A DAILY DIARY EXAMINATION ON THE RELATIONS OF DEPRESSED MOOD AND COPING MOTIVES WITH CANNABIS USE QUANTITY ACROSS THE MENSTRUAL CYCLE: COMPARING CANNABIS USING FEMALES WITH AND WITHOUT PRE-MENSTRUAL DYSPHORIC DISORDER

by

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DEDICATION PAGE

I dedicate the entirety of my thesis to my late grandfather, Brian Francis Joyce, who taught me how to care for others endlessly and to make the best out of every situation. Your unconditional love and guidance have directed me toward the field of psychiatry. I put everything I have into this Masters' degree for you. I hope I am making you proud.

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ABSTRACT

Cannabis is one of the most commonly used drugs in Canada. Though limited, research suggests female, versus male, heavy cannabis users have a higher propensity to develop a cannabis use disorder. Recent research suggests that addictive behaviors, like alcohol use, may change, along with mood states and addictive behavior motives, across the menstrual cycle (MC), particularly during the pre-menstrual and menstrual phases. In this thesis, daily diary methodology was used to examine relations between cannabis use, depressed mood, and coping motives in normally-cycling female cannabis users across the MC. We hypothesized that heightened cannabis use would be associated with depressed mood and coping motives pre-menstrually and menstrually. We also hypothesized that females with a provisional pre-menstrual dysphoric disorder (PMDD) diagnosis would experience stronger relations between cannabis use, depressed mood, and coping motives pre-menstrually and menstrually versus females without PMDD. A sample of 69 normally-cycling female cannabis users (M_{age} = 29.25, SD = 5.66) were recruited and completed daily assessments on cannabis use quantities, depressed mood, and coping-motivated cannabis use. Results from the primary analyses indicated no relationship between cannabis use and depressed mood or coping-motivated cannabis use across the MC in the overall sample or among those without a PMDD diagnosis (n = 50). However, a provisional PMDD diagnosis (n = 19) appeared to be an individual difference factor affecting cannabis use across the MC, with depressed mood predicting heightened cannabis use menstrually, and coping motives predicting heightened cannabis use pre-menstrually and menstrually. Additionally, females with PMDD displayed a greater overall cannabis use quantity during the self-monitoring than females without PMDD. These results add to a growing body of literature pointing to the potential importance of female reproductive hormone variations in accounting for addictive behaviors in females. Findings also have important treatment implications for reproductive-aged females with PMDD who misuse cannabis (e.g., beginning a cannabis cessation/reduction attempt during the ovulatory or luteal phases of the menstrual cycle; training in more adaptive skills for managing depressed affect to be employed during the pre-menstrual and menstrual phases).

LIST OF ABBREVIATIONS USED

CUD	Cannabis Use Disorder
CUDIT-R	Cannabis Use Disorder Identification Test - Revised
DAST	Drug Abuse Screening Test
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (Edition 5)
ELISA	Enzyme-Linked Immuno-Sorbent Assays
EMA	Ecological Momentary Assessment
H_2O	Water
MAAC	Mood, Anxiety, and Addiction Comorbidity
MC	Menstrual Cycle
MCQ	Menstrual Cycle Questionnaire
MMM	Marijuana Motives Measure
PAF-SF	Pre-Menstrual Assessment Form - Short Form
PMDD	Pre-Menstrual Dysphoric Disorder
PMS	Pre-Menstrual Syndrome
REB	Research Ethics Board
SAS	Statistical Analysis Software
SCID-5-RV	Structured Clinical Interview for DSM-5 Disorders - Research Version
SMT	Self-Medication Theory
TMB	3,3',5,5'-Tetramethylbenzidine
TVEM	Time-Varying Effect Models
VAS	Visual Analogue Scale

Weights and Measures

ºC	Degrees Celsius
pg	Picograms
rpm	Rotations Per Minute
mL	Milliliter
nm	Nanometer
g	Acceleration of gravity
µl	Microlitre

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CHAPTER 1 INTRODUCTION

Cannabis is one of the most commonly used drugs in Canada, with a past three-month prevalence rate of 15%, or 4.6 million users, among individuals 15 years and older within the general Canadian population (Statistics Canada, 2018). In the three months following cannabis legalization, the National Cannabis Survey reported Nova Scotia as having the highest rates of cannabis use nationally among individuals 15 years and older (23% of the population; Statistics Canada, 2018). While females report lower rates of overall (18% for males versus 12% for females) and daily (7% for males versus 4% for females) cannabis use than their male counterparts (Statistics Canada, 2018), female cannabis use is of major concern for two main reasons. First, national epidemiological surveys indicate female cannabis users are more apt to develop a cannabis use disorder (CUD) following their first cannabis use relative to males (i.e., telescoping; Khan et al., 2013). Furthermore, females with a CUD report a greater likelihood of having comorbid mood and anxiety disorders versus males (Buckner et al., 2012; Khan et al., 2013). The high prevalence rates of cannabis use in Nova Scotia is concerning given the recent national legalization of cannabis in Canada, as cannabis legalization has been associated with low levels of perceived risk and increased cannabis use in Canada following cannabis legalization relative to one year earlier (i.e., during the first quarter of 2019 18% reported cannabis use versus 14% pre-legalization; Statistics Canada, 2019). Increases in the societal acceptance of cannabis, the recent legalization of cannabis, and the increased risk of developing a CUD along with comorbid mood/anxiety disorders in female cannabis users, relative to male users, suggests more research on female-specific factors influencing cannabis use is warranted.

To date, little is known about female-specific factors affecting addictive behaviors. Females were historically omitted from addiction research given that menstrual cycle (MC)-related rhythmic fluctuations in ovarian hormones were thought to have the potential to impact addictive behavior (Moran-Santa Maria, Flanagan, & Brady, 2014; Hudson & Stamp, 2011). This sex-specific research bias has resulted in an abundance of evidence on the development, nature, and maintenance of addiction in males. Given females' underrepresentation in addiction research thus far, many preventative and therapeutic interventions developed and utilized may not be suitable or optimally effective for females with an addiction. The lack of suitable and/or optimally effective treatment tools for females is alarming given recent cannabis legalization in Canada and some evidence that legalization may be associated with increases in cannabis use (Statistics Canada, 2019).

1.1 THE MENSTRUAL CYCLE

Historically females were often excluded from addictions research due to the potential impact of ovarian hormone fluctuations across their MC on their addictive behaviors. However, in more recent years, researchers have begun assessing the influences of and between addictive behaviors across the MC (for a review, see Moran-Santa Maria et al., 2014; Terner & de Wit, 2006). The MC lasts, on average, 28 days (Münster, Schmidt, & Helm, 1992) with a wide range of individual variability in MC length. As there is currently no standardized method of MC phase designation, the subdivision of the MC results in a combination of two or more of the following phases: the menstrual/early-follicular, follicular/post-menstrual/peri-ovulatory, ovulatory, luteal/post-ovulatory, and pre-menstrual/late-luteal phases. As MC phase categorization

has not been standardized and varies substantially across studies it is difficult to compare results across existing research. Variability in female MC length has been attributed to differing luteal phase lengths (Lenton, Landgren, & Sexton, 1984), although the literature is somewhat mixed (i.e., some literature points toward the follicular phase as contributing to MC variability; Fehring, Schneider, & Raviele, 2006). Attribution of MC length variability to the luteal phase is supported by two facts. First, although the timing of the ovulatory phase may differ on an individual basis, research shows the ovulatory phase typically occurs between MC days 13-16, suggesting little variability prior to ovulation (Fehring et al., 2006). Second, the pre-menstrual phase has been defined as 5 days prior to menstruation (Walsh, Budtz-Olsen, Leader, & Cummins, 1981). Collectively, this literature suggests it is the luteal phase, and not other MC phases, where MC length variability occurs across females. An amalgamation of the existing research on MC phase categorization results in the following five phases: menstrual (days 1-5), follicular (days 6-12), ovulatory (days 13-16), luteal (day 17 to the pre-menstrual phase), and pre-menstrual phases (5 days prior to menstruation; Fehring et al., 2006; Lenton et al., 1984; Walsh et al., 1981).

1.1.1 Ovarian Hormones

These five MC phases have been differentiated based on differing ovarian hormone concentrations (Griffin & Ojeda, 2004; Groome et al., 1996; Levy, Koeppen, & Stanton, 2000). Low estrogen and progesterone concentrations characterize the menstrual phase. During the follicular phase, estrogen concentrations begin increasing. Ovulation, when a female is most fertile, lasts between 24 and 72 hours. Surges in follicle-stimulating and luteinizing hormones are antecedents for ovulation. Ovulation is followed

by declining estrogen and rising progesterone concentrations. During the luteal phase, progesterone concentrations increase, peaking mid-phase. Without fertilization, estrogen and progesterone precipitously decline pre-menstrually.

1.2 ADDICTION AND THE MENSTRUAL CYCLE

MC phases, differentiated based on changes in ovarian hormone concentrations, appear to influence the frequency, quantity and/or use of/involvement in (yes/no) substance use/addictive behaviors in females. Our recent systematic review of the human literature assessed research on the associations between MC phase and substance use and other addictive behaviors (i.e., gambling; Joyce, Good, Tibbo, Brown, & Stewart, under review) to identify MC phase-substance use/addictive behavior relations. Retrieved studies were divided into two sections, consisting of substance use (i.e., alcohol use, cannabis use, nicotine use, and caffeine intake) and other potentially addictive behaviors (i.e., gambling). Interestingly, Joyce et al. (under review) identified the MC phase(s) during which increases or decreases in substance use/other addictive behaviors occur appears dependent on the category of behavior, i.e. either the substance used or the potentially addictive behavior involved.

Potentially addictive behaviors, specifically gambling, varied based on MC phase with heightened gambling behaviors during ovulation and the follicular phase (Joyce et al., under review). Of the three studies identified which assessed gambling behaviors across MC phase, all reported MC phase effects (Chen, Katuščák, & Ozdenoren, 2013; Joyce et al., 2019; Pearson & Schipper, 2013). While the results of individual studies on gambling across MC phase were mixed, the majority of individual findings[1] suggested

[1] Within our review (Joyce et al., under review), several studies found multiple

risky gambling behaviors (e.g., time and money spent gambling) increased during the ovulatory phase versus other MC phases. Overall, our review (Joyce et al., under review) predominantly identified elevations in antecedents of a gambling addiction (i.e., excessive gambling behavior) during the ovulatory phase.

We also identified MC phase effects on all substance use behaviors, with the exclusion of caffeine intake which did not appear to differ by MC phase (Joyce et al., under review). Eighteen studies were identified which assessed alcohol consumption across MC phase (Allen, 1996; Belfer & Shader, 1971; Charette, Tate, & Wilson, 1990; Christensen, Oei, & Callan, 1989; Dumas, Calliet, Tumblin, & King, 1984; Epstein et al., 2006; Griffin, Mello, Mendelson, & Lex, 1987; Harvey & Beckman, 1985; Marks, Hair, Klock, Ginsburg, & Pomerleau, 1994; Martel, Eisenlohr-Moul, & Roberts, 2017; McLeod, Foster, Hoehn-Saric, Svikis, & Hipsley, 1994; Mello, Mendelson, & Lex, 1990; Pastor & Evans, 2003; Pomerleau, Cole, Lumley, Marks, & Pomerleau, 1994; Sutker, Libet, Allain, & Randall, 1983; Svikis et al., 2015; Tate & Charette, 1991; Tobin, Schmidt, & Rubino, 1994). About 71% of individual results reported an effect of MC phase, the slight majority reported heightened alcohol consumption pre-menstrually and menstrually (versus other MC phases), consistent with previously published reviews of the alcohol literature (Carroll, Lustyk, & Larimer, 2015). A total of 10 studies were retrieved which examined nicotine use across MC phase, with ~79% of individual results indicating MC phase effects on nicotine use (Allen, Mooney, Chakraborty, & Allen,

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associations between MC phase and the addictive behavior of interest (e.g., heightened alcohol consumption pre-menstrually and lower alcohol consumption during the follicular phase). Each distinct result was referred to as an "individual finding" and discussed separately. Thus, a single study may have contributed more than one individual finding to our review.

2009; Allen, Allen, & Pomerleau, 2009; Allen et al., 1996; DeBon, Klesges, & Klesges, 1995; Marks et al., 1994; Mello, Mendelson, & Palmieri, 1987; Pomerleau et al., 1994; Sakai & Ohashi, 2013; Snively, Ahijevych, Bernhard, & Wewers, 2000; Steinberg & Cherek, 1989). Interestingly, findings predominantly suggested, yet again, increased nicotine intake pre-menstrually and menstrually versus other MC phases. The same association was found for the three studies identified which assessed relations between cannabis intake and MC phase (Griffin, Mendelson, Mello, & Lex, 1986; Hanzal, Joyce, Tibbo, & Stewart, 2019; Mello & Mendelson, 1985), with the majority of individual results suggesting increased cannabis use pre-menstrually and menstrually. Finally, of the two studies assessing caffeine intake across MC phase, neither study suggested a relationship between caffeine intake and MC phase (Marks et al., 1994; Pomerleau et al., 1994).

Collectively, our in-depth systematic review combining extant literature on substance use and other addictive behaviors across MC phase suggested substance use/other addictive behavior specific MC phase effects (Joyce et al., under review). More specifically, results suggested that substance use increases pre-menstrually and menstrually whereas other addictive behaviors (i.e., gambling) increase during the ovulatory phase.

1.3 SUBSTANCE USE, MOOD, AND THE MENSTRUAL CYCLE

One mechanism by which substance use may differ in normally-cycling females across their MC pertains to mood-related fluctuations (Wharton, Carey, Olson, Carlsson, & Asthana, 2012), specifically changes in levels of depressed mood (Aganoff & Boyle, 1994; Collins, Eneroth, & Landgren, 1985; Reed et al., 2008). Interestingly, depressed

mood increases pre-menstrually and menstrually (relative to other MC phases), alongside elevations in alcohol, cannabis, and nicotine use (Joyce et al., under review). Self-medication theory (SMT; Khantzian, 1997), an emotion-focused theory of substance use, posits that individuals increase their substance use during periods of depressed mood to reduce and/or eliminate depressed mood. SMT thus would predict heightened substance use among normally-cycling females pre-menstrually and menstrually to reduce/eliminate depressed mood during these same MC phases (versus other MC phases).

Increases in depressed mood pre-menstrually and menstrually are suggested to result from changes in ovarian hormone concentrations (not absolute ovarian hormone concentrations; Soares & Zitek, 2008). Increases in depressed mood begin when estrogen and progesterone concentrations decrease during the pre-menstrual phase and this depressed mood begins dissipating soon after the onset of menstruation. Although literature suggests ovarian hormones influence depressed mood, a single underlying mechanism to explain depression-related mood changes across the MC has yet to be identified (Soares & Zitek, 2008).

It has been proposed that changes in ovarian hormones among females have a pronounced MC-related influence on the serotonergic system itself. The monoamine theory of depression, in short, suggests that dysregulation of the serotonergic system explains the development and maintenance of depression (Schildkraut, 1965). One potential mechanism explaining increases in depressed mood across the pre-menstrual and menstrual phases of the MC in females is through the dysregulation of the serotonergic system via ovarian hormones, such as estrogen and progesterone. Ovarian hormones have been shown to bind to and modulate the activity of serotonin receptors,

which are highly expressed in areas of the brain involved in emotion, such as the amygdala (Barth, Villringer, & Sacher, 2015; Sumner & Fink, 1998). Ovarian hormones modulate the generation and efficacy of serotonergic neurotransmission (McEwen, 2004). For instance, research suggests decreasing estrogen may upregulate monoamine oxidase (i.e., the enzyme responsible for degrading serotonin) mRNA expression, which in turn, decreases serotonin levels (Gundlah, Lu, & Bethea, 2002). Importantly, there is a multitude of evidence implicating estrogen and progesterone in the regulation of serotonergic activity menstrually (e.g., Barth et al., 2015; Gundlah et al., 2002; McEwen, 2004; Sumner & Fink, 1998) which may explain depressed mood increases pre-menstrually and menstrually among normally-cycling females.

In addition to ovarian hormone influences on the serotonergic system, the endocannabinoid system, comprised of endocannabinoids, endocannabinoid receptors, as well as other components, modulate a variety of different physiological functions, such as mood (Bassi et al., 2018). For instance, chronic treatment with endocannabinoid receptor 1 antagonists increases both anxiety and depression (Després, Golay, & Sjöström, 2005; Padwal & Majumdar, 2007; Traynor, 2007; Rigotti et al., 2009; Van Gaal, Rissanen, Scheen, Ziegler, & Rössner, 2005), implying the endocannabinoid system is implicated in regulating mood. Additional research suggests that since the endocannabinoid receptor 1 is primarily expressed on presynaptic terminals, along with serotonin receptors, the endocannabinoid system may directly modulate serotonin activity, and as a result, the serotonergic system itself (Bassi et al., 2018). Collectively, the literature suggests that constituents in cannabis (e.g., Δ9-tetrahydrocannabinol), which act on the endocannabinoid system, may have direct and/or indirect antidepressant-like effects on

the serotonergic system (Bassi et al., 2018). As a result of cannabis' influence on the endocannabinoid system, females may use cannabis during the pre-menstrual and menstrual phases to reduce elevations in depressed mood during these phases.

1.3.1 Pre-Menstrual Dysphoric Disorder

Severe increases in depressed mood, comparable to depressed mood reported in individuals with major depressive disorder, are also reported pre-menstrually and menstrually in females with pre-menstrual dysphoric disorder (PMDD) relative to those without. PMDD is a mood disorder diagnosis that is recognized within the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2013) with a prevalence of 3-8% (Halbreich, Borenstein, Pearlstein, & Kahn, 2003). The prevalence of clinically-relevant symptoms, severe enough to promote distress and impairment, however not meeting criteria for a PMDD diagnosis, is much higher (13-19% prevalence rate; Angst, Sellaro, Stolar, Merikangas, & Endicott, 2001; Halbreich et al., 2003; Spitzer, Williams, Kroenke, Hornyak, & McMurray, 2000; Wittchen, Becker, Lieb, & Krause, 2008). Interestingly, selective serotonin reuptake inhibitors are unanimously considered the most efficacious treatment for PMDD (Steiner et al., 2006), consistent with the previously-mentioned influence of ovarian hormone fluctuations on the serotonergic system.

Substance use susceptibility appears greater among those with PMDD. For instance, females with PMDD reported higher levels of alcohol desire, compared to females without PMDD (Reed et al., 2008). It is possible that a PMDD diagnosis may alter substance use risk by increasing susceptibility to depressed mood pre-menstrually and menstrually. The benefits of cannabis products, specifically cannabidiol, are also

marketed toward reducing PMDD-associated symptoms (e.g., pain and depressed/irritable mood; see Potts, 2018, for an example advertisement). This increased substance use susceptibility in females with PMDD (versus those without) and the marketing of cannabis for treating PMDD-associated symptoms might cause an increase in self-medication-motivated substance use pre-menstrually and menstrually among individuals with compared to those without PMDD (Beckman, 1975).

1.4 CANNABIS USE MOTIVATIONS

As with other substances (Cooper, 1994), people use cannabis to obtain various desirable outcomes. In adapting Cooper's (1994) four-factor motivational model from alcohol to a cannabis use context, Simons et al. (1998) identified five distinct motivational factors involved in cannabis use behavior. These five cannabis use motivations are: enhancement (e.g., "I use cannabis to get high"), conformity (e.g., "I use cannabis so that others won't kid me about not using cannabis"), expansion (e.g., "I use cannabis because it helps me be more creative and original"), social (e.g., "I use cannabis to be sociable"), and coping (e.g., “I use cannabis to forget my worries”). Research indicates that coping motivations for cannabis use are particularly risky motives in terms of their specific links to greater levels of cannabis use (Schlossarek, Kempkensteffen, Reimer, & Verthein, 2016). Relations between coping motivations for cannabis use and cannabis use behaviors are stronger among females than males (Simons et al., 1998). Since the endorsement of coping motivations are associated with more severe cannabis use, particularly in females, the examination of coping motivations is of crucial importance in the cannabis use field.

Motivations for using substances, specifically alcohol use, show within-subject variability when examined daily, and are predicted by situational factors, including daily mood (Arbeau, Kuiken, & Wild, 2011). Daily mood may similarly influence one's motivation for using cannabis. Specifically, it is possible that females may use cannabis to cope with increases in depressed mood pre-menstrually and/or menstrually as means of self-medication.

To date, only three studies have assessed variations in substance use motivations across the MC, specifically motives for alcohol consumption (two studies; Joyce et al., 2018; Sutker et al., 1983) and motives for nicotine intake (one study; Allen et al., 2018). The two alcohol studies suggested that drinking motivations differ by MC phase and MC day. Sutker et al. (1983) found normally-cycling females reported drinking to cope more frequently menstrually versus other MC phases. Similarly, we identified that coping motivations for drinking predicted heightened drinking specifically during MC days one to five (i.e., the menstrual phase; Joyce et al., 2018). These findings indeed suggest drinking to cope predicts elevations in alcohol consumption during the menstrual phase, consistent with SMT predictions. In another cross-sectional study, Allen et al. (2018) found higher scores for 15 of 18 nicotine use motives (e.g., affective enhancement) during the menstrual and follicular phases versus the luteal phase. Thus, these findings again suggest that nicotine use motivations differ across the MC, with increases at phases partially consistent with SMT predictions. Other substances of abuse, such as cannabis, must also be examined across the MC to identify MC-related changes in cannabis use, depressed mood, and coping motivations for using cannabis.

1.5 CANNABIS USE ACROSS THE MENSTRUAL CYCLE

Three studies have been published examining the relationship between cannabis use and the MC with mixed findings (Griffin et al., 1986; Hanzal et al., 2019; Mello & Mendelson, 1985). Mello and Mendelson (1985) were the first to assess cannabis acquisition and use patterns across the MC using a 35-day in-patient, in-laboratory design where participants were able to "buy" cannabis using operant conditioning tasks (pressing buttons to earn cannabis). Of the participants, three groups were identified: those who increased cannabis earning pre-menstrually (one-third of the sample), those who decreased cannabis earning pre-menstrually (one-third of the sample) and those who did not experience a change in the amount of cannabis earned pre-menstrually (one-third of the sample) versus other MC phases. Consistent with SMT, participants who reported higher levels of distress pre-menstrually also earned increased quantities of cannabis pre-menstrually. Although Mello and Mendelson's (1985) findings were informative, the study was conducted within a laboratory setting, suggesting the findings may lack ecological validity, and thus highlighting the need for studies in more real-world settings.

Griffin et al. (1986) conducted a daily diary study which examined cannabis use and mood across the MC. Overall, findings indicated that neither cannabis use nor mood differed by MC phase in the total sample. Although these findings suggested that cannabis use may not differ as a function of MC phase, this older study had several methodological limitations in comparison to the methodologies available for such research today (e.g., mailing in surveys versus text message surveys; the mood measure employed, i.e. the Moos Menstrual Distress Questionnaire, was not internally consistent

and did not divide overall negative mood into depression versus anxiety; see Appendix A for a more detailed explanation of the limitations of Griffin et al., 1986).

Finally, we recently conducted a pilot study which assessed the association between stress levels and subsequent cannabis use quantity during the first episode of cannabis use following an earlier stress level assessment (Hanzal et al., 2019). Our findings suggested that the quantity of cannabis used and reported stress levels increased pre-menstrually, versus the follicular/ovulatory and ovulatory phases, respectively, consistent with SMT predictions. Although Hanzal et al. (2019) were able to address many of the previous limitations and methodological flaws identified in Griffin et al. (1986) and Mello and Mendelson (1985), two issues remained which were addressed within the current larger study. First, given the small sample size (n = 14) of this pilot study, Hanzal et al. (2019) assessed early stress levels and subsequent cannabis use quantity across specific MC phases. Although informative, collapsing data across MC phases results in a loss of potentially vital information (Joyce & Stewart, 2018). Second, Hanzal et al. (2019) did not assess the predictive value of mood and cannabis use motivations on cannabis use quantity at various phases of the MC, which is crucial in the development of preventative and therapeutic interventions for reproductive-aged, normally-cycling female cannabis users.

1.6 THE CURRENT STUDY

The current study aimed to fill identified gaps in the literature on female-specific factors contributing to cannabis use. This study examined reports of cannabis use quantity, depressed mood, and coping motivations for using cannabis over an entire MC in 69 normally-cycling female cannabis users via daily diary methodology. The goal was

to determine if the MC influences a female's depressed mood, use of cannabis to cope, cannabis use levels, and/or their inter-relations. This study also acted as a platform to extend Joyce et al. (2018) by examining not only coping motivations as mediators (as done in Joyce et al., 2018), but also depressed mood states, as the inclusion of depressed mood states better tests assumptions of SMT. Findings from this study will enhance our knowledge of female-specific cannabis use factors and improve preventative and therapeutic intervention methods for reproductive-aged females with a CUD. For instance, female cannabis users and, to a greater extent, those with a provisional PMDD diagnosis may use greater cannabis quantities to cope with depressed mood at specific, theoretically-relevant MC phases (i.e., pre-menstrually and menstrually). These findings may be used as a psychoeducational tool for females seeking treatment for their cannabis use, to identify low-risk times of the MC to begin cessation attempts, and to help females with a CUD develop more adaptive/less risky ways of coping with increases in depressed mood through training in cognitive behavioral skills (e.g., cognitive restructuring, mindfulness, distress tolerance, and acceptance).

Two hypotheses were tested which we refer to, in turn, as the self-medication hypothesis and the PMDD hypothesis. Based on previous literature suggesting increases in depressed mood pre-menstrually and menstrually (Aganoff & Boyle, 1994; Collins et al., 1985; Reed et al., 2008), it was hypothesized that normally-cycling females would increase the quantity of cannabis used during the pre-menstrual and menstrual phases relative to other MC phases. This change in cannabis use quantity pre-menstrually and menstrually was predicted to be explained by pre-menstrual and menstrual increases in depressed mood and coping motivations for using cannabis. Finally, based on literature

suggesting females with PMDD experience a greater susceptibility toward substance use versus those without PMDD (Reed et al., 2008) and females with heightened distress pre-menstrually worked to "earn" larger quantities of cannabis than females with low levels of distress pre-menstrually (Mello & Mendelson, 1985), it was predicted that normally-cycling females with a provisional PMDD diagnosis would show stronger relations between depressed mood and cannabis use quantity pre-menstrually and menstrually as compared to females without PMDD. It was also hypothesized that females with a provisional PMDD diagnosis would exhibit more pronounced associations between coping motivations and cannabis use quantity pre-menstrually and menstrually as compared to females without PMDD symptoms.

CHAPTER 2 METHODS

2.1 PARTICIPANTS

Eighty-eight female cannabis users (M_{age} = 28.86 years, *SD* = 6.11, Range = 19-45) were recruited through advertisements in the community, listings on social media, and local newspaper articles (see Appendix B; Kedrosky, 2018; McPhee, 2018). Of the initial 88 participants, 19 were excluded for low survey completion rates (i.e., daily diary completion rate of < 70%; Mundy, 2002)[2], resulting in a final sample of 69 participants (M_{age} = 29.25, *SD* = 5.66, Range = 19-43 years)[3].

To be included, females met a list of inclusion and exclusion criteria. Participants must (1) have been between the ages of 19 and 45 (as 45 years old is the standard upper cut-off for MC research; McKinlay, Brambilla, & Posner, 1992; Treloar, 1981)[4], (2) have owned/had access to a smart phone with data and texting plans to access daily surveys sent via text message, (3) have not had any interference with their MC (i.e., recent [past six months] or current pregnancy, use of hormonal contraceptives, plans of conceiving, breastfeeding, hysterectomy, amenorrhea [i.e., missed periods], or perimenopausal/postmenopausal), (4) have had an average MC length between 25 and 32

[2] The average survey completion rate for all 88 participants was 81.23% while the exclusion of 19 participants with low survey completion rates resulted in an average survey completion rate of 91.80%.

[3] There were no significant differences between participants who were excluded and included on age, race, all five Marijuana Motives Measure subscale scores, Cannabis Use Disorder Identification Test - Revised score, Drug Abuse Screening Test score, Pre-Menstrual Assessment Form - Short Form score, and all current mood disorder diagnoses.

[4] Females in the perimenopausal (beginning around the age of 45) and menopausal stages of life experience permanent cessation of menstruation and changes in ovarian hormone functioning. These ovarian hormone changes are drastically different from normally-cycling females (Burger, Dudley, Robertson, & Dennerstein, 2002; Schmidt & Rubinow, 2009) which has led to the exclusion of females above 45 years of age in MC research.

days (Carroll et al., 2015), (5) not have been diagnosed with a pain disorder or prescribed medicinal cannabis to eliminate females who use cannabis to self-medicate pain (unrelated to their MC; e.g., chronic back pain) or who use cannabis regularly as prescribed, and (6) not have stopped administering hormonal contraceptives within the past three months prior to study participation, as hormonal contraceptives can influence ovarian hormones for up to three months post-use (Klein & Mishell, 1977). Additionally, to increase the probability of and the variability in cannabis use over the course of study participation, females were required to have used cannabis at least four times during the past month. Finally, participants could not be abstaining from, trying to abstain from, or be in treatment for, their cannabis use.

2.2 PROCEDURE

2.2.1 Recruitment and Screening

Study advertisements, posted within the community, via listings on social media, and via local newspaper article coverage of the study (see Appendix B; Kedrosky, 2018; McPhee, 2018) instructed interested prospective participants to contact the Mood, Anxiety, and Addiction Comorbidity Laboratory (MAAC Lab) at Dalhousie University via email. A date/time was scheduled for prospective participants who contacted the MAAC Lab to complete a telephone screening with research personnel to assess eligibility criteria (see Appendix C). Research personnel for this study consisted of the Masters' candidate and three trained volunteers. The telephone screening lasted between 10 and 15 minutes. If eligible and willing to participate, participants were scheduled for in-laboratory sessions one and two, as saliva samples obtained during these two sessions had to be collected during MC days one - seven (theoretically low progesterone

concentrations) or MC days 18-24 (theoretically high progesterone concentrations; Andreano, Arjomandi, & Cahill, 2008; Andreano & Cahill, 2010). The collection of these saliva samples was in no specific order; the first saliva collection occurred during the set of MC days closest to the date of scheduling. Participants began study participation at different times throughout their MC, rather than having all participants beginning the study at the same time in their MC, so any reactivity effects (e.g., a reduction in cannabis use due to self-monitoring) would average out across participants. If the participant's schedule was unreliable and a date/time for the first testing session could not be determined during the telephone screening, the participant was asked to contact the MAAC Lab closer to her optimal date for obtaining the first saliva sample. If the participant's optimal dates for saliva collection drew near and research personnel had not heard from her, research personnel sent a text message to the participant to act as a reminder and the in-laboratory sessions were scheduled if the potential participant was still interested.

2.2.2 First In-Laboratory Session

One day before session one was scheduled, participants were contacted by research personnel via text message reminding them of the date/time of their upcoming session and to provide further information on the saliva sample collection guidelines to be followed prior to session one attendance (see Appendix D).

During the first in-laboratory session, participants reviewed and discussed the informed consent form with research personnel and provided oral consent to participate (see Appendix E). Oral consent was obtained as a precaution to mitigate potential risks to

the study's participants[5]. After obtaining informed consent, the ecological momentary assessment (EMA) training phase took place. Participants were shown how to answer items via smartphone, items similar to those that would be asked of them during the 32-days of EMA. A text message containing a practice survey link was sent to participants from SurveyMonkey. Research personnel showed participants how to complete the practice surveys and answered any questions regarding EMA data collection during this time.

In the following order, participants were administered the interview-based Cannabis Timeline Followback (CTLFB; Robinson, Sobell, Sobell, & Leo, 2014) and several self-reported questionnaires, including: (1) an author-compiled Menstrual Cycle Questionnaire (MCQ; see Appendix F), (2) the Pre-Menstrual Assessment Form - Short Form (PAF-SF; Allen, McBride, & Pirie, 1991), (3) a Demographics Questionnaire (see Appendix G), (4) the Marijuana Motives Measure (MMM; Simons et al., 1998), (5) the Drug Abuse Screening Test (DAST; Skinner, 1982), and (6) the Cannabis Use Disorder Identification Test - Revised (CUDIT-R; Adamson & Sellman, 2003; refer to section 2.3 for details on the measures used). Research personnel remained close by during participants' completion of the self-report measures in case the participants had any questions as they went through the package of measures.

[5] Oral consent was required to gain approval from the Research Ethics Board (REB). The REB was concerned about the collection of illegal activity information (as cannabis was illegal in Canada when the REB application was submitted) and that this illegal activity information, although being collected using a participant code, could still be linked to the participant. The REB required that we implement methods, specifically using oral consent, to mitigate potential risks to the study's participants so that, to the extent possible, a connection between personally identifiable information and study data/samples could not be made.

After participants had become comfortable in the laboratory and with research personnel, the Structured Clinical Interview for DSM-5 Disorders - Research Version (SCID-5-RV; First, Williams, Karg, & Spitzer, 2015) was conducted. The SCID-5-RV was always performed by the Masters' candidate who was thoroughly trained and supervised in the administration of the SCID-5-RV to clinical populations by a licensed clinical psychologist. Given the sensitive nature of the SCID-5-RV, a trained clinical psychologist/psychiatrist was always on-call during administration. The trained clinical psychologist/psychiatrist was to be contacted if a participant indicated being or was thought to be at imminent risk (e.g., suicidal). A list of mood disorder resources was also provided to participants by the Masters' candidate in a sensitive manner upon SCID-5-RV completion whenever mental health concerns were identified (see Appendix H). The Masters' candidate outlined how to access all of the provided resources.

Finally, participants provided a saliva sample[6]. Research personnel described and demonstrated how to passively drool into a saliva collection tube. Participants were then given a new, sterile tube in which to provide their saliva sample. Medical gloves were available for participants and research personnel to wear while handling saliva samples. As session one concluded, participants were asked to contact research personnel if they had any issues with their text message surveys. Session one lasted approximately one hour.

2.2.3 Ecological Momentary Assessment

Participants completed surveys on their cell phone, every day for 32-days using survey software developed by SurveyMonkey (SurveyMonkey Incorporated; San Mateo,

[6] During the first in-laboratory session, saliva samples of 32 participants (46.4%) were collected during MC days one-seven while 37 participants (53.6%) were collected during MC days 18-24.

CA) and programmed by DigitalOcean (Toronto, ON). At 10:30 am each day[7], participants received a text message asking them to complete a daily mood measure (three questions; Grant, Stewart, & Birch, 2007)[8] and to report their MC day (one question), with day one being the first day of menstruation (see Appendix I). If cannabis was used during the previous day, participants were also asked to complete a single question on the total quantity of cannabis used the previous day (one question; in standard joints; Zeisser et al., 2012) and their motivations for using cannabis the previous day (two questions; Simons et al., 1998; see Appendix I)[9]. Daily diary surveys, the 10:30 am and 2:00 pm surveys, took approximately 13 minutes per day to complete (i.e., ~7 hours attributed to EMA in total).

2.2.4 Second In-Laboratory Session

Prior to session two, participants were contacted via text message, acting as a reminder of the date/time for their second in-laboratory session. Within this text message, participants were provided with another reminder of the saliva sample collection guidelines (see Appendix D). Saliva collection was identical to the saliva collection outlined for session one (see section 2.2.3 above); however, the sample was collected during the opposite period of MC days (i.e., during MC days 18 to 24 if the first saliva

[7] Participants received three text message surveys daily. Two text messages included survey links, the first was sent at 10:30 am and the second was sent at 2:00 pm. A third reminder message of the 2:00 pm survey was sent to participants at 6:30 pm. Data from this thesis comes from the first 10:30 am survey and thus, only the 10:30 am survey is described herein.

[8] Participants completed 10 daily mood questions resulting in scores for daily positive, depressed, and anxious mood. For purposes of the present thesis, the three daily depressed mood questions were combined, resulting in an overall depressed affect score.

[9] There were five cannabis use motive items assessed and for the purposes of this thesis, only two questions pertaining to coping motives were assessed within the analyses given their theoretical relevance.

sample was collected during MC days one to seven or vice versa; Andreano et al., 2008; Andreano & Cahill, 2010). Session two lasted approximately 30 minutes.

2.2.5 Third In-Laboratory Session

Following completion of the 32-days of EMA, participants were contacted, via text message, and a date/time was scheduled for an in-laboratory debriefing session. During session three, participants were provided with a full explanation of the study's purpose during which time participants: were encouraged to ask questions and/or express any concerns regarding the study (see Appendix J); answered a debriefing questionnaire (see Appendix J); and received their compensation. The debriefing questionnaire assessed potential reactivity to EMA procedures during the 32-days of self-monitoring from the participant's perspective. Participants were then compensated for their time and effort at a rate of $10.85 CDN/hour (minimum wage in Nova Scotia at the time of study REB approval) for a maximum compensation amount of $97.65. Compensation was calculated based on the number of in-laboratory sessions attended and surveys completed[10]. Once session three came to an end, participants were provided with a list of addiction and mental health resources if they wished to seek treatment for a cannabis use/substance use or mental health disorder after participation (see Appendix K). Research personnel outlined how to access all of the provided resources. Session three lasted approximately 30 minutes.

[10] Compensation totals were determined based on the following times estimated for each session/survey: one-hour for session one ($10.85 CDN), seven hours for EMA completion (13 minutes per day for 32 days = ~seven hours; $75.95 CDN), 30-minutes for session two ($5.43 CDN), and 30-minutes for session three ($5.43 CDN).

2.2.6 Saliva Sample Storage

Once collected from the participant, saliva samples were stored in a research-grade freezer (-30°C) until progesterone enzyme-linked immuno-sorbent assays (ELISAs) were completed. The maximum period of saliva storage (before progesterone assays) was 12 months, as progesterone concentrations remain stable at -30°C without significant degradation during this period (Latendresse & Ruiz, 2009).

2.2.7 Salivary Progesterone Enzyme-Linked Immuno-Sorbent Assays

The Masters' candidate completed six plates of 96 well salivary progesterone ELISAs using Salimetrics (State College, PA) ELISA kits from the same lot number (Lot #: 1902544).

On the day of assay, all reagents were brought to room temperature (20.5°C) and saliva samples were completely thawed. A three-fold dilution series was performed to generate standards with concentrations of: 2430 pg/mL, 810 pg/mL, 270 pg/mL, 90 pg/mL, 30 pg/mL, and 10 pg/mL. Thawed saliva samples were centrifuged at 1500 x *g* for 15 minutes. Centrifuging the saliva samples allowed for the removal of mucins and other particulate matter interfering with antibody-binding which could affect results. After centrifugation, 100 µL of each saliva sample was added to 400 µL of assay diluent. After vortexing to ensure homogeneity, 50 µL of standards, controls (i.e., high [956.65 pg/mL ± 241.66] and low [44.09 pg/mL ± 17.64] progesterone controls), and saliva samples were placed into the appropriate wells. Each standard, control, and saliva sample were assayed in duplicate (i.e., technical replicates). Once all standards, controls, and saliva samples were in the appropriate wells, an enzyme-antibody conjugate (1:800 dilution) was prepared by adding 22.5 µL of the progesterone enzyme-antibody conjugate

with 18 mL of assay diluent. Once vortexed, 150 µL of this enzyme-antibody conjugate was added to each well. Each plate was mixed on a plate shaker (New Brunswick Scientific Classic Series C2; Edison, NJ) continuously at 400 rpm for one hour at room temperature (20.5°C) to incubate.

During incubation, a 1X wash buffer was prepared by combining 100 mL of Wash Buffer Concentrate (10X) and 900 mL of deionized reverse osmosis H_2O (Milli-Q Direct 8/16 System; Molsheim, France). After incubation, the contents of each plate were aspirated and each well was washed four times with 300 µL of the 1X wash buffer. Following each wash, the plate was thoroughly blotted before being turned over. Following washing, 200 µL of 3,3',5,5'-Tetramethylbenzidine (TMB) substrate solution was added to each well. Each plate was then mixed for five minutes at 400 rpm and incubated in sealed foil in the dark at room temperature (20.5°C) for 25 minutes. Once incubation was complete, 50 µL of stop solution was added to each well and the plate was placed on a plate shaker for 3 minutes at 400 rpm. Following this step, each plate was read, within 10 minutes of adding the stop solution, at 450 nm using a plate reader (ThermoScientific Multiskan™ FC Microplate Photometer; Waltham, MA).

2.3 MATERIALS

2.3.1 Session One

2.3.1.1 Cannabis Timeline Followback

To reconfirm cannabis use level eligibility (i.e., cannabis use at least four times within the past month), cannabis use over the prior 30-days was assessed using an interview-based CTLFB (Robinson et al., 2014). Participants were presented with a calendar and asked to provide information pertaining to special/salient occasions during

the past 30 days (e.g., birthdays, holidays) which were recorded on the calendar to act as memory anchors to assist in accurate retrospective recall (Sobell & Sobell, 1992). Robinson et al. (2014) have found acceptable to excellent test-retest reliability (within a one- to two-week period) for the CTLFB over a 30-day period with reliabilities ranging from 0.75 to 0.96. The CTLFB assessed various cannabis use behaviors (e.g., type of cannabis used, amount of cannabis used); for our purposes, days were coded as to whether cannabis was used or not (yes/no). From this, the number of days within the past month where cannabis was used was calculated to re-confirm participant eligibility.

2.3.1.2 Menstrual Cycle Questionnaire

The MCQ is an eight-item author-compiled measure used to ensure no changes in eligibility had occurred since the telephone screening (e.g., females did not begin using hormonal contraceptives; see Appendix F). Four items were designed to capture information on pregnancy (e.g., "Are you currently or have you recently (i.e., past year) been pregnant?") and the use of hormonal contraceptives (e.g., "Are you currently taking any form of hormonal contraception? [e.g., birth control pill, Depo-Provera injection, Evra patch, Implanon implant, NuvaRing ring, hormonal intrauterine device]"); three items captured participant MC length and regularity (e.g., "On average, how long is your entire MC [i.e., time between the start of one "period" to the start of the next "period"]?"); and one item obtained information on the participant's most recent menstruation (e.g., "Thinking back to your last menstrual "period", on what date did your "period" begin? [Count the first day of real blood flow, not days of spotting]?"). The MCQ was administered immediately following the CTLFB, as it was reasoned that the memory

anchors used in the retrospective recall required for the CTLFB would help participants remember previous events (e.g., the first day of their last menstruation) more accurately.

2.3.1.3 Pre-Menstrual Assessment Form - Short Form

The PAF-SF included ten-items pertaining to changes experienced pre-menstrually (e.g., feeling bloated; Allen et al., 1991). The intensity of change experienced pre-menstrually was scored from one ("no change") to six ("extreme change"). The PAF-SF has excellent internal consistency ($\alpha = .95$) and acceptable test-retest reliability ($r = .60 - .70$; Allen et al., 1991). A total score was calculated by summing responses. Additionally, PAF-SF subscale scores - for affect, water retention, and pain - were determined by summing participant responses to specific PAF-SF items. The PAF-SF affect subscale score was the sum of questions two, three, four, and five (e.g., "Feel that I just "can't cope" or am overwhelmed by ordinary demands"; theoretical subscale range = 4-24). The water retention subscale score was the sum of questions seven, nine, and ten (e.g., "Have edema, swelling, puffiness or 'water retention'"; theoretical subscale range = 3-18). Finally, the pain subscale was the sum of questions one, six, and eight (e.g., "Have pain, tenderness, enlargement, or swelling of breasts"; theoretical subscale range = 3-18). These three subscales have acceptable to excellent internal consistency ($\alpha = .74 - .92$; Allen et al., 1991).

2.3.1.4 Demographics Questionnaire

Correlates of adult cannabis use were assessed using seven author-compiled demographic items which examined participants': ethnicity, age, and education level (e.g., "What is your current education level?"; Hawkins, Catalano, & Miller, 1992; see Appendix G). Additionally, as addictions commonly occur among the offspring of

parents with an addiction (Biederman, Faraone, Monuteaux, & Feighner, 2004), the demographics questionnaire was used to ask participants to self-report on their perceptions as to whether either parent had an alcohol, cannabis, and/or gambling problem/disorder.

2.3.1.5 Marijuana Motives Measure

The MMM was a 25-item measure used to assess the frequency (1 = "almost never/never" to 5 = "almost always/always") with which cannabis was used for each of five trait motives including: enhancement ("To get high"), conformity ("To be liked"), expansion ("To know myself better"), coping ("To forget my worries"), and social ("To be sociable"; Simons et al., 1998). Cannabis use motives exhibit good to excellent internal consistency (α = .84 - .94) and are excellent predictors of cannabis use (Simons et al., 1998). Each MMM subscale contained five questions pertaining to each cannabis use motive (coping motives subscale [questions 1, 4, 6, 15, & 17], conformity motives subscale [questions 2, 8, 12, 19, & 20], social motives subscale [questions 3, 5, 11, 14, & 16], enhancement motives subscale [questions 7, 9, 10, 13, & 18], and expansion motives subscale [questions 21, 22, 23, 24, & 25]; Simons et al., 1998). Total subscale scores were the average response rating to each motive subscale. The MMM was used to determine trait motives for cannabis use in the sample for descriptive purposes.

2.3.1.6 Drug Abuse Screening Test

Problematic drug use (including cannabis as well as drugs other than cannabis) was assessed using the ten-item DAST (Skinner, 1982), where each item was scored on a dichotomous scale (1 = yes and 0 = no; e.g., "Do you abuse more than one drug at a time?"). The DAST has excellent internal consistency (α = .92) and acceptable test-retest

reliability between three and 10 days (r = .71; Cocco & Carey, 1998; Skinner, 1982). Responses were summed to determine the degree of problematic drug use (0 = none; 1-2 = low; 3-5 = moderate; 6-8 = substantial; and 9-10 = severe). The DAST was used to describe the severity of participants' problematic drug use across all drugs, not just cannabis use.

2.3.1.7 Cannabis Use Disorder Identification Test - Revised

The CUDIT-R was an eight-item measure, with responses ranging from 0 ("never") to 4 ("daily/almost daily"), used to assess cannabis use disorders amongst at-risk populations (e.g., "Have you thought about cutting down or stopping your use of cannabis?"; Adamson & Sellman, 2003). The CUDIT-R exhibits good internal consistency (α = .84) and test-retest reliability (between six and 12 months; r = .85 - .87, respectively; Adamson & Sellman, 2003). Scores were obtained by summing participant responses. Scores between eight and 11 suggested hazardous cannabis use, while scores of 12 or above suggested a CUD. The CUDIT-R was used to identify participants problematic cannabis use.

2.3.1.8 Structured Clinical Interview for DSM-5 Disorders - Research Version

The SCID-5-RV is the gold standard for mood disorder diagnoses in research settings (First et al., 2015) with good test-retest reliability over one week (r = .76) and very good to excellent inter-rater reliability (κ = .62 - .82; Tolin et al., 2018); the validity of the SCID-5-RV has not yet been determined. The current mood disorder portion of the SCID-5-RV was administered to identify present mood disorders. Specifically, the SCID-5-RV was used to divide participants into those with and those without a provisional

PMDD diagnosis[11] for analyses. PMDD is a relatively new mood disorder which was added to the DSM-5 (American Psychiatric Association, 2013). Thus, an analysis of the reliability and validity of diagnosing PMDD via the SCID-5-RV is lacking. Fortunately, prior to the disorder's addition to the DSM-5, researchers began assessing the reliability of a structured interview for diagnosing PMDD, using questions nearly identical to those on the PMDD diagnosis portion of the SCID-5-RV (e.g., "Feels anxious, tense, keyed up, or on edge" and "Experiences physical symptoms"; Accortt, Bismark, Schneider, & Allen, 2011). Accortt et al. (2011) found a structured interview for PMDD diagnoses has high inter-rater agreement (ICC = 0.86 - 1.00) and reliability ($\kappa = 0.96$).

2.3.2 Ecological Momentary Assessment

Daily diaries have been used to successfully track addictive behaviours, such as nicotine use (Mullane et al., 2008), alcohol use (Joyce et al., 2018), gambling (Joyce et al., 2019), and cannabis use (Hanzal et al., 2019; Tyler, Jones, Black, Carter, & Barrowclough, 2015). Despite the potential burden on participants, a 32-day period of data retrieval was chosen due to MC length variability (i.e., to accommodate females with a longer MC). Twice daily prompts were selected for the overall study based on high compliance rates with this number of prompts in our past work (Grant, Stewart, & Mohr, 2009; Joyce et al., 2019, 2018) and evidence that increasing the number of daily prompts lowers compliance (Battista et al., 2015). Additionally, to avoid having participants complete unnecessary items, a skip pattern was utilized whereby questions on cannabis

[11] A definite PMDD diagnosis is only made if symptoms have been confirmed by prospective daily ratings during at least two symptomatic MCs. For the current thesis, participants in the PMDD group have a provisional PMDD diagnosis on the SCID-5-RV as patterns of self-reported symptoms were not confirmed by prospective daily ratings during at least two symptomatic MCs.

use and cannabis use motives were only prompted if the participant indicated they had used cannabis the previous day.

2.3.2.1 Mood Measure

Participants indicated the extent to which each of three words described their depressive mood using a visual analogue scale (VAS; see Appendix I). Items used by Grant, Stewart, and Birch, (2007) to measure depressed affect (i.e., "sad", "depressed", and "blue") were employed including the anchors “not at all” to “very”. The VAS consisted of a sliding scale where participants moved an icon between the two anchors, leaving the icon at the location on the VAS best reflecting their current mood. For scoring, “not at all” was coded as zero whereas “very” was coded as 100, with possible scores ranging anywhere between these two values. Responses to each depressed affect adjective were averaged to determine overall depressed mood for each MC day. Previous research indicates using a touch screen for implementing a mood VAS produces scores that are internally consistent ($\alpha = 0.89$; Kreindler, Levitt, Woolridge, & Lumsden, 2003). In the present study, internal consistencies for depressed mood were computed for three days representing the middle MC day of the two saliva sample collection sessions (MC days 1-7 [middle MC day = 4; n = 42] and MC days 18-24 [middle MC day = 21; n = 38]) and the middle of the MC (day 14; n = 46). Excellent internal consistencies were found, $\alpha = 0.962$ (MC day 4), 0.963 (MC day 14), and 0.947 (MC day 21). Depressed affect scores were used to assess hypothesized associations between depressed affect and cannabis use across the MC.

2.3.2.2 Menstrual Cycle Day

Participants identified their MC day, with day one being the first day of menstruation (see Appendix I). If the participants' MC day was unknown, participants had the option of selecting ‘unknown’ until menstrual bleeding began. During data analyses, a count forward-backward method (see Wideman, Montgomery, Levine, Beynnon, & Shultz, 2013 for an explination) was employed to specify unknown MC days using the first day of menstrual bleeding as the anchor.

2.3.2.3 Cannabis Use Measure

When participants reported that cannabis was used yesterday, participants indicated the quantity of cannabis used via the number of standard cannabis joints (Zeisser et al., 2012; see Appendix I). A standard joint referred to half of a gram, five bong or pipe hits, and/or 10 puffs (Zeisser et al., 2012). The number of standard cannabis joints per day was selected to identify hypothesized cyclical fluctuations in cannabis use quantities across the MC.

2.3.2.4 Cannabis Use Motives

Coping motives for cannabis use were assessed using two modified questions from a state version of the MMM’s coping motives scale (i.e., "Yesterday I used cannabis because cannabis helps me cope with negative mood" and "Yesterday I used cannabis because cannabis helps me deal with stress"; Simons et al., 1998; see Appendix I). Participants responded to the above questions using a VAS with the anchors "not at all" to "very". For scoring purposes, “not at all” was coded as zero whereas “very” was coded as 100, with possible scores ranging anywhere between these two values. The state coping motives questions asked via the daily diary survey was validated by correlating

average state coping motivations scores (collected via the daily diary survey)[12] to the trait version of the coping motivations subscale (collected via the MMM). Daily coping motivations were significantly and positively correlated with the trait coping motivation subscale on the MMM (moderate effect; $r = 0.580$, $p < 0.001$). Internal consistencies for coping motives were also computed for three days representing the middle MC day of the two saliva sample collection sessions (MC days 1-7 [middle MC day = 4; n = 49] and MC days 18-24 [middle MC day = 21; n = 38]) and the middle of the MC (day 14; n = 41). Good internal consistencies were found, $\alpha = 0.809$ (MC day 4), 0.800 (MC day 14), and 0.802 (MC day 21). State coping motive scores were used to identify the extent to which participants endorsed using cannabis to cope across MC days, specifically during days when cannabis was used.

2.3.3 Salivary Progesterone Enzyme-Linked Immuno-Sorbent Assays

Salivary hormone concentrations identified using salivary ELISAs, specifically progesterone concentrations, correlate with biologically active, unbound free plasma concentrations (Patel, Shaw, MacIntyre, McGarry, & Wallace, 2004) making saliva samples a non-invasive, reliable indicator of MC day. Salivary ELISAs were conducted on saliva samples during times of the MC with known low (MC days one - seven) and high (MC days 18-24) progesterone concentrations, based on an average 28-day MC (Andreano et al., 2008; Andreano & Cahill, 2010) to validate self-reported MC day, consistent with previous research (e.g., Joyce et al., 2019, 2018).

[12] Average state coping motive scores were calculated on a case-by-case bases using all available data (collected on days where cannabis was used) and creating an average state coping motives score for each participant by summing coping motive scores (per day) and dividing this sum by the number of days where coping motives were reported by the participant.

2.3.4 Debriefing Questionnaire

Consistent with previous EMA research in the addiction field (e.g., Hufford, Shields, Shiffman, Paty, & Balabanis, 2002), participants reported, on a 10-point scale (0 = "not at all", 5 = "moderately", 10 = "a great deal"), whether monitoring impacted their mood (i.e., "To what extent did the monitoring impact your mood?") and cannabis use behaviors (i.e., "To what extent did the monitoring impact your cannabis use behaviors?"; see Appendix J). Reactivity measures on the debriefing questionnaire were used to identify potential issues with EMA reactivity, or lack thereof. Since participants began their study participation at different times during their MC, any reactivity effects (e.g., a reduction in cannabis use due to self-monitoring) should have averaged out across participants.

2.4 DATA ANALYSES

2.4.1 Lagging Variables

Since the quantity of cannabis used and coping motives were reported for the previous day, a lag procedure was used for data scoring, where responses to cannabis use quantities and coping motive items were shifted back one day to align with the day during which the cannabis use occurred. A lagging procedure was not used for participant responses to depressed affect or MC day items as these two items assessed present day depressed affect and MC day.

2.4.2 Elimination of Alternative Cannabis Forms

A standard joint as defined herein, i.e., half of a gram, five bong or pipe hits, and/or 10 puffs, does not equate the cannabis flower to other forms of cannabis and research equating cannabis quantity across various forms of cannabis for research

purposes is lacking (e.g., flower, edible, and concentrates; Zeisser et al., 2012). As such, all reported instances of using cannabis edibles and concentrates (4 and 1 out of 1,932 days, respectively) were eliminated prior to MC phase standardization. The reported use of cannabis edibles and concentrates was such a low proportion of the total use and therefore it is unlikely to have a substantive influence on the results, caution nonetheless should be taken in generalizing our results as our findings may not apply to cannabis edibles and concentrates.

2.4.3 Standardization of Menstrual Cycle Data

Differing MC lengths makes it difficult to assess variations in continuously collected variables, such as cannabis use, mood, and cannabis use motivations, across the MC. Analytical approaches in MC research commonly collapse data across MC phase to examine MC phase-related changes. While informative, collapsing data across MC phase results in a loss of potentially vital information. To account for individual variability in MC length, we developed a methodology to standardize the MC to an average 28-day cycle (Joyce & Stewart, 2018). Continuous standardization, as described in Joyce and Stewart (2018) was used to standardize the luteal phase to a seven-day phase, while the remaining phases were held fixed, resulting in a standardized 28-day MC for each participant. MC data standardized using continuous standardization can be analyzed using more intricate statistical analyses, such as time-varying effect models (TVEMs; Dziak, Li, Tan, Shiffman, & Shiyko, 2015; Tan, Shiyko, Li, Li, & Dierker, 2012) which allow for the identification of cyclical changes in cannabis use, mood, cannabis use motivations, and their inter-relations as a function of MC day (using a standardized 28-day MC). Continuous standardization has been used in our previous research to assess

relations between alcohol consumption levels, alcohol use motivations, and their inter-relations continuously across MC day (see Joyce et al., 2018).

2.4.4 Time-Varying Effect Models

Once data was standardized, TVEMs (Tan et al., 2012) were used to analyze data collected via EMA. TVEMs portray changes in the association between predictor and outcome variables across time in a flexible manner. Within this study, TVEM were used to examine how outcome (cannabis use quantity [in standard joints]) and predictor (depressed mood and coping motivation) variables change across MC day and to examine associations between these variables across MC day. Specifically, TVEMs provided a flexible estimation of how the association between the predictor and outcome variable (i.e., the association between depressed mood and cannabis use quantity and the association between cannabis coping motives and cannabis use quantity) fluctuates over time (days of the MC) without assuming the association follows a parametric function. First, intercept-only models were developed to estimate the pattern of change in cannabis use quantity, depressed mood, and coping motivations across MC day. Estimates were then used to determine how each predictor was independently associated with cannabis use quantity across time (days of the MC). Two TVEMs were conducted and fit to the data using the %TVEM normal macro published by The Methodology Center (version 3.1.1; Pennsylvania, US) in Statistical Analysis Software (SAS; version 9; Cary, NC; i.e., one examining associations between depressed mood and cannabis use quantity and the other assessing relations between coping motivations and cannabis use quantity; Dziak, Li, Tan, Shiffman, & Shiyko, 2015).

Two additional sets of TVEM analyses were conducted to assess relations between depressed mood and cannabis use quantity as well as associations between coping motivations and cannabis use quantity in females with versus without PMDD (categorical moderator variable). These TVEMs were conducted identically as those described above with the full sample. Finally, a supplementary sensitivity analysis was conducted to determine whether the inclusion of individuals with mood disorders influenced results in the full sample. This is because individuals with a mood disorder diagnosis have sustained elevations in negative mood across time (e.g., persistent depressive and major depressive disorders) or rhythmic fluctuations in mood irrespective of MC phase (e.g., cyclothymic and hypomanic disorders). Thus, the inclusion of females with mood disorder diagnoses other than PMDD might have masked patterns of variation in depressed mood, coping-motivated cannabis use, and/or cannabis use (or their interrelations) that are associated with variations in ovarian hormones across MC phase. Therefore, a final set of TVEM analyses, as described above, were conducted where females with a mood disorder diagnosis (identified on the SCID-5-RV) were excluded, with the exception of those with only a provisional PMDD diagnosis.

As TVEMs provide too many time-varying coefficients to present in tables, results are presented in figures. Unstandardized regression coefficients are presented on the y-axis and MC day on the x-axis. Black lines present odds ratios while gray lines represent 90% confidence intervals (CIs)[13]. When CIs do not include 0, the association between predictor and outcome is significant on that day (Dziak et al., 2015).

[13] Given the study's small sample size (females with PMDD = 19 participants and females without PMDD = 50 participants) and the lack of prior literature in this area, we chose a CI of 90%. With this decision, we increased our chance of being wrong (i.e., increasing

2.4.5 Independent Samples T-Tests

Independent samples t-tests (two-tailed) were also conducted to assess differences in the average quantity of cannabis used, average levels of depressed mood, and average levels of coping-motivated cannabis use across all days of self-monitoring in females with and without a provisional PMDD diagnosis. The average quantity of cannabis used, average levels of depressed mood, and average levels of coping-motivated cannabis use was calculated separately for each participant. The average quantity of cannabis used (in standard joints) was calculated by summing the quantity of cannabis used across all days of self-monitoring and dividing this sum by the number of days where the participant reported using cannabis. An average depressed affect score was calculated by summing depressed affect scores across all days of self-monitoring and dividing by the number of days were the participant reported their depressed affect. Finally, an average coping-motivated cannabis use score was calculated for each participant by summing each daily coping motive score across all days of self-monitoring (collected only on cannabis using days) and dividing by the number of days where the participant reported using cannabis.

Another set of independent samples t-tests (two-tailed) were conducted on age, MC length, number of daily cannabis uses (via EMA), CUDIT-R total scores, DAST total scores, MMM subscale scores (i.e., coping, enhancement, conformity, social, and expansion), and PAF-SF total score and subscale scores (i.e., affect, water retention, and pain) to identify group differences between females with and without a provisional

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the possibility of false positives) in comparison to a 95% CI (Hair Jr, Black, Babin, & Anderson, 2009; Hazelrigg, 2009). Supplementary analyses were also conducted with a 95% CI, identifying two changes in overall findings when a 90% versus a 95% CI was used. These differences are described in the sections below on the specific findings in question.

PMDD diagnosis. For the PAF-SF and MMM subscales, cumulative subscale scores (see section 2.3.1.3 and 2.3.1.5, respectively) were used.

2.4.6 Chi-Square Tests

Chi-square tests were conducted to determine whether the two PMDD groups (i.e., females without and with PMDD) differ in their proportion of individuals within the following variables: race, ethnicity, education level, cannabis use risk (determined by the CUDIT-R), level of problematic drug use (determined by the DAST), parental addiction, current mood disorder diagnoses and comorbidities (determined by the SCID-5-RV), and cannabis using days (using the CTLFB and EMA surveys). When the count was below 5 for 20% or more cells, Chi-square tests were reported, whereas when the count was over 5 for 20% or more cells, Fisher's Exact Tests were reported.

2.4.7 Menstrual Cycle Validation

Progesterone concentrations obtained using Salimetrics ELISAs were used to validate self-reported MC day. The average of technical replicates was obtained and paired sample t-tests were conducted on these averages to examine differences in salivary progesterone concentrations during times of the MC known to be associated with low (MC days one - seven) and high (MC days 18-24) progesterone concentrations. To validate self-reported MC day in the full sample, progesterone concentrations during MC days one - seven must have been significantly lower than during MC days 18 - 24, consistent with our previous research (Joyce et al., 2019, 2018).

CHAPTER 3: RESULTS AND INTERPRETATION

3.1 Sample Descriptives

The majority of participants identified as a single race (84.1%), Caucasian (83.3%), and college/university graduates (62.3%; see Table 1). The sample average score on the CUDIT-R of 13.42 (*SD* = 6.04) was above the clinical cut-point of 12, suggesting that the average participant likely had a CUD. In fact, 59.4% of the sample scored above the clinical cut-point on the CUDIT-R (Adamson & Sellman, 2003; see Table 1). The frequency of self-reported cannabis use 30 days before study participation did not differ significantly from the frequency of self-reported cannabis use during study participation, $t_{68} = .578$, $p = .565$. Participants retrospectively reported high levels of cannabis use for the 30 days before study participation (*M* = 23.77 cannabis using days, *SD* = 9.18), with the slight majority of the sample (55.1%) being daily cannabis users (see Table 1). Results were similar when cannabis use was collected during the study via EMA (*M* = 23.42 cannabis using days, *SD* = 8.62)[14]. In contrast to the CUDIT-R, on average, the DAST suggested moderate levels of problematic substance use in the sample (*M* = 2.42, *SD* = 1.83; Skinner, 1982; see Table 1). According to the DAST, only 15.9% had no problematic substance use, most had low levels of problematic substance use (43.5%), while a considerable proportion (40.6%) had moderate to substantial levels of problematic substance use (Skinner, 1982). Participants reported, on average,

[14] Please note self-reported cannabis use during the 32-days of EMA is not perfectly representative of the actual amount of days where cannabis was used, but rather the number of days where participants completed daily surveys and indicated using cannabis. For this reason, the proportion of daily cannabis users according to EMA data cannot be determined as the majority of participants missed at least one survey and we cannot be sure whether or not cannabis was used on days where data is missing.

experiencing a typical MC length (*M* = 28.07 days, *SD* = 1.69) and levels of pre-menstrual symptoms consistent with previously tested samples of normally-cycling females on the PAF-SF (*M* = 31.83, *SD* = 9.47; Allen et al., 1991). On average, participants also reported PAF-SF subscale scores in line with previously tested samples of normally-cycling females (affect subscale [*M* = 13.48, *SD* = 4.77], water retention subscale [*M* = 8.10, *SD* = 3.99], and pain subscale [*M* = 10.25, *SD* = 3.18]). On the MMM (Simons et al., 1998) participants, on average, reported high enhancement (*M* = 3.36, *SD* = 0.715) and coping motives (*M* = 2.59, *SD* = 0.878) followed by social (*M* = 2.30, *SD* = 0.978), expansion (*M* = 2.32, *SD* = 1.09), and conformity motives (*M* = 1.09, *SD* = 0.236; see Table 2) comparable to norms reported among cannabis users; however, the relative order of the subscale means are inconsistent with those previously reported (Simons et al., 1998). The mood disorders diagnosed within the present sample on the SCID-5-RV (First et al., 2015) included current: PMDD (27.5%), persistent depressive disorder (17.6%), major depressive disorder (13.2%), cyclothymic disorder (8.8%), and hypomanic episode (1.5%; see Table 1). As addictions commonly occur among the offspring of parents with an addiction (Biederman et al., 2004), participants self-reported whether either parent had an alcohol, cannabis, and/or gambling problem/disorder. Perceived parental problems/disorders were common, with alcohol problems/disorders being the most commonly reported (36.2%), followed by cannabis use problems/disorders (15.9%), and then gambling problems/disorders (10.1%; see Table 1).

3.2 SELF-MEDICATION MODEL HYPOTHESIS IN THE FULL SAMPLE

3.2.1 Cannabis Use Quantity Across Menstrual Cycle Day

Figure 1A shows the estimated mean level of cannabis use quantity across MC day. Consistent with predictions, cannabis use quantity increased menstrually, dipped during the ovulatory and luteal phases, and began increasing again pre-menstrually. The slopes of cannabis use were also much steeper (relative to other MC phases) during the pre-menstrual and menstrual phases. Inconsistent with predictions, cannabis use quantity peaked during the MC phase following the menstrual phase, the follicular phase.

3.2.2 Depressed Mood Across Menstrual Cycle Day

In line with predictions, the estimated mean level of depressed affect increased menstrually, dipped during the ovulatory and luteal phases, and began increasing again pre-menstrually (see Figure 1B). Again, the slopes of depressed mood were much steeper during the pre-menstrual and menstrual phases relative to other MC phases. Inconsistent with predictions, depressed mood peaked during the MC phase following the menstrual phase, the follicular phase.

3.2.3 Cannabis Coping Motives Across Menstrual Cycle Day

Consistent with predictions, the estimated mean level of coping motives increased menstrually, dipped during the ovulatory and luteal phases, and began increasing again pre-menstrually (see Figure 1C). Of interest, the slopes of coping-motivated cannabis use were, yet again, much steeper during the pre-menstrual and menstrual phases versus other MC phases. Inconsistent with predictions, cannabis coping motives peaked during the MC phase following the menstrual phase, the follicular phase.

3.2.4 Depressed Mood and Cannabis Use Quantity Associations by Menstrual Cycle Day

Figure 2A shows the estimated bivariate time-varying associations between daily cannabis use quantity and depressed affect. Inconsistent with SMT predictions, depressed affect was not significantly associated with the quantity of cannabis used on any MC day in the full sample.

3.2.5 Coping Motivation and Cannabis Use Quantity Associations by Menstrual Cycle Day

The estimated bivariate time-varying associations between daily cannabis use quantity and coping-motivated cannabis use are shown in Figure 2B. Coping-motivated cannabis use was, unexpectedly, unrelated to the quantity of cannabis used on any MC day in the full sample.[15]

3.2.6 Supplementary Sensitivity Analysis

A total of 21 females were eliminated from the current sensitivity analysis due to a mood disorder diagnosis on the SCID-5-RV (see Table 5 for further information on mood disorder diagnoses in this group). Of these females with mood disorders other than solely a provisional PMDD diagnosis, the largest group had two mood disorder diagnoses (47.6% of the 21) and the most common current mood disorder diagnosis was persistent depressive disorder (42.9% of the 21; see Table 5).

Results largely remained consistent when these females with mood disorders were eliminated (compared to when females with mood disorders were included; Figures 3 & 4) with the exception of (A) the mean level of cannabis quantity use peaked during the pre-menstrual phase rather than the follicular phase when those with mood disorders were

[15] All SMT findings remain the same regardless of whether 90% or 95% CIs were used.

eliminated (Figure 3A versus Figure 1A); and (B) coping-motivated cannabis use was significantly associated with higher quantities of cannabis use during the luteal and pre-menstrual phases (MC days 17-26) when no effect was previously observed (Figure 4B versus Figure 2B). See Appendix L for all results of the supplementary sensitivity analysis.[16]

3.3 PRE-MENSTRUAL DYSPHORIC DISORDER HYPOTHESIS

3.3.1 Group Descriptives

A total of 19 participants met criteria for a provisional PMDD diagnosis via the SCID-5-RV while 50 did not meet provisional PMDD diagnosis criteria.

Among participants with and without a provisional PMDD diagnosis, the majority were of a single race, specifically Caucasian, and college/university graduates (see Table 3). In both groups, the CUDIT-R (Adamson & Sellman, 2003) suggested that the majority of participants have a CUD (see Table 3). Participants with PMDD were characterized as having low-risk problematic drug use on the DAST (57.9%; Skinner, 1982), whereas the majority of those without PMDD were characterized as either moderate-risk (40%) or low-risk problematic drug users (38%; see Table 3). Of participants reporting parental substance use/addictive behavior involvement, the majority reported having parents with an alcohol use disorder (see Table 3 for more information on differences in demographic variables in participants with and without PMDD). There were no significant differences between females with and without PMDD

[16] The sensitivity analysis findings remained largely the same regardless of whether 90% or 95% CIs were used, however when 95% CIs were implemented, coping motives were associated with higher quantities of cannabis used during MC days 18-25 (versus 17-26 when 90% CIs were used).

on age, MC length, CUDIT-R scores, DAST scores, or MMM subscale scores (see Table 4). All demographic variables were assessed for differences between PMDD groups, i.e. those with and without a provisional PMDD diagnosis. No significant associations were found with the exception of those with PMDD having a higher rate of comorbid mood disorders (i.e., one or more, two or more, or three or more comorbid mood disorders), specifically comorbid persistent depressive disorder, and having a greater number of days where cannabis was used (via the CTLFB; see Table 3).

The SCID-5-RV identified high levels of comorbidity between a provisional PMDD diagnosis and mood disorder diagnoses. Specifically, 57.9% of those with a provisional PMDD diagnosis (n = 11) had one or more mood disorder comorbidities and 21.1% (n = 4) had two or more mood disorder comorbidities (see Table 3). The mood disorder comorbidities identified on the SCID-5-RV were as follows: persistent depressive disorder (36.8% of those with provisional PMDD; n = 7), major depressive disorder (21.2%; n = 4), cyclothymic disorder (15.8%; n = 3), and hypomanic episode (5.3%; n = 1; see Table 3).

While no specific hypotheses were made *a priori* regarding overall PMDD group differences, it is worth noting that we assessed differences in the mean level of cannabis use (quantity), depressed mood, and coping motives across the two groups (i.e., those with and without PMDD). On average, the quantity of cannabis used[17] was significantly higher in females with PMDD (M = 3.44 joint equivalents/day, SD = 2.84) versus those without PMDD (M = 1.85 joint equivalents/day, SD = 1.82; t_{67} = 2.761, p = 0.007; see

[17] The sum of the quantity of cannabis used across all self-monitoring divided by the number of days where the participant reported using cannabis.

Figure 5A). Depressed affect[18], on average, did not differ between those with a provisional PMDD diagnosis (M = 23.42, SD = 16.84) and those without PMDD (M = 24.66, SD = 21.81; t_{67} = 0.224, p = 0.824; see Figure 5B). Similarly, average coping-motivated cannabis use[19] did not differ, on average, between females with (M = 60.48, SD = 23.93) versus without a provisional PMDD diagnosis (M = 55.13, SD = 25.61; t_{65} = 0.784, p = 0.436; see Figure 5C).

Group differences in the quantity of cannabis used, depressed mood, and coping motives were also assessed across MC day. Observable patterns of higher cannabis consumption and depressed affect were shown among the PMDD group compared to the non-PMDD group on at least some days of the MC (see Figures 6A-C). Differences between the PMDD and non-PMDD groups are considered statistically significant at points during the MC where the two sets of CIs are not overlapping (Field, 2012; Mantha, Thisted, Foss, Ellis, & Roizen, 1993)[20]. Using this rule, those with PMDD had higher cannabis consumption than the group without PMDD on MC days 2-24 (i.e., most MC days) and those with PMDD had higher depressed affect than those without PMDD on MC days 4-12, 19-20, and 27-28 (i.e., on the slight majority of MC days; see Figures 6A and 6B, respectively). There were no significant group differences in coping-motivated cannabis use on any MC day (see Figure 6C).

[18] The sum of depressed affect scores across all days of self-monitoring divided by the number of days where the participant reported depressed affect.
[19] The sum of each daily coping motive score across all days of self-monitoring (collected only on cannabis using days) divided by the number of days where the participant reported using cannabis.
[20] The wider CIs for the group of females with versus those without PMDD is expected given the smaller sample size (n = 19 versus n = 50, respectively).

Differences in cyclicity is another notable difference between cannabis use, depressed mood, and coping motives in those with a provisional PMDD diagnosis compared to those without. Specifically, there is visually greater cyclicality among those with PMDD on all three variables versus those without PMDD (see Figures 6A-C). That is, the variation across the cycle is quite minimal for all three variables in the non-PMDD group and widely cyclic in the PMDD group (see Figures 6A-C).

Females with versus those without a provisional PMDD diagnosis on the SCID-5-RV, on average, differed based on their PAF-SF affect subscale scores but not their water retention or pain subscale scores. Specifically, females with a provisional PMDD diagnosis scored significantly higher, on average, than females without a PMDD diagnosis on the affect subscale ($t_{67} = 2.138$, $p = .036$; see Table 3; see Figure 7). Water retention and pain subscale scores did not differ, on average, between those with a provisional PMDD diagnosis compared to those without ($t_{67} = .139$, $p = .890$ and $t_{67} = 1.393$, $p = .168$, respectively).

3.3.2 Cannabis Use Quantity Across Menstrual Cycle Day in Females Without Pre-Menstrual Dysphoric Disorder

Figure 8A shows that among those without PMDD, cannabis use quantity increased menstrually, decreased during the ovulatory and luteal phases, and began increasing again pre-menstrually, consistent with predictions. The slopes of cannabis use were also much steeper (relative to other MC phases) during the pre-menstrual and menstrual phases. Inconsistent with predictions, cannabis use quantity peaked during the MC phase following the menstrual phase, i.e., the follicular phase.

3.3.3 Depressed Affect Across Menstrual Cycle Day in Females Without Pre-Menstrual Dysphoric Disorder

Among those without PMDD, depressed affect increased menstrually, dipped during the ovulatory and luteal phases, and began steadily increasing pre-menstrually, consistent with predictions (see Figure 8B). In line with predictions, the slopes of depressed mood were also much steeper during the menstrual phase (relative to other MC phases). However, inconsistent with predictions, depressed affect peaked during the MC phase following the menstrual phase, the follicular phase.

3.3.4 Cannabis Coping Motives across Menstrual Cycle Day in Females Without Pre-Menstrual Dysphoric Disorder

Coping-motivated cannabis use increased menstrually, decreased during the ovulatory and luteal phases, and experienced an increase again pre-menstrually amongst females without PMDD (see Figure 8C). Consistent with predictions, the slopes of coping-motivated cannabis use were also much steeper (relative to other MC phases) during the pre-menstrual and menstrual phases. Unexpectedly, and inconsistent with predictions, cannabis coping motives peaked during the MC phase following the menstrual phase, i.e., the follicular phase.

3.3.5 Cannabis Use and Depressed Mood Associations by Menstrual Cycle Day in Females Without Pre-Menstrual Dysphoric Disorder

Figure 9A shows the estimated bivariate time-varying associations between daily cannabis use (in quantity of standard joints) and depressed mood. As predicted, depressed mood was not significantly associated with higher cannabis use on any MC day in females without PMDD.

3.3.6 Cannabis Use and Coping Motive Associations by Menstrual Cycle Day in Females Without Pre-Menstrual Dysphoric Disorder

The estimated bivariate time-varying associations between daily cannabis use (in quantity of standard joints) and coping-motivated cannabis use are shown in Figure 9B. Coping-motivated cannabis use was not significantly associated with higher levels of cannabis use on any MC day in females without PMDD, as hypothesized.

3.3.7 Cannabis Use Quantity Across Menstrual Cycle Day in Females with Pre-Menstrual Dysphoric Disorder

As reported in the group of females without PMDD, those with a provisional PMDD diagnosis experienced an increase in cannabis use quantities menstrually. Cannabis use quantities began decreasing during the ovulatory and luteal phases and started increasing again pre-menstrually (see Figure 10A), consistent with SMT. Interestingly, the slopes of cannabis use were also much steeper (relative to other MC phases) during the menstrual phase. Inconsistent with predictions, cannabis use quantity peaked during the MC phase following the menstrual phase, i.e., the follicular phase.

3.3.8 Depressed Mood across Menstrual Cycle Day in Females with Pre-Menstrual Dysphoric Disorder

Self-reported depressed affect began increasing menstrually, dipped during the ovulatory and luteal phases, and began increasing again pre-menstrually among those with a provisional PMDD diagnosis (see Figure 10B), consistent with SMT predictions. Relative to other MC phases, the slopes of depressed mood were also much steeper during the pre-menstrual and menstrual phases. Depressed affect, unexpectedly, peaked during the MC phase following the menstrual phase, i.e., the follicular phase.

3.3.9 Cannabis Coping Motives across Menstrual Cycle Day in Females with Pre-Menstrual Dysphoric Disorder

Consistent with SMT predictions, coping-motivated cannabis use increased menstrually, decreased during the ovulatory and luteal phases, and experienced a slight increase again pre-menstrually amongst females with a provisional PMDD diagnosis (see Figure 10C). The slopes of coping-motivated cannabis use were also much steeper (relative to other MC phases) during the menstrual phase. Inconsistent with predictions, cannabis coping motives peaked during the MC phase following the menstrual phase, i.e., the follicular phase.

3.3.10 Cannabis Use and Depressed Mood Associations by Menstrual Cycle Day in Females with Pre-Menstrual Dysphoric Disorder

Partially consistent with PMDD predictions, depressed mood was significantly associated with higher quantities of cannabis use during the menstrual phase (MC days 1-2), but not the pre-menstrual phase (see Figure 11A).

3.3.11 Cannabis Use and Coping Motive Associations by Menstrual Cycle Day in Females with Pre-Menstrual Dysphoric Disorder

In line with PMDD predictions, coping motives were significantly associated with higher quantities of cannabis used menstrually (MC days 1-3) and pre-menstrually (MC days 25-28; see Figure 11B)[21].

[21] All PMDD hypothesis findings remained the same regardless of whether a 90% or 95% CI was used with two exceptions. Coping-motivated cannabis use was not significantly associated with higher cannabis use quantities pre-menstrually when a 95% CI was implemented; however, at a 90% CI, this association became significant. Additionally, depressed affect was only significantly associated with higher cannabis use quantities menstrually when a 90% CI was used relative to a 95% CI.

3.4 MENSTRUAL CYCLE VALIDATION

The two saliva samples within each set of MC days (MC days 1-7 and MC days 18-24) were highly correlated (r's = 0.96 [MC days 1-7] and 0.94 [MC days 18-24]). As a result, progesterone concentrations were averaged within each set of MC days prior to analysis. Consistent with our prior research (Joyce et al., 2019, 2018), salivary progesterone concentrations were significantly higher during MC days 18-24 (M = 366.00 pg/mL, SD = 236.18) than during MC days 1-7 (M = 214.27 pg/mL, SD = 187.60; $t_{68} = 4.879$, $p < 0.001$; see Figure 12). The R^2 for each assay completed were as follows: 0.993, 0.987, 1.000, 0.997, 0.993, and 0.997, indicating sample concentrations were within the range of standard concentrations as determined by a four-parameter curve fit. Assayed progesterone concentrations, on average, supported the validity of participants' self-reported MC day.

3.5 ECOLOGICAL MOMENTARY ASSESSMENT REACTIVITY

Although no specific hypotheses were made a priori, it is worth noting that following EMA completion participants self-reported little reactivity to EMA on mood (M = 3.43, SD = 2.42; observed and theoretical range = 1-10) and cannabis use behaviors (M = 2.78, SD = 2.35; observed and theoretical range = 1-10)

CHAPTER 4: DISCUSSION

This thesis was the first study to assess relationships between cannabis use, depressed mood, coping-motivated cannabis use, and their inter-relations across the entire MC in normally-cycling female cannabis users. Given the relative dearth of research on females in the addiction field, these findings will enhance our knowledge of female-specific factors influencing cannabis use, which is imperative given Canada's recent legalization of cannabis and female-specific cannabis-related concerns (e.g., female cannabis users being more apt to develop a CUD following their first cannabis use relative to their male-counterparts; Khan et al., 2013). The primary analyses of this thesis support the notion that individual difference variables, specifically a provisional PMDD diagnosis, have a pronounced influence on female cannabis use, depressed mood, coping-motivated cannabis use, and their associations across the MC. Those with a provisional PMDD diagnosis consumed greater quantities of cannabis than those without PMDD. Females with a provisional PMDD diagnosis (versus those without) also showed relations between depressed mood and higher cannabis use quantities menstrually. Similarly, associations between coping motives and higher cannabis use quantities were shown pre-menstrually and menstrually in females with a provisional PMDD diagnosis compared to those without.

4.1 SELF-MEDICATION THEORY

Based on SMT (Khantzian, 1997) and previous literature suggesting increases in depressed mood pre-menstrually and menstrually (Aganoff & Boyle, 1994; Collins et al., 1985; Reed et al., 2008), it was hypothesized that normally-cycling females would increase the quantity of cannabis used pre-menstrually and menstrually relative to other

MC phases. The estimated mean levels of cannabis used increased both pre-menstrually and menstrually and the slopes of cannabis use increases were much steeper pre-menstrually and menstrually versus the other MC phases. These findings substantiate previous literature by Hanzal et al. (2019) and Mello and Mendelson (1985) who showed cannabis use quantities increased pre-menstrually in the entire sample and pre-menstrually in a subsample of participants, respectively.

However, inconsistent with SMT predictions and prior research on addictive behaviors across the MC (see Joyce et al., under review for a review of the literature), cannabis use quantity unexpectedly peaked during the follicular phase, rather than at the premenstrual or menstrual phases as was predicted. First, this discrepancy with theory and with previous research (e.g., cannabis use peaking pre-menstrually among the full sample [Hanzal et al., 2019] and among a subsample of participants [Mello & Mendelson, 1985]) may be the result of the novel statistical analyses used herein. TVEMs were used which examined cyclical variability in dependent variables across days of the MC; however, prior research has collapsed data across days to produce averages for each MC phase which may result in a loss of important information. For example, while the latter allows for comparisons of average levels of use across MC phases, it does not allow one to pinpoint on what days cannabis use peaks, nor does it allow one to examine patterns of change within specific phases – information which is available through the use of TVEMs (see Figure 13). Second, this discrepancy with theory may be secondary to measurement error. Since MC day was determined based on participant self-report, errors in self-reporting may be responsible for our failing to observe peak cannabis use, depressed mood, and coping motives at the pre-menstrual and menstrual phases, and

observing peaks instead during the follicular phase. This explanation seems unlikely given the validation of participants' self-reported MC day using progesterone assays. Nonetheless, future studies should employ additional validation procedures (e.g., identifying the luteinizing hormone surge to pinpoint the timing of ovulation) to better ensure the validity of self-reported MC day.

It was further hypothesized that changes in cannabis use quantity pre-menstrually and menstrually would be associated with pre-menstrual and menstrual increases in depressed mood and coping motives. Inconsistent with this hypothesis, neither depressed affect nor coping motives were associated with heighted cannabis use quantities at any time during the MC among the full sample. This finding is discrepant with our previous research which examined alcohol use across the MC (Joyce et al., 2018). In this previous study, we found that coping motives explained increases in alcohol use menstrually in an unselected sample of female drinkers. One possible explanation for this discrepancy is the social acceptability of alcohol. On a national level, alcohol is more socially acceptable than cannabis (56% acceptability versus 26%, respectively; Government of Canada, 2017). Thus, it may be more socially acceptable for females to consume alcohol to cope with their depressed mood than using cannabis to do so. Another explanation surrounds substance use craving and depression. Specifically, higher levels of depression play a crucial role in substance use craving among females, but not males (Zilberman, Tavares, Hodgins, & El-Guebaly, 2007). Further findings suggest individuals are more likely to drink alcohol than use cannabis to cope (O'Hara, Armeli, & Tennen, 2016). Therefore, females may crave alcohol following depressed mood more readily than

cannabis, explaining why we did not find increases in cannabis use pre-menstrually and menstrually in the full sample.

Overall, findings from the full sample failed to support SMT predictions, as cannabis use peaked during the follicular phase rather than pre-menstrually and menstrually as expected, and there was no association found between cannabis use quantity and depressed mood or coping-motivated cannabis use. One possible explanation for the observed increases in cannabis use quantity during the follicular phase is the influence of ovarian hormones, specifically estrogen, on the mesolimbic dopamine reward pathway (i.e., the brain's reward centre; Dreher et al., 2007; Sakaki & Mather, 2012). Estrogen concentrations increase during the follicular and ovulatory phases (Griffin & Ojeda, 2004; Groome et al., 1996; Levy, Koeppen, & Stanton, 2000) and this increase is associated with a heightened sensitivity to rewards within the mesolimbic dopamine pathway (Dreher et al., 2007; Sakaki & Mather, 2012). In addition to this increased sensitivity to rewards, females experience their most positive mood during the follicular and ovulatory phases of the MC (Collins et al., 1985), suggesting that females may instead be increasing their cannabis use as a result of enhancement motives (i.e., to enhance their positive mood) during these MC phases. A heightened sensitivity to rewards (e.g., the high associated with cannabis use), increase in positive mood, and increased enhancement motives for cannabis use may theoretically explain the observed increase in cannabis use during the follicular phase in the present study.

It was anticipated that the findings in this thesis, given its focus on cannabis, would be in line with findings on the use of other substances across the MC which appear to peak pre-menstrually and menstrually (e.g., alcohol; see Joyce et al., under review for

a literature review). Instead, the findings herein are more in line with putative behavioral addictions (e.g., gambling behavior, sexual behavior, and food consumption) across the MC. As previously highlighted, Joyce et al. (under review) found gambling behaviors predominantly peaked during the ovulatory phase, in line with reward-sensitivity theory. A closer look at other potentially addictive behaviors identified fifteen studies examining the influence of MC phase on sexual behaviors and female-initiated sexual behaviors (Adams, Gold, & Burt, 1978; Bancroft, Sanders, Davidson, & Warner, 1983; Brown, Calibuso, & Roedl, 2011; Bullivant et al., 2004; Burleson, Gregory, & Trevathan, 1995; Burleson, Trevathan, & Gregory, 2002; Caruso et al., 2014; Elaut et al., 2016; Harvey, 1987; Hensel, Fortenberry, Harezlak, Anderson, & Orr, 2004; Matteo & Rissman, 1984; Morotti et al., 2013; Silber, 1994; Spitz, Gold, & Adams, 1975; Wilcox et al., 2004); overall, these studies also lend support for reward-sensitivity theory. Sexual behaviors and female-initiated sexual behaviors heightened during the follicular and ovulatory phases compared to other MC phases. Additionally, six studies assessed food intake across MC phase with half of the individual results pointing toward MC phase effects (Brown, Morrison, Calibuso, & Christiansen, 2008; Dalvit, 1981; Reed, Levin, & Evans, 2008; Tarasuk & Beaton, 1991) and the remaining suggesting no MC phase effects (Allen, Hatsukami, Christianson, & Brown, 2000; Allen, Hatsukami, Christianson, & Nelson, 1996). Findings weakly suggested food intake varies across MC phase, with heightened intake during the follicular/luteal phases versus other MC phases. Results from the present thesis suggest fluctuations in cannabis use quantity across MC phase may be more in line with findings from the putative behavioral addictions (gambling, sex, and food), with cannabis use quantity peaking during the follicular phase.

The supplementary sensitivity analysis suggested that when females with a mood disorder diagnosis (other than those with solely a provisional PMDD diagnosis as identified on the SCID-5-RV) are removed from the full sample, the mean level of cannabis quantity used peaked during the pre-menstrual phase and coping-motivated cannabis use was significantly associated with higher quantities of cannabis use during the luteal and pre-menstrual phases (MC days 17-26) when no effect was previously observed. Overall, the sensitivity analysis suggested that the inclusion of those with mood disorders may have been masking the relationship between coping motives and cannabis use quantity during the luteal and pre-menstrual phases, providing some support for SMT predictions in the full sample.

We further considered that the hypothesized MC-related relationship between cannabis use quantity and depressed mood as well as cannabis use quantity and coping-motivated cannabis use may only be observable among those with greater levels of relevant psychopathology, like those with PMDD. In fact, previous laboratory-based research examining the relationship between cannabis use and self-reported distress across the MC found that females who report higher levels of distress pre-menstrually (an analogue for PMDD) also "earned" more cannabis (by pressing buttons to earn cannabis in a progressive-ratio type task) during the pre-menstrual phase relative to those with low levels of self-reported distress pre-menstrually (Mello & Mendelson, 1985). Collectively, it may be individual difference variables, such as a diagnosis of PMDD, that are relevant moderators of the expected relations between depressed mood and cannabis use quantity as well as between coping motives and cannabis use quantity at relevant phases of the MC.

4.2 PRE-MENSTRUAL DYSPHORIC DISORDER THEORY

Based on prior literature suggesting females with PMDD experience a greater susceptibility toward substance use (Reed et al., 2008) as well as Mello and Mendelson (1985) finding that females with heightened distress pre-menstrually worked to "earn" larger quantities of cannabis than females with low levels of distress pre-menstrually, it was predicted that females with a provisional PMDD diagnosis (determined by the SCID-5-RV) would show stronger relations between depressed mood and cannabis use quantity pre-menstrually and menstrually compared to females without PMDD. It was similarly hypothesized that females with PMDD would exhibit more pronounced associations between coping motivations and cannabis use quantity pre-menstrually and menstrually as compared to females without PMDD. As anticipated, among those without PMDD, neither depressed mood nor coping motives were associated with heightened cannabis use quantities at any point during the MC. Consistent with PMDD predictions, however, depressed mood (menstrually) and coping motives (pre-menstrually and menstrually) explained heightened cannabis use quantities at specific MC phases in females with a provisional PMDD diagnosis. In combination, these findings suggest that a provisional PMDD diagnosis is a female-specific individual difference variable which is related to whether or not depression and coping motives drive elevated cannabis use at certain theoretically relevant points during the MC - namely the pre-menstrual and menstrual phases. Because most previous work failed to examine PMDD diagnoses/symptoms, whether prior research showed elevations in cannabis use pre-menstrually and menstrually (Griffin et al., 1986; Hanzal et al., 2019; Mello & Mendelson, 1985) might

depend on whether or not they had a relatively large representation of females with PMDD in their sample.

The levels of self-reported cannabis use, depressed mood, and coping-motivated cannabis use followed similar patterns across MC phase for those without and with a provisional PMDD diagnosis. All three variables of interest followed the same trend as those reported in the full sample, inconsistent with predictions. These inconsistent findings may be more consistent with predictions of reward-sensitivity theory as previously discussed.

Findings also suggested that females with a provisional PMDD diagnosis used higher quantities of cannabis, on average and across most MC days (i.e., MC days 2-24). If females are using cannabis to reduce symptoms of depression, then it would be expected that elevated cannabis consumption would be restricted to MC phases where those with PMDD have increased levels of depression (i.e., pre-menstrually and menstrually); however, findings suggest increased levels of cannabis use across the entirety of the MC (relative to those without PMDD). Perhaps initially females with PMDD begin using cannabis to cope with increased depressed affect pre-menstrually and menstrually and given cannabis' rewarding (i.e., depression relieving) effects, cannabis use begins generalizing beyond the pre-menstrual and menstrual phases, such that females with PMDD begin using at higher doses across the entire MC even though depressed mood and coping motives only explain cannabis use pre-menstrually and menstrually. Higher doses of cannabis use in females with (versus without) PMDD is consistent with previous literature suggesting greater substance use susceptibility among females with PMDD versus those without (Reed et al., 2008). Additionally, during the

slight majority of MC days, females with (versus without) PMDD reported greater depressed affect (MC days 4-12, 19-20, and 27-28). While it might be expected that those with PMDD would have higher depressed mood during specific days of the MC than those without PMDD, the times that those with PMDD showed increased depressed mood did not correspond precisely with the pre-menstrual and menstrual phases. Interestingly, when collapsed across the entire MC, those with PMDD no longer exhibited greater average depressed mood than those without PMDD. Previous research by McMillan and Pihl (1987) shows that when females who report pre-menstrual depression were monitored prospectively, 39% showed increased depressed mood pre-menstrually (as expected), 36% showed intermittent depression throughout the entire MC, and the remainder did not show changes in depressed mood across the MC. Those with a provisional PMDD diagnosis are likely similarly comprised of these three subgroups, providing a potential explanation for why a mixture of inconsistent increases in depressed mood across the MC were observed rather than these increases being restricted solely to the pre-menstrual and menstrual phases. Finally, there were no group differences in coping-motivated cannabis use either on average or across MC day; however, visually there is a trend for higher levels of coping motives in those with (versus without) a provisional PMDD diagnosis (see Figure 4C) suggesting that this may be a smaller magnitude effect that would prove significant with a larger sample.

Findings also suggested that there is visually greater cyclicality among those with a provisional PMDD diagnosis on all three variables (i.e., cannabis use quantity, depressed mood, and coping motives) versus those without PMDD, such that variation across the cycle is quite minimal for all three variables in the non-PMDD group and

widely cyclic in the PMDD group (see Figures 4A-C) which is expected given the cyclical nature of PMDD symptoms[22].

On average, females with a provisional PMDD diagnosis (n = 19) reported higher affect subscale scores on the PAF-SF than females without PMDD (n = 50); however, water retention and pain subscale scores did not differ between groups. It should be noted that the PAF-SF is used to identify females with pre-menstrual syndrome (PMS) while the SCID-5-RV identifies females with PMDD. PMDD is an established mood disorder diagnosis within the DSM-5 (American Psychiatric Association, 2013) which is associated with drastic increases in depressed mood and physical symptoms pre-menstrually. PMS, without a DSM-5 (American Psychiatric Association, 2013) diagnosis, is also characterized by symptoms nearly identical to those reported in individuals with PMDD, however, these symptoms are reported at drastically lower levels in females with PMS versus those with PMDD (Dickerson, Mazyck, & Hunter, 2003). The self-reported PAF-SF assesses participants' perceived severity of changes in pre-menstrual syndrome symptoms (Allen et al., 1991) while the SCID-5-RV is a more detailed clinical assessment diagnostic interview which ensures individuals meet certain symptom clusters, identifies symptom longevity, and ensures identified symptoms cause significant impairment (First, 2015). While the full length Pre-menstrual Assessment Form (Halbreich, Endicott, Schacht, & Nee, 1982) has been shown to be useful when differentiating clinical populations with PMDD from those without PMDD (Pires & Calil, 2000), even the full length Pre-menstrual Assessment Form does not provide

[22] The greater cyclicity across all three variables of interest in those with versus without a provisional PMDD diagnosis provides some validity to the SCID-5-RV diagnosis.

enough information to make a definitive diagnosis of PMDD (Pires & Calil, 2000). No prior research has assessed relations between the PAF-SF and PMDD diagnoses, so our finding of increased PAF-SF affect scores among those with provisional PMDD diagnoses relative to controls is novel and extends the prior work of Pires and Calil (2000) to the affect subscale of the short form of the PAF. In addition, the fact that there is a convergence between the PAF-SF affect subscale and a provisional PMDD diagnoses provides some independent validation of the PMDD diagnostic group used in the present study.

4.3 MENSTRUAL CYCLE VALIDATION

On average, progesterone concentrations were higher during MC days 18-24 than MC days 1-7. Results thus supported the validity of participants' self-reported MC day. This finding is consistent with prior research where progesterone concentrations peak during MC days 18-24 and dip during MC days 1-7 (Andreano et al., 2008; Andreano & Cahill, 2010; Joyce et al., 2019, 2018). The biological confirmation of MC phase is a strength of the current study relative to many prior studies in this field which do not include such biological confirmation of self-reported MC phase (see Allen et al., 2016 for a review).

4.4 ECOLOGICAL MOMENTARY ASSESSMENT REACTIVITY

Although no a priori hypotheses were made, we assessed participant's self-reported reactivity to EMA on mood and cannabis use behaviors. Receiving twice daily prompts surrounding cannabis use and mood could have influenced the frequency of cannabis use and/or self-reported mood in the sample which would have greatly influenced results. EMA methods may be particularly vulnerable to reactivity as a result

of repeated assessments and the short period of time elapsing between behaviors and self-reporting (Shiffman, 2009). However, to date no research has been conducted to assess cannabis use reactivity to daily EMA self-monitoring. Further, a review of the literature suggests little evidence for reactivity to self-reported mood via EMA self-monitoring (Ebner-Priemer & Trull, 2009). Many health care professionals working in the mental health field use self-monitoring methodology to enhance client's awareness of their substance use and/or mood, while encouraging change (Carter, Day, Cinciripini, & Wetter, 2007; Freedman, Lester, McNamara, Milby, & Schumacher, 2006). Research on EMA reactivity in other areas of addiction, specifically alcohol use, with participants who are not in treatment, have found that the self-monitoring of alcohol use either slightly decreased or had no effect on participants alcohol use (Simpson, Kivlahan, Bush, & McFall, 2005). Thus, we wanted to assess whether participants perceived that EMA self-monitoring influenced our primary variables of interest (i.e., cannabis use quantity and depressed mood). On average, participants self-reported little reactivity of their cannabis use behaviors and mood due to EMA self-monitoring. In combination with our findings suggesting no change in the number of days where cannabis was used 30 days before their study participation versus the 32-days of study participation, results suggest that on average, EMA had very little influence on participants' cannabis use. Future research could make use of prospective self-monitoring of cannabis use to determine whether cannabis use slightly decreases over the month of self-monitoring, consistent with what has been found with alcohol consumption and nicotine use (Shiffman et al., 2002; Simpson et al., 2005).

4.5 POTENTIAL LIMITATIONS AND FUTURE DIRECTIONS

The findings of this thesis should be interpreted with four categories of potential limitations in mind. The first category is comprised of potential limitations in MC assessment. MC day was determined via self-report, which may be subject to respondent error even though it is commonly employed in MC research (e.g., Wideman et al., 2013). Of note, self-reported MC day in this study was validated using salivary progesterone assays - a strong physiological marker of MC phase (Andreano et al., 2008; Andreano & Cahill, 2010). However, as MC phase cannot be definitively verified without measurement of several ovarian hormones, future work should aim to encompass a wider array of ovarian hormones (e.g., estrogen, progesterone, and luteinizing hormone) in order to more precisely identify each MC phase. Researchers must also assess relations between ovarian hormone levels (e.g., progesterone, estrogen, luteinizing hormone) to determine relations between ovarian hormone concentrations and cannabis use. Second, MC phase was determined using an aggregate of prior research as done in our previous work (see Hanzal et al., 2019; Joyce et al., under review, 2019, 2018; Joyce & Stewart, 2018). The field of MC research has not yet reached a consensus on standardized MC phase designations. Future research must work to resolve this lack of consistency in MC phase designations.

The second category of limitations included problems surrounding PMDD and its diagnosis. Long-standing controversy surrounding PMDD as a valid diagnosis remains apparent. Concerns have primarily centered around the natural female response inevitably becoming pathologized and inherently stigmatizing females (Wakefield, 2013). Once known as late luteal phase disorder, PMDD was upgraded to a full disorder status in the

DSM-5 given the effectiveness of selective serotonin reuptake inhibitors in treating this condition (Brown, O'Brien, Marjoribanks, & Wyatt, 2009). Within this thesis, it was assumed that PMDD was a valid diagnosis. Additionally, the PMDD diagnoses used in the present thesis were not checked for reliability as the Master's candidate was the only interviewer conducting SCID-5-RV interviews; however, prior work suggests good interrater reliability for a very similar clinical interview (Accortt et al., 2011), the Master's candidate received appropriate training and supervision, and PMDD diagnoses were validated by self-reported PAF-SF affect scales. In future research, reliability checks should be performed, and the psychometrics of the SCID-5-RV PMDD diagnostic category must be established.

Design limitations comprise the study's third category of limitations. Brief scales were used to measure depressed affect (three items), state coping motives (two items) and cannabis use levels (one item). Such brief scales can introduce measurement error. However, this concern was balanced against issues of participant burden in an EMA study. Internal consistencies were calculated for depressed affect and coping motive items at several time points across the MC. Internal consistencies were excellent for depressed affect and good for state coping motives despite the short scale lengths. Next, although information on daily cannabis use was collected, the assessments that were used were retrospective (a summary of the quantity of cannabis used the previous day). While daily diaries were used to examine behaviors close in time to when they occurred, retrospective biases could still have influenced the study's results (although to a much lesser extent than typical retrospective assessments where participants are asked to recall behaviors that occurred much farther back in time). An alternative approach would be to

have participants track each time they use cannabis and to record how much they use at the time cannabis use is occurring. Of course, this would have been much more demanding of participants and we decided against it in order to minimize participant burden in an already demanding protocol. Finally, although TVEMs add to prior MC research by allowing for the statistical analysis of associations between predictor (i.e., depressed mood and coping motives) and outcome (i.e., cannabis use quantity) variables across the MC, TVEMs do not allow for testing of significant differences in levels of cannabis use quantity, depressed mood, and coping motives across MC day. As such, when reporting TVEM results, findings are discussed with respect to observable trends over time. It is important to note, however, that these observed trends may not represent statistically significant differences in a given variable over time. In future, statistical methods must be developed to determine significant differences in a given variable across time (in our case, MC day) when using TVEMs.

Potential limitations with respect to the participants comprise the fourth category. We aimed to recruit females with varying cannabis use levels for this study but whom would have used cannabis various times across study participation. In order to recruit this type of sample, we required that participants have used cannabis at least four times in the month prior to participation. The final sample were predominantly daily cannabis users and were identified as having a CUD on the CUDIT-R, on average. These sample characteristics suggest that our findings may not generalize to non-problem cannabis users or to non-daily users. Even with this limitation, however, results may very well benefit treatments for daily cannabis users and/or those with a CUD as this population of females would be the most clinically-relevant from a treatment perspective. Second,

females with a provisional PMDD diagnosis reported higher overall cannabis use quantity relative to those without PMDD; however, there were no differences between groups on the CUDIT-R. Despite this, the PMDD group may be at an increased risk of developing a CUD in the future as previous research demonstrates that heavier, early-onset, and persistent cannabis use all predict later cannabis use problems (Swift, Coffey, Carlin, Degenhardt, & Patton, 2008). Finally, given our inclusion of only reproductive-aged females who were normally-cycling, results from the present study may not generalize to post-menopausal females or to reproductive-aged females on hormonal contraceptives. However, Statistics Canada has concluded that only 16% of Canadian females of reproductive age have taken hormonal contraceptives within the prior month (Rotermann, Dunn, & Black, 2015). The highest rates of hormonal contraceptive use are among those 15-19 years old (30%) and the lowest rates are in females 40-49 years of age (3%; Rotermann et al., 2015). Therefore, results from this study may still be applicable to a large proportion of reproductive-aged females within the Canadian population (~84%).

4.6 CLINICAL IMPLICATIONS

The findings of this study have several important clinical implications. Female cannabis users who have a provisional PMDD diagnosis (versus those without PMDD) use cannabis at greater quantities throughout the MC and use this cannabis to cope with depressed mood at specific, theoretically-relevant phases of the MC (i.e., pre-menstrually and menstrually). These findings may be used as a psychoeducational tool for females with PMDD who are seeking treatment for their cannabis use. Moreover, findings from this study may help with the development of preventative and therapeutic interventions for cannabis use among reproductive-aged, normally-cycling female cannabis users with

PMDD. For example, by beginning cannabis cessation/reduction efforts during phases of the MC associated with lower levels of cannabis use (i.e., the ovulatory and luteal phases) and/or phases not linked with depressed mood or coping motives, clinicians may increase the likelihood of cannabis treatment success. Similar recommendations have been made for the timing of tobacco cessation as a result of tobacco smoking behavior variability across MC phase (Mendrek, Dinh-Williams, Bourque, & Potvin, 2014). Clinicians may further enhance treatment for those with PMDD and a CUD by aiding such clients in the development of more adaptive/less risky ways of coping with depressed mood through training in cognitive behavioral skills (e.g., cognitive restructuring, mindfulness, distress tolerance, and acceptance).

4.7 CONCLUSIONS

This study was the first to assess relations between cannabis use, depressed mood, and coping motives across days of a full MC in participants' daily lives. Among the overall sample and those without PMDD, no associations between cannabis use, depressed mood, and coping motives were found. Interestingly, findings from this thesis suggest that a provisional PMDD diagnosis is an individual difference variable influencing cannabis use, depressed mood, and cannabis coping motive levels and/or their interrelations across the MC. More specifically, depressed mood predicted heightened cannabis use menstrually and coping motives predicted heightened cannabis use pre-menstrually and menstrually. In addition, those with (versus without) a provisional PMDD diagnosis demonstrated greater cannabis use levels across the entire MC. Our daily diary methodology combined with the continuous standardization of the MC, novel statistical analyses, and consideration of individual differences (i.e., PMDD),

provide a more in-depth and informative assessment of cannabis use across the MC than prior work. Findings could aid in the development of more effective preventative and therapeutic interventions for reproductive-aged females with CUD/cannabis use problems, particularly those concurrently living with PMDD.

Table 1. Demographic variable percentages among the full sample

Demographic Variable	Percentage
Race	
Single Race	84.1%
Bi-Racial	13.0%
Multi-Racial	2.9%
Ethnicity	
Caucasian	83.3%
Native Canadian	5.8%
Black	2.9%
Other	2.9%
South Asian	2.6%
Latin America	1.2%
Arab/West Asian	0.9%
South East Asian	0.4%
Education Level	
College/University Graduate	62.3%
Some College/University	14.5%
Some High School	8.7%
Some Post-Graduate	5.8%
High School Graduate	4.3%
Post-Graduate Degree	2.9%
Prefer Not to Answer	1.5%
Cannabis Use Risk[a]	
Cannabis Use Disorder	59.4%
Hazardous Cannabis Users	20.3%
Non-problematic Cannabis Users	20.3%
Level of Problematic Drug Use[b]	
Low Risk	43.5%
Moderate Risk	34.8%
No Risk	15.9%
Substantial Risk	5.8%
Parental Addiction	
Alcohol Problem/Disorder	36.2%
Cannabis Problem/Disorder	15.9%
Gambling Problem/Disorder	10.1%
Current Mood Disorder Diagnoses[c]	
Pre-Menstrual Dysphoric Disorder	27.5%
Persistent Depressive Disorder	17.6%
Major Depressive Disorder	13.2%
Cyclothymic Disorder	8.8%

Demographic Variable	Percentage
Hypomanic Episode	1.5%
Manic Episode	0%
Cannabis Using Days (30-Days Pre-Study)[d]	
26 - 30 Days	65.0%
21 - 25 Days	5.8%
16 - 20 Days	7.3%
11-15 Days	7.3%
6 - 10 Days	7.3%
1 - 5 Days	7.3%
Cannabis Using Days (32-Days During Study)[e]	
29 - 32 Days	37.7%
25 - 28 Days	18.9%
21 - 24 Days	20.3%
17 - 20 Days	4.3%
13 - 16 Days	2.9%
9 - 12 Days	2.9%
5 - 8 Days	8.7%
1 - 4 Days	4.3%

[a] Determined by the Cannabis Use Disorder Identification Test - Revised (Adamson & Sellman, 2003)
[b] Determined by the Drug Abuse Screening Test (Skinner, 1982)
[c] Determined by the Structured Clinical Interview for DSM-5 Disorders - Research Version (First et al., 2015)
[d] Determined by the Cannabis Timeline Followback (Robinson et al., 2014)
[e] Determined using ecological momentary assessment prior to rescoring on a standardized 28-day cycle
Note. Cannabis using days during the 32-days of ecological momentary assessment is not perfectly representative of the actual amount of days where cannabis was used, but rather the number of days where participants completed daily surveys and indicated using cannabis.

Table 2. Demographic variable means among the full sample

Demographic Variable	*M (SD)*
MMM Trait Cannabis Use Motive Subscales	
Enhancement Motives	3.36 (0.72)
Coping Motives	2.59 (0.88)
Expansion Motives	2.32 (1.10)
Social Motives	2.30 (0.98)
Conformity Motives	1.09 (0.24)
PAF-SF Subscales	
Affect	13.48 (4.8)
Water Retention	8.10 (4.0)
Pain	10.25 (3.2)

Note. MMM: Marijuana Motives Measure (Simons et al., 1998); PAF-SF: Pre-Menstrual Assessment Form - Short Form (Allen et al., 1991)

Table 3. Demographic variable percentages by those with and without a provisional pre-menstrual dysphoric disorder diagnosis

Demographic Variable	Without PMDD (n = 50)	With PMDD (n = 19)	p-value
Race			
Single Race	88.0%	73.7%	0.161[g]
Bi-Racial	8.0%	26.3%	0.102[g]
Multi-Racial	4.0%	0%	1.000[g]
Ethnicity			
Caucasian	83.7%	81.6%	0.664[g]
Native Canadian	5.0%	7.9%	0.384[g]
Black	1.1%	7.9%	0.182[g]
Other	4.0%	0%	1.000[g]
South Asian	3.7%	0%	0.556[g]
Latin America	0.6%	2.6%	0.478[g]
Arab/West Asian	1.3%	0%	1.000[g]
South East Asian	0.6%	0%	1.000[g]
Education Level			
College/University Graduate	66.0%	52.6%	0.306[h]
Some College/University	16.0%	10.5%	0.715[g]
Some High School	4.0%	21.1%	0.045*[g]
Some Post-Graduate	4.0%	10.5%	0.303[g]
High School Graduate	4.0%	5.3%	1.000[g]
Post-Graduate Degree	4.0%	0%	1.000[g]
Prefer Not to Answer	2.0%	0%	1.000[g]
Cannabis Use Risk[a]			
Cannabis Use Disorder	56.0%	68.4%	0.394[h]
Hazardous Cannabis Users	18.0%	26.3%	0.508[g]
Non-problematic Cannabis Users	26.0%	5.3%	0.091[g]
Level of Problematic Drug Use[b]			
Low Risk	38.0%	57.9%	0.071[h]
Moderate Risk	40.0%	21.1%	0.140[h]
No Risk	18.0%	10.5%	0.491[g]
Substantial Risk	4.0%	10.5%	0.303[g]
Parental Addiction			
Alcohol Problem/Disorder	32.0%	47.4%	0.235[h]
Cannabis Problem/Disorder	16.0%	15.8%	1.000[g]
Gambling Problem/Disorder	8.0%	15.8%	0.384[g]
Current Mood Disorder Diagnoses[c]			
Pre-Menstrual Dysphoric Disorder	0%	100%	-
Persistent Depressive Disorder	10.0%	36.8%	0.028*[g]

Demographic Variable	Without PMDD (n = 50)	With PMDD (n = 19)	p-value
Major Depressive Disorder	10.0%	21.1%	0.253[g]
Cyclothymic Disorder	6.0%	15.8%	0.338[g]
Hypomanic Episode	2%	5.3%	0.279[g]
Manic Episode	0%	0%	-
Mood Disorder Comorbidities			
One or more	20.4%	100%	<0.001* [g]
Two or more	6.1%	57.9%	< 0.001* [h]
Three or more	0%	21.1%	0.005 * [g]
Cannabis Using Days (30-Days Pre-Study)[d]			
26 - 30 Days	58.0%	84.1%	0.041* [h]
21 - 25 Days	8.0%	0%	0.569[g]
16 - 20 Days	10.0%	0%	0.312[g]
11-15 Days	8.0%	5.3%	1.000[g]
6 - 10 Days	8.0%	5.3%	1.000[g]
1 - 5 Days	8.0%	5.3%	1.000[g]
Cannabis Using Days (32-Days During Study)[e]			
29 - 32 Days	36.0%	42.1%	0.640[h]
25 - 28 Days	22.0%	10.5%	0.491[g]
21 - 24 Days	16.0%	31.5%	0.186[g]
17 - 20 Days	6.0%	0%	0.556[g]
13 - 16 Days	2.0%	5.3%	0.478[g]
9 - 12 Days	2.0%	5.3%	0.478[g]
5 - 8 Days	10.0%	5.3%	1.000[g]
1 - 4 Days	6.0%	0%	0.556[g]

[a] Determined by the Cannabis Use Disorder Identification Test - Revised (Adamson & Sellman, 2003)
[b] Determined by the Drug Abuse Screening Test (Skinner, 1982)
[c] Determined by the Structured Clinical Interview for DSM-5 Disorders - Research Version (First et al., 2015)
[d] Determined by the Cannabis Timeline Followback (Robinson et al., 2014)
[f] Determined using ecological momentary assessment prior to rescoring on a standardized 28-day cycle
[g] Pearson chi-square
[h] Fisher's Exact Test
[*] $p < 0.05$
Note. Cannabis using days during the 32-days of ecological momentary assessment is not perfectly representative of the actual amount of days where cannabis was used, but rather the number of days where participants completed daily surveys and indicated using cannabis. Fisher's Exact Tests were used when the count was over 5 for 20% or more of the cells.

Table 4. Demographic variable means by those with and without a provisional pre-menstrual dysphoric disorder diagnosis

Demographic Variables	Without PMDD (n = 50)	With PMDD (n = 19)	p-value
Age (in years)	29.20 (5.70)	29.37 (5.70)	0.913
MC Length (in days)[a]	28.18 (1.62)	27.79 (1.87)	0.396
Cannabis Use (days/month)[b]	23.12 (9.15)	24.21 (7.18)	0.642
CUDIT-R Total Score	12.90 (6.23)	14.79 (5.41)	0.248
DAST Total Score	2.46 (1.82)	2.32 (1.89)	0.772
MMM Trait Cannabis Use Motive Subscales			
Coping	2.53 (0.94)	2.75 (0.69)	0.367
Conformity	1.09 (0.25)	1.07 (0.19)	0.776
Social	2.22 (0.99)	2.52 (0.92)	0.259
Expansion	2.20 (1.08)	2.64 (1.10)	0.135
Enhancement	3.39 (0.66)	3.28 (0.85)	0.594
PAF-SF Total	30.72 (8.75)	34.74 (10.86)	0.116
PAF-SF Subscale Total			
Affect	12.47 (4.33)	15.42 (5.43)	0.036*
Water Retention	8.06 (4.09)	8.21 (3.84)	0.890
Pain	9.92 (2.94)	11.12 (3.68)	0.168

[a] MC Length during ecological momentary assessment prior to rescoring on a standardized 28-day cycle

[b] Number of cannabis use days during ecological momentary assessment

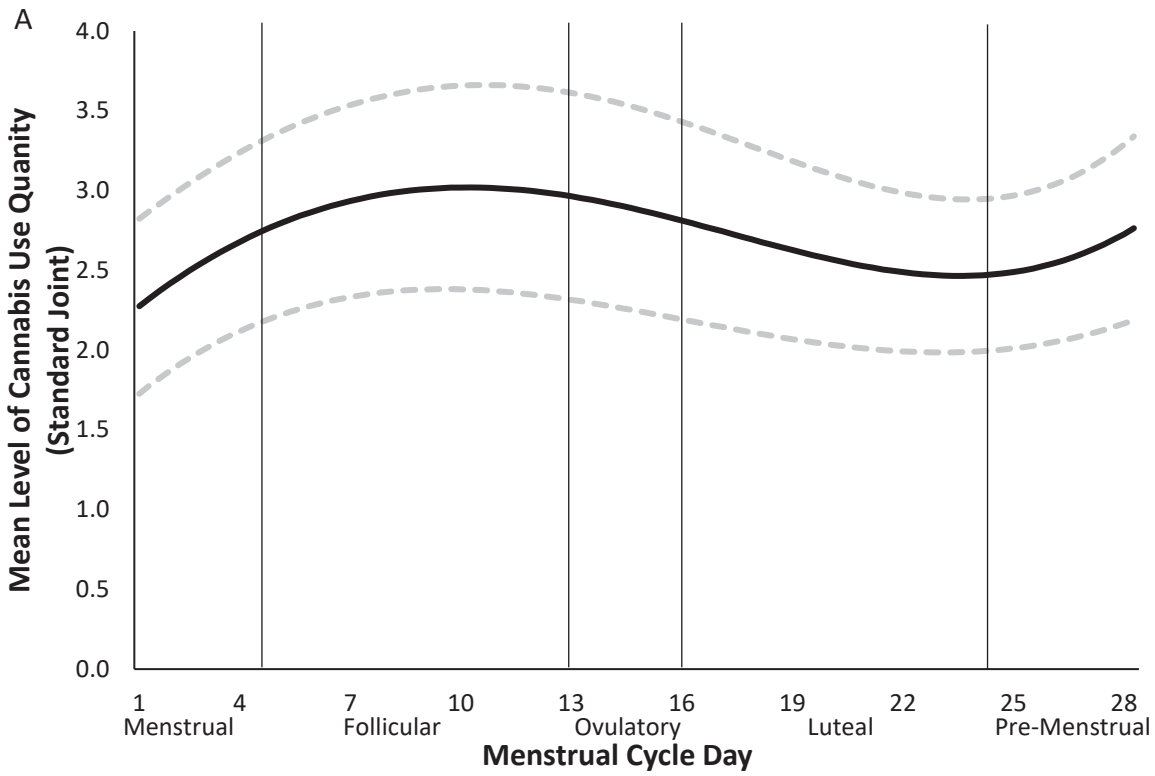
* $p < 0.05$

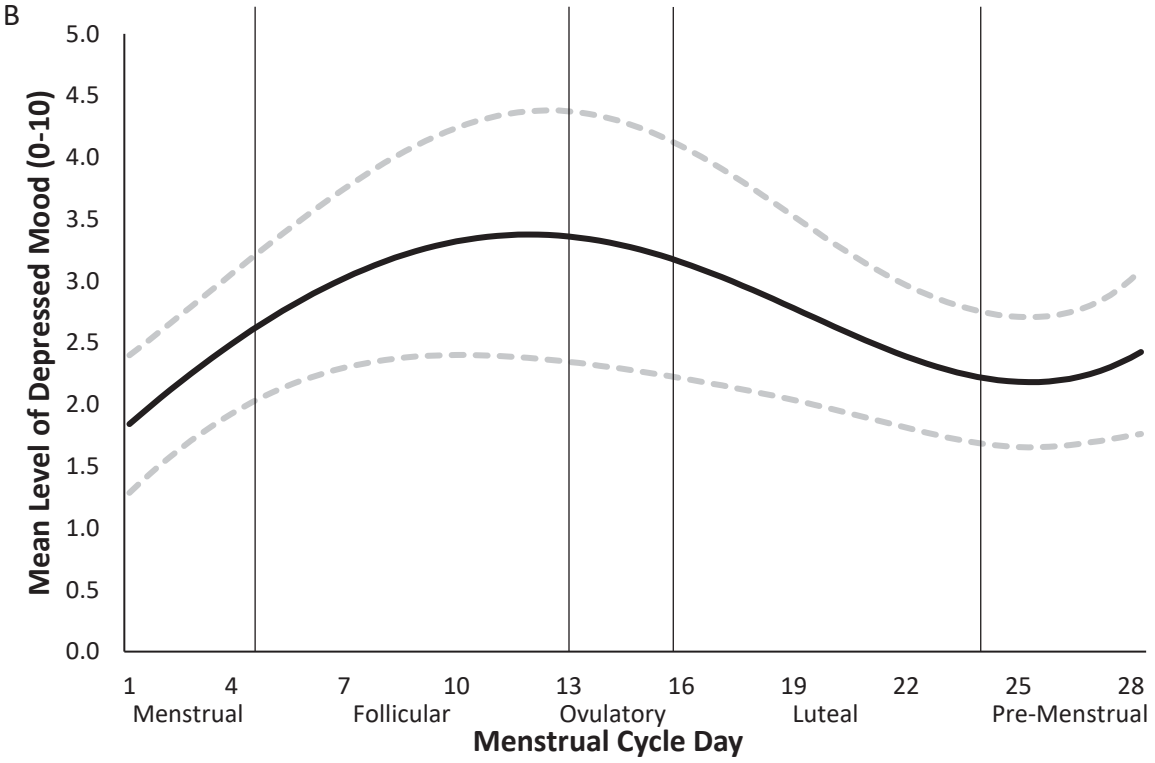
Note. MC: Menstrual Cycle; CUDIT-R: Cannabis Use Disorder Identification Test - Revised (Adamson & Sellman, 2003); DAST: Drug Abuse Screening Test (Skinner, 1982); MMM: Marijuana Motives Measure (Simons et al., 1998); PAF-SF: Pre-Menstrual Assessment Form - Short Form (Allen et al., 1991); Parentheses indicate standard deviations

Table 5. Mood disorder diagnoses of the 21 females excluded in the supplementary sensitivity analysis within the total sample

Demographic Variable	Percentage	n
Current Mood Disorder Diagnoses[a]		
Pre-Menstrual Depressive Disorder	28.2%	11
Persistent Depressive Disorder	30.8%	12
Major Depressive Disorder	23.1%	9
Cyclothymic Disorder	15.4%	6
Hypomanic Episode	2.5%	1
Manic Episode	0%	0
Number of Mood Disorder Diagnoses[b]		
One	33.3%	7
Two	47.6%	10
Three	19.1%	4
Mood Disorder Specific Comorbidities[c]		
Major Depressive Disorder & Persistent Depressive Disorder	21.4%	3
Cyclothymic Disorder & Pre-Menstrual Dysphoric Disorder	21.4%	3
Persistent Depressive Disorder & Pre-Menstrual Dysphoric Disorder	21.4%	3
Major Depressive Disorder & Pre-Menstrual Dysphoric Disorder	7.2%	1
Hypomanic Episode & Persistent Depressive Disorder & Pre-Menstrual Dysphoric Disorder	7.2%	1
Major Depressive Disorder & Persistent Depressive Disorder & Pre-Menstrual Dysphoric Disorder	21.4%	3

[a] Not mutually exclusive categories. Percentages refer to the percentage of the 39 mood disorder diagnoses represented among the 21 females excluded from the sensitivity analyses.
[b] Percentages refer to the percent of the 21 females excluded who met criteria for one, two, or three mood disorders, respectively.
[c] Percentages refer to the percent of the 14 females with comorbidity excluded from the sensitivity analyses who had each particular combinations of mood disorders.


A
Mean Level of Cannabis Use Quanity (Standard Joint)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1 4 7 10 13 16 19 22 25 28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day


B
Mean Level of Depressed Mood (0-10)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1 4 7 10 13 16 19 22 25 28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day

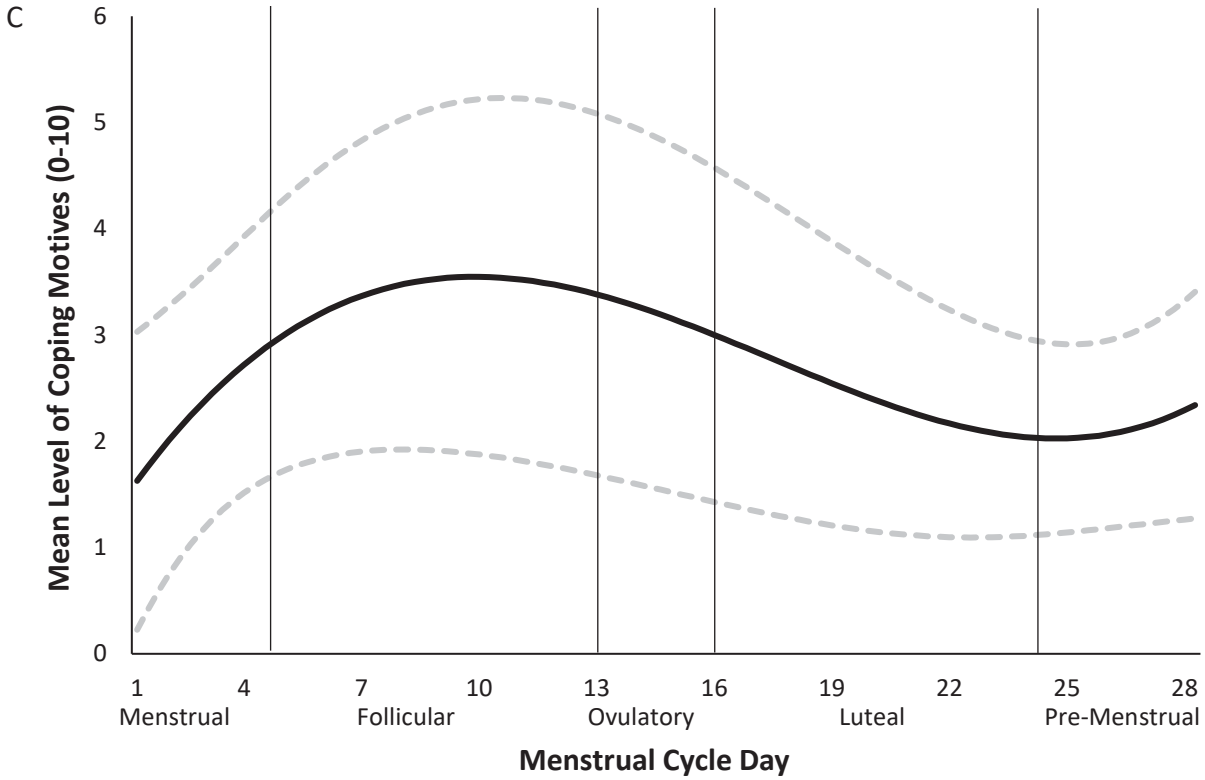


Figure 1. Estimated mean levels of (A) cannabis use quantity, (B) depressed affect, and (C) coping motives across days of the menstrual cycle as estimated by an intercept-only time-varying effect model. Black lines indicate estimated means and gray lines indicate 90% confidence intervals (CIs).

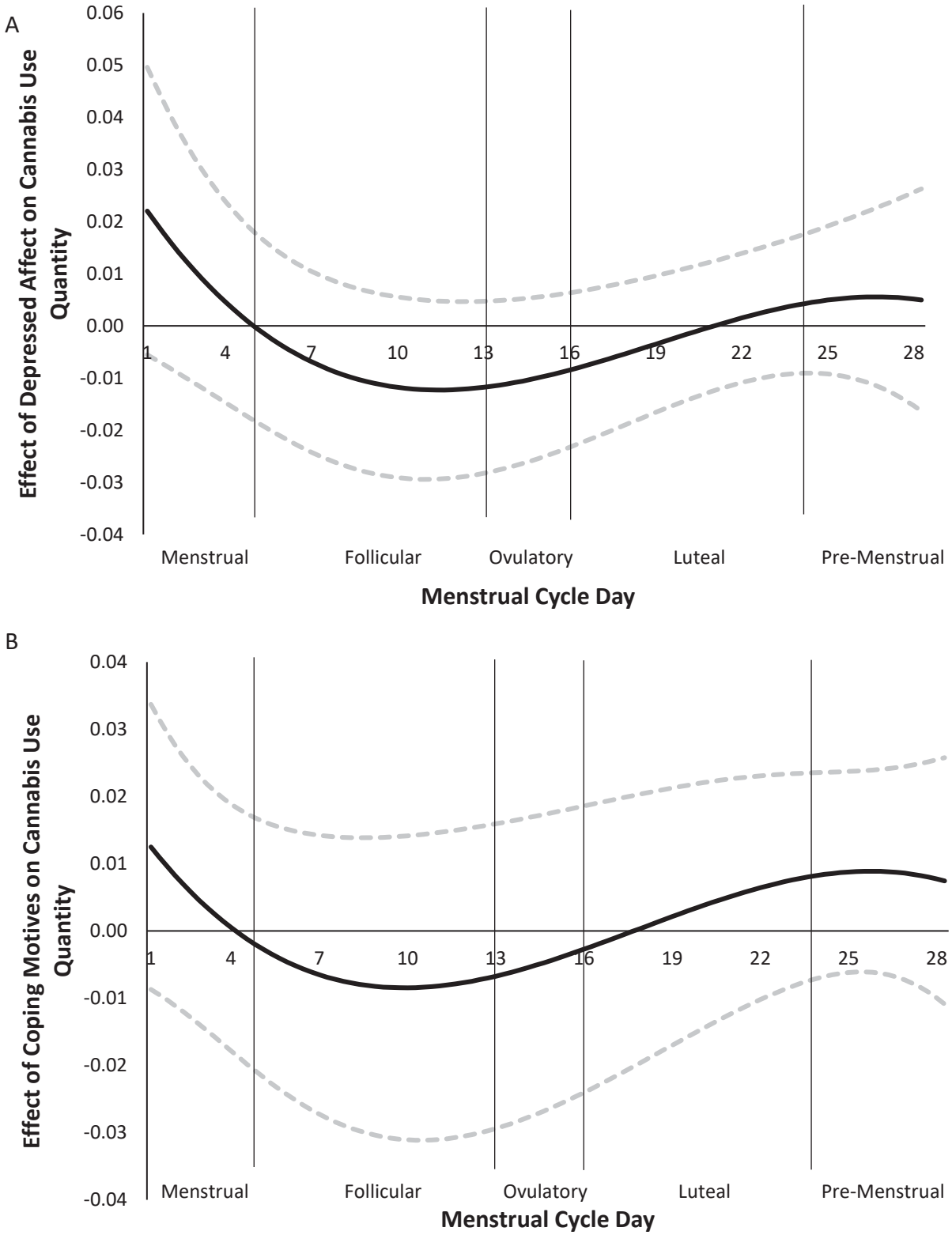
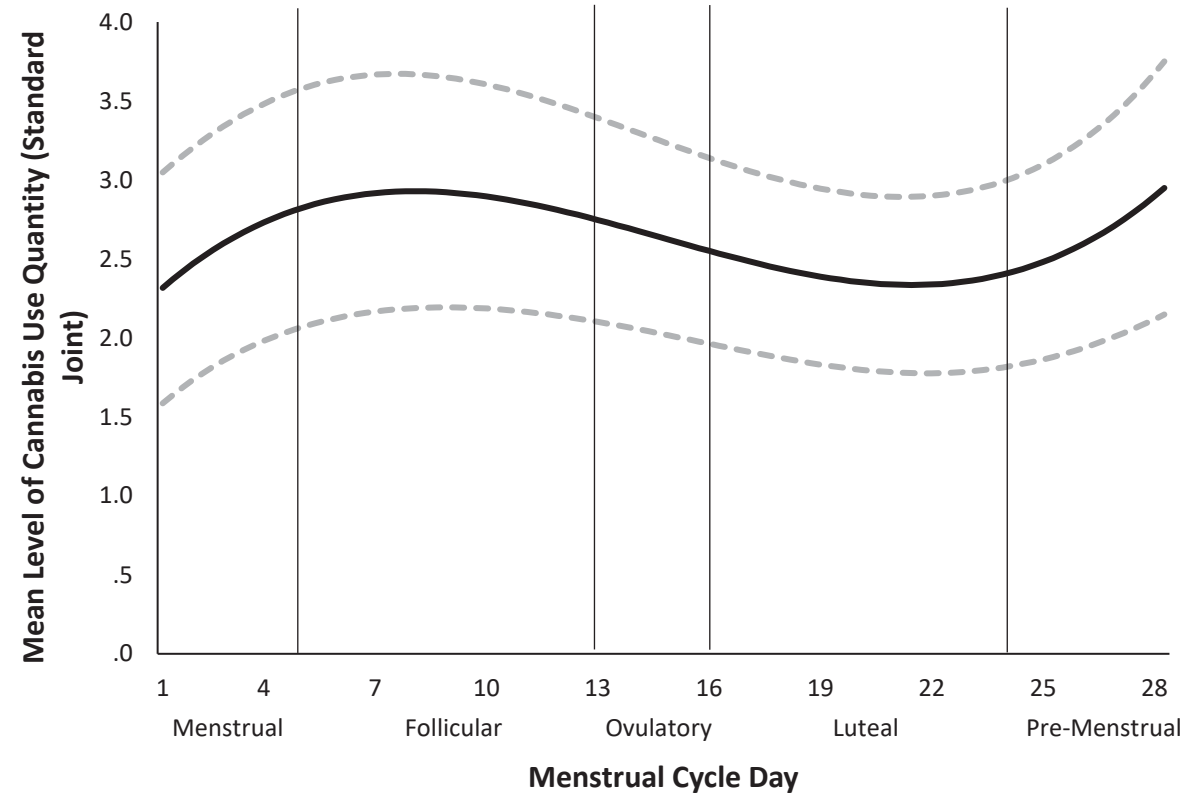
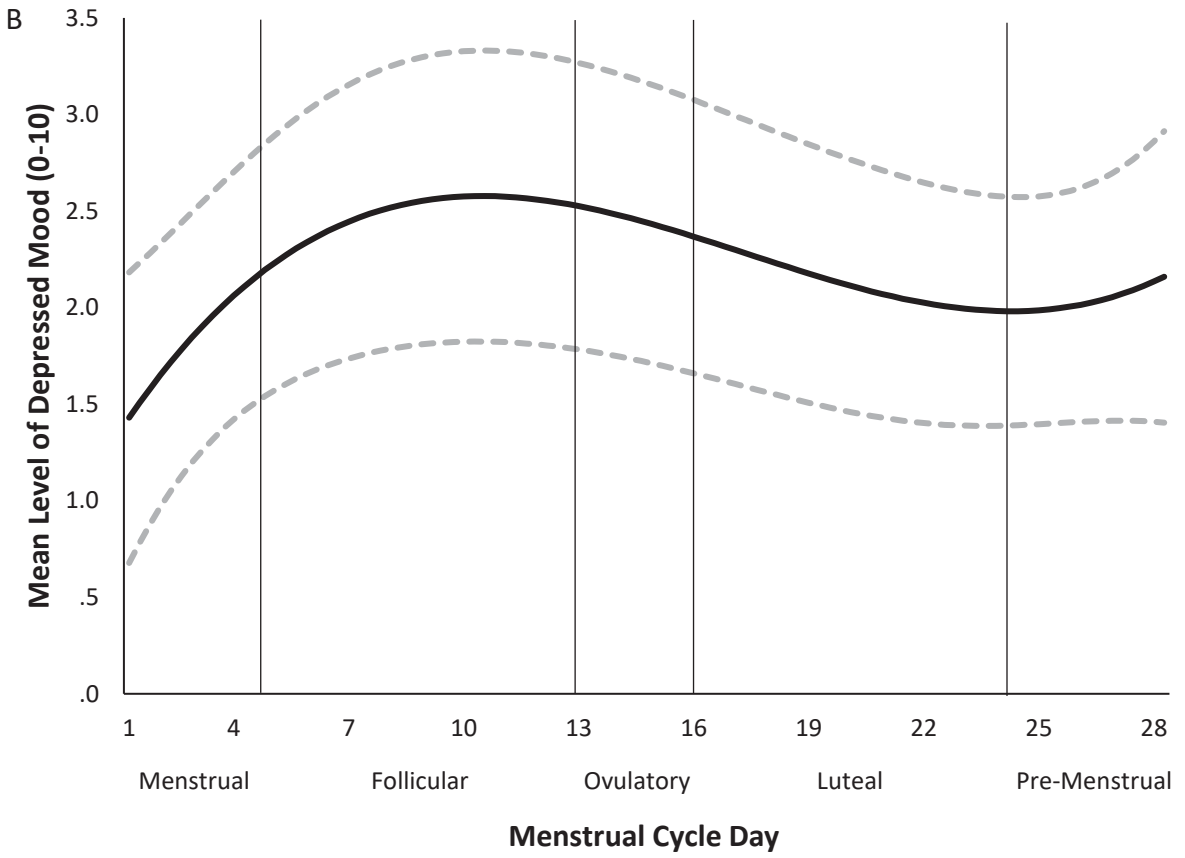


Figure 2. Time-varying effects of (A) depressed affect and (B) coping motives on cannabis use quantity across days of the menstrual cycle. Note: Black lines indicate regression coefficients and gray lines indicate 90% confidence intervals (CIs). CIs that do not include 0 indicate periods of significance.

A


Mean Level of Cannabis Use Quantity (Standard Joint)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
.0
1
4
7
10
13
16
19
22
25
28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day

B


Mean Level of Depressed Mood (0-10)
3.5
3.0
2.5
2.0
1.5
1.0
.5
.0
1
4
7
10
13
16
19
22
25
28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day

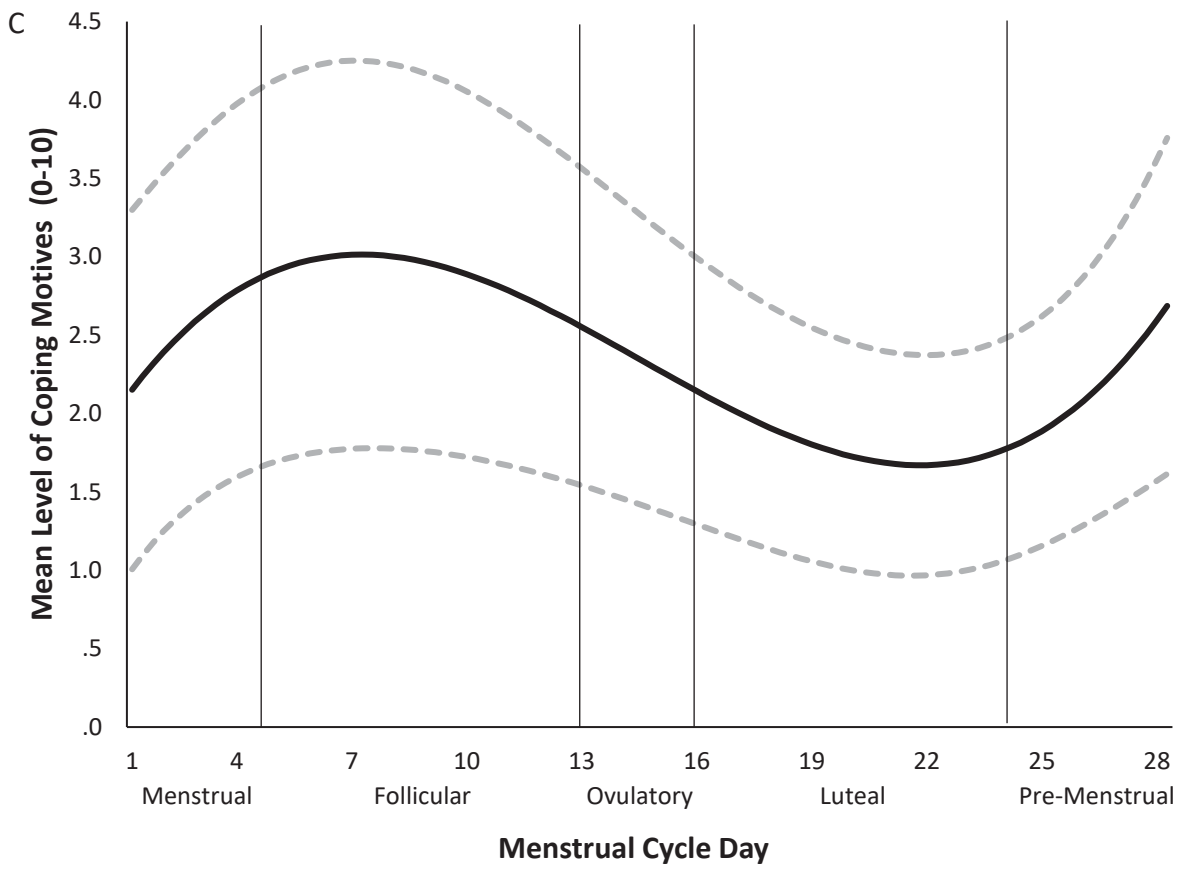


Figure 3. Estimated mean levels of (A) cannabis use quantity, (B) depressed affect, and (C) coping motives across days of the menstrual cycle as estimated by an intercept-only time-varying effect model from the sensitivity analysis. Black lines indicate estimated means and gray lines indicate 90% confidence intervals (CIs).

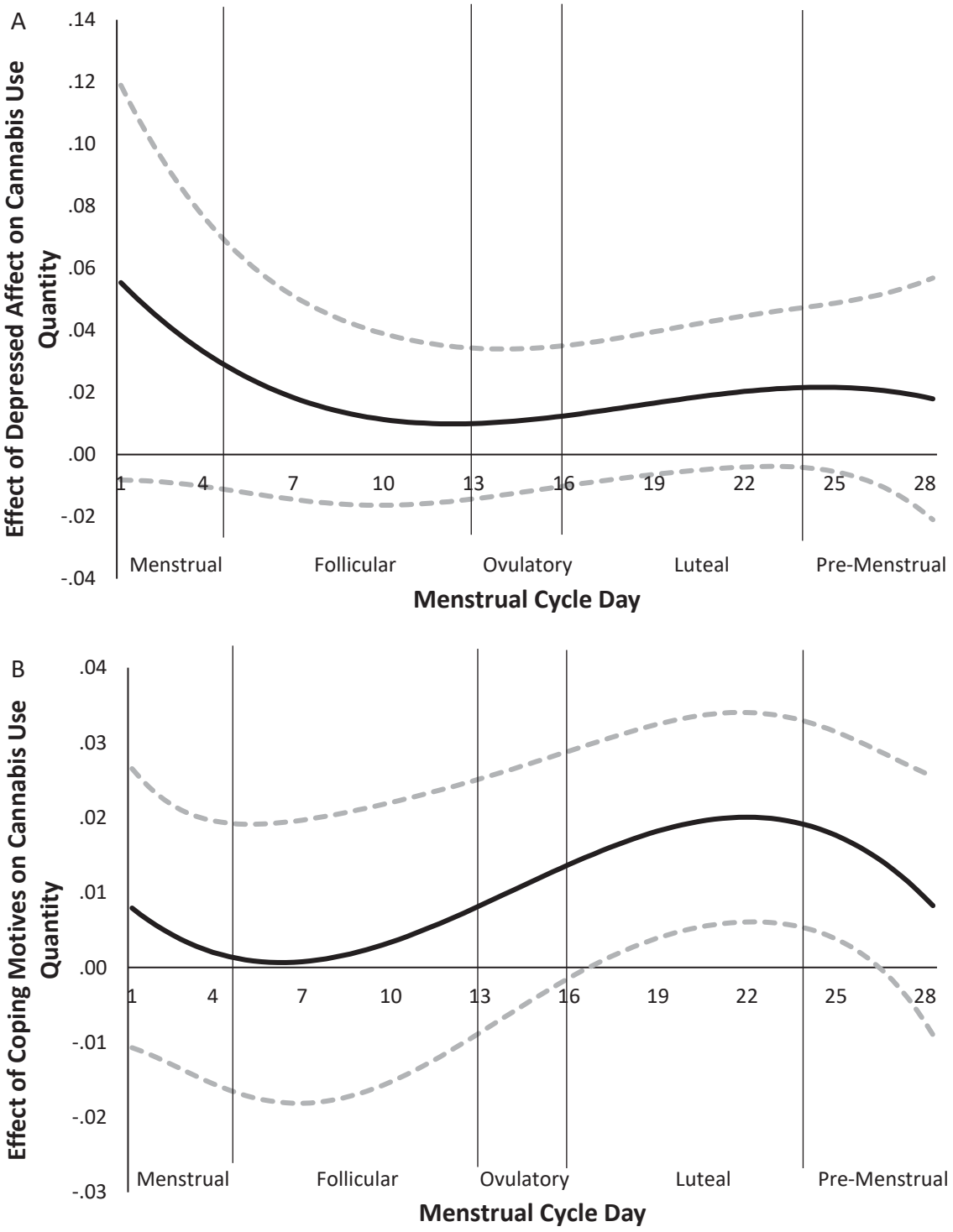


Figure 4. Time-varying effects of (A) depressed affect and (B) coping motives on cannabis use quantity across days of the menstrual cycle from the sensitivity analysis. Note: Black lines indicate regression coefficients and gray lines indicate 90% confidence intervals (CIs). CIs that do not include 0 indicate periods of significance.

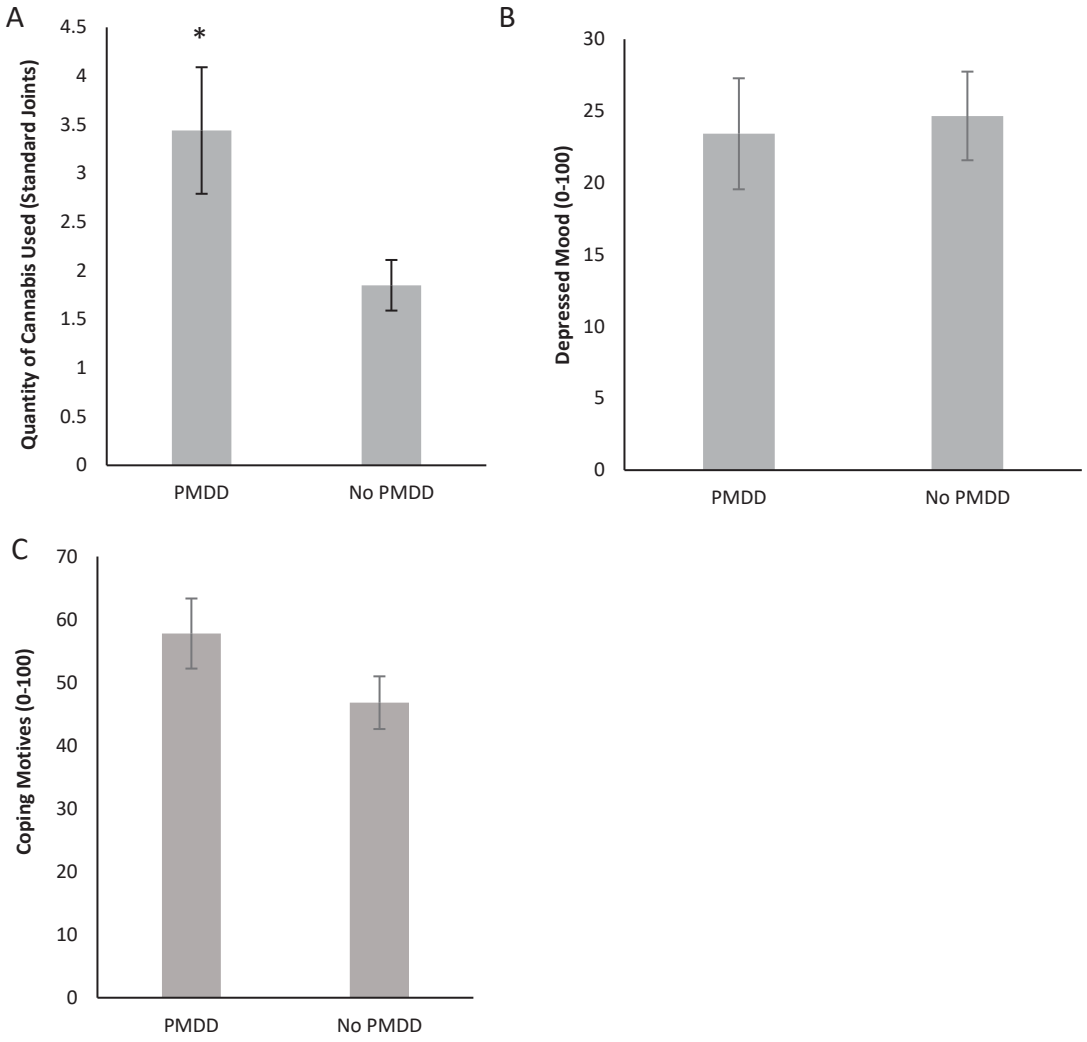
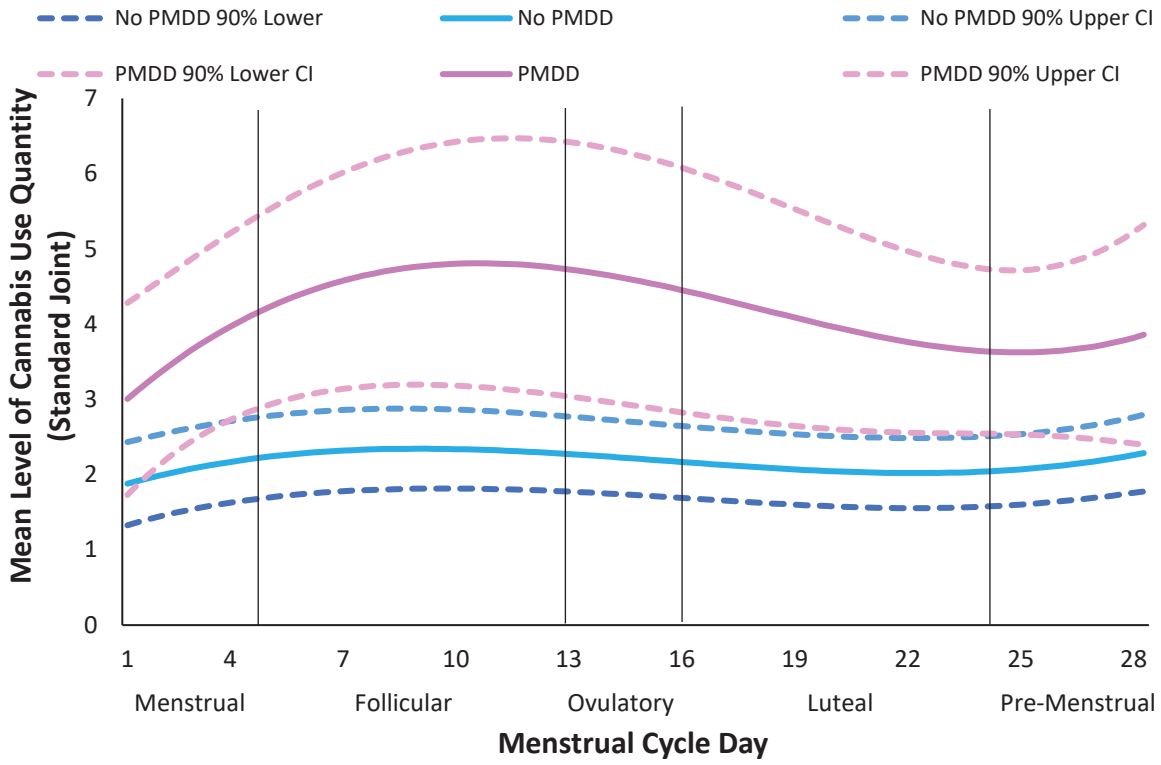
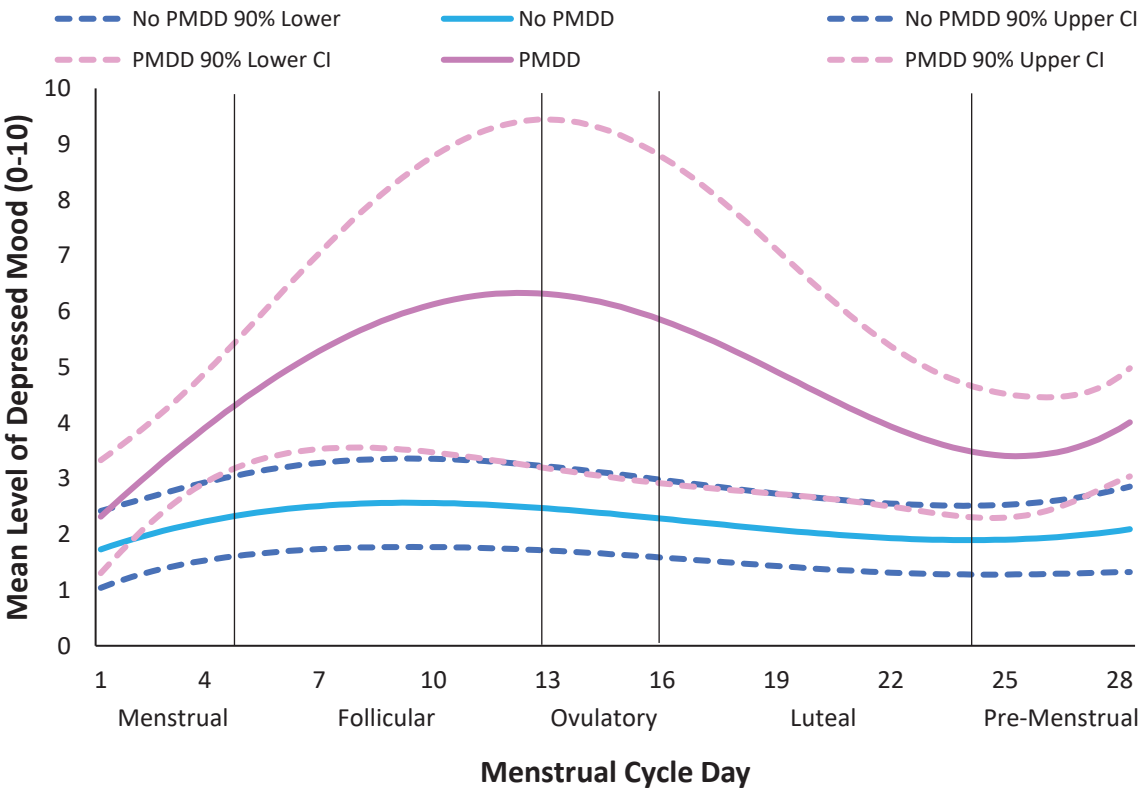


Figure 5. Average levels of (A) cannabis used (in quantity of standard joints), (B) depressed mood, and (C) coping motives across the 32-days of ecological momentary assessment in females with and without pre-menstrual dysphoric disorder (PMDD). Error bars represent standard errors. An asterisk (*) indicates significantly higher levels of cannabis used (in quantity) versus the other group.

A


No PMDD 90% Lower
No PMDD
No PMDD 90% Upper CI
PMDD 90% Lower CI
PMDD
PMDD 90% Upper CI
Mean Level of Cannabis Use Quantity (Standard Joint)
0
1
2
3
4
5
6
7
1
4
7
10
13
16
19
22
25
28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day

B


No PMDD 90% Lower
No PMDD
No PMDD 90% Upper CI
PMDD 90% Lower CI
PMDD
PMDD 90% Upper CI
Mean Level of Depressed Mood (0-10)
0
1
2
3
4
5
6
7
8
9
10
1
4
7
10
13
16
19
22
25
28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day

C

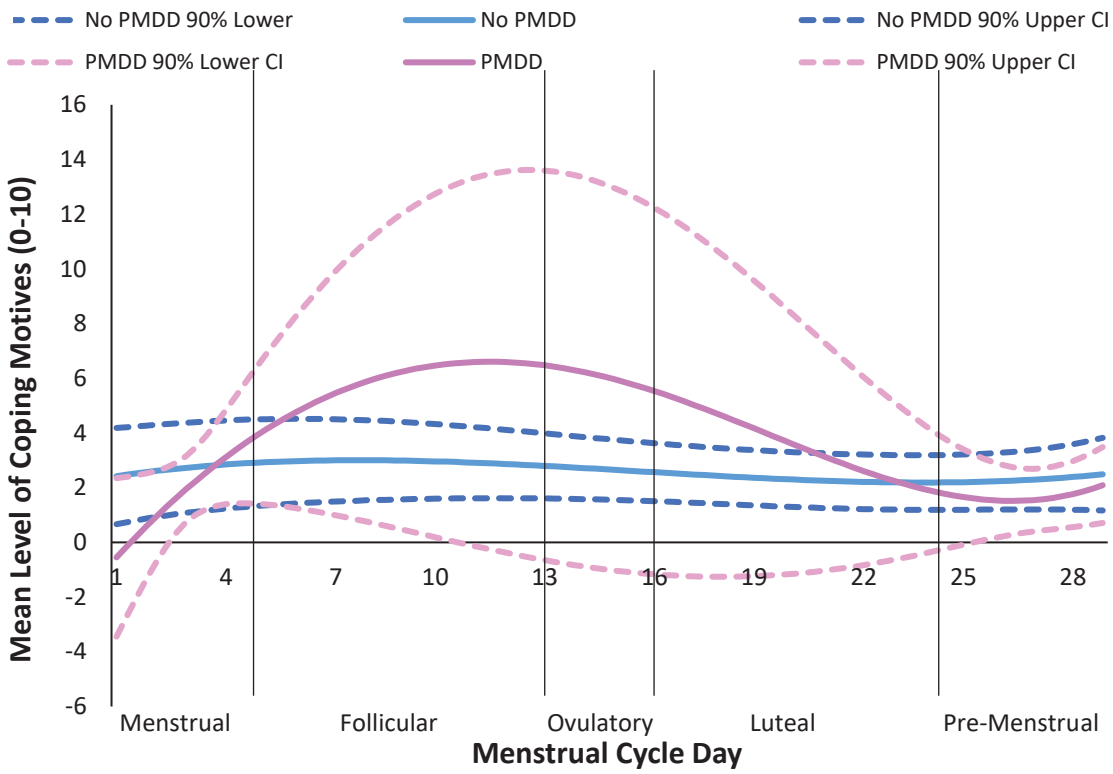


Figure 6. Patterns of (A) cannabis use quantity, (B) depressed affect, and (C) coping motives among females with and without pre-menstrual dysphoric disorder (PMDD) across the menstrual cycle (MC) as estimated by an intercept-only time-varying effect model. Solid lines indicate estimated means and dotted lines indicate 90% confidence intervals (CIs) by PMDD diagnosis (yes/no). The two groups are considered significantly different at points during the MC where the two sets of CIs are not overlapping.

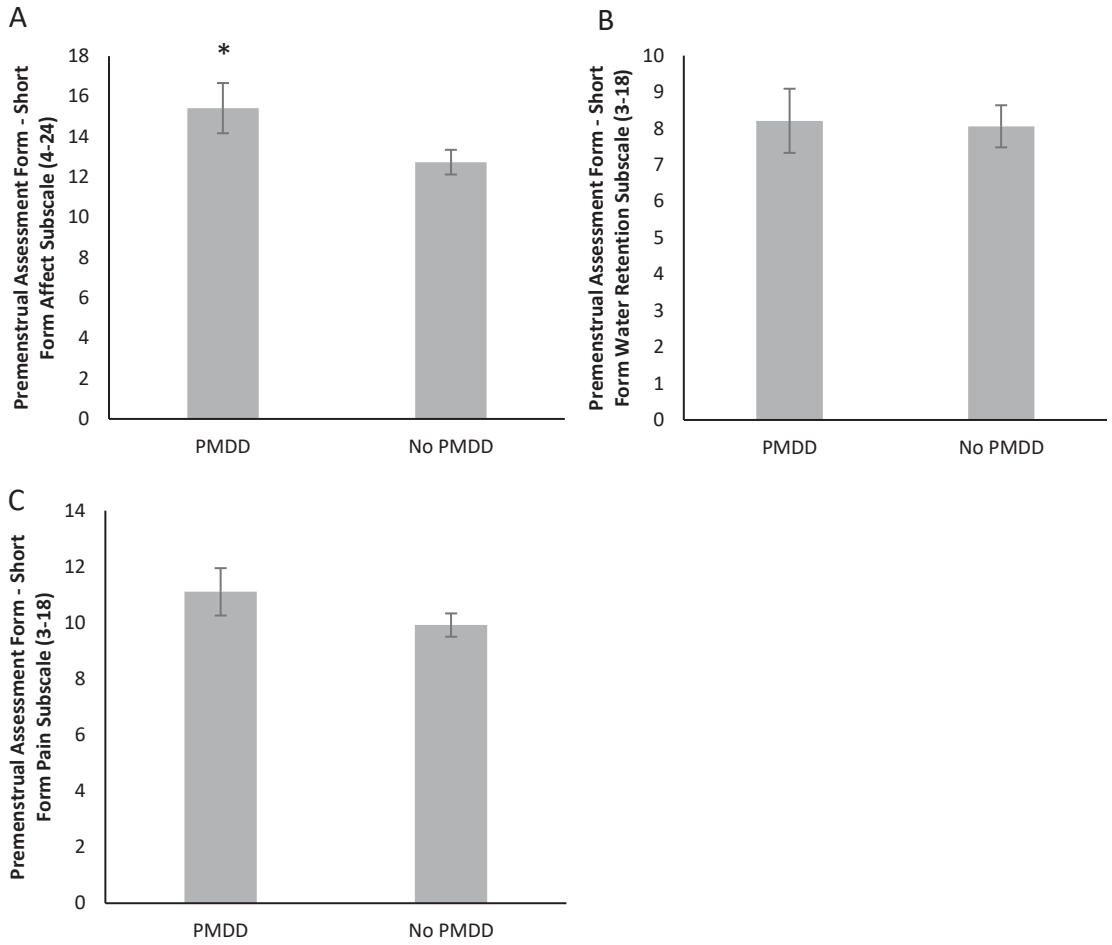
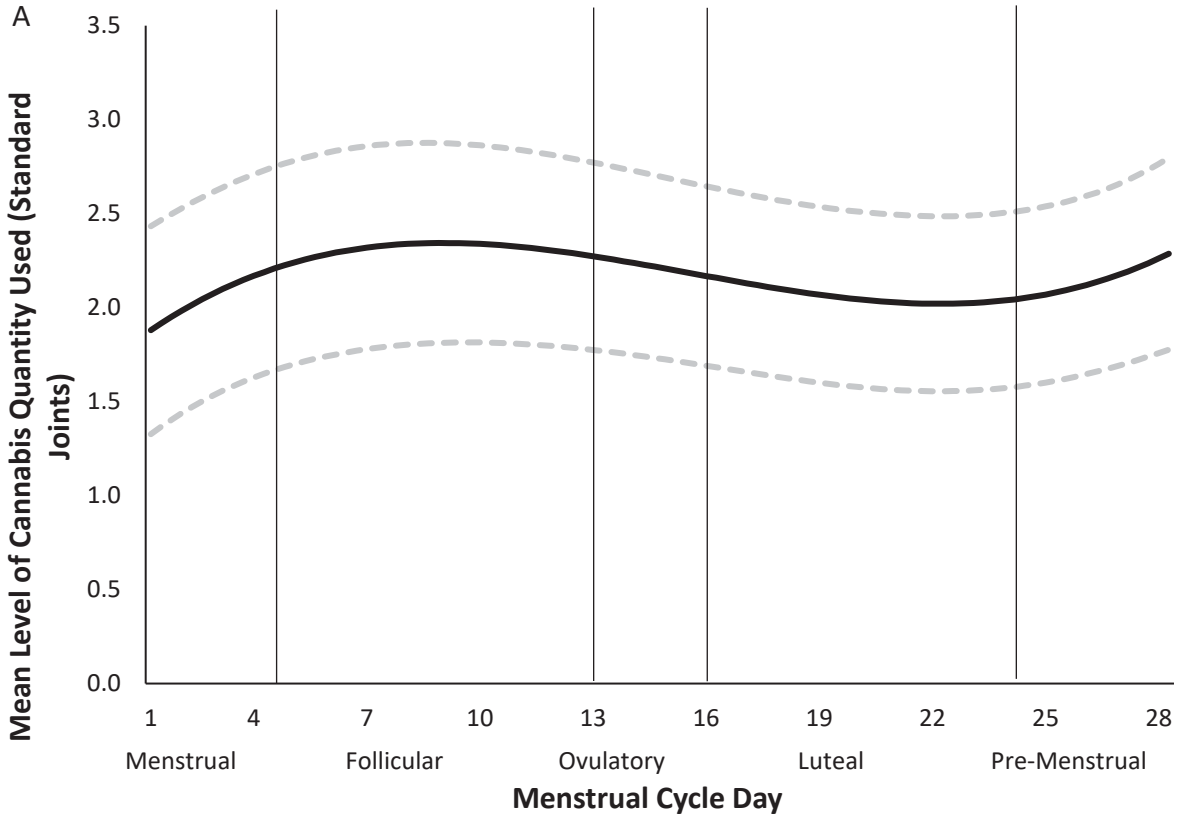
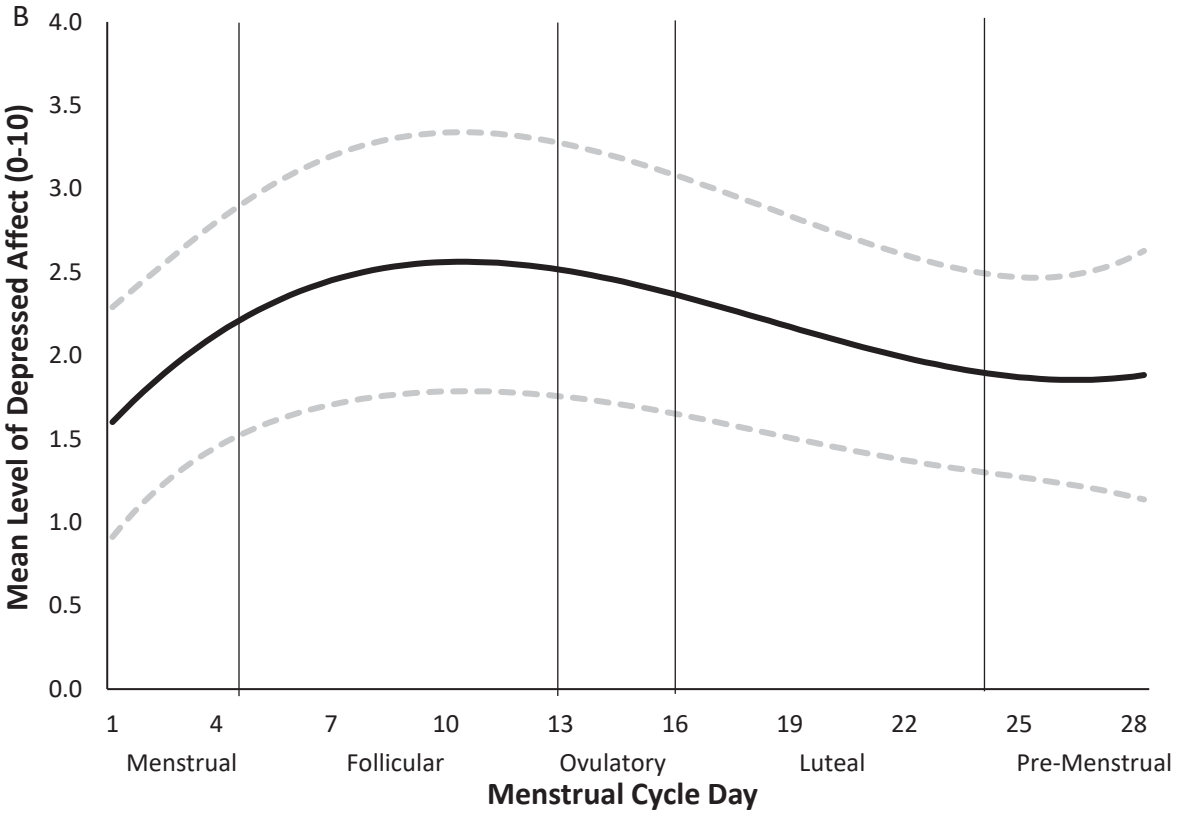


Figure 7. Mean (A) affect, (B) water retention, and (C) pain subscale scores on the pre-menstrual assessment form - short form (PAF-SF; Allen et al., 1991) in females with and without pre-menstrual dysphoric disorder (PMDD). Error bars represent standard errors. An asterisk (*) indicates a significantly higher affect subscale score for females with PMDD versus those without PMDD.


A
Mean Level of Cannabis Quantity Used (Standard Joints)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
4
7
10
13
16
19
22
25
28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day


B
Mean Level of Depressed Affect (0-10)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
4
7
10
13
16
19
22
25
28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day

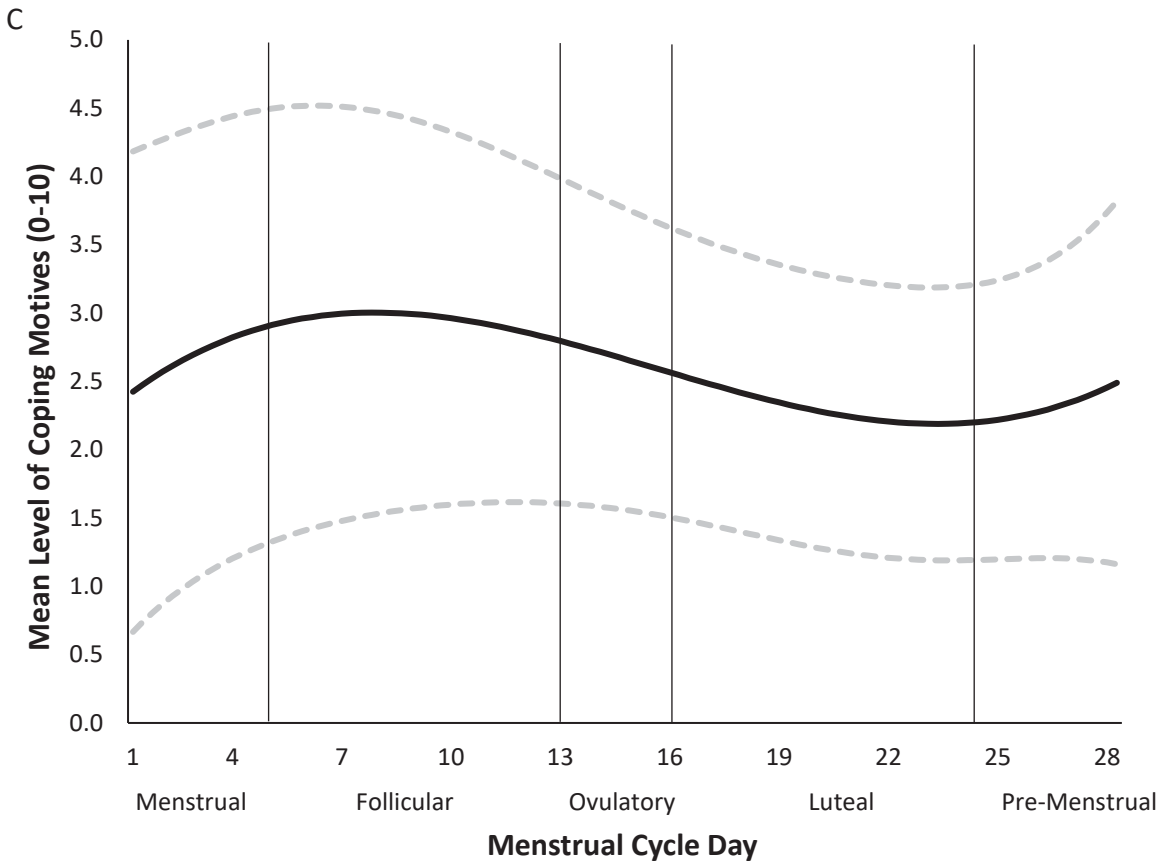


Figure 8. Estimated mean levels of (A) cannabis use quantity, (B) depressed affect, and (C) coping motives across days of the menstrual cycle in females without pre-menstrual dysphoric disorder (PMDD) as estimated by an intercept-only time-varying effects model. Black lines indicate estimated means and gray lines indicate 90% confidence intervals (CIs).

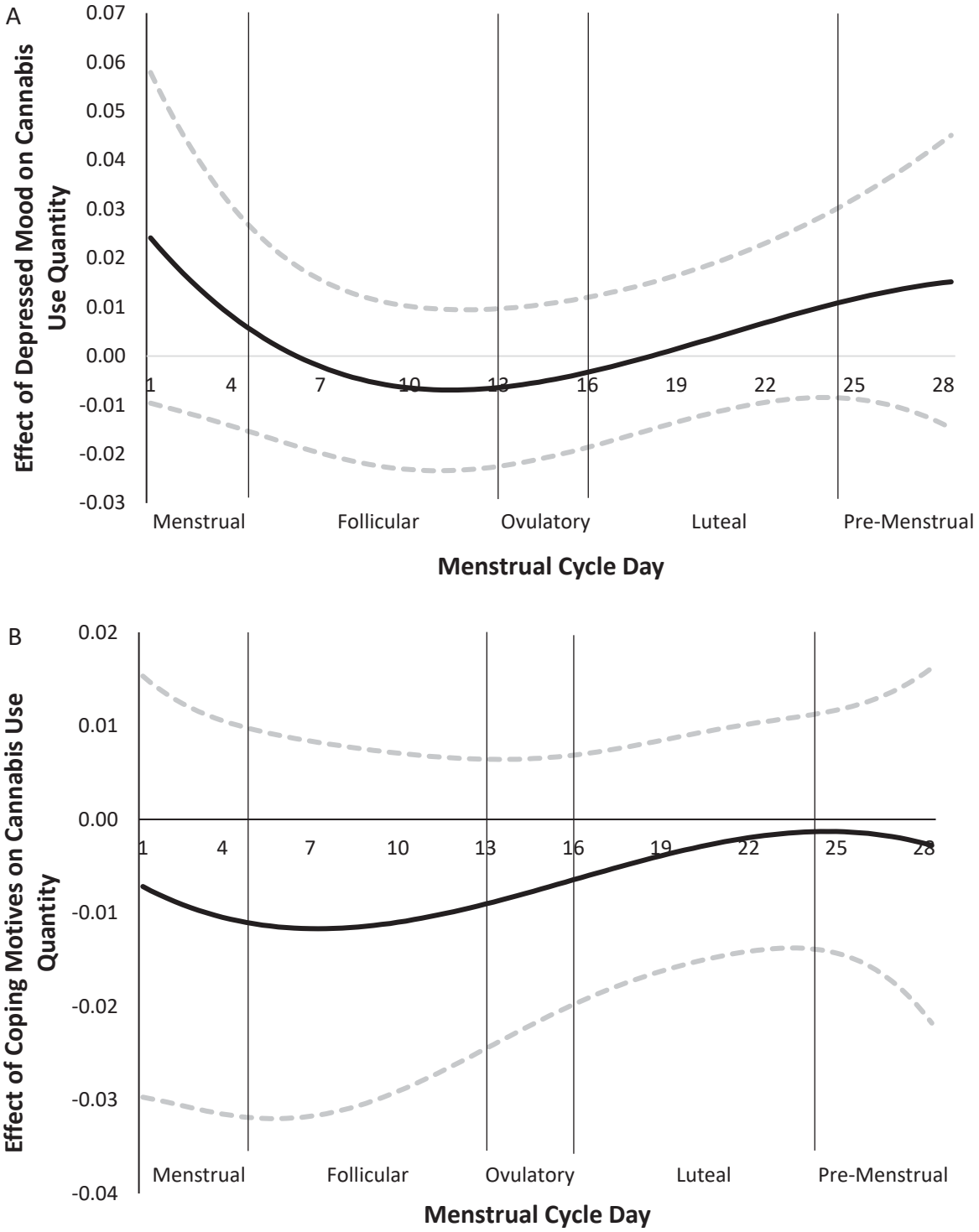
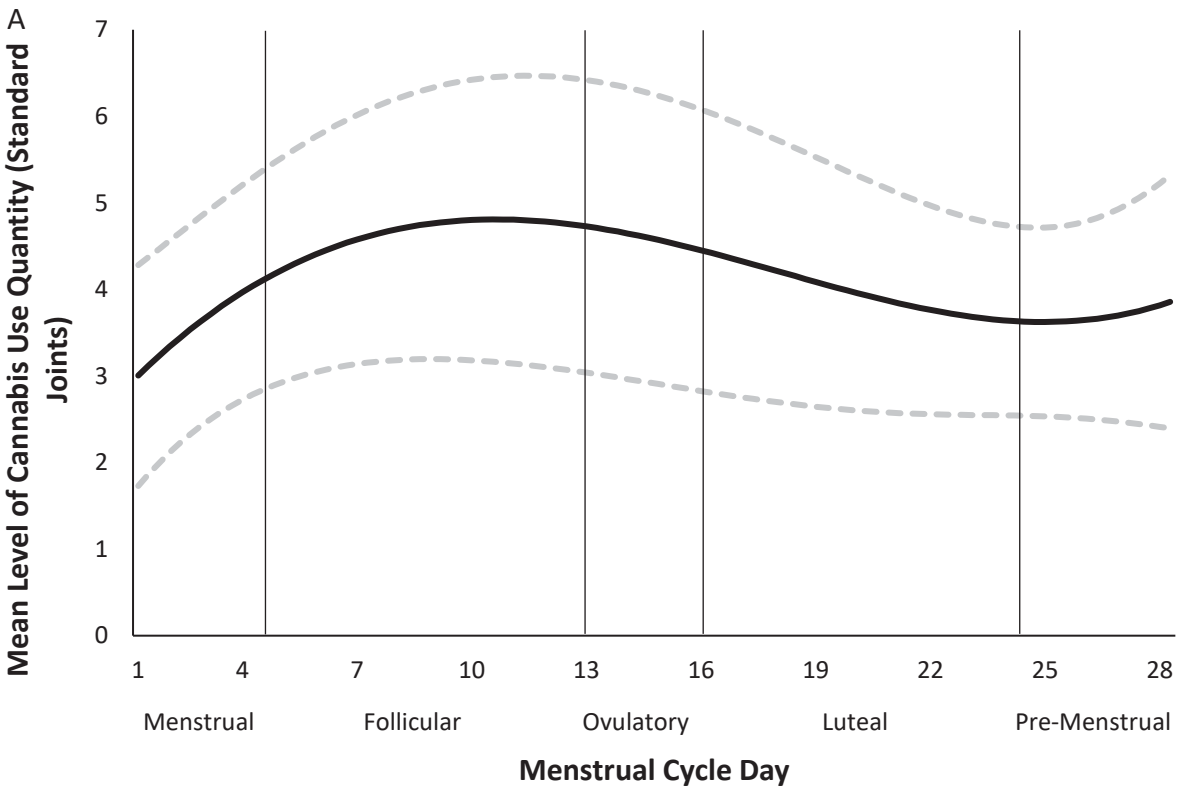
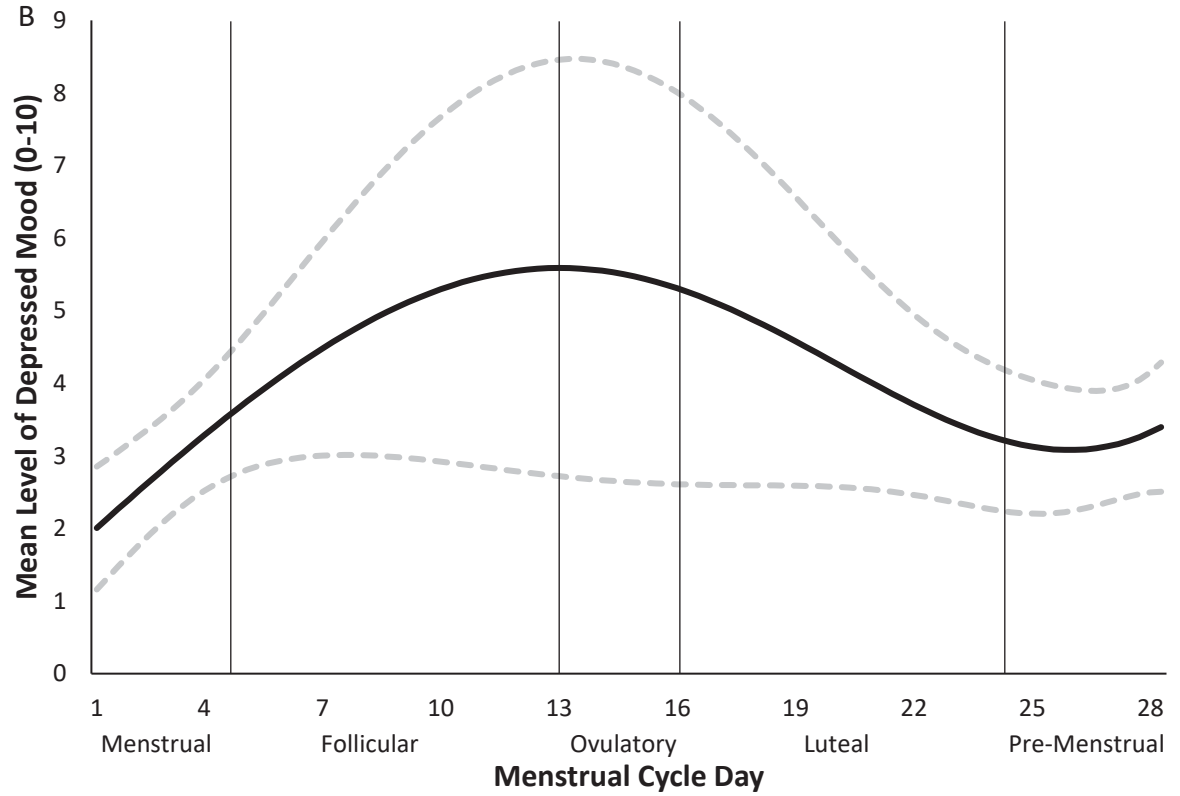


Figure 9. Time-varying effects of (A) depressed affect and (B) coping motives on cannabis use quantity across days of the menstrual cycle in females without pre-menstrual dysphoric disorder (PMDD). Note: Black lines indicate regression coefficients and gray lines indicate 90% confidence intervals (CIs). CIs that do not include 0 indicate periods of significance.


A
Mean Level of Cannabis Use Quantity (Standard Joints)
0
1
2
3
4
5
6
7
1
4
7
10
13
16
19
22
25
28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day


B
Mean Level of Depressed Mood (0-10)
0
1
2
3
4
5
6
7
8
9
1
4
7
10
13
16
19
22
25
28
Menstrual
Follicular
Ovulatory
Luteal
Pre-Menstrual
Menstrual Cycle Day

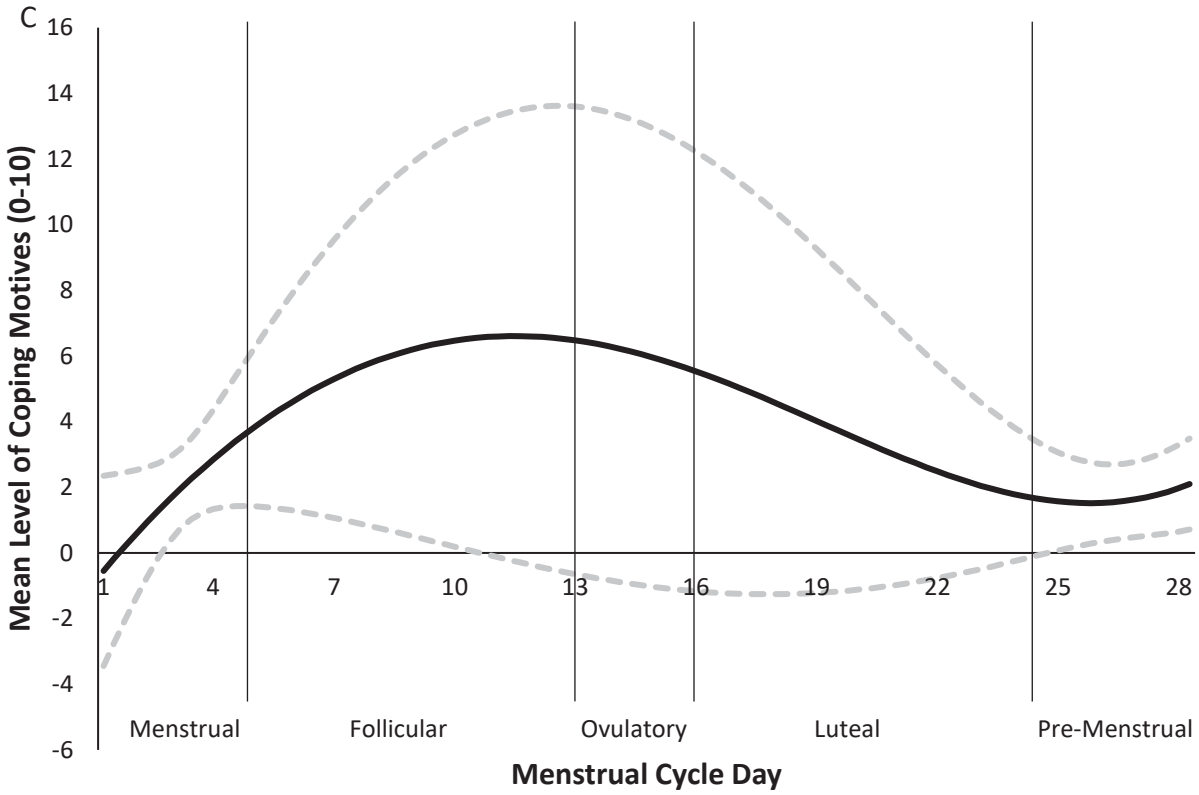


Figure 10. Estimated mean levels of (A) cannabis use quantity, (B) depressed affect, and (C) coping motives across days of the menstrual cycle in females with pre-menstrual dysphoric disorder (PMDD) as estimated by an intercept-only time-varying effects model. Black lines indicate estimate means and gray lines indicate 90% confidence intervals (CIs).

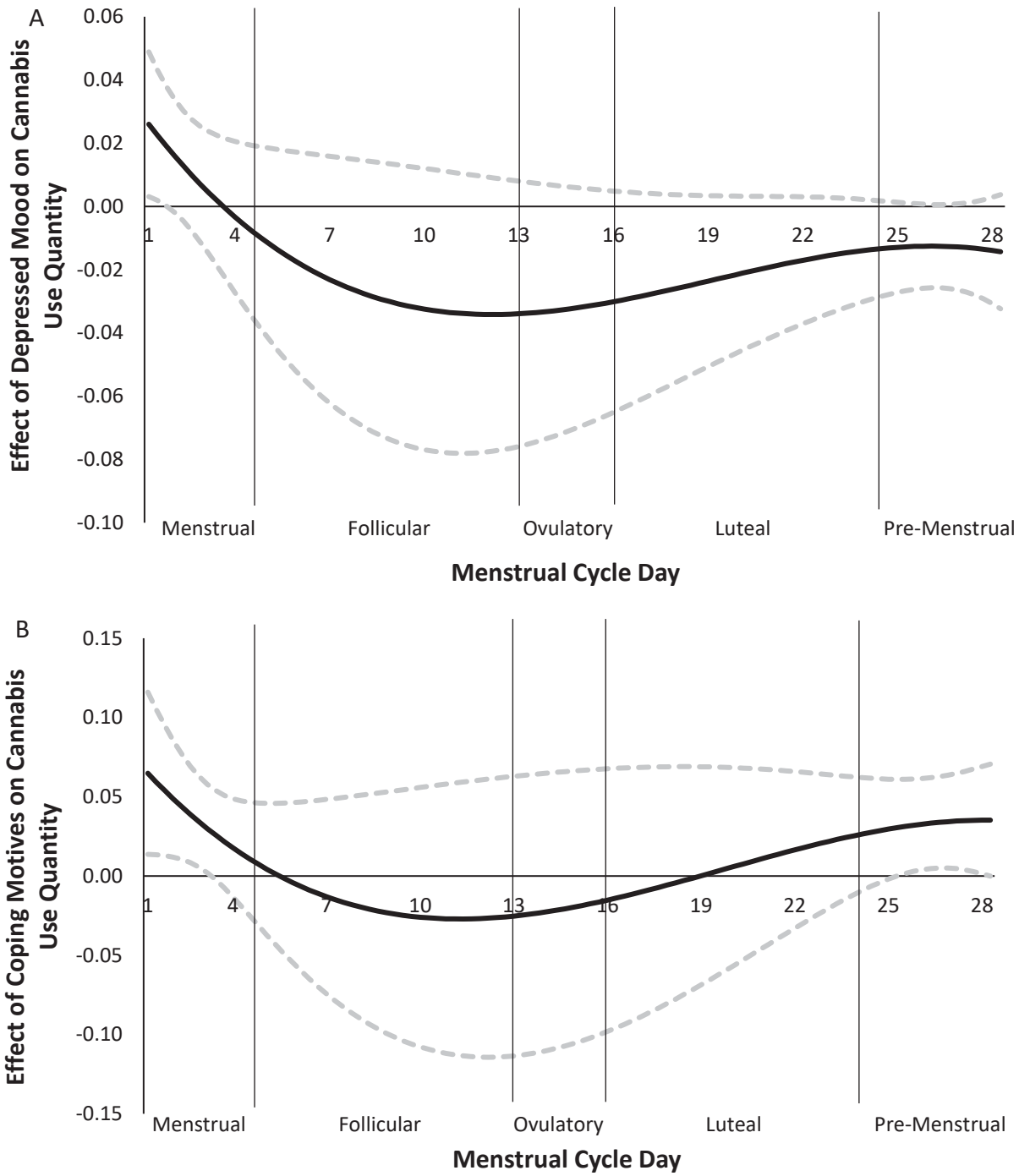


Figure 11. Time-varying effects of (A) depressed affect and (B) coping motives on cannabis use quantity across days of the menstrual cycle in females with pre-menstrual dysphoric disorder (PMDD). Note: Black lines indicate regression coefficients and gray lines indicate 90% confidence intervals (CIs). CIs that do not include 0 indicate periods of significance.

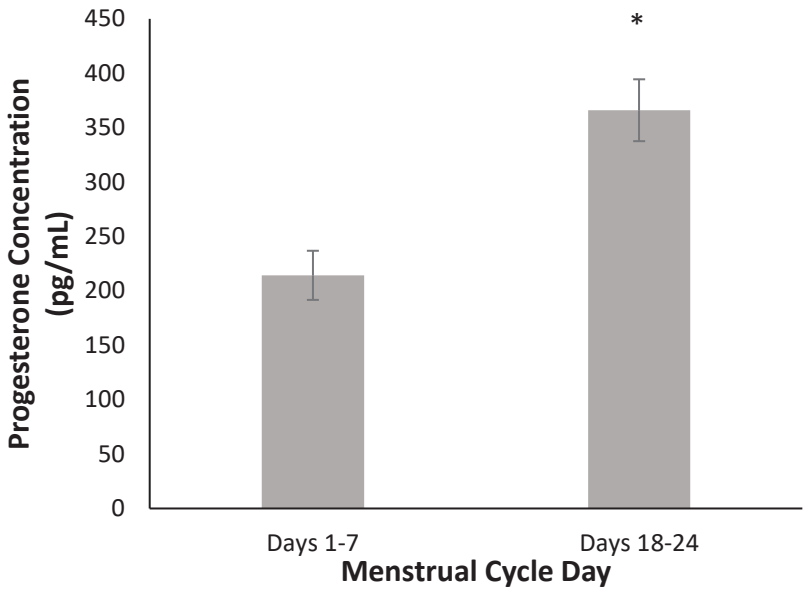


Figure 12. Mean level of salivary progesterone concentrations (pg/mL) during times of the menstrual cycle (MC) known to be associated with low (MC days 1-7) and high (MC days 18-24) progesterone concentrations. Error bars represent standard errors. An asterisk (*) indicates significantly higher levels of progesterone concentrations versus the other group of MC days.

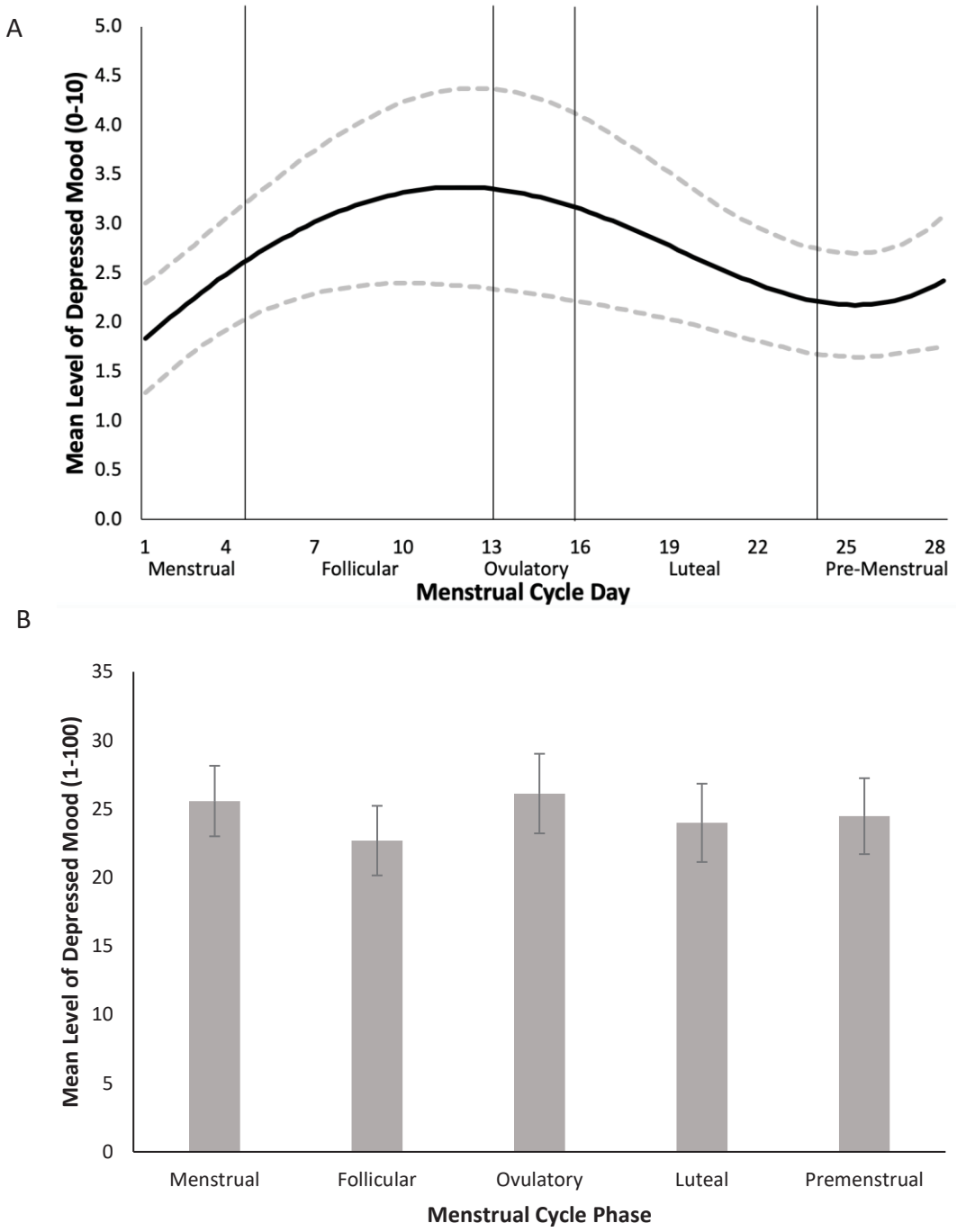


Figure 13. A comparison of the same depressed mood data analyzed across menstrual cycle phase versus menstrual cycle day. (A) intercept-only time-varying effect models and (B) repeated-measure analysis of variance.

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Allen, A. M., McRae-Clark, A. L., Carlson, S., Saladin, M. E., Gray, K. M., Wetherington, C. L., … & Allen, S. S. (2016). Determining menstrual phase in human biobehavioral research: A review with recommendations. *Experimental and Clinical Psychopharmacology, 24*(1), 1–11. doi:10.1037/pha0000057

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APPENDIX A Issues with Griffin et al. (1986)

1. The mood measure employed by Griffin et al. (1986; i.e., the Moos Menstrual Distress Questionnaire) is not internally consistent and does not divide negative affect into depression vs anxiety. The mood measure utilized within the current study is internally consistent and separates negative affect into depression and anxiety. For the purpose of analysis, we only used the depression subscale in our study given its theoretical relevance.

2. Griffin et al. (1986) did not have a temporal separation between their mood and cannabis use measure, as participants reported data together in one questionnaire. Thus, previous cannabis use may have influenced mood when mood was reported at a later point in time (i.e., after having used cannabis). This lack of temporal separation potentially contributed to the authors finding that increases in negative affect caused decreased cannabis use. The current study had a temporal separation between mood measures and cannabis use reporting as this allowed the authors to examine if early day mood predicted cannabis use.

3. Participants in the Griffin et al. (1986) study did not experience a change in negative affect across the MC and experienced relatively stable negative mood altogether, indicating that there would not be an increase in cannabis use to self-medicate (i.e., since they did not experience a change in mood). This lack of negative mood finding is inconsistent with extant literature published (Aganoff & Boyle, 1994; Collins et al., 1985; Reed et al., 2008; Wharton et al., 2012), suggesting potential problems with the mood assessment and emphasizing that further research was needed in this area.

4. In the Griffin et al. (1986) study, the authors did not counterbalance the experimental start date for participants; that is, all participants started recording data on day one of their MC which could influence findings at later phases of the MC due to potential reactivity to the daily monitoring. Within the current study, we had participants begin their daily surveys during the closest period of MC days where a saliva sample could be collected (i.e., either MC days 1-7 or 18-24).

5. Participants in Griffin et al. (1986) recorded data from three MCs and daily prompts about cannabis use may influence the frequency of cannabis (i.e., by reducing or increasing cannabis use) by virtue of self-monitoring. In the current study, participants only completed daily surveys across one MC to minimize the risk of having self-reporting methodologies influencing cannabis use levels and cannabis use reporting relative to studies examining cannabis use across three consecutive menstrual cycles.

5. Of further concern, Griffin et al., (1986) did not report information on how daily dairy surveys were collected and assessed for daily completion. Due to the high retention rate (99.1%) and the high cash payout, it is possible that participants may have completed surveys in bulk. Within the current study, all surveys were time stamped so we could confidently determine when each survey was completed.

6. Griffin et al. (1986) also did not exclude females with abnormally long menstrual cycles (up to 44 days) which suggests some participants were not normally-cycling. Not excluding females who are cycling in an abnormal fashion is problematic as these females have abnormal ovarian hormone fluctuations. The current study only included females who had an average length menstrual cycle (i.e., an average of 28 days [range = 23-35 days; Münster et al., 1992]), suggesting they are normally-cycling.

7. Current literature suggests the luteal phase of the MC is variable which Griffin et al. (1986) did not take into consideration (see review in Joyce & Stewart, 2018). The current study broke the MC down into phases based on more up-to-date literature (Fehring et al., 2006; Lenton et al., 1984; Walsh et al., 1981; see review in Joyce & Stewart, 2018)

APPENDIX B RECRUITMENT POSTER

Daily Diary Study on Cannabis Use in Women

The Dalhousie MAAC Laboratory is conducting a study on MOOD and CANNABIS use.

You may be eligible if you:
Are a woman between the ages of 19 and 45
Are not pregnant
Have a normal length menstrual cycle (i.e., 25 to 35 days)
Own a touchscreen smartphone (with data and texting)

If interested, please e-mail:
k.joyce@dal.ca

DALHOUSIE UNIVERSITY

You will be asked to attend three in-laboratory sessions and respond to two text message surveys daily, for 32 days. This study will take approximately 9 hours of your time across the 32 days.

Replies to this advertisement will be strictly confidential.

This study has been reviewed and approved by the Dalhousie University Health Sciences Ethics Board (REB# 2017-4249)

Daily Diary Study Email: k.joyce@dal.ca

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APPENDIX C TELEPHONE SCREENING

Participants must meet all of the screening criteria to be eligible for this study. Ask the first three questions and if potential participants reply "no" to any of the three questions, they are ineligible. Read instructions below about how to respond.

Dial number, have pen and paper ready, and when person answers the phone, ask:

Step One:

"May I please speak to (Name)?"

If you are not speaking to the person you will be screening, ask:

"Is (Name) available?"

If they are unavailable or they do not answer the phone, do not leave a message with the recipient of the call or on the voicemail. This is because study participation is strictly confidential.

If you are speaking to the person you will be screening, say: "Hi, my name is (Name). I'm a researcher from the Dalhousie University cannabis use study. I am calling as you have expressed interest in participating in this study. Are you still interested in participating?"

If they say "no", say: "Thank you for your time, goodbye."

If they say "yes", say: "Great, do you have approximately 10 minutes to complete a phone screening?"

If they say "yes", skip to step two.

If they say "no", ask: "Is there a better time I can phone you back?"

If they say "no", say: "Thank you for your time, goodbye."

If they say "yes": Record date and time for phone-back, thank them and end call.

Step Two:

Say: "Great, before I get started, I'm going to tell you a bit about the study and ask you some initial questions regarding your demographics, things like your age and cannabis use behaviors. If you're still interested and meet the requirements, I will ask you some further questions to determine your study eligibility.

Please remember, you are free to stop me at any time if you prefer not to continue the screening. All of your information given to me today is completely confidential and your name will not be directly associated with your screening data. You will be assigned a participant identification number that temporarily links your identification number to your identifying information. This is so we can link your data to the information you have given me over the phone and throughout the duration of the study. Your information will be stored in a locked filing cabinet and in a password protected database. Only researchers who are working on this study will have access to the information you give me today over the phone and for the duration of the study.

This study is examining the effects of cannabis use and hormonal changes across the menstrual cycle. The study involves a total of three visits to our lab at Dalhousie University, the collection of two saliva samples, and the completion of 32-daily text message surveys. The first visit to the lab involves you providing consent to participate, the completion of several surveys, and the collection of the first saliva sample. This first session will last approximately 1 hour. During the second visit we will collect a second saliva sample. This session will last approximately 30 minutes. The first two bookings will be scheduled over the phone today if you're eligible. The third visit is booked after you have completed your 32 days of surveys. During this final session you will be debriefed and receive your compensation.

Ask: "Do you have any questions about the study so far?" (Let them ask questions and answer them appropriately)
"Great, is it alright if I continue the phone screening and ask you some questions to determine your eligibility?"

If they say "no", say: "Thank you for your time, goodbye"

If they say "yes", ask:

1. "Are you between the ages of 19 and 45?"

   If they answer "yes", ask: "Could you please tell me your age?" (record) and continue to question two.

   If they answer "no": Kindly state that they are ineligible as we are looking for participants between 19 and 45. Thank them for their time and say goodbye.

2. "Do you own or have access to a smart phone with a data plan and texting?"

   If they answer "no": Kindly state that they are ineligible as we are looking for participants who own a smart-phone with a data plan to participate in daily text message surveys. Thank them for their time and say goodbye.

   If they answer "yes", ask: "Does your smart phone have an unlimited texting plan?"

      If they answer "yes": Continue to question three.

      If they answer "no": Please ask "For the current study, you will be responsible for covering the costs associated with the study's 32 days of text messages. Are you okay with being responsible for these costs?

         If they say "yes": continue to question three.

         If they say "no": Kindly state that they are ineligible as we are looking for participants who can respond to text message surveys. Thank them for their time and say goodbye.

3. "Have you used cannabis four or more times within the past month?"

   If more than four times, continue to step three.

   If less than four times, kindly state that they are ineligible as we are looking for participants who use cannabis on a more frequent basis. Thank them for their time and say goodbye.

Step Three:

If prospective participants answer **yes** to any of questions 4 – 15 or **no** to question 16, they are ineligible for study participation.

4. "Are you taking any form of hormonal contraception?"
5. "Have you stopped taking any form of hormonal contraception within the past 3 months?"
6. "Have you had a recent pregnancy within the last 6 months?"
7. "Are you currently breastfeeding?"
8. "Are you pregnant?"
9. "Are you trying to conceive?"
10. "Have you had a hysterectomy operation?"
11. "Are you menopausal or postmenopausal?"
12. "Do you experience missed periods?"
13. "Have you had a diagnosis of a pain disorder?
14. "Are you prescribed medical marijuana?"
15. "Are you receiving treatment for your cannabis use?"
16. "Do you have a normal length menstrual cycle?" (i.e., between 25 and 32 days from the beginning of one period to the start of a next)."

Step Four:

If they answer yes to any questions between 4-15 or no to question 16, say: "I'm sorry, but our study is looking for individuals with certain characteristics and you unfortunately do not meet the criteria. Thank you for your time. Goodbye." End call.

If they ask why they are not eligible, say:

"It's because the nature of our study requires us to recruit participants with certain characteristics and we have to ensure that participants in our study meet these characteristics." Apologize and thank them for their time.

If they answered no to questions 4-15 and yes to question 16, say: "It appears that you are in the group we are studying, so I'd like to offer you a chance to sign up for the study and schedule you to come into the lab if you are still interested in participating."

If they disagree: thank them for their time, say goodbye, and end the phone call.

If they agree: Go to step five

Step Five:

Say: "As I mentioned to you earlier, I will be booking the first two sessions for you to come into the lab now over the phone. In order for me to schedule these sessions, I must book you in according to where you are in your menstrual cycle. Thus, I need to ask you when the first day of your last period was, with day one being the first day of menstrual bleeding." (Give participants a moment to think about this and when they answer, you will need to do a calculation. See "Instructions on how to calculate cycle day" below).

Once given the dates, say: "Okay, thank you for providing this information to me. I am going to put you on hold so I can calculate the best times for you to come into the lab."

If they don't know which cycle day they are on, you can ask them to call back when their period begins so their sessions can be scheduled accordingly.

Instructions about how to calculate cycle day

We need the saliva samples to be provided during two different phases of the menstrual cycle. Specifically, the early-follicular (days 1-7) and the mid-luteal (days 18-24) phases based on an average 28-day menstrual cycle.

You must book participants once per each phase. Thus, if the first day of their last period was July 17th, you must count July 17th as day one, July 18th as day two and so on. For this participant, they must be booked between July 17th and July 23rd for one sample (early-follicular) and August 3rd to August 9th for the second sample (mid-luteal).

Note: Do not worry about the order in which the saliva samples are obtained, just move forward to the next window of time whether that be the early-follicular or mid-luteal.

Once the dates are calculated, book the participant in between those dates. Ideally, you'd like to book both sessions at once (using the methods previously described); however if for some reason they cannot book session two (e.g., unknown work schedules), tell them

we can schedule session two when they come in for their first session. Write down in the master list the window of days where they must be booked in for their second session

Step Eight:

Finally, ask: "Do you have a paper and pen handy?" and give them time to get one.

Start by telling them you have a few things about the session that would be good for them to write down.

Say: "You are scheduled to come into the lab on (dates) at (times). The lab is located at 1355 Oxford Street. You will be going to the third-floor psychology lounge in the psychology department of the Life Science Centre, Dalhousie University. I will meet you there and bring you to the lab. Also, it is important to note that when you come into the lab and we collect saliva samples there are guidelines you must follow prior to the saliva sample collection. These are:

- Avoid alcohol for 12 hours before sample collection
- Do not eat a major meal within 60 minutes of saliva collection
- Avoid dairy products for 20 minutes before sample collection
- Avoid food with high sugar, acidity, and caffeine content, immediately before sample collection.
- Rinse mouth with water to remove food residue before sample collection and wait at least 10 minutes after rinsing before collection saliva to avoid sample dilution.
- You should not brush your teeth 45 minutes prior to sample collection.
- Dental work should not be performed 48 hours prior to sample collection.
- Do not wear lipstick while collecting sample."

Ask: "Do you have any questions about the study?"

If they answer yes: answer their questions.

Ask: “What is a cell phone number I can reach you at (write down) so I can provide you with a text-message summary of the information I have given you today over the phone?”

Remind them to “Please bring your cell phone for your first session, so we can verify your text message surveys.”

Also say: “I also want to let you know that we schedule your session specifically for you and this session involves bringing researchers into the lab and having clinical psychologists on call. If for some reason you can’t come into the lab during your session, please call us at (902) 494-3793 to let us know and to rebook if that is what you would like to do. Again, thank you and I look forward to meeting you! Goodbye.” End call.

APPENDIX D SALIVA COLLECTION GUIDELINES

Participants:

- Avoid alcohol for 12 hours before sample collection.
- Do not eat a major meal within 60 minutes of sample collection.
- Avoid dairy products for 20 minutes before sample collection.
- Avoid foods with high sugar or acidity, or high caffeine content, immediately before sample collection.
- Rinse mouth with water to remove food residue before sample collection and wait at least 10 minutes after rinsing before collecting saliva to avoid sample dilution.
- Do not brush your teeth 45 minutes prior to sample collection.
- Dental work should not be performed 48 hours prior to sample collection.
- Do not wear lipstick when collecting saliva.

Researchers:

- Saliva samples visibly contaminated with blood should be discarded and recollected.

APPENDIX E INFORMED CONSENT FORM

Project Title: Daily Diary Study of Mood, Cannabis Use Motives, and Cannabis Use Behavior across Females' Menstrual Cycles

Study Investigators
Dr. Sherry H. Stewart, Departments of Psychology and Psychiatry, Dalhousie University
Kayla M. Joyce, Department of Psychiatry, Dalhousie University
Dr. Philip Tibbo, Department of Psychiatry, Dalhousie University
Dr. Kimberley Good, Department of Psychiatry, Dalhousie University
Dr. Kara Thompson, Department of Psychology, St. Francis Xavier University
Dr. Amanda Hudson, Provincial Mental Health and Addictions Programming Lead, Health Prince Edward Island
Dr. Tara Perrot, Department of Psychology, Dalhousie University
Nacera Hanzal, Department of Medical Sciences, Dalhousie University

Contact Person:
Kayla M. Joyce, Master's in Psychiatry Research Student
Laboratory Address: Department of Psychology, MAAC Lab, Dalhousie University, Life Sciences Centre, 1355 Oxford Street, Halifax, Nova Scotia, Canada, B3H 4J1
E-mail: k.joyce@dal.ca

Introduction
You are being invited to take part in a research study being conducted by Kayla M. Joyce, Nacera Hanzal**,** and Dr.'s Sherry H. Stewart, Philip Tibbo, Kimberley Good, Kara Thompson, Amanda Hudson, and Tara Perrot. Your participation in this study is voluntary and you may withdraw from the study at any time. The study is described below. This description tells you about the risks, inconveniences, or discomforts that you might experience during your participation. Participating in this study might not benefit you, but we might learn things that will benefit others. You should discuss any questions you have about this study with the researcher reviewing this consent form.

Purpose of the Study
The purpose of this study is to look at whether and how mood, cannabis use motives, and cannabis use change over the course of females' menstrual cycles.

Study Design
You are being asked to take part in this study because you responded to an advertisement and were then interviewed by a research assistant over the phone. This interview was done to determine whether you met the requirements for the study and to see if you were interested in further participation. For this study, we will have 80 community-recruited female cannabis users from Nova Scotia. There is some research suggesting that mood plays an important role in people's reasons for using cannabis and that people use cannabis differently depending on their mood. Our study is intended to closely examine the relationship between mood and cannabis use by having people tell us about their mood, their reasons for using cannabis, and cannabis use in their natural environments.

We hope to learn more about how cannabis use is linked with mood as people go about their everyday lives. We also hope this study will help us develop new ways of assessing cannabis use to help with future research. Your feedback and participation in this study is important to help us understand how to best measure cannabis use.

This study involves five phases, each described in more detail below:

1. **Phase One:** You have previously completed a telephone screening where you were found to be eligible for the current study
2. **Phase Two:** Today, you will complete two questionnaires with a researcher, answer questions regarding your cannabis use and mood, and then answer seven questionnaires in an online survey. You will also be shown how to use your smart phone to complete online surveys. Finally, you will provide the researcher with a saliva sample.
3. **Phase Three:** For 32 days, you will self-monitor (using questionnaires) your cannabis use, mood, and menstrual cycle on your smart phone.
4. **Phase Four:** You will come back to the lab to provide a second saliva sample. This sample will have to be given during a specific time of your menstrual cycle.
5. **Phase Five:** Finally, you will return to Dalhousie University to fill out one final questionnaire, receive an explanation of the study, and receive your compensation.

Who can Participate in the Study?

You may participate in this study if you are an adult female between 19 and 45 years of age (standard cut-off for menstrual cycle research). To participate, you must have used cannabis at least 4 times in the past month. Additionally, you are eligible to complete the current study if you have not stopped taking hormonal contraceptives within the past three months, you are not abstaining from or trying to quit cannabis use, if you are able to learn to use your smart phone to respond to online questionnaires, and if you can read and write English. To participate, you cannot be pregnant or trying to conceive, cannot have had a hysterectomy operation, cannot be menopausal, and cannot experience missed periods. Participants must also own a touch screen smartphone (that has a data plan and texting) in order to receive survey links. Although you are not required to have a cell phone plan with free texting to participate, you must be willing to cover the costs associated with the daily text messages you will be receiving.

Who will be Conducting the Research?

Kayla M. Joyce (a Masters' Student working under Dr. Sherry Stewart) and/or Nacera Hanzal (an undergraduate student working under Dr. Sherry Stewart), will be administering the questionnaires to you, training you on how to use a smart phone to complete daily questionnaires and gather your saliva samples.

Dr. Sherry H. Stewart is the Principal Investigator on this study and Kayla M. Joyce as well as Drs. Phil Tibbo, Kimberely Good, Kara Thompson, Amanda Hudson, and Tara Perrot are co-investigators.

What you will be asked to do?

Study Overview

If you choose to participate, this study includes five phases. The first phase has already taken place. The second phase will take place today and involves an initial interview, seven questionnaires, saliva collection, and an orientation to the study. The third phase will involve 32-days of daily-monitoring (questionnaires on a smart phone). Phase four will involve you returning to the lab to provide a final saliva sample. The final phase will involve one final questionnaire and a debriefing/compensation.

Phase One: Telephone Screening

Before coming into the lab today, you completed a telephone screening with one of the research assistants at the lab. This telephone screening was to determine your eligibility for the current study.

Phase Two: The Initial Interview

This will involve an interview with a research assistant regarding your cannabis use, menstrual cycle, and current mood. You will then fill out four questionnaires on a computer regarding demographic information as well as your cannabis and drug use. After you have finished the online questionnaire, you will meet with the research assistant again who will provide you with training on how to use your smart phone to complete the questionnaires during the 32-day self-monitoring (phase three). To end this phase, you will be asked to provide the research assistant with a saliva sample. Hormones from the saliva samples provided will be used to determine which day of your menstrual cycle you are on. In total, phase one should take 60 minutes or 1 hour.

Phase Three: Daily Monitoring (Questionnaires) for 32 days

The daily monitoring will be done electronically on a smart phone. You will be texted to complete two daily questionnaires, that you will complete by clicking on the link in the text message. The first survey will be sent daily at 10:30 am, and the second will be sent at 2:00 pm, with a reminder text message to complete your 2:00 pm survey sent again at 6:30 pm. It is intended that the first survey (10:30 am) be completed sometime in the morning, before using cannabis, but the second survey (2:00 pm) should be completed after using cannabis just prior to using cannabis, or before bed (if no cannabis use took place).

Both surveys will ask questions about your cannabis use, mood, and stressors in your life. If you used cannabis the day before (10:30 am survey) or are planning to use cannabis (2:00 pm survey) the survey will ask you questions about your cannabis use (e.g. how long you were using cannabis for and how much money you spent on cannabis) and your reasons for using cannabis. The 10:30 am survey will also ask if you plan to use cannabis later in the day. Additionally, you will receive a question each day (at 10:30 am) about where you are in your menstrual cycle. In total, phase three will take approximately 13 minutes to complete daily (13 minutes x 32 days = 416 minutes or approximately 7 hours).

You may call or e-mail us at the lab if you have any questions about the study after leaving here today. Starting tomorrow, you will begin receiving daily text messages for a period of 32 days.

During the 32 days you are completing the self-monitoring, a research assistant may contact you to see how you are doing with the self-reporting and answer any questions you might have.

Phase Four: Second Saliva Sample
This phase will involve you coming into the lab to provide the second, and last, saliva sample. This saliva sample will be given during a specific time of your menstrual cycle. This phase will last approximately 30 minutes.

Phase Five: The Final Meeting
Once the 32 days of self-monitoring are over, you will be invited to attend a final meeting at the research laboratory where you will be given one final questionnaire. This questionnaire will examine the effects of monitoring your mood, motives, and cannabis use. You will receive a debriefing and be given your compensation. This phase will last approximately 30 minutes.

Possible Risks and Discomforts
Harms associated with participating in this study are low. By completing the self-monitoring of your mood and cannabis use, you may begin to notice some patterns that were not apparent before. At the end of the study, we will provide you with some information on places you can get support for substance use disorders. Additionally, we will conduct an interview with you regarding your current mood. The likelihood of becoming distressed while being interviewed is low; however, if you become distressed due to your participation in this study, trained psychologists are available to assist you. You will also be provided with the contact information of important places and services you can get support for your mental health if required.

To reduce risks associated with admitting to illegal activities, this study will collect minimal identifying and demographic information from you. Your name will never be recorded or linked to any of the data we collect. There will be a link between your participant identification number and cell phone number, although this link will be eliminated once compensation is collected.

You are free to withdraw from this study at any time. If you decide to participate now, but then later decide you are no longer interested, you may still withdraw from the study. To withdraw from the study, please contact Kayla M. Joyce, and let her know that you'd like to withdraw from the study and whether you would like your data removed from the study. Once you receive your compensation, you will be unable to withdraw your data from the current study, as we will be unable to identify your data/samples.

Possible Benefits

There may also be a benefit to participating in the study. You might get a better understanding of how your mood is related to your cannabis use. Having a list of resources and information on substance use disorders may also be helpful to you in the future.

Your participation in this study will also help us gain a better understanding of what kinds of treatments might be best for certain cannabis users and how we can support people who are looking for help with their cannabis use disorders.

Compensation / Reimbursement

This study requires you to take a few minutes out of your day, every day, for 32 days. We will compensate you based on a rate of $10.85 per hour for a total of 9 hours (totaling to a maximum compensation of $97.65). Your final compensation will be based on the number of phases you attend and the number of surveys you complete. All surveys must be completed on the correct day to be fully compensated. All compensation will be provided during the final debriefing session. You will be paid based on the following:

- Phase two will last approximately one hour (**$10.85**)
- Phase three will take approximately 13 minutes per day to complete daily diary surveys (13 minutes x 32 days = ~7 hours or **$75.95**)
- Phase four will take approximately 30 minutes (**$5.43**)
- Phase five will take approximately 30 minutes (**$5.43**)

If you decide to withdraw from the study before the end of the 32-day self-monitoring period, you will still receive compensation based on the number of sessions and daily diary surveys completed (see above compensation breakdown). Once you receive your compensation, you will be unable to withdraw your data from the current study, as we will be unable to identify your data/samples.

Confidentiality & Anonymity

All information gathered during this study will remain confidential, unless otherwise required by law and/or the Dalhousie Research Ethics Board.

You will not be required to write your name on any of the actual questionnaires and no names will be used on any reports or presentations that arise from this study. All data collected through daily diary surveys will be linked to your participant identification number to maintain your confidentiality. All data we collect from you (via questionnaires) will be entered into a password protected computer file and this file will not contain any names. Additionally, all daily dairy data will be password protected. Only the investigators listed above will have access to your information. In any published report or presentation about the results of this project, your name will never be mentioned, nor will any information that could identify you. Additionally, all saliva samples will be stored for up to three years, after which time your samples will be destroyed by incineration.

Use of your data may occur in the future for theses or graduate student projects. This data will be completely anonymous with no identifiers. The data will be kept for 5 years post-publication. Should you wish to receive a copy of the written report you can contact Pam Collins (Dr. Stewart's research assistant) at (902)-494-6488.

Questions

Should you have any questions about this study, or if any issues arise because of your participation in the study, please feel free to contact the Principal Investigator (Dr. Sherry Stewart) or Masters' Student (Kayla M. Joyce).

Dr. Sherry H. Stewart
Departments of Psychology and Psychiatry, Dalhousie University
Telephone: (902)-494-3793; E-mail: sstewart@dal.ca

Kayla M. Joyce
Department of Psychiatry, Dalhousie University
E-mail: k.joyce@dal.ca

Problems or Concerns

You will receive a copy of this consent form for your records. Please feel free to address any question you may have to the Masters' Student or investigators either now or after you have participated. You may contact Dr. Sherry Stewart at (902)-494-3793.

If you have any ethical concerns about your participation in this research, you may also contact Dalhousie University's Research Ethics at (902)-494-1462 or email ethics@dal.ca (and reference REB file #2017-4249).

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Signature Page – Participant Copy

Daily Diary Study of Mood and Cannabis Use

I have read the explanation about this study. I have been given the opportunity to discuss it and my questions have been answered to my satisfaction. I consent to take part in this study. However, I realize that my participation is voluntary and that I am free to withdraw from the study at any time.

Please check the options that apply below:

____ I have read all of the information outlined above and;

____ I understand that I will receive a copy of the Consent Form including contact information of whom to call if I have questions in the future.

____ I give my consent to participate in this study

_____ _____

Signature of Researcher Date

DALHOUSIE UNIVERSITY
Inspiring Minds

_____ **Participant ID**

Signature Page – Researcher Copy

Daily Diary Study of Mood and Cannabis Use

I have read the explanation about this study. I have been given the opportunity to discuss it and my questions have been answered to my satisfaction. I consent to take part in this study. However, I realize that my participation is voluntary and that I am free to withdraw from the study at any time.

Please check the options that apply below:

____ I have read all of the information outlined above and;

____ I understand that I will receive a copy of the Consent Form including contact information of whom to call if I have questions in the future.

____ I give my consent to participate in this study

_____ _____

Signature of Researcher Date

APPENDIX F MENSTRUAL CYCLE QUESTIONNAIRE

1. Are you currently or have you recently (i.e., past year) been pregnant?

Yes	No	I Don't Know

2. Are you currently trying to conceive?

Yes	No	I Don't Know

3. Are you currently taking any form of hormonal contraception? (e.g., birth control pill, Depo-Provera injection, Evra patch, Implanon Implant, NuvaRing ring, Hormonal intrauterine device)?

Yes	No
If so, what kind?	

4. Are you currently taking any form of hormonal replacement therapy for pre-menopause?

Yes	No

5. Would you say that you experienced regular menstrual cycles during the last 3 months (i.e., the same number of days each month ranging between 25 and 35 days)?

Yes	No	I Don't Know

6. On average, how long is your entire menstrual cycle (i.e., time between the start of one "period" to the start of the next "period")?

of days:

7. On average, how long is your "period" (i.e., days that you experience menstrual bleeding)?

of days:

For this next set of questions, we would like you to estimate the start and end dates of your past "period". If you have brought this information with you today, please notify the researchers. If not, please look at the cannabis use calendar you completed to help you estimate these dates.

8(a). Thinking back to your last menstrual "period", on what date did your "period" begin? (Count the first day of real blood flow, not days of spotting)

Date:

8(b) Please indicate how confident you are about this date by circling the appropriate number.

1	2	3	4	5	6	7	8	9	10
Not at All Confident				Neutral					Extremely Confident

8(c). On what date did your MOST RECENT menstrual "period" end? (Record the last day of real blood flow, not spotting)

Date:	My most recent period has not ended

8(b) Please indicate how confident you are about this date by circling the appropriate number.

1	2	3	4	5	6	7	8	9	10
Not at All Confident				Neutral					Extremely Confident

APPENDIX G DEMOGRAPHIC QUESTIONNAIRE

1. People sometimes identify themselves by ethnicity or race. Do you consider yourself (please check):

Single Race
Bi-racial
Multi-racial (3 or more)
Prefer not to answer

2. Check all the boxes that show how you identify yourself:

Native Canadian/First Nations Group/Band:
Caucasian
Chinese
Filipino
Latin American
Japanese
Korean
Black (e.g., African, Haitian, Jamaican, Somali)
South Asian (e.g., East Indian, Pakistani, Punjabi, Sri Lankan
Arab/West Asian (e.g., Armenian, Egyptian, Iranian, Lebanese, Moroccan
South East Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese)
Other:
Prefer not to answer

3. How old are you?

Years:	Prefer not to answer

4. What is your current level of education?

Completed elementary school
Some high school
High school graduate
Some college/university
College/university graduate
Some post-graduate
Post-graduate degree (e.g., Master's PhD, LLB, MD)
Prefer not to answer

5. As far as you know, did either of your parents ever have a problem with gambling or receive treatment for problem gambling?

Yes	No	Prefer Not to Answer

6. As far as you know, did either of your parents ever have a problem with alcohol or receive treatment for alcohol abuse?

Yes	No	Prefer Not to Answer

7. As far as you know, did either of your parents ever have a problem with cannabis use or receive treatment for cannabis abuse?

Yes	No	Prefer Not to Answer

APPENDIX H STRUCTURED CLINICAL INTERVIEW FOR DSM-5 DISORDER RESEARCH VERSION (EDITION 5) RESOURCES

Please note that you can contact/refer to the following agencies if you need to talk to someone regarding concerns about your mood and/or mental health.

Name	**Contact Information**
Mental Health Crisis Line	*Call:* 1-888-429-8167 (Toll-free; available 24 hours a day, 7 days a week)
Canadian Mental Health Association (Nova Scotia Division)	*Website:* http://www.novascotia.cmha.ca *Call:* 1-877-466-6606 (Toll-free)
Nova Scotia Health Authority	*General Website:* http://www.nshealth.ca/mental-health-addictions *Contact information for your nearest location:* http://www.nshealth.ca/service-details/Community%20Mental%20Health%20Services
Dalhousie Student Counselling Services (For Dalhousie University Students)	*Call:* 1-902-494-2171 to make an appointment

APPENDIX I ECOLOGCAL MOMENTARY ASSESSMENT SURVEYS

Mood Measure:
Touch the horizontal line at the point that best reflects your mood today (VAS scale).

1. Sad
Not at all <- - - - - - - - - - - - - - > Very

2. Depressed
Not at all <- - - - - - - - - - - - - - > Very

3. Blue
Not at all <- - - - - - - - - - - - - - > Very

Cannabis Use Details
1. Did you use cannabis yesterday? (pull down)
Yes
No (If no, then the remaining cannabis use questions and cannabis use motive questions are skipped)

2. How much cannabis did you use? (number of joints) Please note a standard joint refers to 0.5 grams, five bong or pipe hits, and/or 10 puffs.

Cannabis Use Motives
We would like to have a better understanding of why individuals choose to use cannabis. For the reason listed below, please touch the horizontal line at the point which best reflects the reason you used cannabis yesterday.

1. Yesterday I used cannabis because cannabis helps me cope with negative mood (e.g., because it helps when you are feeling nervous, depressed, or anxious).
Not at all <- - - - - - - - - - - - - - > Very much so

2. Yesterday I used cannabis because cannabis helps me deal with stress (e.g., to relax or to unwind).
Not at all <- - - - - - - - - - - - - - > Very much so

Daily Menstrual Cycle Day
1. Please indicate your menstrual cycle day, if known. If unknown, please select unknown. Day 1 is considered the first day of menstruation. (choose from a list of numbers/pull-down)

APPENDIX J DEBRIEFING FORM

First of all, I want to thank you very much for participating in this investigation. The purpose of this study was to help us understand the relationship between mood, cannabis use and how differences in females' reasons for using cannabis influence their cannabis use across the menstrual cycle. In this study we were measuring whether or not there are individual differences in how much females use cannabis after they experience different mood states. We have a hypothesis that an individual's cannabis use motives (or reasons for using cannabis) will influence how much they use cannabis on days when they are in a sad mood state. Hopefully, this research will help us to understand how emotions can serve as triggers for using cannabis. Your participation in this study will help us gain a better understanding of what kinds of treatments might be best for certain female cannabis users and how we can support females who are looking for help with substance use disorders.

We will use your saliva samples to help validate your progesterone levels, which is a valid indicator of your menstrual cycle. We are interested in knowing where you were in your menstrual cycle throughout the course of the month because research has shown that some potentially addictive behaviours are influenced by ovarian hormones. This relationship has never before been investigated with cannabis use behaviours.

Finally, if you could answer the following questions about the daily diary study:

1. To what extent did the monitoring impact your mood?

1	2	3	4	5	6	7	8	9	10
Not at All				Moderately					A Great Deal

2. To what extend did the monitoring impact your cannabis use behaviour?

1	2	3	4	5	6	7	8	9	10
Not at All				Moderately					A Great Dealt

3. How satisfied were you with the design of this study?

1	2	3	4	5	6	7	8	9	10
Not at All				Moderately					A Great Dealt

4. What did you like best about the study?

5. What did you like least about the study?

APPENDIX K DEBRIEFING RESOURCES

Lastly, please note that you can contact/refer to the following agencies if you need to talk to someone regarding concerns about your substance use behaviours and/or mental health.

Name	**Contact Information**
Addictions Services	*Website:* http://www.nshealth.ca/mental-health-addictions
Canadian Mental Health Association (Nova Scotia Division)	*Website:* http://www.novascotia.cmha.ca *Call:* 1-877-466-6606 (Toll-free)
Mental Health Crisis Line	*Call:* 1-888-429-8167 (Toll-free; available 24 hours a day, 7 days a week)
Nova Scotia Health Authority	*Website:* http://www.nshealth.ca/mental-health-addictions

APPENDIX L SUPPLEMENTARY SENSITIVITY ANALYSIS RESULTS

Cannabis Use Quantity Across Menstrual Cycle Day

Figure 3A shows the estimated mean level of cannabis use quantity across MC day. Cannabis use quantity increased during the menstrual and follicular phases, dipped during the ovulatory and luteal phases, and peaked pre-menstrually. This peak in cannabis use quantity during the pre-menstrual phase was not observed in the main analysis. The slopes of cannabis use were also much steeper (relative to other MC phases) during the menstrual phase.

Depressed Mood Across Menstrual Cycle Day

The estimated mean level of depressed affect increased menstrually, dipped during the ovulatory and luteal phases, and began increasing again pre-menstrually (see Figure 3B). The slopes of depressed mood were much steeper during the menstrual, but not the pre-menstrual phase, compared to other MC phases. Inconsistent with predictions, depressed mood peaked during the MC phase following the menstrual phase, the follicular phase.

Cannabis Coping Motives Across Menstrual Cycle Day

The estimated mean level of coping motives increased menstrually, dipped during the ovulatory and luteal phases, and began increasing again pre-menstrually (see Figure 3C). Of interest, the slopes of coping-motivated cannabis use were, yet again, much steeper during the pre-menstrual and menstrual phases versus other MC phases. Cannabis coping motives peaked during the MC phase following the menstrual phase, the follicular phase.

Depressed Mood and Cannabis Use Quantity Associations by Menstrual Cycle Day

The estimated bivariate time-varying associations between depressed affect and daily cannabis use quantity are shown in Figure 4A. Depressed mood was unrelated to the quantity of cannabis used on any MC day.

Coping Motivation and Cannabis Use Quantity Associations by Menstrual Cycle Day

Figure 4B shows the estimated bivariate time-varying associations between coping motives and daily cannabis use quantity. Coping-motivated cannabis use was significantly associated with higher quantities of cannabis use during the luteal and pre-menstrual phases (MC days 17-26).