, this sequestering of lipophilic chemicals increases the total body burden through bioaccumulation and may have long term negative effects through continual internal exposure.[108] These chemicals will be released into the bloodstream slowly over time, which may be further exacerbated during weight loss.[108,110] Fortunately, for some POPs, the POP body burden may decrease by 15% through weight loss.[108,110]

1.4.3 Exercise and Reproductive Health

As weight effects menstrual patterns, several studies have looked at exercise as a possible treatment for both heavy bleeding and painful periods in women.[24,27] Atta *et al*. found that 54.6% of female students that did not exercise at all or had low physical activity suffered from dysmenorrhea.[32] Although it seems exercise has a positive impact on dysmenorrhea, the type of exercise varies greatly in such studies, as do their results. In 2017, Banu *et al*. found that there seemed to be no association with heavy bleeding and BMI; instead, they found that secondary causes of menorrhagia were more likely, such as uterine fibroids.[45] However, Mariam *et al*. found abnormal uterine bleeding to be the main cause of menorrhagia, which may be a result of the age of the participants, as older women are less likely to develop fibroids than younger women.[111] In other studies Mohebbi Dehnavi *et al*. and Motahari-Tabari et al. found that regular and continuous aerobic exercise or stretching may reduce or eliminate heavy menstrual bleeding.[24,27] Additionally, physical activity may increase the length of the menstrual cycle so that there are a greater number of days between menses.[112] This increase in cycle length could be caused by a decrease in FSH, which in turn causes follicles to mature more slowly and thus increase the length of the follicular phase, ultimately delaying ovulation.[112] In another study Nieczuia-Dwojacka *et al*. found that women have shorter menstrual cycles when they are physically active.[29]

It seems more studies have been done on the effect of exercise on primary dysmenorrhea. Mohebbi Dehnavi *et al*. found that primary dysmenorrhea may be reduced through moderate intensity aerobic exercise, though improvement is only seen when an individual exercises consistently three times a week for thirty minutes or more.[24] This effect is likely due to the decrease in serum aldosterone levels seen in women when active, which is caused by decreased levels of renin and increased levels of estrogen and progesterone.[24] Additionally, sports exercise may increase blood circulation to the pelvis, resulting in the elimination of wastes and prostaglandins from the uterus more effectively during exercise, resulting in a delayed onset of pain.[24,27] This increase in blood circulation also increases endorphins due to a decrease in stress levels experienced while exercising.[24] The timing of exercise may also be important, as Motahari-Tebari *et al*. found that the prevalence of dysmenorrhea was reduced in women that had regularly exercised before the onset of menarche.[27] Stretching exercises that consisted of a five-minute

warmup and ten-minutes of stomach and pelvic stretches three times a week were also found to reduce dysmenorrhea just as well as mefenamic acid.[27] However, exercise took longer to reduce pain and was not as effective as mefenamic acid until after one month of consistent exercise.[27] Although it seems regular exercise can be effective at reducing pain from primary dysmenorrhea, its effectiveness largely depends on the duration of exercise, as well as the intensity and quality of exercise done, where more vigorous exercise causes the greatest decrease in pain intensity.[27] These stretching exercises are thought to increase endorphin levels and cause hormonal changes in the epithelial tissues of the uterus.[27] Exercise in general helps the body to maintain homeostasis in relation to regulation of hormones and the menstrual cycle.[32]

Exercise may also be beneficial by inducing perspiration, as may eliminate some phthalates from the body, including DEHP and MEHP.[13] Other activities that induce perspiration, such as sauna use, may also be beneficial at eliminating these chemicals.[13] In addition, the loss of fat that is often a result of regular exercise and caloric restriction may result in the mobilization of stored chemicals from adipose tissue to the fat stores of the skin, which may act as an alternative storage.[13]

1.4.4 Smoking and Reproductive Health

Smoking may also have an impact on the menstrual cycle, where smoking may increase the risk of dysmenorrhea[28] and a longer, heavier menstrual flow.[113] Some researchers have found that this risk increases the longer an individual has been a smoker and the more they smoke.[37,113] Ju *et al*. found that the earlier an individual starts smoking the greater the risk of developing chronic dysmenorrhea, where girls who started smoking before menarche and girls 13 or younger had up to 60% higher odds.[37] However, there is some evidence that dysmenorrhea symptoms caused by smoking may be reversed after cessation of smoking, though further research is needed.[37] Smoking likely contributes to dysmenorrhea because smoking causes vasoconstriction and may limit blood flow to the endometrium.[37,113] Additionally, by increasing the duration of menstruation, individuals are at an increased risk for experiencing dysmenorrhea.[37,113] This longer period of menstruation may be caused by smoking's effect on the endocrine system.[37] Other researchers have found that smoking may cause shorter, more frequent menstruation[54], leading to early

menopause.[107,112] This early menopause is likely due to an increase in FSH, which causes follicles to mature more quickly and results in the early depletion of oocytes.[112] There are several other suggested theories as to why smoking may cause dysmenorrhea, such as through interference with the binding of estrogens to its receptors, enhancing the metabolism of alternative estrogen sources that are not produced by the body itself, or by reducing the conversion of androgens in the body to estrogens.[37] There are also other less plausible theories, such as smoking causes ovarian atrophy, which is unlikely since the cessation of smoking can reverse dysmenorrhea symptoms experienced due to smoking.[37]

1.4.5 Alcohol and Reproductive Health

The consumption of alcohol in even moderate amounts may cause menstrual and reproductive irregularities such as infertility, amenorrhea, and early menopause.[114,115] Liu *et al*. found that the cycle length of women who consumed alcohol was shorter than those who did not, which can cause more frequent menstruation.[112] Alcohol disrupts the reproductive system through hypothalamic-pituitary-ovarian axis dysfunction, ovarian dysfunction, and the dysfunction of various regulation mechanisms.[114] Augustyńska *et al*. found that prolactin levels were significantly increased in alcoholic women during the entire cycle.[114] This increase in prolactin disrupts the pituitary-ovarian axis, which in turn disrupts reproductive function and stimulates a decrease in LH secretion.[114] Additionally, many of the women studied were found to have increased progesterone levels during the follicular phase and decreased LH levels during the ovulation phase.[114] Testosterone levels also increased during the luteal phase and were positively associated with the length of time of alcohol dependency prior to the study.[114] Decreased LH secretion, or lack thereof, leads to anovulation or irregular ovulation and is a common cause of infertility.[114,115] Testosterone can also influence the hypothalamic-pituitary axis, leading to dysfunction of the menstrual cycle.[114] This increase in testosterone may be further increased when alcohol is consumed while taking oral contraceptives.[114] Estrogen levels may also increase due to alcohol, likely due to metabolic dysfunction in the liver, leading to an increase in nicotinamide adenine dinucleotide (NAD) + hydrogen (H) (NADH) that affects estradiol-estrone conversion.[114] Schliep

et al. found that consumption of wine and liquor led to an increase in estradiol, testosterone, and LH when one or more alcoholic drinks were consumed per day, while beer and spirits seemed to have no effect.[116] These results were further magnified when binge drinking was involved.[116] Parazzini *et al*. also found that the heavy consumption of wine and/or beer may decrease an individual's risk of dysmenorrhea[113], though this is likely due to the cessation of a period altogether, as other researchers have found the consumption of alcohol to cause dysmenorrhea.[28]

Alcohol consumption may also impact puberty, where Emanuele *et al*. found that low levels of estrogen in 12- to 18-year-old girls that remained low for up to two weeks after moderate drinking, which may impact the maturation of the reproductive system.[115] In research done with rhesus monkeys, alcohol increased the time between menstruations, which may result in the development of irregular menstrual patterns.[115]

1.4.6 Sleep and Reproductive Health

Sleep may also have an impact on the menstrual cycle, where circadian rhythm disruption can affect menstrual function.[117,118] A disrupted circadian rhythm, such as in shift workers, may cause irregular and longer menstrual cycles.[117] Baker and Driver found that 50% of menstruating women doing shift work reported menstrual irregularities, as compared to 20% in the general population.[117] These menstrual irregularities may be caused by changes in the amplitude and frequency of the pulsatile secretions of LH and dysfunction of the hypothalamic-pituitary-ovarian axis due to added stress on the body.[117] Sleep causes a natural nocturnal decrease in LH levels, as well as a decrease in LH pulsatile frequency during the follicular phase.[117] However, shift work disrupts this pattern, as most shift workers get less sleep that is more fragmented.[117] Short sleep duration may also lead to menstrual irregularities.[13] Figà-Talamanca also found that women working irregular hours or shift work increased their risk of spontaneous abortion, along with other reproductive issues.[118] However, this was not the case if women working nights had consistent sleep schedules.[118]

1.4.7 Workplace and Reproductive Health

Stress and anxiety may be linked to dysmenorrhea, where Atta *et al*. found that female students who suffered from stress and anxiety were 81.8% more likely to have dysmenorrhea.[32] Also, Nieczuja-Dwojacka *et al*. linked high stress levels with dysmenorrhea, where dysmenorrhea was more severe and frequent in those with high stress levels than in those who were not highly stressed.[29] Other researchers found high levels of stress in the work environment caused anovulation and changes in menstrual cycle length, as well as spontaneous abortion and preterm births.[118]

The workplace may also impact chemical exposure, where many jobs, such as energy production or manufacturing, often use chemicals during production that are retained within the products, exposing both workers and consumers.[1] Women working in the plastic industry are also at higher risk of chemical exposure than men, as women often have lower positions with more chemical exposure risk.[4] Chemicals women are exposed to in the plastic industry may have estrogenic effects and cause endocrine disruption.[119] DEHP is one such chemical and has been found in workers at significantly higher levels than in the general population, even when air samples at the workplace found DEHP in trace amounts below typical exposure standard levels.[120] This is because DEHP has a low evaporation rate.[61] Another high-risk job is agricultural work, where exposure to pesticides and other chemicals is common.[1,2] Immigrant workers are at even greater risk of chemical exposure, as they often work jobs with high hazardous exposure levels in greater numbers than do a country's own citizens.[2] It has been documented that pesticide exposure in women can cause health problems in offspring, infertility, and spontaneous abortion, among other issues.[118] Other high-risk industries with regular chemical exposure include dry cleaners, nail salons, hair salons, house cleaning, health care, and factory work.[121]

1.4.8 Ethnicity and Socioeconomic Status and Reproductive Health

Ethnicity and socioeconomic status may also impact dysmenorrhea, though this area is less studied. For example, although dysmenorrhea prevalence in women of reproductive age ranges from 16 to 91%, a meta-analysis and systematic review by Saei Ghare Naz *et al*. found that for

Iranian women, this statistic is closer to 71%.[20] Banikarim *et al*. found that Hispanic teenage girls had higher rates of dysmenorrhea compared to previously reported rates in African American and Caucasian girls by up to three times their pain.[122]

Socioeconomic status of women in South Korea was associated with education and household income, where women who had lower education or women with high household incomes were found to have the highest rates of menstrual irregularities.[123] A higher education is likely associated with a decreased risk of dysmenorrhea due to an individual having more access to information, medical services, greater medical service quality, better living conditions, and better occupational and housing environments.[123] However, an individual's job may also have an impact on dysmenorrhea, where high stress jobs with poor working conditions, temporary employment, or irregular hours may increase an individual's risk of developing menstrual irregularities.[123] Though surprising at first, Kwak *et al*. found that women with higher incomes had greater rates of menstrual irregularities, though this was attributed to the types of jobs women with high incomes usually have.[123] For example, many high paying jobs are managerial or specialized in nature and are often high stress positions; these types of jobs are known for their irregular schedules and can cause mental and physical exhaustion, dietary changes, and sleep issues.[123] Women who had not gone through childbirth and women who were either unmarried, widowed, divorced, or not living with their spouse may also be more likely to suffer from menstrual irregularities than women with children or were married living in the same household.[123]

Culture may have an impact on menstrual pain as well. For example, most women in Western cultures say they experience menstrual pain, while only one-quarter of rural Mayan women do.[21] This may not necessarily mean than Mayan women experience less menstrual pain than women from Western cultures. Cultural influences can have a profound impact on how the menstrual cycle is perceived, which may affect the number of women who report experiencing menstrual pain.[21] For instance, some cultures may consider discussing the menstrual cycle as taboo[23] or may consider a menstruating woman impure and thus unable to partake in certain religious practices, which may lead to under reporting of dysmenorrhea.[21] With this in mind, De Sanctis *et al*. reviewed the prevalence of dysmenorrhea from around the world between 2010 and

2015, which varied greatly between countries, ranging from as high as 94% in Oman and as low as 0.9% in Korea.[123]

In addition to dysmenorrhea, race and status may also play a role in the amount of chemical exposure an individual experiences. For example, according to the American Lung Association, poorer people and certain ethnic groups have the highest exposure to pollutants.[125] This disparity can be attributed to the living situation of many minority groups, who often live in poor neighborhoods with lower quality housing due to a range of factors including racism, class bias, and low social position, among others.[125]

1.4.9 Mental Health and Reproductive Health

Mental health status may also be associated with menstrual irregularities.[126] Mental health may impact the menstrual cycle, where Patel *et al*. found that as levels of anxiety and depression increased, so did pain caused by dysmenorrhea.[127] Women who have experienced emotional disturbances[38] or high levels of somatization may also experience higher rates of dysmenorrhea, though studies on these topics are generally small.[21] Rowland *et al*. found that women suffering from depression often had longer and more irregular cycles than those without depression and they also experienced bleeding between menses.[54] These menstrual irregularities could be attributed to several factors, including depression itself, the medical treatment for depression, or the stress associated with depression.[54]

1.4.10 Confounding Variables

Treatments for dysmenorrhea typically involve relieving pain or other symptoms either by masking them or by directly affecting the mechanisms involved in causing the pain, such as by reducing or inhibiting prostaglandin synthesis.[28] Some of these treatments are also affective in reducing bleeding.

There are many drugs or treatment options that can, for reasons mentioned above, impact the results of our study. There are also drugs or treatments for other unrelated conditions that have secondary effects that can impact the menstrual cycle. These include, but are not limited to, non-steroidal anti-inflammatory drugs (NSAIDs)[128], oral contraceptives[26,30], GnRH agonists[129], aromatase inhibitors[129], antispasmodics[129], calcium channel blockers[28,129], vasopressin antagonists [28,130], nitroglycerin[28,129], antifibrinolytic drugs[46], and progestins[129].

In terms of contraceptives, combined oral contraceptives (both continuous and cyclical) both work to treat primary dysmenorrhea after six months of use, though the use of continuous oral contraceptives for secondary dysmenorrhea is more effective.[26] However, not all contraceptives are effective at reducing dysmenorrhea and may even increase menstrual pain and bleeding. The use of a copper intrauterine device (IUD), which is inserted into the vagina, is one such example.[128,131] Common side effects of copper IUDs include increased menstrual flow and duration, pelvic pain[128], and dysmenorrhea.[28,131] These side effects are often the cause of discontinued use and premature removal of copper IUDs.[25,128,131] An alternative to the copper IUD is the hormonal IUD, which reduces prostaglandin synthesis in the endometrial tissue.[40] This may lead to a decrease in dysmenorrhea and menorrhagia through the reduction of uterine blood flow and a decrease in endometrial thickness.[21,25] Another type of contraceptive that may decrease dysmenorrhea and menorrhagia is the depot medroxyprogesterone acetate (DMPA) injection,[132] which is injected intramuscularly every three months; this results in anovulation for seven to nine months.[21] However, there is a chance of increasing uterine bleeding through the use of the DMPA shot in the short-term, though amenorrhea becomes more likely after three months.[132] Since the use of contraceptives is quite common among women and have varying affects on the menstrual cycle, women who use these contraceptives were still included in our study.

There are many secondary causes of dysmenorrhea, menorrhagia, and other menstrual irregularities. Secondary dysmenorrhea is associated with many other issues including painful intercourse[21,133], pelvic inflammatory disease[21,28], adenomyosis[21,28], uterine fibroids[21,28], endometriosis[21,28], ovarian cysts[21], intrauterine polyps[21], inflammation of the cervix[21], and bleeding between periods[21]. Other possible causes of secondary dysmenorrhea include neural or hormonal issues.[21]

Some evidence suggests that exposure to phthalates[61] and PCBs[74] may increase the risk of developing endometriosis.[1,10,61,74] Polycystic ovary syndrome (PCOS), another common disorder that can cause dysmenorrhea, may be associated with fetal exposure to some EDCs.[10] Endocrine hormones also help to regulate the function of the immune system and EDCs may disrupt their effect on this system[1] and lead to immune system disorders.[3] Inflammation is often linked with diseases that cause infertility, such as pelvic inflammatory disease, and EDCs such as dioxin-like PCBs have been associated with an increased risk of developing endometriosis.[1]

Heavy menstrual bleeding may also be caused by many other conditions which include ovarian cysts, uterine cancer, uterine polyps, bleeding disorders, cervical inflammation, and uterine prolapse, to name a few.[45] Many hormonal conditions can also have an impact of the menstrual cycle. Hyperthyroidism and hypothyroidism, both thyroid disorders, can lead to altered menstrual function[58,134,135] by impacting the metabolism of androgens and estrogens.[136]

Type two diabetes mellitus may also cause menstrual irregularities, where diabetes has been found to increase the odds that a woman will experience an irregular and longer cycle.[54] Additionally, women who had either an irregular cycle or a long cycle were twice as likely to develop type two diabetes mellitus than women who did not experience an irregular or long cycle.[54] It is important to note that DEHP exposure may increase insulin resistance in elderly populations[61] and many DEHP metabolites have been positively linked to insulin resistance and diabetes.[109]

Aside from the above-mentioned conditions, there are many other illnesses and diseases that can have an impact on the menstrual cycle, as can the medications that are often used to cope with such conditions. For these reasons, individuals with certain medical conditions were excluded from our study.

1.5 Objectives

The objective of the proposed research is to see which exposure routes and additional factors may contribute to menstrual irregularities, and which may not. Each category will also be ranked to see which have the greatest positive and negative effects on reproductive health.

This research addresses the hypothesis that higher levels of exposure to harmful EDCs are more likely to result in higher reports of reproductive issues in women, such as increased pain and bleeding during menstruation, compared to women with low EDC exposure levels, where high chemical exposure is defined as exposure to chemicals in large quantities, for long periods of time, and/or in high frequencies. High chemical exposure was chosen as our measure due to multiple EDCs mentioned previously having known reproductive effects at high doses, such as phthalates, while low doses are not often considered. This research also addresses the hypothesis that various factors can either increase or decrease a woman's risk of experiencing pain and/or can increase or decrease bleeding during menstruation.

This research will provide insight into the effect of EDCs and other chemicals on the female reproductive system, in particular the menstrual cycle.

Chapter 2: Methods

2 Study Design and Participants

Approval for the study was granted by the Thompson Rivers University Research Ethics Board (ID 102783). Written informed consent was given by all participants.

We aimed to recruit between 2000-3000 menstruating women volunteers between the ages of 18-35 for our study, which consisted of a one-time online survey. Our sample population ended up being 178, after a total of 97 participants were excluded for various reasons, which can be found in table 2A. The participants in this study had to be between the ages of 18 and 35, currently experience a menstrual cycle, and could not be pregnant during the time of completing the survey. Additionally, only women who lived in Canada and had access to a computer with internet were considered for participation in the study. Women who had a medical condition that could impact the reproductive system on its own or through medication use for treating the condition were also excluded post survey in the data analysis phase of the study.

Women were recruited through online advertising, which was sent to all major universities across Canada. In addition, further advertisement was done through local and provincial news outlets and the researcher's Facebook and Instagram pages. A copy of this ad can be found in the appendix.

2.1 Online Survey

The survey link was provided to potential participants and included a consent form for potential participants to review before partaking in the survey. This consent form outlined what was expected of participants and can be found in the appendix. The survey also contained a built-in screening process, where anyone who was not female, menstruating, and was not between the ages of 18-35 were automatically excluded. The survey itself contained just over 95 questions and was estimated to take between 45-60 minutes to complete. The survey did not have to be completed in one sitting and participants could edit their answers prior to submission. Any surveys that were not fully completed were not considered for data analysis. Questions included in the survey

covered socioeconomic status, reproductive health, general health, mental health, product use, and additional factors. This survey is contained in the appendix. Within the survey, pain was measured using the Andersch and Milson Pain Scale (AMS) (which is a scale used to assess the severity of menstrual pain), and stress levels were measured using the Perceived Stress Scale (PSS). Both of these scales can be found in the appendix (A4, A5). The AMS was used to assess pain due to its simplistic, easy to interpret design that could easily be included in our survey without adding multiple questions to the already broad survey.

2.2 Analysis

After survey results were collected, questions that pertained to a single variable, such as alcohol consumption, were combined into a single score. Each response was ranked, where, in our example of alcohol consumption, 0 would indicate low use and a higher number, such as 2, would indicate high use. Questions were normalized so that each question pertaining to a single variable were weighted the same. For example, the number of standard alcoholic drinks an individual has in a week was weighted the same as how many years an individual has been drinking for, so that both contribute equally to the overall alcohol consumption score used for data analysis.

By condensing questions into a single score, we used a total of 21 variables in our analysis. These variables were age, BMI, hormone medication use, age at menarche, cycle regularity, vaping status, alcohol consumption, drug use, sleep, caffeine use, stress, chemical exposure, smoking status, psychological medication use, relationship status, place of residence (urban, rural, etc.), pregnancy history, sexual activity, number of days between menstrual cycles, number of days the menstrual cycle lasts, and stress levels.

Alcohol consumption was calculated based on a participant's alcohol use status, if participants consumed alcohol before their first period or when they were younger than 18, how many drinks they had per week, and how long they have consumed alcohol for.

Drug use was calculated based on a participant's drug use status, if participants used drugs before their first period or when they were younger than 20, and how long they have used drugs for.

Stress scores were calculated based on the PSS that can be found in the appendix (A4).

Chemical exposure was calculated based on a participant's menstrual product use (inorganic/organic, scented/unscented), use of other vaginal hygiene products, use of personal care products, diet type (vegetarian/vegan/unrestricted, organic/unrestricted), consumption of canned foods/foods and beverages stored in plastic bags/bottles/containers, and frequency of consumption of canned/plastic exposed foods.

Vaping status, Drug status, and smoking status all had small sample sizes for moderate and high use, so these categories had to be collapsed into one category of moderate/high use in order to run the logistic regression model that was used. The smallest vaping category was moderate use with 8 participants, the smallest drug use category was high use with 18 participants, and the smallest smoking category was high use with 3 participants. As a result, a binary comparison was made where we compared low/no use in these three categories with moderate/high use.

Several questions from our survey were not used in our analysis for a variety of reasons. Some questions were excluded due to having insufficient data for analysis, such as having too many "I am unsure" responses or blank answers, while others were excluded due to being outside the scope of our study. Other questions were excluded due to the questions not being specific enough and a high likelihood of misinterpretation by participants (such as "how frequently are you exposed to chemicals at work, home, or school," where the participant may not know they are exposed to chemicals at all and no further information was provided to participants to help them provide an informed response).

After survey results were condensed into 21 total variables, the data collected was analyzed using a proportional odds logistic regression model to see if chemical exposure and different additional factors may contribute to menstrual irregularities, and which may not. Separate analyses were done for pain and bleeding, respectively. The absolute risk of significant variables was also calculated to see which variables may have the greatest effects on reproductive health within our participants. The effect size of all variables was visualized using a Forest Plot.

Relative risk of experiencing dysmenorrhea was obtained by taking the average percentage of women affected by dysmenorrhea in multiple studies, which ranged from 16 to 95% of

reproductive aged women, to get 56%.[20–28] Relative risk of experiencing menorrhagia was based on the CDCs assessment that 20% of American women experience heavy menstrual bleeding.[137]

Chapter 3: Results

3 Results

3.1 Pain During Menstruation

In our study, less than 6% of participants experience no pain during their menstrual cycles. Most participants experience moderate pain (40%), followed by some pain (35%), and severe pain (19%).

Table 1. Participant pain experience.

Participant Response	Number of Participants
No Pain	10
Some pain	62
Moderate pain	72
Severe pain	34

Outside of our study, dysmenorrhea is reported to affect anywhere from 16 to 95% of reproductive aged women,[20–28] resulting in an average of 56% of these women, which was used as an estimate in our risk assessments below.

3.1.1 Pain Variable Summary

A summary of dysmenorrhea results is visualized in Figure 1, where the number of days of menstrual bleeding, high chemical exposure, and age were the only variables considered that were found to have a correlation with dysmenorrhea experienced in the study population.

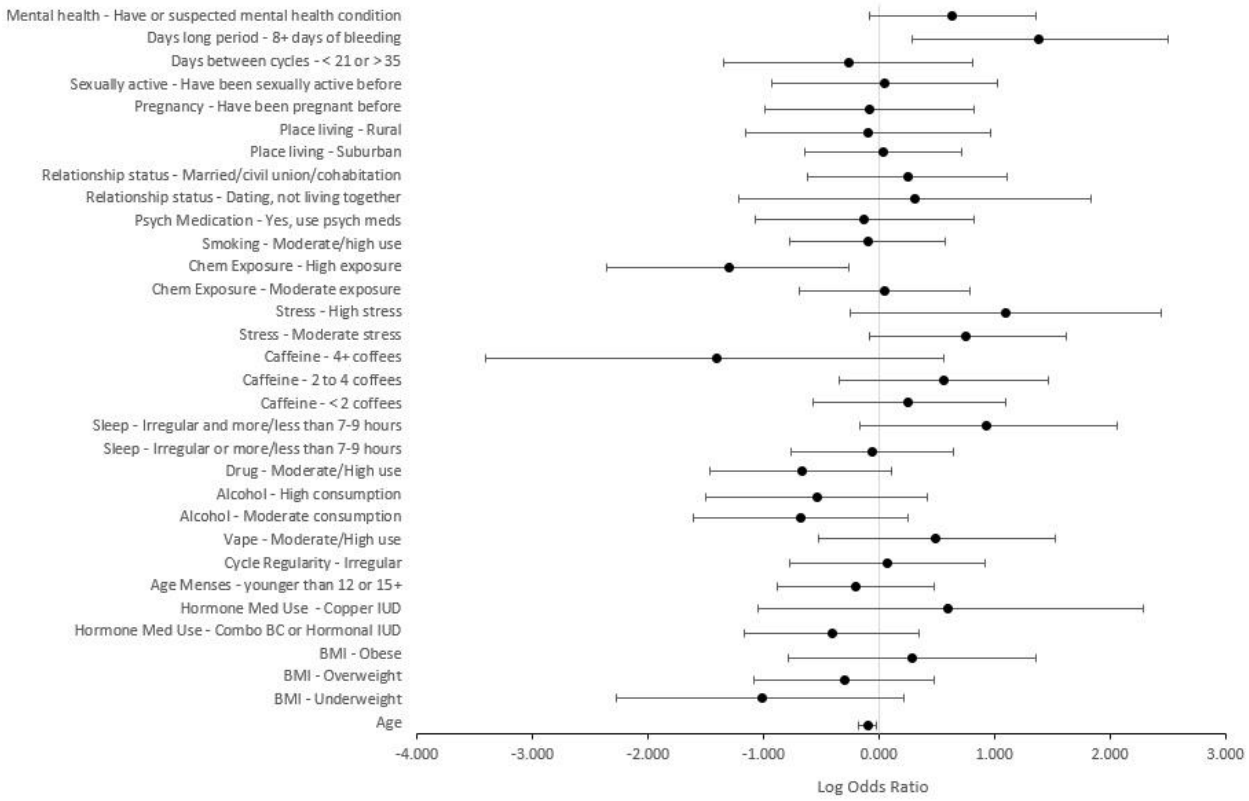

Figure 1. Impact of variables on dysmenorrhea with 95% confidence intervals.

Figure 1 illustrates the correlation of each of our study variables with dysmenorrhea with 95% confidence intervals. The x axis shows the log odds ratio of each variable, where any variable that crosses the 0.000 line do not have an impact on dysmenorrhea in our study participants. Any variables that do not cross the 0.000 line on the left decrease dysmenorrhea and any variables that do not cross the 0.000 line on the right increase dysmenorrhea.

3.1.2 Age

Age was negatively correlated with the pain experienced during menstruation, where the odds of experiencing pain during menstruation are reduced as age increases (p=0.016, OR=0.907). With an average of 56% of reproductive aged women experiencing dysmenorrhea, the risk of

experiencing dysmenorrhea is reduced to 45% (odds ratio*absolute risk = relative risk: 0.907*56% = 45%) as age increases in our study population.

3.1.3 Chemical Exposure

High chemical exposure was negatively correlated with the pain experienced during menstruation, where the odds of experiencing pain during menstruation are reduced with high chemical exposure (p=0.015, OR=0.274) compared to low chemical exposure. With an average of 56% of reproductive aged women experiencing dysmenorrhea, the risk of experiencing dysmenorrhea is reduced to 14% (odds ratio*absolute risk = relative risk: 0.274*56% = 14%) with high chemical exposure in our study population.

3.1.4 Length of Menstruation

Menstruation that lasted eight or more days was positively correlated with the pain experienced during menstruation, where the odds of experiencing pain during menstruation was increased with periods that last eight or more days (p=0.014, OR=3.969) compared to menstruation lasting 7 or less days. With an average of 56% of reproductive aged women experiencing dysmenorrhea, the risk of experiencing dysmenorrhea is increased to 100% (odds ratio*absolute risk = relative risk: 3.969*56% = 100%) with menstruation events eight or more days long in our study population.

3.1.5 Additional Variables

BMI was not correlated to pain experienced during menstruation in our study population (underweight (p=0.107), overweight (p=0.454), obese (p=0.600)). Hormone medication use was not correlated with pain experienced during menstruation in our study population (use of combination birth control or hormonal IUD (p=0.290), use of copper IUD (p=0.477)). Cycle regularity was not correlated with pain experienced during menstruation in our study population

(p=0.856). Vape status was not correlated with pain experienced during menstruation in our study population (p=0.343). Alcohol consumption was not correlated with pain experienced during menstruation in our study population (moderate consumption (p=0.152), high consumption (p=0.270)). Drug use was not correlated with pain experienced during menstruation in our study population (p=0.094). Sleep was not correlated with pain experienced during menstruation in our study population (irregular sleep or more/less than 7-9 hours (p=0.863), irregular sleep and more/less than 7-9 hours (p=0.099)). Caffeine consumption was not correlated with pain experienced during menstruation in our study population (<2 coffees (p=0.544), 2-4 coffees (p=0.226), 4+ coffees (p=0.163)). Stress levels were not correlated with on pain experienced during menstruation in our study population (moderate stress (p=0.080), high stress (p=0.109)). Smoking status was not correlated with pain experienced during menstruation in our study population (p=0.775). Psychological medication use was not correlated with pain experienced during menstruation in our study population (p=0.794). Relationship status was not correlated with pain experienced during menstruation in our study population (dating but not living together (p=0.686), married/civil union/cohabitation (p=0.572)). Place of residence was not correlated with pain experienced during menstruation in our study population (suburban (p=0.913), rural (p=0.863)). Previous experience with pregnancy was not correlated with pain experienced during menstruation in our study population (p=0.858). Sexual activity was not correlated with pain experienced during menstruation in our study population (p=0.927). The length of time between cycles was not correlated with pain experienced during menstruation in our study population (p=0.629). Stress levels were not correlated with pain experienced during menstruation in our study population (p=0.085).

3.2 Bleeding During Menstruation

In our study, less than 8% of participants experience heavy bleeding during their menstrual cycles. Most participants experience light bleeding (72%), followed by moderate bleeding (20%).

Table 2. Participant bleeding experience.

Participant Response	**Number of Participants**
Light bleeding	128
Moderate bleeding	36
Heavy bleeding	14

Outside of our study, menorrhagia is reported to affect 20% of reproductive aged women,[137] which was used as an estimate in our risk assessments below.

3.2.1 Bleeding Variable Summary

A summary of menorrhagia results is visualized in Figure 2, where the number of days of menstrual bleeding, moderate stress, moderate to high drug use, moderate alcohol consumption, and irregular periods were the only variables found to be correlated with bleeding experienced in the study population.

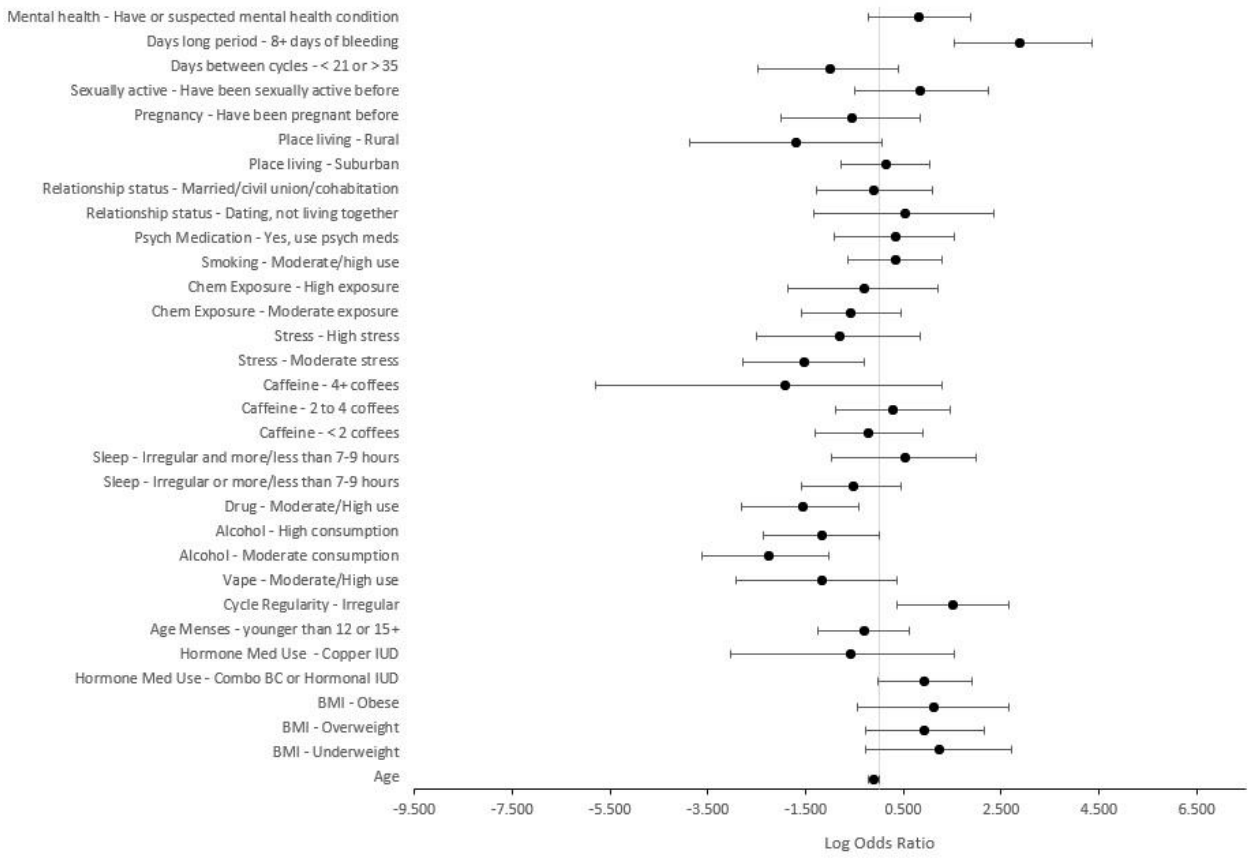

Figure 2. Impact of variables on menorrhagia with 95% confidence intervals.

Figure 2 illustrates the correlation of each of our study variables on menorrhagia with 95% confidence intervals. The x axis shows the log odds ratio of each variable, where any variable that crosses the 0.000 line do not have an impact on menorrhagia in our study participants. Any variables that do not cross the 0.000 line on the left decrease menorrhagia and any variables that do not cross the 0.000 line on the right increase menorrhagia.

3.2.2 Cycle Regularity

Having an irregular cycle was positively correlated with the bleeding experienced during menstruation, where the odds of experiencing menorrhagia was increased with irregular cycles ($p=0.010$, $OR=4.480$) compared to regular cycles. With an average of 20% of reproductive aged women experiencing menorrhagia, the risk of experiencing menorrhagia is increased to 90% (odds

ratio*absolute risk = relative risk: 4.480*20% = 90%) with cycle irregularity in our study population.

3.2.3 Alcohol Consumption

Alcohol consumption was negatively correlated with the bleeding experienced during menstruation, where the odds of experiencing menorrhagia was decreased with moderate alcohol consumption (p=0.001, OR=0.106) compared to low or no alcohol consumption. With an average of 20% of reproductive aged women experiencing menorrhagia, the risk of experiencing menorrhagia is decreased to 2% (odds ratio*absolute risk = relative risk: 0.106*20% = 2%) with moderate alcohol consumption in our study population.

3.2.4 Drug Use

Drug use was negatively correlated with the bleeding experienced during menstruation, where the odds of experiencing menorrhagia was decreased with moderate to high drug use (p=0.010, OR=0.210) compared to low or no drug use. With an average of 20% of reproductive aged women experiencing menorrhagia, the risk of experiencing menorrhagia is decreased to 4% (odds ratio*absolute risk = relative risk: 0.210*20% = 4%) with moderate to high drug use in our study population.

3.2.5 Stress Levels

Moderate stress was negatively correlated with bleeding experienced during menstruation, where the odds of experiencing menorrhagia was decreased with moderate stress (p=0.016, OR=0.220) compared to low stress. With an average of 20% of reproductive aged women experiencing menorrhagia, the risk of experiencing menorrhagia is decreased to 4% (odds ratio*absolute risk = relative risk: 0.220*20% = 4%) with moderate stress in our study population.

3.2.6 Length of Menstruation

Menstruation that lasted eight or more days was positively correlated with the bleeding experienced during menstruation, where the odds of experiencing menorrhagia was increased with periods that last eight or more days ($p<0.001$, OR=17.943) compared to menstruation that lasts 7 or less days. With an average of 20% of reproductive aged women experiencing menorrhagia, the risk of experiencing menorrhagia is increased to over 100% (odds ratio*absolute risk = relative risk: 17.943*20% = 100%) with menstrual events that last eight or more days long in our study population.

3.2.7 Additional Variables

Age was not correlated with menorrhagia experienced during menstruation in our study population ($p=0.102$). BMI was not correlated with menorrhagia experienced during menstruation in our study population (underweight ($p=0.106$), overweight ($p=0.130$), obese ($p=0.146$)). Hormone medication use was not correlated with menorrhagia experienced during menstruation in our study population (use of combination birth control or hormonal IUD ($p=0.060$), use of copper IUD ($p=0.604$)). Vape status was not correlated with menorrhagia experienced during menstruation in our study population ($p=0.161$). Sleep was not correlated with menorrhagia experienced during menstruation in our study population (irregular sleep or more/less than 7-9 hours ($p=0.296$), irregular sleep and more/less than 7-9 hours ($p=0.473$)). Caffeine consumption was not correlated with menorrhagia experienced during menstruation in our study population (< 2 coffees ($p=0.697$), 2-4 coffees ($p=0.644$), 4+ coffees ($p=0.273$)). Chemical exposure was not correlated with menorrhagia experienced during menstruation in our study population (moderate chemical exposure ($p=0.272$), high chemical exposure ($p=0.686$)). Smoking status was not correlated with menorrhagia experienced during menstruation in our study population ($p=0.496$). The use of psychological medications was not correlated with menorrhagia experienced during menstruation in our study population ($p=0.590$). Relationship status was not correlated with menorrhagia experienced during menstruation in our study population (dating but not living together ($p=0.560$), married/civil union/cohabitation ($p=0.865$)). Place of residence was not

correlated with menorrhagia experienced during menstruation in our study population (suburban (p=0.768), rural (p=0.084)). Previous experience with pregnancy was not correlated with menorrhagia experienced during menstruation in our study population (p=0.444). Sexual activity was not correlated with menorrhagia experienced during menstruation in our study population (p=0.224). The length of time between cycles was not correlated with menorrhagia experienced during menstruation in our study population (p=0.171). Stress levels were not correlated with menorrhagia experienced during menstruation in our study population (p=0.129).

Chapter 4: Discussion

4 Discussion

4.1 Dysmenorrhea

In our study, eight or more days of menstrual bleeding, high chemical exposure, and age were correlated with dysmenorrhea experienced in the study population.

Age seems to reduce an individual's risk of experiencing dysmenorrhea, where those who are younger have a higher risk of dysmenorrhea than those who are older. In our study population, risk of experiencing dysmenorrhea decreased from 56% to 45% as age increased. This finding is supported with previous research.[13,23,28] After a woman has experienced roughly 30 years of menstruation[28], or has given birth to children[30], menstrual pain caused by primary dysmenorrhea typically decreases. This decrease in pain is likely caused by hormone shifts that occur with age, specifically, a decrease in estrogen levels. Reduction in estrogen concentrations may reduce its stimulating effects on the endometrium, thus limiting the growth of tissues that play a role in prostaglandin synthesis.[100]

Unexpectedly, high chemical exposure also seems to reduce an individual's risk of experiencing dysmenorrhea compared to those who had low or moderate chemical exposure. In our study, risk of experiencing dysmenorrhea decreased from 56% to 15% with high chemical exposure as compared to low chemical exposure in our study population. It is surprising that we did not see a difference in effect between moderate chemical exposure in comparison to low chemical exposure, since EDC effects are known to follow a nonlinear U-shaped dose response curve.[3] All evidence previously presented seems to contradict our results. However, it is important to note that EDCs do not only affect the reproductive system, but also other systems in the body where hormones are present. One of these systems is the immune system, which is closely linked to the reproductive system. EDCs may act as estrogens or antiestrogens[138] and they can interfere with cytokine and immunoglobulin synthesis, inflammatory mediators, and activation and survival of immune cells.[139] As a result, EDCs may reduce or increase the bodies natural immune response[139], which includes the inflammatory response. Interestingly, estrogen has both pro-inflammatory and anti-inflammatory influence, which may play a role in our results. Novella *et al*.

(2012) found that the effect of estrogen is bidirectional in certain inflammatory biomarkers based on age in postmenopausal women.[140] It was found that estrogen had anti-inflammatory effects on the arteries of women in their early stages of menopause and pro-inflammatory effects on the arteries of women in late menopause, which may be associated with estrogen receptor-β expression. As far as we are aware, research has not been done on estrogen's anti-inflammatory effects on premenopausal women. As inflammation plays a role in the menstrual pain women experience, it is possible that the specific EDCs our participants were exposed to have an anti-inflammatory effect, though it is unclear what other health impacts these EDCs might have had on our participants. Further research regarding the estrogenic effects EDCs can have in pre-menopausal women is needed.

Menstruation that lasts 8 or more days seemed to increase an individual's risk of experiencing dysmenorrhea, where those that menstruate for 8 or more days have a higher risk of menorrhagia than those who menstruate for less than 8 days. In our study, risk of experiencing dysmenorrhea increased from 56% to 100% with menstruation that lasts 8 or more days in our study population. Since both heavy menstrual bleeding, either in quality or duration, and dysmenorrhea can be caused by hormone imbalances, [21,24,32,141] it does stand to reason that both menorrhagia and dysmenorrhea would occur at the same time. Excessive uterine blood loss as well as primary dysmenorrhea can both result from increased levels of PGE_2,[21,27,28,49] so it is likely that study participants who experience menstruation that lasts 8 or more days have elevated PGE_2 levels.

Of the significant variables, it seems high chemical exposure has the biggest impact on reducing pain, with increasing age having a much smaller affect. Long menstruation events that last eight or more days was the only variable found to increase the risk of experiencing pain.

Many variables tested were not correlated in our study population, although other researchers mentioned in chapter 1 have found contradictory results. These differences may be due to small sample sizes, small control sizes (or heavily skewed compared to sample size), not having a representative sample population, and counting each normalized question as just as powerful as any other for a variable. Despite reaching out to universities across Canada and multiple news

outlets, we were unsuccessful in reaching our desired sample size of roughly 30 participants per study question, only getting a fraction of the participants we had hoped for. As a result of this, control and sample sizes for some variables were skewed, where the control was typically the "null" response (e.g. low/no alcohol consumption, low stress, etc.). With a larger sample size, each variable would have had a more even representation of participants. In addition, due to most of the respondents coming from the Kamloops, British Columbia, TRU student population, this was not a representative sample of women across Canada. Therefore, the results found would only apply to the TRU female student population, though it is unclear if this sample consisted of an even mix of domestic and international students, which could have also had an impact on the results due to differences in ethnic backgrounds and socioeconomic status, among other things. In addition, since there is very little data on many of the variables studied, it was unclear if some questions should have held more weight than others when condensing related questions into a single variable. For instance, we considered the amount of alcohol consumed to have just as much weight as the age at which a participant started to consume alcohol when calculating the alcohol consumption score, when one of these might have played a greater role in the dysmenorrhea and/or menorrhagia experienced by the participant than the other.

4.2 Menorrhagia

In our study, we found that eight or more days of menstrual bleeding, cycle irregularity, moderate stress, moderate to high drug use, and moderate alcohol consumption were all correlated with menorrhagia experienced in the study population.

Moderate alcohol consumption seemed to decrease an individual's risk of experiencing menorrhagia compared to those who had low or high alcohol consumption. Though not significant, it is worth noting that high alcohol consumption exhibited a trend towards significant correlation ($p=0.052$, $OR=0.310$). In our study, risk of experiencing menorrhagia decreased from 20% to 2% with moderate alcohol consumption in our study population. Alcohol metabolism increases estrogen levels[143] and decreases progesterone levels[144] in the body, which disrupts the bodies regular hormonal fluctuations, depending on when drinking occurs during the menstrual cycle.

This disruption can lead to anovulation,[114,115] which cause also cause hypomenorrhea, or light periods.[145]

Moderate to high drug use seemed to decrease an individual's risk of experiencing menorrhagia compared to those who had low or no drug use. In our study, risk of experiencing menorrhagia decreased from 20% to 4% with moderate to high drug use in our study population. Though drug use was not an original part of our literature review due to the lack of research done on drug use and its effects on menstruation, we had decided to include questions on drug use in our survey due to Canada's current opioid crisis[146] and the recent legalization of marijuana by the Canadian Government in 2018.[147] Despite a lack of research in terms of recreational drug use and menorrhagia, there has been research that shows drug use can cause other cycle irregularities, such as anovular menstruation.[148,149] We did not specify the types of drugs used in our study and only defined drug use in general terms, including the use of prescription drugs recreationally. As such, further research should be done in this area.

Moderate stress seems to decrease an individual's risk of experiencing menorrhagia compared to those who had low or high stress. Though not significant, it is worth noting that the high stress variable had a small sample size (n=19) compared to moderate stress (n=122) and the control, low stress (n=37), which is likely the cause for high stress not being significantly correlated. In our study, risk of experiencing menorrhagia decreased from 20% to 4% with moderate stress in our study population. Previous researchers have found that stress levels can cause anovulation and changes in menstrual cycle length.[118] The most likely cause of the reduction in bleeding is the stress hormone cortisol, which has already been shown to cause irregular or missed periods,[150] although the affect of cortisol is dependent on when during the menstrual cycle stress occurs.[151] For instance, the timing of the stress might cause a delay in ovulation as well as the menstrual cycle, it may cause a disruption in flow, or, in prolonged cases of stress, may lead to the absence of a period all together.[151]

Cycle irregularity seemed to increase an individual's risk of experiencing menorrhagia, where those who have more irregular cycles have a higher risk of menorrhagia. In our study, risk of experiencing menorrhagia increased from 20% to 90% with irregular cycles in our study

population. One of the most common causes of menorrhagia is irregular ovulation, which in turn causes cycle irregularity.[152] Both cycle irregularity and menorrhagia are often treated using hormone therapy.[152] So it is likely that cycle irregularity and menorrhagia seen in our participants is a result of hormone imbalances. [40,47-50]

Menstruation that lasts 8 or more days seems to increase an individual's risk of experiencing menorrhagia, where those that menstruate for 8 or more days have a higher risk of menorrhagia than those who menstruate for less than 8 days. In our study, risk of experiencing menorrhagia increased from 20% to certainty with menstruation that lasts 8 or more days in our study population. This variable was used as a control, where we expected to see an increase in bleeding experienced the more days a woman experienced menstrual bleeding.

Of the significant variables, it seems moderate alcohol consumption has the biggest impact on reducing menstrual bleeding, followed by moderate to high drug use and moderate stress. It is important to note that there may be a link between alcohol consumption and the stress levels reported, as alcohol consumption has been shown to dampen the stress response.[153] This may be one reason why alcohol consumption has a greater impact on reducing menstrual bleeding in our participants, as a lower stress level may have been reported in those who moderately consumed alcohol, though further analysis would be needed to confirm this. Alcohol may also have a more disruptive effect on the endocrine system than the stress response does. Long menstruation events that last eight or more days had the greatest impact on increasing menstrual bleeding, followed by cycle irregularity.

Many variables tested were not significantly correlated with menorrhagia in our study population, although other researchers mentioned in chapter 1 have found contradictory results. These differences may be due to small sample sizes, small control sizes (or heavily skewed compared to sample size), not having a representative sample population, and counting each normalized question as just as powerful as any other for a variable, all of which were discussed in the previous section on dysmenorrhea.

4.3 Strengths and Limitations

Our greatest limitation in this research study was our broad topic coverage, which did not allow us to go in depth in the variables that were found to be significant. Future research would be required to look at significant variables in more depth to determine exact causes for our results. In addition, some of the survey questions were on topics regarding the participants past experiences or family history (such as if they had been exposed to chemicals at a young age, if there is a history of dysmenorrhea in the family, etc.), where a majority of participants were unsure, and thus some questions had to be cut from our analysis. Other questions were on sensitive topics, where, even in an anonymous study, participants might not have felt comfortable sharing information and there is a chance answers are not completely accurate. Besides this, self-reporting also could impact the accuracy of information collected. Our study design was also a limitation, where we were only able to consider correlations and not causation. Our correlational study was limited by the use of non-validated measures and a limited sample size that was required for logistic regression without collapsing categories. Despite these limitations, our study considered many different variables that have not been considered in a single study, which may help encourage further research in a field where women's studies are limited.

4.4 Future Directions

Our study is the first study, to our knowledge, that looks at the effects of various factors in addition to chemical exposure.

We hoped to collect information on whether there were known chemical exposures during childhood or at work, home, or school, but many participants were unsure of their exposures in these areas. This could be due to a lack of knowledge of an individual's own upbringing but is most likely due to the fact individuals are exposed to chemicals they are not even aware of in daily life through seemingly insignificant means, such as touching or handling receipt paper.[142] Prenatal and early childhood exposure can have long lasting effects on health later in life, so not tracking this information left a gap in our research. The timing of chemical exposures is extremely important when looking at their effects on the body, where the human reproductive system is

especially vulnerable to chemicals during critical windows of development,[3] including infancy, childhood, and adolescence, due to the many developmental changes that occur during this time.[11] As it is possible for long term health effects to arise even after harmful chemical exposure as a zygote,[1] further research is required that takes a more in depth look at prenatal and early childhood exposure to determine the true effects on the female reproductive system, including the menstrual cycle.

We hope this study can act as a steppingstone for future research that looks at this topic in more detail.

Chapter 5: Conclusion

5 Conclusion

In our study, we found that high chemical exposure does have an impact on the female reproductive system, where high chemical exposure decreased the risk of experiencing dysmenorrhea. We also found that, of the additional factors that were significant, moderate alcohol consumption had the biggest impact on reducing menstrual bleeding, followed by moderate to high drug use and moderate stress. Other factors that played a role in menstrual irregularities included increasing age decreases the risk of dysmenorrhea, long menstruation events lasting eight or more days increase the risk of dysmenorrhea and menorrhagia, and irregular cycles increase the risk of menorrhagia.

Our study aims to encourage future research in the field of women's health, where research in this area is often limited, especially regarding research looking at women's health under a more holistic lens.

Chapter 6: References

6 References

1. *Environmental Impacts on Reproductive Health and Fertility*. (Cambridge University Press, 2010). doi:10.1017/CBO9780511674686.
2. (ACOG) American College of Obstetrics and Gynecology. Exposure to toxic environmental agents. Committee Opinion NO 575. *Obstetrics and Gynecology.* **122**, 931–935 (2013).
3. UNEP & WHO. State of the science of endocrine disrupting chemicals - 2012. An assessment of the state of the science of endocrine disruptors. *UNEP & WHO*. (2013).
4. DeMatteo, R.S. *et al.* Chemical exposures of women workers in the plastics industry with particular reference to breast cancer and reproductive hazards. *New Solutions.* **22**, 427–448 (2012).
5. Endocrine Society. *Endocrine Disrupting Chemicals*. (2009).
6. Thomas Zoeller, R. *et al.* Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society. *Endocrinology.* **153**, 4097–4110 (2012).
7. The American College of Obstetricians and Gynecologists. *Companion Piece to Committee Opinion #575 Exposure to Toxic Environmental Agents.* (2013).
8. Mnif, W. *et al.* Effect of endocrine disruptor pesticides: a review. *International Journal of Environmental Research and Public Health.* **8**, 2265–2303 (2011).
9. Vitku-Kubatova, J. *et al.* Endocrine disruptors of the bisphenol and paraben families and bone metabolism. *Physiological Research.* **67**, S455–S464 (2018).
10. Diamanti-Kandarakis, E. *et al.* Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocrine Reviews.* **30**, 293–342 (2009).
11. Sutton, P. *et al.* Toxic environmental chemicals: The role of reproductive health professionals in preventing harmful exposures. *American Journal of Obstetrics and Gynecology.* **207**, 164–173 (2012).
12. Gore, A. Organocholrine pesticides directly regular gonadotropin-releasing hormone gene expression and biosynehtsis in the GT1-7 hypothalamic cell line. *Molecular and Cellular Endocrinology*. **192**: 157-170 (2002).
13. Genuis, S.J, Beesoon, S, Lobo, R.A, & Birkholz, D. Human elimination of phthalate compounds: Blood, urine, and sweat (BUS) study. *The Scientific World Journal.* **2012**, 1–10 (2012).
14. DeMatteo, R. Chemical exposure and plastics production: issues for women's health. *National Network on Environments and Women's Health*. (2011).

15. McCormick, K & Abdel-Rahman, MS. The role of testosterone in trichloroethylene penetration in vitro. *Environ. Res*. **54**, 82-92 (1991).

16. Gao, C. J. & Kannan, K. Phthalates, bisphenols, parabens, and triclocarban in feminine hygiene products from the United States and their implications for human exposure. *Environment International.* **136**, 105465 (2020).

17. Ritter R, Scheringer M, MacLeod M, Moeckel C, Jones KC, Hungerbuhler K. Intrinsic human elimination half-lives of polychlorinated bisphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom. *Environmental Health Perspectives*. **119**(2): 225-231 (2011).

18. Woodruff, TJ, Zota, AR, & Schwartz, JM. Environmental chemicals in pregnant women in the United Statse: NHANES 2003-2004. *Environ. Health Perspect*. **199**, 878-885 (2011).

19. Mendola, P, Messer, LC, & Rappazzo, K. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. *Fertil. Steril*. **89**(2 Suppl), e81-94. (2008).

20. Saei Ghare Naz, M. *et al.* The effect of micronutrients on pain management of primary dysmenorrhea: a systematic review and meta-analysis. *Journal of Caring Sciences.* **9**, 47–56 (2020).

21. Tu, F, Bettendorf, B, & Shay, S. Dysmenorrhea: contemporary perspectives. *PAIN Clinical Updates.* **15**, 1–4 (2007).

22. Grandi, G. *et al.* Prevalence of menstrual pain in young women: what is dysmenorrhea? *Journal of Pain Research.* **5**, 169–174 (2012).

23. Berkley, K. Primary dysmenorrhea: an urgent mandate. *Pain.* **21**, 1–8 (2013).

24. Mohebbi Dehnavi, Z, Jafarnejad, F, & Kamali, Z. The effect of aerobic exercise on primary dysmenorrhea: a clinical trial study. *Journal of Education and Health Promotion.* **7**, 1–6 (2018).

25. Ramazanzadeh, F, Tavakolianfar, T, Shariat, M, Firuzabadi S.J.P, & Hagholahi, F. Levonorgestrel-releasing IUD versus copper IUD in control of dysmenorrhea, satisfaction and quality of life in women using IUD. *Iranian Journal of Reproductive Medicine.* **10**, 41–46 (2012).

26. Dmitrovic, R, Kunselman, A.R., & Legro, R.S. Continuous compared with cyclic oral contraceptives for the treatment of primary dysmenorrhea: a randomized controlled trial. *Obstetrics and Gynecology.* **119**, 1143–1150 (2012).

27. Motahari-Tabari, N, Shirvani, M.A, & Alipour, A. Comparison of the effect of stretching exercises and mefenamic acid on the reduction of pain and menstruation characteristics in primary dysmenorrhea: A randomized clinical trial. *Oman Medical Journal.* **32**, 47–53 (2017).

28. Proctor, M. & Farquhar, C. Diagnosis and management of dysmenorrhoea. *British Medical Journal.* **332**, 1134–1138 (2006).

29. Nieczuja-Dwojacka, J, Borowska, B, Janiszewska, A, & Kozieł, S. Socioeconomic factors and lifestyle affecting the variability of menstrual cycle characteristics in women from Central Poland. *Anthropological Review.* **82**, 327–338 (2019).

30. Latthe, P, Champaneria, R, & Khan, K. Dysmenorrhea. *American Family Physician.* **85**, 386–387 (2012).

31. Smith, K. *et al.* Urinary paraben concentrations and ovarian aging among women from a fertility center. *Environmental Health Perspectives*. **121**, 1299–1305 (2013).

32. Atta, K, Jawed, S, & Zia, S. Correlating primary dysmenorrhea with its stressors: a cross sectional study investigating the most likely factors of primary dysmenorrhea and its effects on quality of life and general well being. *Journal of University Medical and Dental College.* **7**, 43–51 (2016).

33. Widmaier, E.P., Raff, H, & Strang, K.T. Vander's Human Physiology: The mechanisms of body function. (McGaw Hill Education, 2016).

34. Powell, A, Chan, WY, Alvin P, & Litt, I. Menstrual-PGF2α, PGE2, and TXA2 in normal and dysmenorrheic women and their temporal relationship to dysmenorrhea. *Prostaglandins*. **29** (2), 273-289 (1985).

35. Taylor, H, Pal, L, & Seli, E. *Speroff's Clinical Gynecologic Endocrinology and Infertility*. 9th ed. Philadelphia: Lippincott Williams & Wilkins (2019).

36. Fajrin, I, Alam, G, & Usman, A. Prostaglandin level of primary dysmenorrhea pain sufferers. *Enfermeria Clinica*. **30** (2), 5-9 (2020).

37. Ju, H., Jones, M. & Mishra, G. D. Smoking and trajectories of dysmenorrhoea among young Australian women. *Tobacco Control.* **25**, 195–202 (2016).

38. Gosselin, M. (Editor). Menstrual cycle: signs and symptoms, psychological/behavioural changes and abnormalities. (Nova Biomedical, 2013).

39. Berkley, K.J. & McAllister, S.L. Don't dismiss dysmenorrhea! *Pain.* **152**, 1940–1941 (2011).

40. Burns, S. & Parapia, L.A. Haematological causes of menorrhagia. *Reviews in Gynaecological Practice.* **5**, 8–14 (2005).

41. Knudtson, J. & McLaughlin, J. Female reproductive endocrinology. *Merck Manual Professional Version.* https://www.merckmanuals.com/en-ca/professional/gynecology-and-obstetrics/female-reproductive-endocrinology/female-reproductive-endocrinology (2019).

42. Thiyagarajan, D, Basit, H, & Jeanmonod, R. Physiology, menstrual cycle. *StatPearls [Internet]*. (StatPearls Publishing, 2020).

43. Prior, J. Very heavy menstrual flow. Cemcor. https://www.cemcor.ubc.ca/resources/very-heavy-menstrual-flow (2017).

44. Trasi, S, Pathare, A, Shetty, S, Gosh, K, Salvi, V, & Mohanty, D. The spectrum of bleeding disorders in women with menorrhagia: a report from Western India. *Ann Hematol*. **84**: 339-342 (2005).

45. Banu, F, Pandit, U, Ahmad, S, & Singh, G. Assessment of causes and clinical symptoms of menorrhagia and its co-relation with BMI in western Nepalese women - an observational study. *Journal of Krishna Institute of Medical Sciences University.* **6**, 42–48 (2017).

46. Bryant-Smith, A.C, Lethaby, A, Farquhar, C, & Hickey, M. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews.* **2018**, 1–79 (2018).

47. Gleeson, N. Cyclic changes in endometrial tissue plasminogen activator and plasminogen activator inhibitor type 1 in women with normal menstruation and essential menorrhagia. *Am J Obstet Gynecol*. **171** (1), 178-183 (1994).

48. Tsang, B, Domingo, M, Spence, J, Garner, P, Dudley, D, & Oxorn, H. Endometrial prostaglandins and menorrhagia: influence of a prostaglandin synthetase inhibitor in vivo. *Can J Physiol. Pharmacol*. **65** (10), 2081-2084 (1987).

49. Smith, SK, Abel, MH, Kelly, RW, & Baird, T. Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. *Br. J. Obstet. Gynaecol*. **88**, 434 (1981a).

50. Smith, SK, Kelly, RW, Abel, MH, & Baird, T. A role for prostacyclin (PGi2) in excessive menstrual bleeding. *Lancet.* **1**(8219), 522-524 (1981b).

51. Beric, M. & Fraser, I. Immunology of normal and abnormal menstruation. *Women's Health (Lond).* **9** (4), 387-395 (2013).

52. Eckert-Lind, C, Busch, AS, Petersen, JH, *et al*. Worldwide secular trends in age at pubertal onset assessed by breast development among girls: a systematic review and meta-analysis. *JAMA Pediatr*. **174** (4), e195881 (2020).

53. Liu, T. *et al.* Effects of di-(2-ethylhexyl) phthalate on the hypothalamus-uterus in pubertal female rats. *International Journal of Environmental Research and Public Health.* **13**, 1130 (2016).

54. Rowland, A.S. *et al.* Influence of medical conditions and lifestyle factors on the menstrual cycle. *Epidemiology*. **13**, 668–674 (2002).

55. Roth CL, DiVall S. Consequences of early life programing by genetic and environmental influences: a synthesis regarding pubertal Timing. *Endocr Dev.* **29**:134–52 (2016).

56. Martini, F, Nath, J, & Bartholomew, E. Fundamentals of anatomy and physiology. (Peason Education Inc., 2018).

57. Gao, C.J, Wang, F, Shen, H.M, Kannan, K, & Guo, Y. Feminine hygiene products - a neglected source of phthalate exposure in women. *Environmental Science and Technology.* **54**, 930–937 (2020).

58. Reed, B. & Bruce, R. The normal menstrual cycle and the control of ovulation. *Endotext [Internet]*. (2018).

59. Jacobson, M.H. *et al.* Thyroid hormones and menstrual cycle function in a longitudinal cohort of premenopausal women. *Paediatric and Perinatal Epidemiology.* **32**, 225–234 (2018).

60. Holesh, J, Bass, A. & Lord, M. Physiology, ovulation. *StatPearls [Internet]*. (2021).

61. Rowdhwal, S. & Chen, J. Toxic effects of Di-2-ethylhexyl Phthalate: An overview. *BioMed Research International.* **2018**, 1–10 (2018).

62. Bulun, S.E. *et al.* Endometriosis. *Endocrine Reviews.* **40**, 1048–1079 (2019).

63. Smith, RP. The role of prostaglandins in dysmenorrhea and menorrhagia. *Dysmenorrhea and Menorrhagia: A Clinician's Guide*. 75-88 (Springer, 2018).

64. Rudel, R.A. *et al.* Food packaging and bisphenol A and bis(2-ethyhexyl) phthalate exposure: findings from a dietary intervention. *Environmental Health Perspectives.* **119**, 914–920 (2011).

65. Chi, Y, Huang, Q, Zhang, H, Chen, Y, & Dong, S. In situ combined chemical and biological assessment of estrogenic pollution in a water recycling system. *Journal of Environmental Sciences (China).* **43**, 216–223 (2016).

66. Ji, K, Lim Kho, Y, Park, Y, & Choi, K. Influence of a five-day vegetarian diet on urinary levels of antibiotics and phthalate metabolites: a pilot study with "Temple Stay" participants. *Environmental Research.* **110**, 375–382 (2010).

67. Park, C.J. *et al.* Sanitary pads and diapers contain higher phthalate contents than those in common commercial plastic products. *Reproductive Toxicology.* **84**, 114–121 (2019).

68. Sathyanarayana, S. *et al.* Unexpected results in a randomized dietary trial to reduce phthalate and bisphenol A exposures. *Journal of Exposure Science and Environmental Epidemiology.* **23**, 378–384 (2013).

69. Schmidt, J.S, Schaedlich, K, Fiandanese, N, Pocar, P, & Fischer, B. Effects of Di(2-ethylhexyl) phthalate (DEHP) on female fertility and adipogenesis in C3H/N Mice. *Environmental Health Perspectives.* **120**, 1123–1129 (2012).

70. Vogel, S.A. The politics of plastics: the making and unmaking of bisphenol A "safety." *American Journal of Public Health.* **99 Suppl 3**, 559–567 (2009).

71. Rytel, L, Gonkowski, S, Janowski, T, Wojtkiewicz, J, & Pomianowski, A. The effects of bisphenol A (BPA) on sympathetic nerve fibers in the uterine wall of the domestic pig. *Reproductive Toxicology*. **84**, 39–48 (2019).

72. Qiu, W. *et al.* The occurrence, potential toxicity, and toxicity mechanism of bisphenol S, a substitute of bisphenol A: a critical review of recent progress. *Ecotoxicology and Environmental Safety*. **173**, 192–202 (2019).

73. DeVito, M.J. & Schecter, A. Exposure assessment to dioxins from the use of tampons and diapers. *Environmental Health Perspectives.* **110**, 23–28 (2002).

74. Woo, J. *et al.* Systematic Review on Sanitary Pads and Female Health. *The Ewha Medical Journal*. **42**, 25 (2019).

75. Hait, A. & Powers, S.E. The value of reusable feminine hygiene products evaluated by comparative environmental life cycle assessment. *Resources, Conservation and Recycling.* **150**, 104422 (2019).

76. Halden, R.U. *et al.* The Florence statement on triclosan and triclocarban. *Environmental Health Perspectives.* **125**, 1–13 (2017).

77. Lin, N. *et al.* Volatile organic compounds in feminine hygiene products sold in the US market: A survey of products and health risks. *Environment International.* **144**, 105740 (2020).

78. Adeniran, J, Yusuf, R, Mustapha, S, & Sonibare, J. Exposure to total volatile organic compounds from household spray products. *Environmental Research, Engineering, and Management*. **73** (4), 21-30 (2017).

79. Women's Voices for the Earth (WVE). Testing reveals toxic chemicals in Procter & Gamble's Always pads. *WVE*. https://womensvoices.org/2014/10/13/testing-reveals-toxic-chemicals-in-procter-gambles-always-pads/ (2014).

80. Smith-Spangler, C. *et al.* Are organic foods safer or healthier than conventional alternatives? A systematic review. *Annals of Internal Medicine.* **157**, 348–366 (2012).

81. Environmental Justice Foundation (EJF). The deadly chemicals in cotton. *EJF*. (2007).

82. Lu, C, Kedan, G, & Fisker-Andersen, J. *et al*. Multipathway organophosphorus pesticide exposures of preschool children living in agricultural and nonagricultural communities. *Environ Res*. 96, 283-289 (2004).

83. Nicole, W. A question for women's health: Chemicals in feminine hygiene products and personal lubricants. *Environmental Health Perspectives.* **122**, 70–75 (2014).

84. ANSES. OPINION of the French Agency for Environmental and Occupational Health Safety on the safety of 60eminine hygiene products. *Public Health* (2018).

85. Cobellis L, Colacurci N, Trabucco E, Carpentiero C, Grumetto L. Measurement of bisphenol A and bisphenol B levels in human blood sera from healthy and endometriotic women. *Biomed Chromatogr*. **23**(11):1186–1190 (2009).

86. Takeuchi T, Tsutsumi O, Ikezuki Y, Takai Y, & Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. *Endocrine Journal* **51**(2): 165-169, (2004).

87. World Health Organization (WHO). Dioxins and their effects on human health. *WHO* (2016). Available at: https://www.who.int/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health

88. Schettler, T, Solomon, G, Kaplan, J, Valenti, M, Burns, P, & Huddle, A. Generations at risk: how environmental toxicants may affect reproductive health in California. *Physicians for Social Responsibility and The California Public Interest Research Group Charitable Trust*. (1997).

89. Ouyang, F, Perry, MJ, Venners, SA, Chen, C, Wang, B, Yang, F, *et al*. Serum DDT, age at menarche, and abnormal menstrual cycle length. *Occup Environ Med*. **62**:878–84 (2005).

90. Farr, SL, Cooper, GS, Cai, J, Savitz, DA, & Sandler, DP. Pesticide use and menstrual cycle characteristics among premenopausal women in the Agricultural Health Study. *Am J Epidemiol*. **160**:1194–204 (2004).

91. Windham, GC, Lee, D, Mitchell, P, Anderson, M, Petreas, M, & Lasley, B. Exposure to organochlorine compounds and effects on ovarian function. *Epidemiology*. **16**:182–90 (2005).

92. Perry, MJ, Ouyang, F, Korrick, SA, Venners, SA, Chen, C, Xu, X, *et al*. A prospective study of serum DDT and progesterone and estrogen levels across the menstrual cycle in nulliparous women of reproductive age. *Am J Epidemiol*. **164**:1056–1064 (2006).

93. Akkina, J, Reif, J, Keefe, T, & Bachand, A. Age at natural menopause and exposure to organochlorine pesticides in Hispanic women. *J Toxicol Environ Health.* **67**:1407–1022 (2004).

94. Bae, J, Kwon, H, & Kim, J. Safety evaluation of absorbent hygiene pads: A review on assessment framework and test methods. *Sustainability (Switzerland).* **10**, 1–17 (2018).

95. Huang, Q. *et al.* Dioxin-like rather than non-dioxin-like PCBs promote the development of endometriosis through stimulation of endocrine–inflammation interactions. *Archives of Toxicology.* **91**, 1915–1924 (2017).

96. Cooper G, Klebanoff M, Promislow J, Brock J, & Longnecker M. Polychlorinated bisphenyls and menstrual cycle characteristics. *Epidemiology*. **16**(2):191-200 (2005).

97. Lu, C. *et al.* Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. *Environmental Health Perspectives.* **114**, 260–263 (2006).

98. Zhang, Y. *et al.* Oral intake exposure to phthalates in vegetables produced in plastic greenhouses and its health burden in Shaanxi province, China. *Science of the Total Environment.* **696**, 133921 (2019).

99. Barnard, N.D, Scialli, A.R., Hurlock, D, & Bertron, P. Diet and sex-hormone binding globulin, dysmenorrhea, and premenstrual symptoms. *Obstetrics and Gynecology*. **95**, 245–250 (2000).

100. Barnard, N, Scialli, A.R., Bertron, P, Hurlock, D, & Edmunds, K. Acceptability of a therapeutic low-fat, vegan diet in premenopausal women. *Journal of Nutrition Education and Behavior*. **32**, 314–319 (2000).

101. Ricciotti, E. & Fitzgerald, G.A. Prostaglandins and inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology*. **31**, 986–1000 (2011).

102. Isaza, A. Natural interventions for dysmenorrhea as an alternative to NSAIDS. Commentary on the available research. *Nutrition Perspectives: Journal of the Council of Nutrition of the American Chiropractic Association.* 29–31 (2019).

103. Guarda A. Eating disorders. *American Psychiatric Association*. https://www.psychiatry.org/patients-families/eating-disorders/what-are-eating-disorders (2021).

104. Huhmann, K. Menses requires energy: a review of how disordered eating, excessive exercise, and high stress lead to menstrual irregularities. *Clinical Therapeutics.* **42**, 401–407 (2020).

105. Perkins, R, Hall J, & Martin, K. Neuroendocrine abnormalities in hypothalamic amenorrhea: spectrum, stability, and response to neurotransmitter modulation. *The Journal of Clinical Endocrinology & Metabolism*. **85** (6), 1905-1911 (1999).

106. Dars, S, Sayed, K, & Yousufzai, Z. Relationship of menstrual irregularities to BMI and nutritional status in adolescent girls. *Pakistan Journal of Medical Sciences.* **30**, 140–144 (2014).

107. Kwak, J.I, Nam, S.H, Kim, D, & An, Y.J. Comparative study of feminine hygiene product regulations in Korea, the European Union, and the United States. *Regulatory Toxicology and Pharmacology.* **107**, 104397 (2019).

108. La Merrill, M. *et al.* Toxicological function of adipose tissue: Focus on persistent organic pollutants. *Environmental Health Perspectives.* **121**, 162–169 (2013).

109. Jackson, E, Shoemaker, R, Larian, N, & Cassis, L. Adipose tissue as a site of toxin accumulation. *Comprehensive Physiology.* **7**, 1085–1135 (2018).

110. Jandacek, R.J. & Tso, P. Factors affecting the storage and excretion of toxic lipophilic xenobiotics. *Lipids.* **36**, 1289–1305 (2001).

111. Mariam, A, Ali, HA, Babar, M, Saroona, H, Naveen, F, Muzzammil, EM *et al*. Clinical pattern and spectrum of endometrial pathologies in patients with abnormal uterine bleeding in Pakistan:

need to adopt a more conservative approach to treatment. *BMC Women's Health BMC Series*. **14**:132 (2014).

112. Liu, Y, Gold, E.B., Lasley, B.L, & Johnson, W.O. Factors affecting menstrual cycle characteristics. *American Journal of Epidemiology.* **160**, 131–140 (2004).

113. Parazzini, F. *et al.* Cigarette smoking, alcohol consumption, and risk of primary dysmenorrhea. *Epidemiology*. **5**, 469–472 (1994).

114. Augustyńska, B. *et al.* Menstrual cycle in women addicted to alcohol during the first week following drinking cessation - changes of sex hormones levels in relation to selected clinical features. *Alcohol and Alcoholism.* **42**, 80–83 (2007).

115. Emanuele, M.A., Wezeman, F, & Emanuele, N. Alcohol's effects on female reproductive function. *Alcohol Research and Health.* **26**, 274–281 (2002).

116. Schliep, K.C. *et al.* Alcohol intake, reproductive hormones, and menstrual cycle function: a prospective cohort study. *American Journal of Clinical Nutrition.* **102**, 933–942 (2015).

117. Baker, F.C. & Driver, H.S. Circadian rhythms, sleep, and the menstrual cycle. *Sleep Medicine.* **8**, 613–622 (2007).

118. Figà-Talamanca, I. Occupational risk factors and reproductive health of women. *Occupational Medicine.* **56**, 521–531 (2006).

119. Yang C, Yaniger S, Jordan C, Klein D, & Bittner G. Most plastic products release estrogenic chemicals: A potential health problem that can be solved. *Environmental Health Perspectives* **119**(7): 989-996 (2011).

120. Gaudin R, Marsan P, Robert A, Ducos P, Pruvost A, Levi M, & Bouscaillou P. Biological monitoring of occupational exposure to di(2-ethylhexyl)phthalate: Survey of workers exposed to plastisols. *International Archives of Occupational and Environmental Health* **8**:959-966 (2008).

121. Scott, D. (Editor). Our chemical selves. (UBC Press, 2015).

122. Banikarim, C, Chaco, MR, & Kelder, SH. Prevalence and impact of dysmenorrhea on Hispanic female adolescence. *Arch Pediatr Adolesc Med*. **154**, 1226-1229 (2000).

123. Kwak, Y, Kim, Y, & Baek, K. Prevelance of irregular menstruation according to socioeconomic status: a population-based nationwide cross-sectional study. *PLoS ONE* **14** (3), e0214071. (2019).

124. De Sanctis, V, Soliman, AT, Elsedfy, H, Soliman, NA, Soliman, R,E, & Kholy, M. Dysmenorrhea in adolescents and young adults: a review in different country. *Acta Bio Medica Atenei Parmensis* **87**:233-246 (2016).

125. American Lung Association (ALA). Disparities in the impact of air pollution. *ALA*. https://www.lung.org/clean-air/outdoors/who-is-at-risk/disparities (2022).

126. Yamamoto, K, Okazaki, A, Sakamoto, Y, & Funatsu, M. The relationship between premenstrual symptoms, menstrual pain, irregular menstrual cycles, and psychological stress among Japanese college students. *Journal of Physiological Anthropology*. **28**, 129-136 (2009).

127. Patel, V, Tanksale, V, Sahasrabhojanee, M, Gupte, S, & Nevrekar, P. The burden and determinants of dysmenorrhoea: a population-based survey of 2262 women in Goa, India. *BJOG: An International of Obstetrics and Gynecology*. **113**, 453-463 (2006).

128. Godfrey, E.M, Folger, S.G, Jeng, G, Jamieson, D.J, & Curtis, K.M. Treatment of bleeding irregularities in women with copper-containing IUDs: a systematic review. *Contraception.* **87**, 549–566 (2013).

129. Oladosu, F.A., Tu, F.F. & Hellman, K.M. Nonsteroidal anti-inflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment. *American Journal of Obstetrics and Gynecology*. **218**, 390–400 (2018).

130. Brouard, R, Bossmar, T, Fournié-Lloret, D, Chassard, D, & Åkerlund, M. Effect of SR49059, an orally active V1a vasopressin receptor antagonist, in the prevention of dysmenorrhoea. *BJOG: An International Journal of Obstetrics and Gynaecology*. **107**, 614–619 (2000).

131. Mutlu, I, Demir, A, & Mutlu, M.F. Can uterine artery Doppler parameters predict copper intrauterine device-induced side effects? *European Journal of Contraception and Reproductive Health Care.* **19**, 51–56 (2014).

132. Best Practice Advocacy Centre New Zealand (BPAC). Depot medroxyprogesterone acetate (DMPA) injections: an intermediate option. *BPAC NZ.* 25–29 https://bpac.org.nz/2019/contraception/depot.aspx (2019).

133. Rizk, B. *et al.* Recurrence of endometriosis after hysterectomy. *Facts, Views & Vision in ObGyn.* **6**, 219–27 (2014).

134. Nasir, S, Khan, M.M., Ahmed, S, Alam, S, & Ziaullah, S. Role of thyroid dysfunction in infertile women with menstrual disturbances. *Gomal Journal of Medical Sciences.* **14**, 20–24 (2016).

135. Dittrich, R. *et al.* Thyroid hormone receptors and reproduction. *Journal of Reproductive Immunology*. **90**, 58–66 (2011).

136. Krassas, G.E. Thyroid disease and female reproduction. *Fertility and Sterility*. **74**, 1063–1070 (2000).

137. Centers for Disease Control and Prevention (CDC). Heavy menstrual bleeding. *CDC.* (2022). https://www.cdc.gov/ncbddd/blooddisorders/women/menorrhagia.html

138. Ahmed S. The immune system as a potential target for environmental estrogens (endocrine disrupters): a new emerging field. *Toxicology* **150**:191e206 (2000).

139. Kuo CH, Yang SN, Kuo PL, & Hung CH. Immunomodulatory effects of environmental endocrine disrupting chemicals. *Kaohsiung J Med Sci*. **28**(7, Suppl):S37–S42 (2012).

140. Novella S, Heras M, Hermenegildo C, & Dantas AP. Effects of estrogen on vascular inflammation: A matter of timing. *Arteriosclerosis, Thrombosis, and Vascular Biology*. **32**(8): 2035-2042 (2012).

141. The Society of Obstetricians and Gynaecologists of Canada (SOGC). Abnormal pain and menstrual bleeding: Hormonal causes of HMB. *SOGC*. (2003). https://www.yourperiod.ca/abnormal-pain-and-menstrual-bleeding/heavy-menstrual-bleeding/hormonal-causes-of-heavy-menstrual-bleeding/

142. Bernier, M. & Vandenberg, L. Handling of thermal paper: Implications for dermal exposure to bisphenol A and its alternatives. *PLoS One.* **12**(6): e0178449. (2017).

143. Mendelson, J, Mello, N, Cristofaro, P, Ellingboe, J, Skupny, A, Palmieri, S, Benedikt, R., and Schiff, I. Alcohol effects on naloxone-stimulated luteinizing hormone, prolactin and estradiol in women. *Journal of Studies on Alcohol* **48**, 287–294 (1987).

144. Sarkola T, Makisalo H, Fukunaga T, Eriksson C. Acute effect of alcohol on estradiol, estrone, progesterone, prolactin, cortisol, and luteinizing hormone in premenopausal women. *Alcohol Clin Exp Res*. **23**(6): 976-982 (1999).

145. SheCares Editorial Team. Hypomenorrhea: Light periods. *She Cares*. (2022). https://www.shecares.com/menstruation/hypomenorrhea

146. Government of Canada. Canada's opioid crisis (fact sheet). *Government of Canada*. (2019). https://www.canada.ca/en/health-canada/services/publications/healthy-living/canada-opioid-crisis-fact-sheet.html

147. Health Canada. Taking stock of progress: Cannabis legalization and regulation in Canada. *Government of Canada*. 2022. https://www.canada.ca/en/health-canada/programs/engaging-cannabis-legalization-regulation-canada-taking-stock-progress/document.html

148. Shen, W, Zhang, Y, Li, L, Liu, Y, Huang, X, Chen, L, & Zhou, W. Long-term use of methamphetamine disrupts the menstrual cycles and hypothalamic-pituitary-ovarian axis. *J Addict Med*. **8**(3): 183-188. (2014).

149. Centre of Excellence for Women's Health (CEWH). Women and prescription opioids. *CEWH*. (2017). https://cewh.ca/wp-content/uploads/2018/03/InfoSheet-Women-Opioids0308.pdf

150. Sonnier, S. How stress can affect your menstrual cycle. *UTHealth Houston*. (2022). https://www.utphysicians.com/how-stress-can-affect-your-menstrual-cycle/

151. Elara Care. How cortisol affects women's health and the menstrual cycle. Elara Care. (2023). https://elara.care/hormones/how-cortisol-affects-womens-health-and-the-menstrual-cycle/#:~:text=Stress%20can%20make%20your%20periods,ovulation%2C%20anovulation%2C%20or%20amenorrhea.

152. Gynecological & Obstetric Associates, SC. Heavy and irregular menstrual bleeding. *Gynecological & Obstetric Associates, SC*. Accessed 2023. https://www.gyneandob.com/patient-services/gynecological-care/heavy-and-irregular-menstrual-bleeding#:~:text=The%20most%20common%20cause%20of,time%20or%20be%20unusually%20heavy.

153. Levenson RW, Sher KJ, Frossman LM, Newman J, Newlin DB. Alcohol and stress response dampening: pharmacological effects ,expectancy, and tension reduction. Journal of Abnormal Psychology. 1980. 89(4): 528-538.

Chapter 7: Appendix

7 *Appendix*

A1. Recruitment email.

Hello,

My name is Kyley Drach and I am a Master's student at Thompson Rivers University in Kamloops, British Columbia. I am doing research of chemical exposure and its effects on the female reproductive system. My study is looking at various areas of potential chemical exposure in a woman's life and how this can impact her reproductive health. If it is found that chemical exposure can influence female reproductive health, we will aim to determine which routes of chemical exposure seem to have the greatest effect.

I am seeking female participants for this study between the ages of 18 to 35 who still currently experience a menstrual cycle. The study consists of a one-time survey, which will take between 45-60 minutes to complete. The survey does not need to be completed in one sitting and responses can be edited until the survey is submitted. Questions include the areas of reproductive health, product use, and general health.

I am wondering if you would be able to share this information within your institution to assist in recruitment of women across Canada. I have provided the link to the survey below, where more information will also be provided regarding the study.

https://www.surveymonkey.ca/r/chemical_exposure

If you have any questions about this study, please feel free to contact me at:
Kyley-drach@mytru.ca

Thank you for your time and assistance,
Kyley Drach

A2. Consent form.

Consent Form

This study is entitled Chemical Exposure and Female Reproductive Health and will be conducted by Kyley Drach (email: kyley-drach@mytru.ca). This study examines various areas of potential chemical exposure in a woman's life and how this can impact her reproductive health. If it is found that chemical exposure can influence reproductive health, we will aim to determine which routes of chemical exposure seem to have the greatest effect. There is no direct benefit to you by partaking in this study, but the data collected will provide researchers with a better understanding of whether chemical exposure is related to women's reproductive health. This information can help to shape future research projects related to this topic.

As a participant in this study, you will be asked to complete the following one-time survey, which will take between 45-60 minutes to complete. You are not required to complete the entire survey in one sitting, and you may come back later to edit your questions or continue the survey. There are a total of 6 pages with various numbers of questions per page, where one full page is submitted at a time. If you do not submit a full page of responses at a time, some of your responses might not be saved. After you have submitted your survey in full you will not be able to go back and edit your responses. Questions include the areas of reproductive health, product use, and general health. There are no known risks associated with participating in this study. However, there are questions in this survey that may cause emotional distress in certain individuals including questions on alcohol consumption, drug use, and mental health. If these questions are at all distressing to you, please feel free to withdraw at any point within the study. You can also reach out to the counselling service that are listed below for help.

Mental Health:

Crisis Services Canada

https://www.crisisservicescanada.ca/en/looking-for-local-resources-support/

Alcohol and Drug Use:

Canadian Centre on Substance Use and Addiction

https://www.ccsa.ca/addictions-treatment-helplines-canada

Data will be recorded in a secure online database and subjects will be identified only by an assigned number.

The data collected will be summarized and used for the researcher's master's thesis, which will be submitted to the faculty supervisor and master's committee for review. If applicable, this research may be published in a scientific journal. The only individuals who will have access to the raw data will be the students who conduct this research and her faculty supervisor and master's committee. All data collected will be archived anonymously for potential further study.

This initial agreement does not obligate you in any way to fully complete the online survey if you later decide you do not wish to participate. If the study is not fully completed, your data will be removed from the study. You can withdraw from the study at any time without any negative repercussions.

If you have any questions about this study or need clarification on any questions, please contact Kyley Drach (researcher) at kyley-drach@mytru.ca. If you have any concerns about this study, please contact Dr. Gregory Anderson (TRU Dean of Science) at ganderson@tru.ca or 250.852.7137, or the Chair of the Research Ethics Board (REB) at TRU-REB@tru.ca or 250.828.5000.

A3. Survey.

THOMPSON RIVERS UNIVERSITY

Chemical Exposure & Female Reproductive Health

1. Study Information and Consent

This study is entitled Chemical Exposure and Female Reproductive Health and will be conducted by Kyley Drach (email: kyley-drach@mytru.ca), a Master's student at Thompson Rivers University, under the supervision of Dr. Heidi Huttunen-Hennelly, Dr. Kingsley Donkor, and Dr. Mark Rakobowchuk. This study examines various areas of potential chemical exposure in a woman's life and how this can impact her reproductive health. If it is found that chemical exposure can influence reproductive health, we will aim to determine which routes of chemical exposure seem to have the greatest effect. There is no direct benefit to you by partaking in this study, but the data collected will provide researchers with a better understanding of whether chemical exposure is related to women's reproductive health. This information can help to shape future research projects related to this topic.

As a participant in this study, you will be asked to complete the following one-time survey, which will take between 45-60 minutes to complete. You are not required to complete the entire survey in one sitting and you may come back later to edit your questions or continue the survey. There are a total of 6 pages with various numbers of questions per page, where one full page is submitted at a time. If you do not submit a full page of responses at a time, some of your responses might not be saved. After you have submitted your survey in full you will not be able to go back and edit your responses. The questions in this survey are divided into the following sections: General Personal Information, Socioeconomic Status, Reproductive Health, Product Use, General Health, and Mental Health. There are no known risks associated with participating in this study. However, there are questions in this survey that may cause emotional distress in certain individuals including questions on alcohol consumption, drug use, and mental health. Sensitive questions will have an option of "prefer not to say" if you are uncomfortable answering these questions. If these

questions are at all distressing to you, please feel free to withdraw at any point within the study. You can also reach out to the counselling services that are listed below for help.

Mental Health:

Crisis Services Canada

https://www.crisisservicescanada.ca/en/looking-for-local-resources-support/

Alcohol and Drug Use:

Canadian Centre on Substance Use and Addiction
https://www.ccsa.ca/addictions-treatment-helplines-canada

(Click "Next" to continue to the second page of Study Information and Consent)

2. Study Information and Consent

Data will be recorded in a secure online database and subjects will be identified only by an assigned number.

The data collected will be summarized and used for the researcher's master's thesis, which will be submitted to the faculty supervisor and master's committee for review. If applicable, this research may be published in a scientific journal. The only individuals who will have access to the raw data will be the students who conduct this research and her faculty supervisor and master's committee. All data collected will be archived anonymously for potential further study.

This initial agreement does not obligate you in any way to fully complete the online survey if you later decide you do not wish to participate. If the study is not fully completed, your data will be removed from the study. You can withdraw from the study at any time without any negative repercussions.

If you have any questions about this study or need clarification on any questions, please contact Kyley Drach (researcher) at kyley-drach@mytru.ca or Dr. Mark Rakobowchuk (secondary investigator) at mrakobowchuk@tru.ca. If you have any concerns about this study, please contact Dr. Gregory Anderson (TRU Dean of Science) at ganderson@tru.ca or 250.852.7137, or the Chair of the Research Ethics Board (REB) at TRU-REB@tru.ca or 250.828.5000.

1. I consent to participate in this research study

- ◡ Yes
- ◡ No

3. Participant Eligibility

2. What is your birth sex?

- ◯ Female
- ◯ Male

3. Do you currently have a menstrual cycle each month?

- ◯ Yes, monthly
- ◯ I have a menstrual cycle, but not every month
- ◯ I do not have a menstrual cycle

4. Are you currently pregnant?

- ◯ Yes
- ◯ No

5. Are you either under the age of 18 or over the age of 35?

- ◯ Yes
- ◯ No

4. General

6. What is your race or ethnicity?

- ◯ Asian
- ◯ Black or African American
- ◯ Hispanic or Latino
- ◯ Middle Eastern or North African
- ◯ Multiracial or Multiethnic
- ◯ Indigenous
- ◯ Caucasian
- ◯ Another race or ethnicity, please describe below

Self-describe below:

7. How old are you?

8. What is your height in either feet and inches or meters?

Feet and Inches (e.g. 5'6" or 5 foot 6 inches)

Centimeters (e.g. 168 cm)

9. What is your current weight in pounds?

10. Which of the following best describes your current relationship status?

- Married
- Widowed
- Divorced
- Separated
- In a domestic partnership or civil union
- Single, but cohabiting with a significant other
- Single, never married
- Polyamorous
- Other (please specify)

11. What is the highest level of education you have completed?

- Did not attend school
- Some high school
- High school diploma
- Post-secondary certificate
- Post-secondary diploma
- Bachelors
- Masters
- PhD
- Other (please specify)

12. What is your approximate household income?

- $0-$24,999
- $25,000-$49,999
- $50,000-$74,999
- $75,000-$99,999
- $100,000-$124,999
- $125,000-$149,999
- $150,000-$174,999
- $175,000-$199,999
- $200,000 and up
- I am unsure
- Prefer not to say

13. What is your current housing situation?

- Single family home
- Condominum
- Apartment
- Townhouse
- Other (please specify)
- Mobile home
- Share House
- Prefer not to say

14. How many people currently live in your household?

15. Is your place of residence urban (city core or highly populated area), suburban (outside of city core or moderately populated), or rural (country or area with a low population)?

- Urban
- Suburban
- Rural
- I am unsure

16. What province or territory do you live in?

- British Columbia
- Alberta
- Saskatchewan
- Manitoba
- Ontario
- Quebec
- New Brunswick
- Nova Scotia
- Prince Edward Island
- Newfoundland and Labrador
- Nunavut
- Northwest Territories
- Yukon
- If you do not live in Canada, please state where you currently live in the textbox below.

5. Reproductive Health

17. Have you ever been pregnant or given birth to children?

- ◯ Yes
- ◯ No
- ◯ Prefer not to say

18. Are you sexually active?

- ◯ Yes
- ◯ No
- ◯ Prefer not to say

19. Do you have any known diseases or infections that may influence the reproductive system, such as a sexually transmitted infection?

- ◯ Yes
- ◯ No
- ◯ Prefer not to say

20. Do you currently take any medications that can influence hormones, such as birth control, hormone replacement therapy, or an intrauterine device (IUD)?

- ◯ Yes
- ◯ No
- ◯ I am unsure

21. What type of IUD, birth control, hormone therapy, or other hormonal medications do you take? Check all boxes that apply.

- ☐ Copper IUD (e.g. Paragard)
- ☐ Hormonal IUD (e.g. Mirena, Skyla, Liletta, Kyleena)
- ☐ Combination birth control pill (containing estrogen and progestin)
- ☐ Progestin-only birth control pill (does not contain estrogen)
- ☐ I do not take any sort of hormone medication
- ☐ If you are on hormone replacement therapy or any other type of hormone medication, please list them below. If you do not wish to disclose this information, please put "N/A" in the textbox below.

22. Do you have a gynecological disorder, such as endometriosis, ovarian cysts, ovarian/uterine cancers, fibroids, pelvic inflammation, infertility, or any other illnesses, such as a pain disorder, that can affect the pain and/or bleeding you experience during your period?

- Yes
- No
- I am unsure

23. Do you have a blood disorder, such as hemophilia, or a platelet disorder or other disease that affects your ability to clot blood?

- Yes
- No
- I am unsure

24. Do you have a family or extended family history of any gynecological or blood disorders?

- Yes
- No
- I am unsure

25. Approximately how old were you when you experienced your first period in years?

26. On average, how many days are there between the start of each of your periods?

28. How many days long is your period on average? This includes all days where bleeding is present, no matter how little.

29. Do you regularly experience menstrual pain at any point during your period?

- Yes, always
- Yes, sometimes
- No, never

30. How bad is the worst menstrual pain you experience while you are on your period?

- ◯ I do not experience pain during menstruation and my daily activities are unaffected
- ◯ I experience mild pain during menstruation but it rarely stops me from participating in my normal daily activities
- ◯ I experience moderate pain during menstruation and use medication to relieve my pain. My daily activities are affected but my pain rarely causes me to miss work, school, or other activities
- ◯ I experience severe pain during menstruation and medication does not fully relieve my pain. My daily activities are inhibited and my pain stops me from participating in work, school, and other activities

31. How many days during your period does your worst pain last?

32. Which of the following do you use for pain relief during your period? Select all that apply.

- ☐ Pain medication (e.g. Advil, Tylenol, Midol)
- ☐ Exercise
- ☐ Heat (e.g. heat packs)
- ☐ Dietary changes
- ☐ Water intake
- ☐ None
- ☐ Other (please specify)

33. Do you have a family history of painful periods?

- ◯ Yes
- ◯ No
- ◯ I am unsure

34. How would you describe the bleeding you experience on the heaviest days of your period?

- ◯ Light. I barely bleed and usually only require liners or light absorbency sanitary products. I have to change my products every several hours. I rarely experience leaks
- ◯ Moderate. When I bleed I require moderate absorbency sanitary products. I have to change my products every few hours. I sometimes experience leaks
- ◯ Heavy. When I bleed I require heavy absorbency sanitary products. I have to change my products hourly. I often experience leaks

35. For how many days during your period do you have your heaviest flow?

36. Do you have a family or extended family history of irregularly heavy or light menstrual bleeding?

- Yes
- No
- I am unsure

37. Do you ever experience breakthrough bleeding (spotting, mid-cycle bleeding) between your periods?

- Yes
- No

38. How often do you experience breakthrough bleeding?

- In between every period
- Once every few months
- Once a year or less
- Never

39. Have you ever been hospitalized or had to go to the emergency room due to the pain and/or bleeding you experience during your period?

- Yes
- No
- Prefer not to say

40. Have you ever seen a doctor or a gynecologist about your reproductive health?

- Yes, I see my doctor or gynecologist for my reproductive health more than once a year
- Yes, I see my doctor or gynecologist for my reproductive health once a year
- Yes, I see my doctor or gynecologist for my reproductive health every 2-5 years
- Yes, but I only see my doctor or gynecologist for my reproductive health every 6 or more years
- No, I have never seen my doctor or gynecologist for my reproductive health
- I do not have a doctor or gynecologist

41. If you have been diagnosed or treated for a gynecological issue (such as painful periods, heavy bleeding, or endometriosis), how long did it take to receive your diagnosis and/or treatment?

- I still have not received a diagnosis and/or treatment for my gynecological issues after several visits
- I had to visit my medical provider several times and it was difficult to get a diagnosis and/or treatment
- I had to visit my medical provider a few times and it was not difficult to get a diagnosis and/or treatment
- I have never visited a medical provider for my gynecological issues
- I do not have gynecological issues

42. Do you feel your doctor or gynecologist takes your concerns regarding your reproductive health seriously?

- Yes, my medical provider always listens to my concerns
- Yes, but my medical provider doesn't always listen to what I have to say
- No, I do not feel listened to by my medical provider
- I have not seen a doctor or gynecologist for my reproductive health

43. Do you feel you have received the treatment you need from your doctor or gynecologist regarding your reproductive health?

- Yes
- No
- N/A

6. Product Use

44. What type of menstrual products do you use from the following list? Choose all that apply.

- [ ] Disposable pads (e.g. Kotex, Always, Stayfree)
- [ ] Organic disposable pads (e.g. made of 100% organic cotton, such as Natracare)
- [ ] Disposable tampons (e.g. Playtex, Tampax, Kotex, O.B. original)
- [ ] Organic disposable tampons (e.g. made of 100% organic cotton, such as Natracare or O.B. organic regular without plastic applicator)
- [ ] Reusable pads (e.g. Lucky Pads, Hannah Pads, Aisle, New Moon Pads)
- [ ] Organic reusable pads (e.g. made of 100% organic cotton, such as GladRags organic cotton line)
- [ ] Menstrual cup (e.g. DivaCup, Lily Cup)
- [ ] None (e.g. free bleeding)
- [ ] Other (please specify)

45. Are the sanitary products you use scented or unscented?

- ○ Scented
- ○ Unscented
- ○ I am unsure
- ○ I don't use sanitary products

46. Do you use any other types of feminine hygiene products aside from menstrual products on a monthly basis? These include feminine wipes, douches, or other products that come in contact with the vaginal area.

- ○ Yes, every month
- ○ Yes, but not every month
- ○ No, never
- ○ Prefer not to say

47. Describe the personal care products you use from the below options. (Personal care products include shampoo/conditioner, body wash, deodorant, moisturizer, shaving cream, hair products, cosmetics etc.)

- ◯ I don't put any restrictions on the personal care products I buy
- ◯ I try to buy natural products that are free of chemicals (such as parabens, sulphates, phthalates, volatile organic compounds (VOCs), and artificial fragrances)
- ◯ I exclusively buy natural products that are free from chemicals (such as parabens, sulphates, phthalates, volatile organic compounds (VOCs), and artificial fragrances)

48. Are you exposed to chemicals at work, home, or school?
(possible exposure routes include the use of cleaning products, pesticides, detergents, manufacturing chemicals, and/or solvents, or working in an industry that often handles receipts or that uses chemicals, such as hair salons, nail salons, dry cleaners, house cleaners, farming, manufacturing, cosmetology, etc.)

- ◯ Yes
- ◯ No
- ◯ I am unsure

49. How frequently are you exposed to chemicals at work, home, or school?
(possible exposure routes include the use of cleaning products, pesticides, detergents, manufacturing chemicals, and/or solvents, or working in an industry that often handles receipts or that uses chemicals, such as hair salons, nail salons, dry cleaners, house cleaners, farming, manufacturing, cosmetology, etc.)

- ◯ Every day
- ◯ A few times a week
- ◯ About once a week
- ◯ A few times a month
- ◯ Once a month
- ◯ Rarely ever, or never
- ◯ I am unsure

50. From the below list, check all that apply regarding where you experience chemical exposure

- ☐ Home
- ☐ Work
- ☐ School
- ☐ Other (please specify)
- ☐ I am unsure
- ☐ I do not experience chemical exposure that I am aware of

51. Were you ever exposed to chemicals during key development windows, such as while you were still in the womb, during childhood, or during puberty?
(examples include the consumption of alcohol or smoking by your mother while you were in the womb, or being in an environment where chemicals were frequently present/having a high level of exposure to chemicals in one sitting as a child or during puberty. For example, having a cleaning job in your teenage years where proper safety protocol was not followed, allowing inhalation of chemicals or absorption through the skin.)

- Yes
- No
- I am unsure

7. General Health

52. Do you currently or have you ever smoked or been exposed to second-hand smoke from others? Check all that apply. (This includes cigarettes and cigars)

- [ ] Yes, I currently smoke
- [ ] Yes, I am currently exposed to second-hand smoke from others
- [ ] I used to smoke
- [ ] I used to be exposed to second-hand smoke from others
- [ ] No, I have never smoked
- [ ] No, I have never been exposed to second-hand smoke from others
- [ ] Prefer not to say

53. Do you currently or have you ever smoked marijuana?

- ◯ Yes, I currently smoke marijuana
- ◯ I used to smoke marijuana
- ◯ No, I have never smoked marijuana
- ◯ Prefer not to say

54. Do you currently or have you ever vaped?

- ◯ Yes, I currently vape
- ◯ I used to vape
- ◯ No, I have never vaped
- ◯ Prefer not to say

55. Did you start smoking/vaping or were you exposed to second-hand smoke either before you had your first period or when you were 13 years old or younger?

- ◯ Yes
- ◯ No
- ◯ N/A
- ◯ I am unsure

56. How long have you been a smoker for if you are still currently smoking?

- Less than 1 year
- 1 to 5 years
- 6 to 15 years
- 16 to 25 years
- More than 25 years
- N/A

57. How much do you smoke in a day?

- Half a pack of cigarettes or less
- Half a pack to 1 pack of cigarettes a day
- 1 to 2 packs of cigarettes a day
- More than 2 packs of cigarettes a day
- I only one or two cigarettes occasionally
- N/A

58. How long have you been exposed to second-hand smoke from others?

- Less than 1 year
- 1 to 5 years
- 6 to 15 years
- 16 to 25 years
- More than 25 years
- N/A

59. How long have you smoked marijuana for if you still currently smoke marijuana?

- Less than 1 year
- 1 to 5 years
- 6 to 15 years
- 16 to 25 years
- More than 25 years
- N/A

60. How often do you smoke marijuana?

- Every day
- A few times a week
- About once a week
- A few times a month
- Once a month
- Once every few months
- Once a year or less
- N/A

61. How long have you vaped for if you are still currently vaping ?

- Less than 1 year
- 1 to 5 years
- 6 to 15 years
- 16 to 25 years
- More than 25 years
- N/A

62. How often do you vape?

- Every day
- A few times a week
- About once a week
- A few times a month
- Once a month
- Once every few months
- Once a year or less
- N/A

63. Do you currently or have you ever drank alcohol?

- Yes, I currently drink
- Yes, I have had alcohol in the past but I do not currently drink
- No, I have never drank
- Prefer not to say

64. Did you start consuming alcohol before you had your first period or when you were younger than 18?

- Yes
- No
- N/A
- I am unsure

65. How many standard alcoholic drinks do you have in a week? (A standard drink is one can of beer, one shot of liquor, or a 5 oz/147mL glass of wine)

- I have 19 or more drinks per week
- I have 15 to 18 drinks per week
- I have 11 to 14 drinks per week
- I have 7 to 10 drinks per week
- I have 3 to 6 drinks per week
- I have less than 3 drinks per week
- I only drink on special occasions
- I don't drink

66. How long have you been drinking for, if you are currently still drinking?

- Less than 1 year
- 1 to 5 years
- 6 to 15 years
- 16 to 25 years
- More than 26 years
- I don't drink

67. What types of alcohol do you consume?

- [ ] Wine
- [ ] Liquor
- [ ] Beer
- [ ] Other (please specify)
- [ ] Spirits
- [ ] N/A

68. Do you currently or have you ever used drugs recreationally (including legal and/or illegal substances)?

- ◯ Yes
- ◯ No
- ◯ Prefer not to say

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69. Did you start using drugs recreationally before you had your first period or when you were 19 years old or younger (including legal and/or illegal substances)?

- ◯ Yes
- ◯ No
- ◯ N/A
- ◯ I am unsure
- ◯ Prefer not to say

70. How long have you been using drugs recreationally if you are still currently a recreational drug user (including legal and/or illegal substances)?

- ◯ Less than 1 year
- ◯ 1 to 5 years
- ◯ 6 to 15 years
- ◯ 16 to 25 years
- ◯ More than 25 years
- ◯ N/A
- ◯ Prefer not to say

71. How often do you use drugs recreationally (including legal and/or illegal substances)?

- ◯ Daily
- ◯ Weekly
- ◯ Monthly
- ◯ Yearly
- ◯ Less than yearly
- ◯ N/A
- ◯ Prefer not to say

72. Do you have any hormonal issues, such as a thyroid disorder, adrenal gland disorder, or diabetes?

- ◯ Yes
- ◯ No
- ◯ I am unsure

73. Do you suffer from any chronic diseases or health issues, such as pain disorders or cardiovascular disease?

- ◯ Yes
- ◯ No
- ◯ I am unsure

Please list all chronic diseases or health issues you suffer from below. If you do not have a chronic disease or health issue, please type "N/A" below:

74. Do you currently take medication for a physical health condition?

- ◯ Yes
- ◯ No

Please list the medications you are currently taking below. If you are not taking any medications or do not wish to disclose these medications, please respond with "N/A" in the textbox below:

75. Do you have a regular sleep schedule, where you wake up and go to sleep at around the same time each night?

- ◯ Yes
- ◯ No, my sleep schedule is always changing

76. On average, how many hours of sleep do you get each night?

77. What type of diet most closely matches your food consumption from the below list?

- ◯ Unrestricted diet
- ◯ Vegetarian
- ◯ Vegan
- ◯ Ketogenic diet
- ◯ Other (please specify)
- ◯ Mediterranean diet
- ◯ Blue zone diet
- ◯ Paleo diet

78. How long have you been on the above-mentioned diet, rounded to the nearest number of years? If you have transitioned to this diet less than a year ago, respond with a "0"

79. Is the food you consume on a daily basis organic?

- Yes, I only consume organic food
- Yes, at least half the food I consume is organic
- I only occasionally consume organic food
- No, I never consume organic food
- I am unsure

80. How long have you been consuming organic food, rounded to the nearest year? If you have not been consuming organic food, respond with "N/A" in the textbox below

81. Do you have any dietary restrictions or food allergies?

- Yes
- No

If you responded "Yes", please list any restrictions or allergies below. If you do not have restrictions or food allergies, type "N/A" in the textbox below.

82. Do you consume canned foods or foods and/or beverages stored in plastic containers, plastic packaging, plastic bags, or plastic bottles?

- Yes
- No

83. How often do you consume either canned foods or foods and/or beverages that have been stored in plastic containers, plastic packaging, plastic bags, or plastic bottles?

- Every day
- A few times a week
- About once a week
- A few times a month
- Once a month
- Never

84. On average, how many mg of caffeine do you consume in a day? (An average coffee contains 95 mg, an average tea contains 47mg, an average can of soda contains 40mg, and an average caffeinated energy drink contains 180mg)

- ◯ More than 400mg per day (more than 4 coffees)
- ◯ 200mg to 400mg per day (2 to 4 coffees)
- ◯ 1mg to 199mg per day (less than 2 coffees)
- ◯ I consume caffeine on occasion, but not daily
- ◯ I don't consume caffeine

85. How many hours of high-intensity exercise do you perform each week, including during work and leisure time? If less than one hour, enter "0" in the textbox below. (during high-intensity exercise, you will not be able to say more than a few words without pausing for a breath)

86. How many hours of moderate-intensity exercise do you perform each week, including during work and leisure time? If less than one hour, enter "0" in the textbox below. (during moderate-intensity exercise, you will be able to talk, but not sing during the activity)

87. How many hours of low-intensity exercise do you perform each week, including during work and leisure time? If less than one hour, enter "0" in the textbox below. (during low-intensity exercise, you can easily talk and sing during the activity)

88. Within the last year, have you gained or lost a significant amount of weight (more than 5% of your usual body weight)?

- ◯ Yes
- ◯ No
- ◯ I am unsure
- ◯ Prefer not to say

8. Mental Health

89. Have you been diagnosed with any of the following mental health conditions? Check all that apply.

- [ ] Anxiety
- [ ] Bipolar
- [ ] Depression
- [ ] Schizophrenia
- [ ] Obsessive compulsive disorder (OCD)
- [ ] N/A
- [ ] Other (please specify)

90. If you have not received an official diagnosis, are there any mental health conditions you think you may have?

- ◯ Yes
- ◯ I am unsure
- ◯ No
- ◯ Prefer not to say
- ◯ I have an official diagnosis

If yes, please specify below what mental health condition(s) you think you may have. If you do not think you have a mental health condition or prefer not to say, respond with "N/A" below.

91. Do you currently take medication for a mental health condition?

- ◯ Yes
- ◯ No

Please list the medications you are currently taking below. If you are not taking any medications or prefer not to indicate which medications you are taking, please respond with "N/A" in the textbox below:

92. Aside from medication, do you receive any other treatment for your mental health condition?

- Yes
- No
- N/A
- Prefer not to say

If you answered "Yes", please specify what these treatments are (e.g. therapy). If you do not want to share what treatments you are receiving or if you are not receiving treatment, please respond with "N/A" below.

93. In the past month, how often have you felt difficulties were piling up so high that you could not overcome them?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

94. In the past month, how often have you been angered because of things that happened that were outside of your control?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

95. In the past month, how often have you felt that you were on top of things?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

96. In the past month, how often have you been able to control irritations in your life?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

97. In the past month, how often have you found that you could not cope with all the things that you had to do?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

98. In the past month, how often have you felt that things were going your way?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

99. In the past month, how often have you felt confident about your ability to handle your personal problems?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

100. In the past month, how often have you felt nervous and stressed?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

101. In the past month, how often have you felt you were unable to control the important things in your life?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

102. In the past month, how often have you been upset because of something that happened unexpectedly?

- Never
- Almost never
- Sometimes
- Fairly often
- Very often

9. Available Resources

Mental Health:
Crisis Services Canada
https://www.crisisservicescanada.ca/en/looking-for-local-resources-support/

Alcohol and Drug Use:
Canadian Centre on Substance Use and Addiction
https://www.ccsa.ca/addictions-treatment-helplines-canada

103. Thank you for completing this survey. If you have any feedback, feel free to leave it in the comment box below.

A4. Perceived Stress Scale (PSS).

Perceived Stress Scale

A more precise measure of personal stress can be determined by using a variety of instruments that have been designed to help measure individual stress levels. The first of these is called the **Perceived Stress Scale**.

The Perceived Stress Scale (PSS) is a classic stress assessment instrument. The tool, while originally developed in 1983, remains a popular choice for helping us understand how different situations affect our feelings and our perceived stress. The questions in this scale ask about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer fairly quickly. That is, don't try to count up the number of times you felt a particular way; rather indicate the alternative that seems like a reasonable estimate.

For each question choose from the following alternatives:
0 - never 1 - almost never 2 - sometimes 3 - fairly often 4 - very often

_____ l. In the last month, how often have you been upset because of something that happened unexpectedly?

_____ 2. In the last month, how often have you felt that you were unable to control the important things in your life?

_____ 3. In the last month, how often have you felt nervous and stressed?

_____ 4. In the last month, how often have you felt confident about your ability to handle your personal problems?

_____ 5. In the last month, how often have you felt that things were going your way?

_____ 6. In the last month, how often have you found that you could not cope with all the things that you had to do?

_____ 7. In the last month, how often have you been able to control irritations in your life?

_____ 8. In the last month, how often have you felt that you were on top of things?

_____ 9. In the last month, how often have you been angered because of things that happened that were outside of your control?

_____ 10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Figuring Your PSS Score

You can determine your PSS score by following these directions:

- First, reverse your scores for questions 4, 5, 7, and 8. On these 4 questions, change the scores like this:

  0 = 4, 1 = 3, 2 = 2, 3 = 1, 4 = 0.

- Now add up your scores for each item to get a total. **My total score is _____.**

- Individual scores on the PSS can range from 0 to 40 with higher scores indicating higher perceived stress.
  - ► Scores ranging from 0-13 would be considered low stress.
  - ► Scores ranging from 14-26 would be considered moderate stress.
  - ► Scores ranging from 27-40 would be considered high perceived stress.

The Perceived Stress Scale is interesting and important because your perception of what is happening in your life is most important. Consider the idea that two individuals could have the exact same events and experiences in their lives for the past month. Depending on their perception, total score could put one of those individuals in the low stress category and the total score could put the second person in the high stress category.

***Disclaimer**: The scores on the following self-assessment do not reflect any particular diagnosis or course of treatment. They are meant as a tool to help assess your level of stress. If you have any further concerns about your current well being, you may contact EAP and talk confidentially to one of our specialists.*

A5. Tables

Table 1A. Andersch and Milson Pain Scale.

Grade	Description
0	I do not experience pain during menstruation and my daily activities are unaffected.
1	I experience mild pain during menstruation but it rarely stops me from participating in my normal daily activities.
2	I experience moderate pain during menstruation and require analgesics to relieve my pain; my daily activities are affected but my pain rarely causes me to miss work, school, or other activities.
3	I experience severe pain during menstruation and analgesics do not fully relieve my pain; my daily activities are inhibited and my pain stops me from participating in work, school, and other activities.

(modified from Parra-Fernandez et al. 2020)

Table 2A. Reasons for exclusion of potential participants.

Outside of age range	7
Taking medications that influence hormones (besides IUD or birth control) or reproductive system	48
Has a diagnosed gynecological disorder	17
Does not have a period	3
Contradicting responses to questions	4
Has a hormonal issue	7
Has a chronic disease	33

Table 3A. Questions excluded due to insufficient data.

What is the highest level of education you have completed	Too few questions to adequately measure socioeconomic status
What is your approximate household income	Too few questions to adequately measure socioeconomic status
How many people currently live in your household	Too few questions to adequately measure socioeconomic status
Do you have a family or extended family history of any gynecological or blood disorders?	Too many unsure responses
Do you have a family history of painful periods?	Too many unsure responses
Do you have a family or extended family history of irregularly heavy or light menstrual bleeding	Too many unsure responses
Are you exposed to chemicals at work, home, or school?	Too many unsure responses
How frequently are you exposed to chemicals at work, home, or school?	Too many unsure responses
From the below list, check all that apply regarding where you experience chemical exposure (work, home, school)	Too many unsure responses
Were you ever exposed to chemicals during key development windows, such as while you were still in the womb, during childhood, or during puberty?	Too many unsure responses
Do you currently or have you ever smoked marijuana?	Outside study scope
How long have you smoked marijuana for if you still currently smoke marijuana?	Outside study scope
How often do you smoke marijuana?	Outside study scope
Within the last year, have you gained or lost a significant amount of weight?	Outside study scope