PRENATAL CANNABIS EXPOSURE AMONG PREGNANT PEOPLE IN TWO MICHIGAN SAMPLES

By

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ABSTRACT

PRENATAL CANNABIS EXPOSURE AMONG PREGNANT PEOPLE
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This dissertation will address three study aims: **Aim 1** will estimate the size of a suspected causal influence of prenatal cannabis exposure on a set of inter-related birth outcomes: birth size, gestational age, 5-minute Apgar score, and neonatal intensive care unit admission. **Aim 2** will investigate the degree to which morning sickness might be associated with higher odds of cannabis use. **Aim 3** is to conduct a feasibility study to assess the recruitment and retention of pregnant people who regularly use cannabis, measured by willingness to participate and complete the study survey; willingness to provide urine samples; the percentage of participants who are cannabis-only users; and the percentage of pregnant people retained for the three follow-up assessments.

Aims 1 and 2 use data for the Michigan Archive for Research on Child Health, a prospective cohort of pregnant people recruited from 11 sites across Michigan between 2017 and 2021. Aim 1 and Aim 2 analytic sample sizes are n= 584 and n= 826, respectively. Results of Aim 1 suggest a modest but statistically significant association between prenatal cannabis exposure and birth size z-score after model adjustment for potential confounding variables ($beta_{model4}$= -0.3; 95% CI: -0.5, -0.003).

Results of Aim 2 suggest higher odds of prenatal cannabis use with increasing morning sickness severity (OR_{model4}= 1.2; 95% CI: 1.1, 1.2). Sensitivity analyses indicate higher odds of using cannabis during the first trimester with increasing morning sickness severity (OR_{model4}= 1.1; 95% CI: 1.01, 1.2). Similarly, findings indicate higher odds of cannabis use in the second or

third trimester of pregnancy with increasing morning sickness severity (OR_{model4}= 1.2; 95% CI: 1.1, 1.4). Sensitivity analyses also suggest an association between pre-pregnancy and prenatal cannabis use and morning sickness severity ($beta_{model4}$= 0.1; 95% CI: 0.003, 0.2 and $beta_{model4}$= 0.2; 95% CI: 0.1, 0.2, respectively).

For Aim 3, Cannabis Legalization in Michigan-Maternal & Infant Health, a prospective feasibility study, was designed to better understand the recruitment and retention of pregnant people who regularly use cannabis. The study recruited n= 77 baseline participants of which n= 15 were prospectively followed and assessed during each trimester of pregnancy and once post-delivery. Of the participants recruited at baseline, 42% reported using cannabis during pregnancy, of which 87% were cannabis-only users (*i.e.,* no reported polysubstance use). All prospective participants were willing to provide urine samples; the concordance between self-reported cannabis use and urinalysis was 100% in the first and second trimesters and 92% in the third trimester of pregnancy. Study retention of the prospective sample was 80%; of n= 15 first trimester participants, n= 3 were loss-to-follow-up. Of the remaining 12 participants, 83% had complete data across all four timepoints.

Findings from this dissertation reveal that pregnant people are willing to participate in a study that explores the health effects of prenatal cannabis use on birth outcomes and maternal health. Larger studies are warranted to assess the association between prenatal cannabis exposure and fetal growth and development, as well as the relationship between morning sickness and cannabis use. This dissertation also detected an association between prenatal cannabis exposure and lower birth size, suggesting that pregnant people, or people contemplating pregnancy, should be cautioned against using cannabis until more studies are conducted to establish causality between prenatal cannabis use and neonatal health.

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KEY TO ABBREVIATIONS

US	United States
THC	Tetrahydrocannabinol
CB1	Cannabinoid-1
CB2	Cannabinoid-2
ECS	Endocannabinoid System
AEA	Anandamide
2-AG	2-Arachidonoylglycerol
CB1R	Cannabinoid-1 Receptor
CB2R	Cannabinoid-2 Receptor
FAAH	Fatty Acid Amide Hydrolase
PTB	Preterm Birth
LBW	Low Birth Weight
BPM	Beats Per Minute
NICU	Neonatal Intensive Care Unit
PRAMS	Pregnancy Risk Assessment Monitoring System
SGA	Small-For-Gestational-Age
NVP	Nausea and Vomiting of Pregnancy
HG	Hyperemesis Gravidarum
hCG	Human Chorionic Gonadotropin
SSRI	Selective Serotonin Reuptake Inhibitor
FDA	Food and Drug Administration

CNS	Central Nervous System
GIT	Gastrointestinal Tract
CHS	Cannabinoid Hyperemesis Syndrome
PUQE	Pregnancy-Unique Quantification of Emesis
NSDUH	National Survey on Drug Use and Health
DC	District of Columbia
CBD	Cannabidiol
MARCH	Michigan Archive for Research on Child Health
LMP	Last Menstrual Period
BMI	Body Mass Index
SES	Socioeconomic Status
GLM	Generalized Linear Models
GEE	Generalized Estimating Equations
OR	Odds Ratio
CI	Confidence Interval
ACOG	American College of Obstetricians and Gynecologist

CHAPTER 1. BACKGROUND & DISSERTATION AIMS

1.1. Cannabis Legalization and Liberalization

The widespread legalization of cannabis in the United States (US) has contributed to the rise in cannabis use prevalence. Although not federally legal, many states across the nation have legalized the medical and/or recreational use of cannabis; Michigan became the first state in the Midwest to legalize the recreational use of cannabis among adults 21 years and older in December 2018. Cannabis policy reform continues to evolve, and liberalization of its use may contribute to the perception that cannabis use is safe and efficacious in treating a variety of health conditions. Relative to past-year cannabis use prevalence among US adults in 2002-03, prevalence increased by approximately 170% in 2018-19.[1] Further, cannabis use among pregnant people has doubled in recent years.[2] It is worth noting the four-fold increase in cannabis potency,[3,4] measured by delta-9-tetrahydrocannabinol (THC), the main psychoactive constituent of the cannabis plant.

1.2. Historical Roots of Cannabis

Archeological records of cannabis pollen, cannabis achene (*i.e.,* seeds), and hemp fibers suggests human use of cannabis as early as 8000 BP (*i.e.,* 8000 years before present) in Eurasia. 'Human use' in this context does not necessarily translate to human consumption. Rather, some of the first known records indicate that the cannabis plant was cultivated for its fibers and used to produce textiles. It has been suggested that inhalation of cannabis began as early as 5000 BP in Eastern Europe.[5,6] In western China, evidence indicates the earliest use of cannabis as a psychoactive substance around 2450 BP; wooden braziers excavated from ancient burial sites and tested for compounds using gas chromatography and mass spectrometry revealed high levels of THC, indicating the burning of cannabis for inhalation near those at burial sites.[7] The ancient

Chinese used cannabis medicinally to treat ailments including rheumatic pain, intestinal constipation, and disorders of the female reproductive system. In India, cannabis was widely used for both medicinal and religious reasons. In fact, cannabis is listed as one of the five sacred plants in Atharvaveda texts. Medicinal treatments in India included cannabis use as an anticonvulsant, tranquilizer, and anti-inflammatory. It wasn't until the 19th century that cannabis was introduced to Western medicine. Dr. William B. O'Shaughnessy of Ireland, known as a distinguished expert in medicinal cannabis from his extensive work in India, conducted experiments that supported the use of cannabis (*i.e.*, Indian hemp) as a treatment for cholera, tetanus, rheumatic diseases, alcohol withdrawal delirium, and infantile convulsions.[6,8,9] During the same time period, Dr. Jacques-Joseph Moreau, a French psychiatrist, experimented with the psychoactive and therapeutic effects of cannabis for mental illness. Both O'Shaughnessy and Moreau contributed greatly to the introduction of cannabis to Western medicine in the late 19th and early 20th centuries.[6,8,9] In fact, cannabis was a patented medication according to the 1850 United States Pharmacopeia. However, the Marihuana Tax Act of 1937 federally prohibited the use and sale of cannabis. It was not until 1996 that California became the first state to permit physician-supervised medicinal use of cannabis.[10]

Experiments on cannabinoids in the US were first carried out in the 1940s; however, it wasn't until the mid-1980s that evidence contributed to the existence of cannabinoid receptors. Allen Howlett's laboratory concluded that cannabinoids act through G-protein-coupled receptors. Howlett and William A. Devane later detected receptor sites using a radiolabeled ligand of a synthetic cannabinoid, developed by Pfizer, that mimics THC. Confirmation that cannabinoids act on G-protein-coupled receptors came in the early 1990s with the cloning of cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors in both rat and human experiments.[11,12]

1.3. The Endocannabinoid System

The endocannabinoid system (ECS) is a biological network that plays a role in maintaining homeostasis. It influences and is influenced by multiple signaling pathways. The ECS consists of endogenous cannabinoids (*i.e.,* endocannabinoids), cannabinoid receptors, and enzymes responsible for the synthesis and degradation of endocannabinoids. Cannabinoid receptors are found throughout the body, including the brain. The cannabinoid receptor is the most abundant receptor in the brain, and can impact motor coordination, cognition, sleep, mood, pain, and inflammatory and immune responses.[13] Another role of endocannabinoids is to regulate the stress response. In fact, one endocannabinoid, anandamide (AEA), is derived from the Sanskrit word, *ananda*, and translates to 'bliss.'[14] Another major endocannabinoid found naturally in humans is 2-arachidonoylglycerol (2-AG); both AEA and 2-AG are the most well-studied endocannabinoids.[15] The two main endocannabinoid receptors are the cannabinoid-1 receptor (CB1R) and cannabinoid-2 receptor (CB2R). CB1R is primarily found in the brain while CB2R is found in immune cells.[16]

1.4. The Endocannabinoid System in Pregnancy

The ECS plays a role in pregnancy via fertilization, implantation, embryo development, and immune regulation. The two main endocannabinoids previously mentioned, AEA and 2-AG, affect events in pregnancy. Fatty acid amide hydrolase (FAAH) is responsible for metabolizing AEA to arachidonic acid and ethanolamine. It has been implied that FAAH is a factor for a healthy pregnancy; FAAH controls levels of AEA, and it has been suggested that the downregulation of AEA is linked to implantation. However, THC, an exogenous cannabinoid that crosses the fetal-placental barrier, results in a signaling cascade that might adversely affect pregnancy.[17]

1.5. Birth Outcomes

1.5.1. Birth Weight and Gestational Age

Adverse measures of neonatal health, including preterm birth (PTB) and low birth weight (LBW) are important public health issues. PTB, defined as delivery prior to 37 weeks' gestation, is more common in the US than in other industrialized countries,[18] and PTB among Black neonates is almost double that of their white counterparts.[19] In developed countries, preterm delivery and intrauterine growth restriction are the principal causes of LBW, defined as weight less than 2500 grams at birth.[18] Both PTB and LBW are associated with neonatal mortality and morbidity. LBW babies are at higher risk of disability later in life, such as neurodevelopmental disorders and cerebral palsy.[18] Common concerns in LBW neonates are low oxygen levels, difficulty feeding and gaining weight, and difficulty maintaining body temperature. Major complications include a higher risk of sudden infant death and infant respiratory distress syndrome.[20]

When studying fetal growth, sex-specific birth weight and gestational age must be taken into consideration. Weight-for-gestational age charts were first introduced in 1963 by Lubchenco and colleagues.[21] The use of these charts has vastly improved the determination of fetal growth, as birth weight alone does not accurately depict birth size; weight-for-gestational age charts use sex-specific weight and gestational age at birth to distinguish neonates who may be small because they are born early, from neonates who are born later in gestation but who are small relative to others at the same gestational age.[22] Determination of birth size using birth weight for gestational age references is useful in medicine to identify neonates at risk of restricted or excessive fetal growth. Additionally, this information is used in epidemiology to identify birth

sizes to be used as indicators of fetal health, including for the prediction of future health consequences.[23]

1.5.2. The Apgar Score

The Apgar score, coined by Dr. Virginia Apgar in 1953, is a composite clinical measure used to evaluate the condition of the newborn. The Apgar score was developed to provide a classification of neonatal health 60 seconds after birth.[24] The score consists of five measures: 1) heart rate, 2) respiratory effort, 3) reflex irritability, 4) muscle tone, and 5) color. An individual score ranging from 0-2 is assigned to the neonate for each of the five measures; scores are summed and reflect an overall measure of neonatal health following birth. For example, the neonate's heart rate is first assessed one minute following birth. A score of 2, the best possible score, is assigned to a neonatal heart rate of 100-140 beats per minute (BPM); a score of 1 is given to a heart rate less than 100 BPM; and a score of 0, the worst possible score, is assigned to a heart rate of 0 BPM. A similar pattern is followed for each of the four remaining measures. A composite Apgar score of 7-10 is defined as reassuring in terms of the neonate's physiological condition; a score of 4-6 is defined as moderately abnormal; a score of 0-3 is defined as low.[25,26] Not only is an Apgar score reported one minute after birth but it is again reported at five minutes. In neonates with scores less than 7 at five minutes, additional Apgar scores are reported in five-minute intervals until the 20-minute mark.[25,26] This scoring system is used to assess the effects of various resuscitation efforts, compare births between hospitals, evaluate modes of delivery (e.g., induction vs. cesarean section), assess the effects of maternal anesthesia and pain relief medications on the neonate, predict survival of the neonate, and later, the Apgar score was used as a predictor of neonatal health in research.[27] It is important to note that the Apgar score alone cannot be used to predict the survival or morbidity of an individual. Some components of the

Apgar score are subjective (e.g., interobserver variability). Additionally, the Apgar score is affected by other variables such as maternal factors, resuscitation, and gestational age at birth.[25,26]

1.5.3. Neonatal Intensive Care Unit

The neonatal intensive care unit (NICU) was not conceived until 1960. Prior to then, newborn care was partitioned into term and preterm care, and medically well and unwell newborn care. Neonates who were born at term but who were unwell were cared for on pediatric floors; neonates who were well but preterm were cared for in premature infant nurseries. Neonates who were unwell and premature were cared for either on pediatric floors or in isolated rooms. Care in isolation rooms was often provided by obstetric nurses who were not trained in the treatment of premature neonates. The rationale for this division was due to the spread of *Staphylococcus aureus* (*i.e.*, staph infection) among newborns.[28]

It is worth noting the history prior to the development of the NICU. Dr. Stephane Tarnier, an obstetrician, pioneered the first human incubator for newborns, which was put into use at the Paris Maternity Hospital in 1880. Dr. Martin A. Couney, a neonatologist, and colleagues, advanced Tarnier's incubator. Couney 'showcased' these newborn incubators at exhibitions around the world, where he and his nursing staff demonstrated how the incubators functioned to care for premature neonates. Public audiences paid admission to observe this innovative care. It wasn't until the early 1900s that Couney's work reached medical and research communities. Later, Dr. Julius Hess, a pediatrics professor and physician, introduced premature neonatal care into the medical literature, shaped by Couney's exhibition neonatology contributions. Although oftentimes ethically questioned, Couney's exhibitions were eventually observed by clinicians and researchers to better understand the behavior of premature newborns. Ultimately, Couney's work along with the research of many others led to the formation of the first NICU in 1960 at

Yale-New Haven Hospital. Dr. Louis Gluck, also known as the father of neonatology, is credited with the development of the NICU, which led to major advancements in fetal-maternal-neonatal medicine.[28]

1.6. Public Health Importance of Studying Birth Outcomes

Birth outcomes have also been linked to the risk of adverse health in adulthood. The Barker Hypothesis, also known as the Fetal Origins of Adult Disease, posits that fetal malnutrition, indexed by LBW, is related to the risk of disease later in life. LBW may result from PTB or intrauterine growth restriction and is associated with chronic diseases such as coronary artery disease and Type II diabetes mellitus. The mechanism by which events of intrauterine origin may influence disease in adulthood is via sensitive periods, which is responsible for alterations in structure and function of certain organs upon environmental stimuli (e.g., poor maternal nutrition). The fetus adapts in response to in-utero stimuli to increase its chances of survival. However, when this adaptation is no longer functional in the postnatal environment, these physiologic changes that may be difficult to reverse, may be related to adult diseases.[29,30]

1.7. Prenatal Cannabis Exposure and Birth Outcomes

Prior research indicates mixed findings on the association between prenatal cannabis exposure and birth outcomes.[31,32] While some studies conclude null findings,[33,34,35] others report statistically significant associations.[36,37,38] The majority of previous research uses a retrospective study design which induces limitations including recall bias. One study, by Chabarria et al., retrospectively investigated the association of prenatal cannabis exposure and birth outcomes from a large perinatal database. Cannabis and tobacco use information was ascertained via an in-person interview at the time of delivery. Additionally, maternal and neonatal outcomes were extracted from the electronic medical record. The authors found that cannabis use alone was not

associated with adverse birth outcomes, however, concurrent use of cannabis and tobacco resulted in a significant association with PTB and decreased birth weight.[33] Ko et al. retrospectively analyzed data for the Pregnancy Risk Assessment Monitoring System (PRAMS). After adjustment for tobacco use and other confounding variables, the authors found no appreciable difference in gestational age or birth weight between people who used cannabis during pregnancy and people who did not.[34] Nguyen et al. also retrospectively analyzed data for PRAMS to assess the effect of prenatal cannabis exposure on LBW, small-for-gestational-age (SGA), and PTB. After adjustment for potential confounding variables, the odds of SGA and PTB were significantly higher in people who used cannabis during pregnancy compared to those who did not.[39]

On the other hand, Kharbanda et al. conducted an observational study of a cohort from a large health care system. The authors suggested a relationship between prenatal cannabis exposure and SGA, independent of potential confounding variables.[40] Corsi et al. used a retrospective cohort design to investigate self-reported cannabis use and birth outcomes. The authors found that the rate of PTB was significantly higher in people who used cannabis during pregnancy compared to those who did not.[38]

A minority of studies used a prospective cohort study design to assess the relationship between prenatal cannabis exposure and birth outcomes. El Marroun et al. conducted a large, population-based prospective study of pregnant people residing in the Netherlands. Timing and frequency of substance use were measured using a questionnaire at enrollment. Authors concluded prenatal cannabis exposure may be associated with restricted fetal growth trajectories.[37] Another prospective study by Michalski et al., estimated the association between maternal cannabis use in pre-/early pregnancy and birth outcomes including LBW, SGA, and

PTB. Pregnant people at least 18 years of age were recruited to the Ontario Birth Study within their first or early second trimester of pregnancy. The sample consisted of a homogeneous population, with the majority of people reporting high educational attainment, high income, and low rates of polysubstance use. It is worth noting, as acknowledged by the authors, that homogenous samples limit the generalizability of research findings. The authors concluded that compared to people who did not use cannabis within the three months prior to learning of pregnancy, those who did had two times the odds of giving birth to a SGA infant.[41]

1.8. Nausea and Vomiting of Pregnancy

Nausea and vomiting of pregnancy (NVP), also referred to as 'morning sickness,' is common during the first trimester of pregnancy, affecting 70-80% of pregnant people in the US.[42,43] The term 'morning sickness' should be interpreted with caution, as NVP is not limited only to the morning hours.[44,45] NVP is typically experienced very early in pregnancy, around 4-6 weeks' gestation, and is at its worst around 8-12 weeks' gestation. Typically, NVP can be expected to resolve early in the second trimester of pregnancy,[43] although about 10% of pregnant people experience NVP throughout pregnancy.[46] NVP can range from mild to moderate to severe illness. A distinct form of NVP that elicits debilitating nausea and vomiting is called hyperemesis gravidarum (HG) and is defined as excessive vomiting, dehydration, ketonuria, and greater than 5% body weight loss.[47] HG is far less common than NVP with a prevalence of 1-3%.[45]

Although NVP does not usually result in health consequences to the developing fetus, NVP can have major maternal psychosocial implications. For instance, NVP may result in absence from the workplace, decreased participation in social activities, irritability, sleep disturbances, and depressed mood.[48,49,50] In terms of fetal health, prior research suggests a

protective effect of NVP; that is, compared to those without NVP, pregnant people who experience nausea and vomiting are less likely to have a miscarriage[51] or preterm delivery.[52]

NVP is thought to be related to endocrine, sex, and pregnancy hormone fluctuation. Human chorionic gonadotropin (hCG) has been suggested to be correlated with NVP.[42,44] Briefly, hCG is produced by trophoblasts, cells that surround the embryo and eventually develop the placenta, and is the hormone detected in urine or blood to confirm pregnancy. Levels of hCG are measured at prenatal care visits and peak around 9-12 weeks' gestation.[53] NVP typically peaks around 12 weeks' gestation, correlating with hCG levels. Prior studies have suggested that NVP is often more severe in individuals with conditions that result in high hCG levels, such as multiple gestations.[42,54] Moreover, increased hCG levels may stimulate transient hyperthyroidism, which is sometimes characteristic of NVP or HG pregnancies. Sex hormones, estrogen and progesterone, are also thought to play a role in NVP. Progesterone slows gastrointestinal contractility, which may induce nausea. Estrogen stimulates the synthesis of nitric oxide, relaxing smooth muscle; gastric motility is slowed, gastric emptying is delayed, and nausea and vomiting may result.[44]

NVP may also be linked to medication used to treat mood disorders. Research suggests that depression and anxiety among pregnant people are common; nearly 13% of pregnant people are diagnosed with major depressive disorder while 37% of pregnant people report depressive symptomology.[55] Selective serotonin reuptake inhibitors (SSRIs) are sometimes prescribed to treat depression and anxiety disorders; SSRIs inhibit the reuptake of serotonin, increasing serotonin levels, which in turn increases the risk of emesis.[56]

1.9. History of Antiemetics in Pregnancy

Research on antiemetic medications used during pregnancy is lacking, partially as a result of the unsettling history associated with serious fetal side effects. In the 1950s, thalidomide was marketed as safe and efficacious for use during pregnancy in Germany, although it was later determined that the drug was associated with devasting birth defects. In the US, a drug marketed to treat NVP, Bendectin (a combination of doxylamine and pyridoxine), was prescribed to pregnant people for roughly 30 years until studies suggested its association with congenital malformations. It wasn't until 2013 that Diclegis became available for the treatment of NVP. To date, epidemiological studies have not found significant associations with birth defects. Due to the lack of access and its ineffectiveness in treating severe NVP, ondansetron is most often prescribed to treat NVP despite its lack of Food and Drug Administration (FDA) approval for use during pregnancy.[57]

1.10. Cannabinoids and Emesis

Brain regions of the central nervous system (CNS) play a major role in emesis. Via the dorsal vagal complex, the vagovagal reflex controls gastrointestinal muscle contraction. Both CB1R and CB2R are expressed in the vagovagal neural pathway, although less is known about the role of CB2R.[58] Binding of cannabinoids to CB1R blocks nausea and vomiting.[59] Moreover, CB1R and CB2R are expressed in the gastrointestinal tract (GIT), although CB1R is expressed at elevated levels. The binding of cannabinoids to CB1R in the GIT produces a delay in gastric emptying, which can induce vomiting.[60,61] This delay in gastric emptying is paradoxical to the antiemetic effects of cannabis.[62] Clinical literature has recently (2004) identified patients presenting with cannabinoid hyperemesis syndrome (CHS), in which individuals experience

severe hyperemesis. These patients are chronic, heavy cannabis users and symptoms resolve upon discontinued use of cannabis.[63,64,65]

1.11. Cannabis and NVP

Historically, cannabis has been used medicinally for its antiemetic properties. In fact, two prescription drugs, dronabinol and nabilone, contain synthetic THC and have been approved since the mid-1980s for the treatment of nausea among cancer patients receiving chemotherapy. However, cannabis is not approved for use in pregnancy in the US.

In the US and Canada, small qualitative studies indicate that individuals who used cannabis during pregnancy reported doing so to alleviate morning sickness. One study recruited pregnant and postpartum people who used cannabis either daily or occasionally while pregnant. The authors indicated five themes that emerged from the data including, "continued use for healthcare management." One form of healthcare management reported by study participants included using cannabis to self-medicate morning sickness. Another theme was "ongoing evaluative process" in which participants weighed the benefits and risks of using cannabis versus pharmaceutical drugs for nausea and vomiting.[66] Hesitancy of using prescription antiemetics given the disconcerting history[57] seemed to play a role in the decision to use cannabis during pregnancy.[66] Another small qualitative study derived main themes from their semi-structured interviews with pregnant people who either self-reported cannabis use during pregnancy or who had a positive urine screen for THC. One of the themes described motives to use cannabis during pregnancy; participants described using cannabis to control nausea, vomiting, and appetite.[67] One study recruited a convenience sample of pregnant people to better understand the views of participants who used cannabis during pregnancy. Of those who continued to use cannabis during pregnancy, 96% reported doing so to treat nausea. Further, among participants who quit

using cannabis, 31% indicated using in the first trimester,[68] when morning sickness is most common.[69] A Canadian study recruited pregnant people who used cannabis for medicinal purposes from compassion societies. Of participants who retrospectively reported using cannabis during pregnancy, 77% reported NVP, of which 68% treated morning sickness symptoms with cannabis.[70]

To date, only three epidemiological studies explore the relationship between NVP and cannabis use.[71,,72,73] Roberson et al. (2014) conducted a secondary analysis of Hawaii PRAMS data in which participants were asked to retrospectively recall cannabis use as well as severe nausea, vomiting, or dehydration during their most recent pregnancy. Authors found that participants who reported severe nausea were nearly four times more likely to report using cannabis compared with participants who did not report severe nausea.[71] Moreover, Young-Wolff et al. (2018) abstracted data from electronic health records of pregnant people who had completed a substance use survey and had a urinalysis in the first trimester of pregnancy. Compared to those without NVP, pregnant people who reported severe NVP had nearly four times the odds of using cannabis, while those who reported mild NVP had just over two times the odds of using cannabis during pregnancy.[72] Finally, a recent study by Metz et al. (2022) investigated the odds of NVP among cannabis-using pregnant people compared to non-users. Authors conducted a secondary analysis of a prospective study that administered the Pregnancy Quantification of Emesis and Nausea (PUQE) tool to assess morning sickness severity. Cannabis use was measured via urine assays. Participants with urine assays positive for THC were associated with more severe and frequent NVP. Further, higher THC concentrations were associated with increased odds of nausea and vomiting.[73]

1.12. Dissertation Aims

This dissertation is comprised of three aims. **Aim 1** will estimate the size of a suspected causal influence of prenatal cannabis exposure on a set of inter-related birth outcomes: birth size, gestational age at birth, 5-minute Apgar score, and NICU admission. I hypothesize that using cannabis during pregnancy will result in adverse birth outcomes including SGA, decreased gestational age at birth, poor 5-minute Apgar score, and NICU admission following birth.

Aim 2 will investigate the degree to which NVP, also known as morning sickness, might be associated with increased odds of cannabis use. I hypothesize an increase in the odds of prenatal cannabis use with increasing morning sickness severity.

Finally, **Aim 3** is to conduct a feasibility study to assess the recruitment and retention of pregnant people who regularly use cannabis, measured by willingness to participate and complete the study survey; willingness to provide urine samples; the percentage of participants who are cannabis-only users; and the percentage of pregnant people retained for the three follow-up assessments. I will measure the concordance between self-reported cannabis use and urine toxicology analysis among pregnant people, explore the characteristics of cannabis-using pregnant people compared to non-cannabis-using pregnant people, and measure the proportion of individuals who use cannabis during pregnancy with varying severity levels of morning sickness.

CHAPTER 2. THE HEALTH EFFECTS OF PRENATAL CANNABIS EXPOSURE ON BIRTH OUTCOMES

2.1. Background

Cannabis use prevalence has doubled among pregnant people in the US[2] According to the National Survey on Drug Use and Health (NSDUH), the estimated prevalence of cannabis use among pregnant people aged 12-44 years old increased from 3% in 2004-2005 to 6.3% in 2019-2020.[1] Cannabis is the most commonly used internationally regulated substance in pregnancy,[74] as it is classified as a Schedule I substance at the federal level. However, evolving state-level cannabis policy might influence the liberalization and risk perception of cannabis use.[75] As of April 1, 2022, 37 states in addition to the District of Columbia (DC), Puerto Rico, Guam, and the US Virgin Islands have legalized cannabis for medicinal use, and 18 states plus DC, Guam, and the Northern Mariana Islands have legalized cannabis for recreational use.[76] The rising number of states legalizing cannabis may contribute to the relaxed view of using cannabis both in the general and pregnant populations.

The two main receptors of the ECS are CB1R and CB2R, both of which are found in the female reproductive system. CB1R is of particular importance in pregnancy, as it is located in the oviduct, uterus, and the developing embryo.[77] Cannabis is an exogenous cannabinoid and contains THC, the main psychoactive constituent of cannabis, and cannabidiol (CBD) but also contains over 100 other cannabinoids.[6] THC interferes with critical factors of embryo development such as folic acid uptake, cellular growth, and neural development, resulting in potential neonatal health consequences.[78] THC readily crosses the placenta due to its lipophilic nature and can interact with functional cannabinoid receptors in the fetus as early as 14 weeks' gestation.[77,79,80] Further, THC is stored in maternal adipose tissue and places the developing

embryo at risk even after initial exposure to cannabis.[77] Fetal exposure to cannabis may have detrimental effects on growth and maturation, potentially leading to adverse neonatal health.

Prior research findings on cannabis exposure during pregnancy and birth outcomes are mixed, and therefore, current evidence of an association is inconclusive.[32] The majority of studies use retrospective designs, which may be susceptible to recall bias. Other studies are cross-sectional in nature, resulting in the inability to discern temporality. Many studies extract data from medical charts, which are sometimes incomplete. Further, confounding from polysubstance use proves problematic in existing studies, as an abundance of literature has established the adverse implications of substance use, primarily tobacco and alcohol use, during pregnancy on fetal growth and development.[81,82,83,84,85,86]

In the current study, I estimate the size of a suspected causal influence of prenatal cannabis exposure on a set of birth outcomes including birth size, PTB, 5-minute Apgar score, and NICU admission. Further, the effects of first trimester cannabis exposure on birth outcomes will be assessed in a sensitivity analysis.

2.2. Methods

2.2.1. Participants and the Study Sample

In the current study, I analyzed data for the Michigan Archive for Research on Child Health (MARCH) cohort, recruited between 2017 and 2021. MARCH began recruiting pregnant people in 2017 from 11 sites across Michigan including Hutzel Women's Hospital, Detroit; Beaumont Hospital, Dearborn; St. John Hospital, Novi; Sinai Grace Hospital, Detroit; St. Joseph Mercy Hospital, Ann Arbor; University of Michigan Hospital, Ann Arbor; McLaren Port Huron Hospital, Port Huron; Covenant Healthcare, Saginaw; Hurley Medical Center, Flint; Munson Healthcare, Traverse City; and Spectrum Health, Grand Rapids. MARCH implemented a

probability-based sampling approach to achieve a population-based prospective cohort study. A random stratified sample of ten of the 84 hospitals located in Michigan's lower peninsula was selected, in addition to ten hospitals to be used as a backup sample. To do this, hospitals were first categorized into quintiles by the percentage of African American births. Two hospitals were then randomly selected from each of the five strata, resulting in ten recruitment sites. Birth attendants were grouped into their prenatal practices, and two practices that delivered largely in the sampled hospitals were selected using a proportional-to-size algorithm. Hurley Hospital and two of its affiliated prenatal clinics were included from the backup sample and added to the MARCH study in consideration of the Flint Water Crisis.

MARCH is an ongoing study that plans to recruit 1000 participants. Pregnant patients are recruited through physician offices at participating prenatal practices. MARCH excludes pregnant people who are under the age of 18 and those who do not speak English. Each eligible participant receives a recruitment packet containing consent forms, HIPPA forms, and study surveys. Data are collected by interviewing the participant in person or by telephone. Participants complete up to two prenatal surveys throughout pregnancy. Although MARCH recruits participants at the first prenatal visit, eligibility criteria do not differentiate according to trimester of pregnancy (*i.e.*, trimester at recruitment is not restricted). As such, while the goal is for each participant to complete both prenatal surveys, some participants only complete prenatal survey one due to late recruitment into the study or loss-to-follow-up. MARCH collects a urine sample during each assessment and two blood samples throughout pregnancy. Newborn data are abstracted from the medical record, birth certificate, placenta samples, and newborn dried blood spots. Retention of the study sample is achieved via social media, messaging, frequent mail and telephone contact, and participant birthday cards sent from the MARCH study group.

Additionally, participants receive a $25 gift card after the first survey and a $10 gift card for surveys thereafter as a token of appreciation for study participation.[87]

2.2.2. Study Population

The current analysis includes singleton birth outcomes only and excludes participants who did not: have data on cannabis use in at least one prenatal survey; have birth record data on gestational age, birth weight, 5-minute Apgar score, or NICU admission; or have data on maternal age, US census-based race/ethnicity, recruitment site, level of education, health insurance, pre-pregnancy BMI, tobacco smoking status, or alcohol drinking status. The final analytic sample size was n= 584 participants. This study has been approved by the Michigan State University institutional review board for protection of human subjects and has been determined exempt under 45 CFR 46.104(d) 4(ii).

2.2.3. Cannabis Use During Pregnancy

Cannabis use was measured via self-report by answering the following prenatal survey question: “Have you used marijuana (pot) or cannabis including medically prescribed cannabis, at all during this pregnancy?” The same cannabis survey item was asked on both prenatal surveys. A response of ‘yes’ to the cannabis survey item on either survey qualified the participant as a prenatal cannabis user in the current study. This means that completion of prenatal survey 1 and prenatal survey 2 do not necessarily correspond to the first and second trimesters of pregnancy.

2.2.4. Birth Outcomes

Birth outcome measures included birth size, gestational age at birth, 5-minute Apgar score, and NICU admission following birth. All outcome variables were retrieved from state-archived birth records. Birth size was defined as sex-specific birth weight for gestational age (in

weeks). I used a US birth weight reference that corrected for implausible gestational age estimates to derive birth size.[23] To better understand the reference used in this dissertation, the following describes the approach by Talge et al.: the authors implemented an algorithm originally developed by Basso and Wilcox in which last menstrual period (LMP) and/or obstetric/clinical estimates (e.g., ultrasound) of gestational age and birth weight were used to determine errors in birth size using US live birth files from the National Center for Health Statistics. Briefly, if both LMP and obstetric/clinical gestational age estimates were available and within two weeks of one another, birth weight z-scores were calculated based on the LMP estimate for gestational age. If the birth weight z-score estimate was considered plausible for gestational age (see footnotes in Talge et al. for definition of plausibility), the LMP estimate was retained. If the birth weight z-score was not considered plausible for gestational age, a birth weight z-score based on obstetric/clinical gestational age was calculated instead, and if considered plausible, the obstetric/clinical-based gestational age was retained. If LMP-based gestational age and obstetric/clinical-based gestational age were greater than two weeks apart, the birth weight z-score based on obstetric/clinical gestational age was calculated first, and the same protocol based on z-score birth weight plausibility was followed.[23] Talge et al. generated means, standard deviations, and smoothed percentiles for birth weight for gestational age, which were used here for the calculation of continuous and categorical measures of birth size. To calculate sex- and gestational age-specific birth weight z-scores in the MARCH study sample, I subtracted reference mean birth weights from the sample birth weights and divided the difference by the reference standard deviation. Using this information, I calculated a three-level categorical measure of birth size. I categorized SGA as MARCH sample birth weights at or less than the 10th percentile reference birth weight for gestational age. Next, I categorized LGA as sample birth

weights at or above the 90th percentile reference for gestational age. Of note, only one measure of gestational age was available in MARCH birth record data; the Michigan Department of Health and Human Services birth records contain estimates of gestational age based on obstetric/clinical measures, which were used in the current study.

Gestational age was measured as a continuous variable to increase statistical power. I performed a skew-normal distribution method followed by a log transformation, a method outlined by Sauzet et al., to normalize the distribution.[88] Gestational age measured in weeks is left-skewed, as fewer mothers deliver preterm compared to term newborns. Additionally, the upper limit of gestational age is restricted to around 44 weeks, as medical intervention (*i.e.*, induction) prevents a longer pregnancy.[89] To improve the distribution, each neonatal gestational age in the sample was subtracted from 45 weeks and log transformed. Next, I used linear regression to identify studentized residuals. If the absolute value of a residual was greater than 3, then the observation was considered an outlier.[90] Here, n= 10 outliers were observed and subsequently removed. Moreover, gestational age was measured as a categorical variable (*i.e.*, PTB vs. not PTB), in which PTB was defined as birth at less than 37 weeks' gestation.

Five-minute Apgar score was assessed five minutes after birth. According to the Neonatal Encephalopathy and Neurologic Outcome, Apgar score is defined as reassuring (7-10), moderately abnormal (4-6), or low (0-3). Finally, NICU admission was defined as infant admission to the NICU following birth (measured as a binary yes/no variable).

2.2.5. Covariates

I adjusted for covariates including maternal age (continuous), US census-based race/ethnicity (non-Hispanic White, non-Hispanic Black, and other), recruitment site (Southeast Michigan, Mid-Michigan, and Northern Michigan), education level (no high school diploma,

high school diploma and/or some college, and college degree), health insurance (government plan/none and non-government plan), pre-pregnancy body mass index (BMI) (obese defined as BMI ≥30 kg/m^2 and not obese defined as BMI <30 kg/m^2), tobacco smoking (non-smoker, quit smoking upon pregnancy, and active smoker), and alcohol drinking (non-drinker and active drinker). To justify the conceptualization of these factors as confounders of the association between prenatal cannabis exposure and birth outcomes, I will present evidence on each potential confounding variable. Compared to people in older age groups, younger individuals have a higher prevalence of cannabis use, thus the inclusion of maternal age as a potential confounder in the current analyses. Estimates for year pair 2018-2019 from the NSDUH indicate that past-month cannabis use was highest among pregnant people aged 18-25 years old.[1] Further, prior research suggests adverse birth outcomes in teen mothers as well as older mothers.[91,92,93,94] This trend can be thought of as a U-shaped curve in which neonates born to younger and older mothers are at increased risk of birth outcomes including PTB.[92,94]

It has been well-established that low socioeconomic status (SES) is associated with adverse health and behavioral outcomes. SES is used as a predictor of health disparities and common indicators include educational attainment, household income, neighborhood-level income, and race/ethnicity.[95] Research suggests that maternal educational attainment is linked to adverse birth outcomes.[96,97] One study investigated the effects of maternal education in a country where healthcare was available to everyone regardless of SES. Results suggest that lower education levels were associated with adverse outcomes including PTB, LBW, and SGA.[97]

Race and ethnicity are linked to SES via the substantial inequities among disadvantaged groups in the US. Socioeconomically disadvantaged groups (e.g., non-Hispanic Black and Hispanic groups) have lower household income and lower educational attainment compared to

socioeconomically advantaged groups (e.g., non-Hispanic Whites). Although its mechanistic role in poor health consequences is sometimes unclear, race as a social construct helps to explain health disparities.[98]

Compared to non-Hispanic White individuals of high SES, non-Hispanic Black individuals of high SES continue to have an increased risk of PTB, LBW, and infant mortality.[98] This finding suggests that racism (which may be institutional, interpersonal, internalized, or cultural) is a chronic stressor and a key factor in poor birth outcomes. .[98 100,101,102] Relevant to the inclusion of race as a covariate in this analysis, race is also associated with cannabis use.[103]

Pre-pregnancy BMI is an important consideration of the prenatal cannabis exposure- birth outcomes association. Prior studies suggest a relationship between pre-pregnancy BMI and the effects on birth weight and preterm delivery. Individuals with a pre-pregnancy BMI less than 25 kg/m^2 were more likely to deliver an infant of LBW.[104] On the other hand, obese individuals (>30 kg/m^2) are less likely to deliver an LBW infant, and gain less weight during pregnancy than underweight and normal-weight individuals,[104] but are at increased risk of gestational diabetes mellitus, gestational hypertension, and PTB.[105,106] Colloquial knowledge suggests that using cannabis might induce weight gain via increased food consumption, yet studies have found a lower prevalence of cannabis use among overweight and obese individuals.[107,108]

The association between tobacco smoking during pregnancy and birth weight was first reported in 1957 and has since been validated by numerous studies.[83] Further, a dose-response has been established; the more cigarettes smoked per day, the larger the decrease in birth weight.[109,110,82,84] It has been suggested that the link between tobacco smoking and LBW and SGA is attributed to intrauterine growth restriction,[83] thus alluding to the role of tobacco exposure on fetal growth and maturation. It has also been well-established that heavy alcohol use is

associated with adverse birth outcomes, as it was deemed a teratogen in the 1970s.[85] Adverse birth outcomes including fetal alcohol syndrome, LBW, SGA, and PTB are associated with heavy alcohol drinking, however, low to moderate levels of alcohol drinking on birth outcomes are not as clear, although some studies have found significant associations.[85,86]

Cannabis is the number one internationally regulated drug used in pregnancy.[111] Polysubstance use among cannabis users, especially tobacco use, is common during pregnancy.[74] I chose to add tobacco and alcohol status to the model as potential confounding variables due to their relationship with birth outcomes[112] as well as with cannabis use, as prior studies have indicated the high prevalence of co-drug use among cannabis users.[113]

2.2.6. Analysis Plan

The analysis plan consists of the main analysis and four sensitivity analyses. The main analysis investigates the association between prenatal cannabis exposure (any trimester) and birth outcomes. The first sensitivity analysis assesses the association between first trimester cannabis exposure and birth outcomes. The second sensitivity analysis assesses the relationship between prenatal cannabis exposure (any trimester) and birth outcomes, restricting the sample to exclude: 1) tobacco users, 2) alcohol users, and 3) tobacco and alcohol users. The third sensitivity analysis assesses relationship between prenatal cannabis exposure (any trimester) and birth outcomes while considering twin clusters. Lastly, the fourth sensitivity analysis assesses the relationship between prenatal exposure (any trimester) and birth outcomes while considering participants nested within recruitment sites.

In the main analysis, I estimated associations using unadjusted and adjusted generalized linear models (GLM). The prenatal cannabis exposure-birth size association was examined using both linear and multinomial logistic regression models to accommodate continuous and

categorical (SGA, AGA, and LGA) definitions of birth size, respectively. The prenatal cannabis exposure-gestational age relationship was also measured on continuous (*i.e.*, weeks' gestation) and categorical (*i.e.*, PTB vs not PTB) scales. The association between prenatal cannabis exposure and 5-minute Apgar score was analyzed using Poisson regression. Finally, the association between prenatal cannabis exposure and NICU admission was assessed using logistic regression due to the binary scale of the outcome. For the first and second sensitivity analyses, I repeated all the previous analyses and 1) limited the sample to individuals in their first trimester of pregnancy at study recruitment and 2) removed alcohol users, tobacco users, and both alcohol and tobacco users. A note regarding the first sensitivity analysis: the investigation of the trimester-specific (*i.e.*, beyond the first trimester) relationship between prenatal cannabis exposure and birth outcomes is not possible in the current study. The cannabis survey item is not specific in terms of the recency of cannabis use. Each of the two prenatal survey cannabis items asks whether or not the participant used cannabis at any time during pregnancy. For the third and fourth sensitivity analyses, I used generalized estimating equations (GEE) to estimate the association between prenatal cannabis exposure and birth outcomes while considering twin clusters as well as participants nested within recruitment sites, respectively. SAS® version 9.4 was used to perform all statistical analyses.

2.3. Results

As of January 2022, the MARCH dataset consisted of n= 866 participants. The final analytic sample of the current study is n= 584 participants, of whom n= 90 used cannabis during pregnancy. The following describes missingness in the sample: n= 255 participants were missing data on birth size and gestational age. An additional participant was missing on NICU admission (n= 1) and another participant was missing on 5-minute Apgar score (n= 1). Further, n= 4

participants were missing on cannabis; n= 2 were missing on recruitment site; n= 3 were missing on education level; n= 4 were missing on health insurance; n= 9 were missing on pre-pregnancy BMI; and n= 3 were missing on alcohol status. Not all participants who completed the survey(s) had given birth at the time of this analysis, resulting in missing derived from the birth record. Of note, the analysis of the association between prenatal cannabis use and gestational age measured on a continuous scale had an analytic sample n= 574 due to the removal of n= 10 outliers, as previously mentioned in the Methods section.

Table 2.1 describes the characteristics of a sample of pregnant people in Michigan who do and do not use cannabis during pregnancy. Approximately 15% of pregnant people in the sample used cannabis and on average, were 26 years old. The majority of participants who used cannabis during pregnancy were recruited from clinics in southeast Michigan (53%), had government health insurance (83%), identified as non-Hispanic Black (56%), had attained at least a high school diploma but may have also completed some college courses without earning a degree (71%), were not obese (59%), and reported no alcohol use during pregnancy (77%). Although the majority of prenatal cannabis users reported no active cigarette smoking (either non-smoker or quit upon learning of pregnancy), 39% reported active tobacco smoking.

Table 2.2 describes the results of the association between prenatal cannabis exposure and birth outcomes. Among neonates who were not exposed to cannabis during pregnancy, the mean birth weight was equal to 3294 grams (standard error= 26.5 grams); among neonates prenatally exposed to cannabis, the mean birth weight was equal to 3030 grams (standard error= 62.8 grams). Among neonates prenatally exposed to cannabis, the unadjusted odds of being born SGA, compared to AGA, was 2.2 times as large as neonates who were not prenatally exposed to cannabis (Odds Ratio $(OR)_{model1}$= 2.2; 95% Confidence Interval (CI): 1.1, 4.2). Results remained

significant after adjusting for maternal age; however, upon adjustment for other covariates, results were no longer statistically significant (OR_{model4}= 1.5; 95% CI: 0.7, 3.2). Covariates that had the largest effect on the association were determined by adding each covariate to the main effects model, one-by-one, and noting the OR and 95% CI change in the association between prenatal cannabis exposure and SGA. Covariates that attenuated the estimate and resulted in a null association as indicated by the 95% CI are as follows: US census-based race/ethnicity (OR= 1.7; 95% CI: 0.9, 3.4), education level (OR= 1.7; 95% CI: 0.8, 3.4), and smoking (OR= 1.7; 95% CI: 0.8, 3.7). Moreover, there was no association detected between prenatal cannabis exposure and neonates born LGA (OR_{model4}= 0.3; 95% CI: 0.1, 1.1). Although birth size, measured as a categorical variable, was not significantly different between neonates exposed and unexposed to cannabis during pregnancy, birth size z-score suggested otherwise. Results of linear regression indicate that prior to model adjustment, the birth size z-score was lower among neonates exposed to prenatal cannabis compared to unexposed neonates ($beta_{model1}$= -0.4; 95% CI: -0.6, -0.2). After adjustment for potential confounders, findings suggest that birth size z-score remained lower in neonates who were prenatally exposed to cannabis compared to those who were not ($beta_{model4}$= -0.3; 95% CI: -0.5, -0.003). The mean birth size z-score among the prenatal cannabis exposure group was equal to -0.34 (standard error= 0.1), while among the non-exposed group, the mean z-score was equal to 0.07 (standard error= 0.04).

After full model adjustment, findings indicated no significant association between prenatal cannabis exposure and gestational age ($beta_{model4}$= 0.1; 95% CI: -0.01, 0.1). Similarly, there was no association detected between prenatal cannabis exposure and PTB ($beta_{model4}$= 1.1; 95% CI: 0.5, 2.4), and no association between prenatal cannabis exposure and 5-minute Apgar score ($beta_{model4}$= 0.01; 95% CI: -0.1, 0.1). However, study findings indicated a significant

association between prenatal cannabis exposure and NICU admission. Specifically, neonates prenatally exposed to cannabis had 2.1 times the odds of being admitted to the NICU compared to non-exposed neonates (OR_{model1}= 2.1; 95% CI: 1.2, 3.8). However, after model adjustment, results were attenuated and the relationship no longer persisted (OR= 1.2; 95% CI: 0.6, 2.4). Again, covariates that had the largest effect on the association were determined by adding each covariate to the main effects model, one-by-one. Covariates that attenuated the estimate and resulted in a null association between prenatal cannabis exposure and NICU admission as indicated by the 95% CI are as follows: US census-based race/ethnicity (OR= 1.7; 95% CI: 0.9, 3.1), education level (OR= 1.7; 95% CI: 0.9, 3.1), health insurance (OR= 1.6; 95% CI: 0.9, 3.0), and smoking (OR= 1.6; 95% CI: 0.8, 3.1).

I performed a sensitivity analysis to explore how first trimester cannabis exposure might be associated with birth outcomes. Table 2.3 describes a sample of participants who completed the prenatal survey during their first trimester of pregnancy. The analytic sample included n= 378 participants in their first trimester, 11% of whom used cannabis during pregnancy. Participants who used cannabis were, on average, 26 years old. The majority of participants were recruited from southeast Michigan (61%) and were non-Hispanic Black (54%). Eighty-eight percent of people who used cannabis during pregnancy completed high school; 83% had government health insurance; and the mean BMI was 29 kg/m^2. Finally, 76% of participants did not use alcohol while pregnant and 63% did not actively smoke tobacco.

Table 2.4 describes the results of the sensitivity analysis of the association between first trimester cannabis exposure and birth outcomes. After model adjustment, findings indicated no association between first trimester cannabis exposure and birth size. Specifically, compared to neonates born AGA, there was no association between first trimester cannabis exposure and

SGA (OR_{model4}= 1.8; 95% CI: 0.6, 5.9), nor between first trimester cannabis exposure and LGA (OR_{model4}= 0.2; 95% CI: 0.03, 2.0). The fully adjusted model indicated no association between first trimester cannabis exposure and birth size z-score ($beta_{model1}$= -0.2; 95% CI: -0.6, 0.2). Recall that due to the non-normal distribution of gestational age, I had performed the skew-normal distribution method. Here, among people in their first trimester of pregnancy, n= 9 outliers were removed from the sample resulting in a sample size n= 369. Results suggest no association between first trimester cannabis exposure and gestational age at birth ($beta_{model4}$= 0.03; 95% CI: -0.1, 0.1). Further, first trimester cannabis use was not associated with PTB (OR_{model4}= 0.8; 95% CI: 0.3, 2.4). Similarly, there was no meaningful difference in 5-minute Apgar score among neonates exposed to first trimester cannabis use compared to unexposed neonates ($beta_{model4}$= -0.003; 95% CI: -0.1, 0.1). Finally, even after adjustment for maternal age, neonates exposed to cannabis during the first trimester of pregnancy had 2.6 times the odds of being admitted to the NICU compared to non-exposed neonates (OR_{model2}= 2.6; 95% CI: 1.1, 5.8). After further model adjustment, the estimate was attenuated and findings were no longer statistically significant (OR_{model4}= 1.3; 95% CI: 0.5, 3.1). Covariates that attenuated the estimate and resulted in a null association as indicated by the 95% CI are as follows: health insurance (OR= 1.8; 95% CI: 0.8, 4.2) and smoking (OR= 1.9; 95% CI: 0.8, 4.6).

In a second sensitivity analysis, I considered the impact of non-independence as a result of twin clusters. The study sample included n= 597 pregnant people of whom n= 14 delivered twins. Of note, although 14 participants gave birth to twins, data were for n= 27 twins, as one twin was missing birth record data. I employed the GENMOD procedure in SAS® version 9.4. The estimates, confidence intervals, and standard errors produced by GEE were nearly identical to results from the main analysis, which considered singleton births only. Likely due to the small

number of twins in the study, twin pairs did not influence confidence intervals. It is important to comment on the issue of the small sample of twins in this study, as only three participants who delivered twins used cannabis during pregnancy. Pearson correlation coefficients indicated a high correlation between twins among pregnant people who used cannabis and all birth outcomes (e.g., the Pearson correlation coefficient for birth weight, measured in grams, was 0.9999).

In a third sensitivity analysis, I examined how pregnant people clustered within recruitment sites might be similar to one another. I employed the GENMOD procedure in SAS® 9.4 and used GEE in consideration of the potential non-independence between participants. Non-independence could be due to similarities among participants living in a particular geographic area. For example, socioeconomic proxies (e.g., household income) might be similar within recruitment sites. Findings produced using GEE were nearly identical to results in the main analysis. For instance, results of the unadjusted GEE analysis investigating the association between prenatal cannabis use and birth size z-score was beta= -0.4; 95% CI: -0.6, -0.3 while unadjusted findings from the main analysis were beta= -0.4; 95% CI: -0.6, -0.2.

In a fourth sensitivity analysis, I explored how excluding alcohol users, tobacco users, and both alcohol and tobacco users from the analysis impacted study findings. The analytic sample size after excluding prenatal alcohol users only was n= 502. After excluding prenatal tobacco users only, the sample size was n= 435. Finally, after removing all polysubstance use (*i.e.,* both alcohol and tobacco users), the sample size was n= 384. After adjustment for potential confounding variables, no differences were detected in estimates compared to Table 2.2 results. To illustrate, Table 2.2 suggests no association between prenatal cannabis exposure and PTB (OR_{model4}= 1.1; 95% CI: 0.5, 2.4). Upon removal of participants who used alcohol, used tobacco, or used both alcohol and tobacco, people who used cannabis during had the following odds of

PTB compared to non-users: OR_{model4}= 1.1 (95% CI: 0.4, 2.8), OR_{model4}= 0.7 (95% CI: 0.2, 2.6), and OR_{model4}= 0.8 (95% CI: 0.2, 2.9), respectively.

Table 2.1. Prenatal Cannabis Use by Maternal Characteristics, MARCH (n= 584)

	Prenatal Cannabis Use	
	No n= 494	**Yes** n= 90
	n (column %)[ρ] or mean (standard error)	
Mean Maternal Age, Years	29 (0.3)	26 (0.5)
Recruitment Site		
Southeast MI	314 (63.6)	48 (53.3)
Mid MI	96 (19.4)	31 (34.4)
Northern MI	84 (17.0)	11 (12.2)
US Census-Based Race/Ethnicity		
Non-Hispanic White	302 (61.1)	34 (37.8)
Non-Hispanic Black	140 (28.3)	50 (55.6)
Other	52 (10.5)	6 (6.7)
Education Level		
No high school diploma	46 (9.3)	16 (17.8)
High school diploma and/or some college	189 (38.3)	64 (71.1)
College degree	259 (52.4)	10 (11.1)
Health Insurance		
Government plan/none	220 (44.5)	75 (83.3)
Non-government plan	274 (55.5)	15 (16.7)
Pre-pregnancy BMI		
Not obese	322 (65.2)	53 (58.9)
Obese	172 (34.8)	37 (41.1)
Tobacco Smoking		
Non-smoker	404 (81.8)	31 (34.4)
Quit smoking upon pregnancy	48 (9.7)	24 (26.7)
Active smoker	42 (8.5)	35 (38.9)
Alcohol Drinking		
Non-drinker	433 (87.7)	69 (76.7)
Active drinker	61 (12.4)	21 (23.3)

[ρ] Percentages may not add to 100% due to rounding.
*Indicates statistical significance.

Table 2.2. The Association Between Prenatal Cannabis Exposure and Birth Outcomes, MARCH (n= 584)

Prenatal Cannabis Exposure and Birth Outcomes Odds Ratio (OR) or β Estimate (95% Confidence Interval)				
Birth outcomes	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Birth size[α]				
Small-for-gestational age	2.2* (1.1, 4.2)	2.0 (1.0, 3.9)	1.7 (0.8, 3.5)	1.5 (0.7, 3.2)
Large-for-gestational age	0.3 (0.1, 1.0)	0.3 (0.1, 1.0)	0.3 (0.1, 1.1)	0.3 (0.1, 1.1)
Birth size z-score[δ]	-0.4* (-0.6, -0.2)	-0.4* (-0.6, -0.1)	-0.3* (-0.6, -0.1)	-0.3* (-0.5, -0.003)
Preterm birth (<37 weeks)[α]	1.1 (0.5, 2.3)	1.1 (0.5, 2.2)	0.9 (0.4, 1.9)	1.1 (0.5, 2.4)
Gestational age (weeks)[δ] *(n= 574)*	0.1* (0.01, 0.1)	0.1* (0.01, 0.1)	0.1 (-0.01, 0.1)	0.1 (-0.01, 0.1)
NICU admission (yes)[α]	2.1* (1.2, 3.8)	1.9* (1.01, 3.4)	1.5 (0.8, 2.7)	1.2 (0.6, 2.4)
5-minute Apgar score[ε]	-0.01 (-0.1, 0.1)	-0.01 (-0.1, 0.1)	-0.01 (-0.1, 0.1)	-0.01 (-0.1, 0.1)

*Indicates statistical significance at 0.05 level.

[α] Categorical variable (OR)

[δ] Continuous variable (β)

[ε] Discrete variable (β)

[a] Model 1: Unadjusted.

[b] Model 2: Adjusted for maternal age.

[c] Model 3: Adjusted for maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, and pre-pregnancy BMI.

[d] Model 4: Adjusted for maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, pre-pregnancy BMI, alcohol drinking, and tobacco smoking.

Table 2.3. First Trimester Cannabis Use by Maternal Characteristics, MARCH (n= 378)

	First Trimester Cannabis Use	
	No n= 337	**Yes** n= 41
n (column %)[ρ] or mean (standard error)		
Mean Maternal Age, Years	30 (0.3)	26 (0.7)
Recruitment Site		
Southeast Michigan	254 (75.4)	25 (61.0)
Other	83 (24.6)	16 (39.0)
US Census-Based Race/Ethnicity		
Non-Hispanic White	221 (65.6)	17 (41.5)
Non-Hispanic Black	81 (24.0)	22 (53.7)
Other	35 (10.4)	2 (4.9)
Education Level		
No high school diploma	21 (6.2)	5 (12.2)
Diploma or higher education	316 (93.8)	36 (87.8)
Health Insurance		
Non-government plan	217 (64.4)	7 (17.1)
Government plan/none	120 (35.6)	34 (82.9)
Mean Pre-pregnancy BMI, kg/m^2	28.5 (0.4)	29.4 (1.2)
Tobacco Smoking		
Non-smoker	318 (94.4)	26 (63.4)
Active smoker	19 (5.6)	15 (36.6)
Alcohol Drinking		
Non-drinker	299 (88.7)	31 (75.6)
Active drinker	38 (11.3)	10 (24.4)

[ρ] Percentages may not add to 100% due to rounding.

Table 2.4. The Association Between First Trimester Cannabis Exposure and Birth Outcomes, MARCH (n= 378)

First Trimester Cannabis Exposure and Birth Outcomes Odds Ratio or β Estimate (95% Confidence Interval)				
Birth outcomes	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Birth size[α]				
Small-for-gestational age	2.1 (0.8, 5.6)	1.8 (0.7, 4.8)	1.9 (0.7, 5.3)	1.8 (0.6, 5.9)
Large-for-gestational age	0.2 (0.03, 1.8)	0.2 (0.03, 1.8)	0.2 (0.03, 1.9)	0.2 (0.03, 2.0)
Birth size (z-score)[δ]	-0.3 (-0.7, 0.04)	-0.2 (-0.6, 0.1)	-0.2 (-0.6, 0.1)	-0.2 (-0.6, 0.2)
Gestational age (weeks)[δ] *(n= 369)*	0.1 (-0.02, 0.1)	0.1 (-0.02, 0.1)	0.04 (-0.04, 0.1)	0.03 (-0.1, 0.1)
Preterm birth (<37 weeks)[α]	1.2 (0.4, 3.2)	1.1 (0.4, 3.0)	0.7 (0.2, 2.1)	0.8 (0.3, 2.4)
5-minute Apgar score[ε]	-0.005 (-0.1, 0.1)	-0.003 (-0.1, 0.1)	-0.01 (-0.1, 0.1)	-0.003 (-0.1, 0.1)
NICU admission (yes)[α]	3.0* (1.3, 6.6)	2.6* (1.1, 5.8)	1.7 (0.7, 3.9)	1.3 (0.5, 3.1)

* Indicates statistical significance at 0.05 level.

[α] Categorical variable (OR)

[δ] Continuous variable (β)

[ε] Discrete variable (β)

[a] Model 1: Unadjusted.

[b] Model 2: Adjusted for maternal age.

[c] Model 3: Adjusted for maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, pre-pregnancy BMI, and weight gain.

[d] Model 4: Adjusted for maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, pre-pregnancy BMI, and weight gain, level, alcohol drinking, and tobacco smoking.

2.4. Discussion

The current study investigated the association of prenatal cannabis exposure with a set of birth outcomes, including birth size, gestational age, 5-minute Apgar score, and NICU admission. In this sample of Michigan pregnant people, prenatal cannabis exposure was not associated with gestational age, 5-minute Apgar score, or NICU admission. However, findings suggest that neonates exposed to cannabis during pregnancy had lower birth size z-scores compared to neonates who were not prenatally exposed to cannabis ($beta_{model4}$= -0.3; 95% CI: -0.5, -0.003).

In a subsample of first trimester participants, prenatal cannabis exposure was not significantly associated with birth outcomes. Post-analysis restriction of the sample by excluding combinations of other drug use (*i.e.*, alcohol drinkers, tobacco smokers, and alcohol drinkers and tobacco smokers) did not significantly alter results. GEE analyses determined that twin clusters as well as pregnant people nested within recruitment sites did not have an effect on estimates.

Few studies assessed birth size via z-scores. However, Koto et al. investigated the relationship between prenatal cannabis exposure and birth outcomes, including birth size measured as a z-score.[114] The authors detected a statistically significant association between using cannabis during pregnancy and lower birth size z-score after controlling for potential confounding variables (beta= 0.23; 95% CI: 0.19, 0.27). These results were similar to the findings of this dissertation research. However, Koto et al. also detected an association between prenatal cannabis use and birth size measured on a categorical scale; compared to non-users, people who reported cannabis use during pregnancy had higher odds of delivering an SGA neonate (OR= 1.52; 95% CI: 1.34, 1.71). The authors' findings also suggested a significant association between prenatal cannabis use and 5-minute Apgar score as well as NICU

admission.[114] Koto et al. utilized a large perinatal database, which consisted of an analytic sample size of over 100,000 participants, while the MARCH analytic sample consisted of only 584 participants. It is likely that the current analysis was underpowered and therefore limited in its ability to detect a statistically significant difference between people who used cannabis during pregnancy and those who did not.

Another study, conducted by Sturrock et al. in the United Kingdom, assessed the relationship between prenatal cannabis exposure and birth size z-score. The authors did not report a significant mean difference in z-score (via Student's t-test) between people who used cannabis during pregnancy and people who did not (-0.255 vs. 0.064, respectively; p-value= 0.087).[115] Of note, the authors only included term newborns (37-41 weeks' gestation) in the analysis, whereas the current study included births prior to 37 weeks' gestation. Sturrock et al. excluded preterm births in the association between prenatal cannabis use and birth size.

Moreover, Corsi et al. detected a significant association between prenatal cannabis use and PTB <37 weeks' gestation (RR= 1.41; 95% CI: 1.36, 1.47), SGA (RR= 1.41; 95% CI: 1.36, 1.45), NICU admission (RR= 1.40; 95% CI: 1.36, 1.44), and 5-minute Apgar score (RR= 1.28; 95% CI: 1.13, 1.45).[38] The authors used a large Canadian perinatal registry which included n= 661,617 study participants, an adequately powered sample. Further, Kharbanda et al. found that compared to no exposure, prenatal cannabis exposure was associated with SGA (RR= 1.69; 95% CI: 1.22, 2.34), while no association was detected between prenatal cannabis exposure and PTB (RR= 1.06; 95% CI: 0.64, 1.77).[40] It might be that a significant association was detected between using cannabis during pregnancy and SGA due to the large sample size (n= 3435 participants), and may also be attributed to the objective measure used to capture prenatal cannabis use (*i.e.*,

urinalysis). It could be that social desirability bias attributed to an underreporting of cannabis use during pregnancy in studies that only utilize self-report.

In the full analytic sample, prenatal cannabis exposure was associated with lower birth size z-scores compared to neonates who were not exposed to cannabis during pregnancy. Although modest, this finding suggests that fetal exposure to cannabis during pregnancy might play a role in fetal growth and maturation. Previous literature indicates health consequences of SGA neonates including cardiometabolic morbidities[116,117] and problems with intellectual performance in school-age children,[118] and that prenatal cannabis exposure is associated with these same outcomes. However, it is unclear the extent to which birth size mediates these associations and represents a direction for future research.

2.4.1. Limitations

There are several limitations to this study. First, birth size was measured as a multinomial variable – AGA, SGA, and LGA – and also on a continuous scale by using z-scores to estimate the change in the standard deviation of sex-specific birth weight for gestational age. Likewise, gestational age was measured as a binary variable (*i.e.*, PTB) and continuously as weeks' gestation at birth. Categorizing variables that can be analyzed on a continuous scale offers the advantage of simpler interpretation in clinical research. However, a resulting limitation is the loss of information through categorization, leading to reduced statistical power. A study of low power decreases the probability of detecting a true effect.[121] Additionally, not all participants had delivered at the time of this analysis, reducing the sample size and statistical power.

Another limitation is the constraint on statistical precision due to the small sample size. Because MARCH is an ongoing study, recruitment is incomplete. An additional limitation is that prenatal cannabis use was measured via self-report by MARCH study staff. Self-reported

substance use may introduce social desirability bias, which may be further exacerbated in a scientifically complex[122] study population (*i.e.*, pregnant people). Stigma and fear related to legal repercussions of substance use during pregnancy might hinder truthful participant responses. A scoping review that explored the validity of self-report measures and biological samples among women of reproductive age concluded that agreement between the measures was poor, and that self-reported cannabis use was underreported.[123]Moreover, MARCH did not restrict trimester eligibility upon study recruitment, and this limited our ability to conduct well-powered, trimester-specific analyses.

Lack of detailed substance use survey items restricted statistical analyses. The cannabis use survey item in prenatal surveys one and two did not inquire about recency of cannabis use, as the question measured cannabis use at any time during pregnancy. Further, no survey items measured the frequency of cannabis use. The significance of studying prenatal cannabis exposure and birth outcomes in terms of recency and frequency is related to well-established evidence attesting to the harmful effects of tobacco smoking during pregnancy. Prior literature suggests dose-response effects of tobacco smoking in pregnancy; increasing the number of cigarettes smoked, specifically in the third trimester, decreases birth weight.[124] Exploring the presence of a dose-response of cannabis use would be clarifying. Another limitation of the current study is that tobacco and alcohol use questions did not measure the recency of use and therefore, these potentially confounding variables may not have been adequately adjusted for.

2.4.2. Strengths

A strength of this study includes its prospective ascertainment of cannabis use, which reduces recall bias. Further, MARCH relied on state-archived birth records for birth outcome data. Birth records are a reliable source of birth outcome data. Finally, the skew-normal

distribution method resulted in a normal distribution of gestational age. This is a strength of the current study because the distribution of gestational age is often left-skewed.

2.4.3. Conclusions

Future studies that investigate the effects of prenatal cannabis exposure on birth outcomes are warranted, particularly with prospectively designed studies with comprehensive assessment of substance use biomarkers. Current recommendations from the American College of Obstetricians and Gynecologists discourage clinicians from advising and/or prescribing cannabis for use during pregnancy due to the lack of evidence exhibiting the benefits of its use on the developing fetus.[31] The majority of prior literature suggests null associations or reports modest adverse effects of prenatal cannabis exposure on birth outcomes. Given the effect of prenatal cannabis exposure on birth size in the current study, people who are pregnant or who are contemplating becoming pregnant should be weary of using cannabis in pregnancy until more prospective studies are conducted.

CHAPTER 3. HOW MIGHT MORNING SICKNESS SEVERITY INFLUENCE THE ODDS OF PRENATAL CANNABIS USE?

3.1. Background

Nausea and vomiting of pregnancy, also known as morning sickness, is common among pregnant people in the first trimester. Although undertreated,[69] NVP affects 70-80% of pregnant people[42] and varies in severity, ranging from mild and moderate symptoms to a severe form of NVP called hyperemesis gravidarum.[43] NVP can result in a lessened quality of life by inducing mood changes, poor sleep, and decreased social interactions.[43,50] A meta-analysis exploring the prevalence of NVP in the US found that one-quarter of individuals reported morning sickness during late pregnancy, a finding that suggests a large proportion of people continue to experience nausea and vomiting, although the vast majority of clinical literature indicates that NVP subsides around 12 weeks' gestation.[43] With limited pharmaceutical drugs marketed for NVP,[57] pregnant people experiencing morning sickness might contemplate using cannabis, as it has a history of use as an antiemetic,[62] for self-medicated treatment of symptoms.[57,67,68]

Past-month cannabis use has more than doubled among pregnant people aged 12-44 years old in the US between 2004-2005 (3.0%) and 2019-2020 (6.3%).[1] Cannabis legalization in many states across the nation may contribute to the decreased risk perception of cannabis use among pregnant people.[70] Scant research on the health effects of cannabis use during pregnancy may leave physicians unable to counsel pregnant patients with certainty given the lack of evidence-based findings. At present, the American College of Obstetricians and Gynecologists (ACOG) instructs physicians to recommend against the use of cannabis during pregnancy. Small qualitative studies, however, suggest that pregnant people believe that cannabis use during pregnancy is efficacious and safe.[66,67,70]

Dickenson et al. conducted a cross-sectional study in Colorado that sought to better understand recommendations from cannabis dispensaries regarding first trimester cannabis use among pregnant people. Findings indicated that about 70% of dispensaries recommended cannabis products for the treatment of morning sickness. The majority of dispensaries based their recommendations on personal opinion, and a minority of dispensaries recommended consulting a physician without being prompted by the caller first.[125]

Given the high prevalence of morning sickness, the lack of available prescription drugs for the treatment of NVP, the two-fold increase in cannabis use among pregnant people, the perception that cannabis is safe to use in pregnancy, and the reinforcing recommendations of the safety and efficacy of cannabis use to treat morning sickness by dispensary employees (and not medical professionals), I aim to estimate the degree to which NVP might be associated with prenatal cannabis use in a sample of Michigan pregnant people, a state where medical and recreational cannabis use is legal.

3.2. Methods

3.2.1. Study Population and Sample

Here, I analyzed data for the Michigan Archive for Research on Child Health (MARCH) cohort, recruited between 2017 and 2021. MARCH is a prospective study that began recruiting pregnant people in 2017 from 11 sites across Michigan using probability-based sampling. Pregnant patients were recruited through physician offices at participating prenatal practices. MARCH excludes pregnant people who are under the age of 18 and those who do not speak English. Upon participant consent, data were collected by interviewing the participant in person or via telephone. Participants completed up to two prenatal surveys throughout pregnancy. Although study participants are recruited at the first prenatal visit, the trimester of recruitment

was not restricted. As such, while the goal was for participants to complete both prenatal surveys, some only completed prenatal survey one due to late recruitment into the study, or loss-to-follow-up.[87] A more detailed description of the MARCH study protocol can be found in the Chapter 2 Methods section of this dissertation. This study has been approved by the Michigan State University institutional review board for protection of human subjects and has been determined exempt under 45 CFR 46.104(d) 4(ii).

3.2.2. Nausea & Vomiting of Pregnancy (NVP)

In the current analysis, I examined data from prenatal survey one only. This survey was completed by all study participants and was the only survey containing the Pregnancy-Unique Quantification of Emesis and Nausea tool (*i.e.,* prenatal survey two did not contain the PUQE tool). The PUQE scoring system was validated by Koren et al. in 2005 in an effort to simplify the tool previously used to assess the severity of nausea and vomiting. This tool, the Rhodes' score, was originally developed for a sample of cancer patients receiving chemotherapy, and according to Koren et al., was complex and not specific to pregnancy, which led to the implementation of a scoring system specific to pregnancy. The PUQE tool consisted of three questions that asked patients or participants (as the tool was intended for both clinical practice and research) about the number of hours they felt nauseated, the number of times they had vomited, and the number of times they had experienced retching or dry heaving in the prior 12 hours. Scores for each question ranged from one to five and were summed to yield a composite score. Based on the composite score, the patient/participant was categorized as having mild (≤ 6), moderate (7-12), or severe NVP (13-15).[126] A few years after the validation of the 12-hour PUQE scoring system, Ebrahimi et al. validated the 24-hour PUQE tool to account for time spent asleep.[127] Figure 1 illustrates the scoring system

Figure 3.1. PUQE-24 Scoring System

Items	Response (Score)
In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all (1) 1 hour or less (2) 2-3 hours (3) 4-6 hours (4) More than 6 hours (5)
In the last 24 hours have you vomited or thrown up?	I did not throw up (1) 1-2 times (2) 3-4 times (3) 5-6 times (4) 7 or more times (5)
In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?	None (1) 1-2 times (2) 3-4 times (3) 5-6 times (4) 7 or more times (5)
PUQE-24 Score: Mild ≤ 6; Moderate = 7–12; Severe = 13–15	

MARCH used the 24-hour PUQE scoring system (Figure 3.1), which asked the following three questions: 1) "On average in a day, for how long do you feel nauseated or sick to your stomach?" 2) "On average in a day, how many times do you vomit or throw up?" 3) "On average in a day, how many times do you have retching or dry heaves without bringing anything up?" Although MARCH used the PUQE scoring system, it may be worth noting the minor differences in language between the validated tool and MARCH survey items. Whereas the PUQE scoring system asked about symptoms in the last 24 hours, MARCH asked about symptoms "on average in a day."

3.2.3. Cannabis Use During Pregnancy

Cannabis use was measured via self-report on prenatal survey one by answering the following survey item: "Have you used marijuana (pot) or cannabis including medically

prescribed cannabis, at all during this pregnancy?" A response of 'yes' to the cannabis survey item indicated prenatal cannabis use.

3.2.4. Covariates

Covariates adjusted for in the current analysis include maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, pre-pregnancy BMI, tobacco smoking, alcohol drinking, and trimester of pregnancy. Existing literature regarding NVP risk and race/ethnicity are mixed. Some studies found NVP risk to be lower among Black pregnant people,[128,129] while others suggested that White pregnant people were less likely to experience NVP.[130] Moreover, cannabis use prevalence is higher among Black individuals compared to their White counterparts.[103] Further, one study found that individuals with NVP were more likely to be young[131] and another study reported that NVP risk decreased in older age groups.[129] Interestingly, one study suggested that increasing maternal age was associated with delayed onset of NVP.[132] Trends in prenatal cannabis use, however, indicate a higher prevalence of use among younger pregnant people.[1] Socioeconomic status may also play a role in NVP risk; one study found that women with less education and low, but not the lowest, level of income were more likely to report NPV and more severe NVP.[133] Other studies found that low income and less education were linked to a greater risk of NVP.[42,131,134,128] Prior studies indicate an increased prevalence of cannabis use among groups who are socioeconomically disadvantaged.[135] Some research suggests that NVP is more likely in pregnant people with low BMI.[136] Although anecdotal evidence suggests that increased appetite and weight gain may be associated with cannabis use, studies have found a lower prevalence of cannabis use among overweight and obese individuals.[107] Furthermore, while tobacco smoking is more often than not associated with poor health outcomes, especially in pregnancy, some research suggests that smoking prior to

pregnancy[137] is protective against NVP.[129] An epidemiological study suggested an association between tobacco smoking before pregnancy and decreased risk of NVP. Authors also determined an interaction between alcohol drinking, tobacco smoking, and NVP; participants who smoked and who were regular alcohol drinkers before pregnancy were significantly less likely to experience NVP compared with non-smokers. However, there was no association between non-smokers who drank alcohol before pregnancy and NVP risk.[138] Another study found an association between alcohol consumption before pregnancy and decreased risk of NVP.[130]

Prior research indicates issues of confounding resulting from polysubstance use among cannabis users.[33,144,145] Lastly, I controlled for trimester of morning sickness given that NVP is most common early in pregnancy and typically resolves by 20 weeks' gestation.[42,44]

3.2.5. Analysis Plan

The current study consists of four analyses – one main analysis and three sensitivity analyses. In the main analysis, I estimate the association between morning sickness severity and the odds of prenatal cannabis use. In the first sensitivity analysis, I estimate the association between trimester-specific morning sickness and the odds of prenatal cannabis use. In the second sensitivity analysis, I assess the association between prenatal cannabis use and morning sickness severity. Finally, in the third sensitivity analysis, I assess the relationship between pre-pregnancy cannabis use, defined as use in the three months prior to pregnancy, and first trimester morning sickness severity.

For the main analysis, I estimated associations using covariate-adjusted generalized linear models. Specifically, I used logistic regression to estimate the odds of prenatal cannabis use with increasing morning sickness severity. I measured morning sickness severity on a continuous scale, ranging from 0-15, to increase statistical power. As such, morning sickness was not

categorized into mild, moderate, and severe, as illustrated in Figure 1. However, this reference allows the reader to better understand the meaning behind the PUQE-24 score. For the first sensitivity analysis, I repeated the previous analyses but investigated whether trimester-specific morning sickness might be associated with the odds of prenatal cannabis use. Because NVP is more prevalent in the first trimester compared to later trimesters of pregnancy, and due to the small sample size of third trimester recruitment, this analysis compared the odds of cannabis use during the first trimester to the combined sample of second and third trimester participants. For the second sensitivity analysis, I used Poisson regression to assess the association between prenatal cannabis exposure and morning sickness severity, and also used the same analysis for the third sensitivity analysis in which I restricted the sample to pre-pregnancy cannabis use and first trimester morning sickness.

3.3. Results

The MARCH dataset consisted of n= 866 participants in total. The final analytic sample for the current study was n= 826 pregnant people. Thirty-nine participants were excluded due to missing data on the exposure, outcome, or covariates. Specifically, n= 5 participants were missing data on cannabis; n= 6 were missing data on the PUQE; n= 3 were missing data on recruitment site; n= 3 were missing data on education level; n= 1 was missing data on health insurance; n= 14 were missing data on pre-pregnancy BMI; n= 2 were missing data on smoking status; n= 1 was missing on trimester; there was no missingness on maternal age or US census-based race/ethnicity.

Table 3.1 describes prenatal cannabis use by maternal characteristics. Descriptive statistics indicate that 14% of the sample used cannabis during pregnancy and were on average, 27 years old. The majority of prenatal cannabis users were recruited from Southeast Michigan

(57%), had a high school diploma and may have additionally completed some college (72%), were insured under a government health insurance plan (80%), and had an average pre-pregnancy BMI of 29 kg/m^2 (64% of the sample was not obese). Nearly half of prenatal cannabis users were non-Hispanic Black (49%), although non-Hispanic White pregnant people (40%) made up a large proportion of the sample as well. The vast majority of people who used cannabis during pregnancy did not concurrently drink alcohol (84%), although 36% of prenatal cannabis users smoked cigarettes during pregnancy.

Table 3.1. Prenatal Cannabis Use by Maternal Characteristics, MARCH (n= 826)

	Prenatal Cannabis Use	
	No n= 714	**Yes** n= 112
	n (column %)[ρ] or mean (standard error)	
Mean PUQE Score	6.1 (0.1)	7.4 (0.3)
Mean Maternal Age, Years	29 (0.2)	27 (0.5)
Recruitment Site		
Southeast MI	450 (63.0)	64 (57.1)
Mid MI	171 (24.0)	38 (33.9)
Northern MI	93 (13.0)	10 (8.9)
US Census-Based Race/Ethnicity		
Non-Hispanic White	425 (59.5)	45 (40.2)
Non-Hispanic Black	209 (29.3)	55 (49.1)
Other	80 (11.2)	12 (10.7)
Education Level		
No high school diploma	63 (8.8)	20 (17.9)
High school diploma and/or some college	308 (43.1)	81 (72.3)
College degree	343 (48.0)	11 (9.8)
Health Insurance		
Non-government plan	378 (52.9)	23 (20.5)
Government plan/none	336 (47.1)	89 (79.5)
Mean Pre-pregnancy BMI, kg/m²	28.5 (0.3)	28.8 (0.9)
Pre-pregnancy BMI		
Not obese	455 (63.7)	72 (64.3)
Obese	259 (36.3)	40 (35.7)
Tobacco Smoking		
Non-smoker	588 (82.4)	44 (39.3)
Quit smoking upon pregnancy	59 (8.3)	28 (25.0)
Active smoker	67 (9.4)	40 (35.7)
Alcohol Drinking		
Non-drinker	651 (91.2)	94 (83.9)
Active drinker	63 (8.8)	18 (16.1)

[ρ] Percentages may not add to 100% due to rounding.

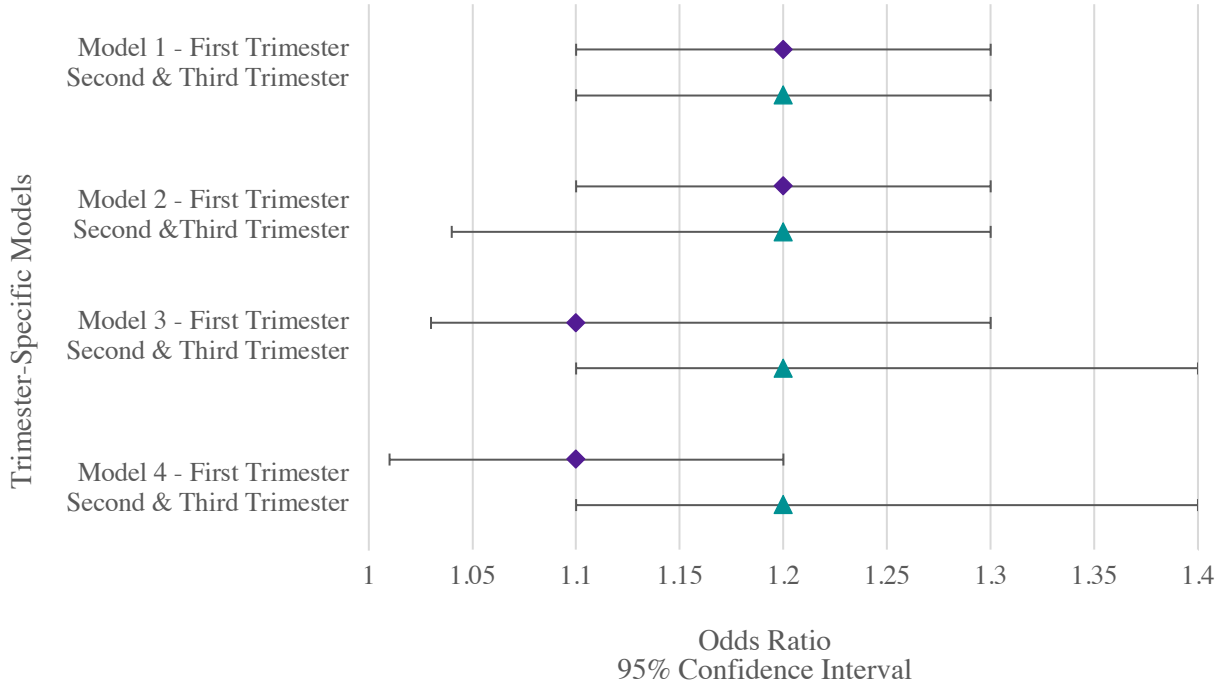
Table 3.2 illustrates the results from multiple logistic regression models estimating the association between morning sickness severity and prenatal cannabis use. After model adjustment for potential confounding variables, for each one-point increase in the PUQE score, pregnant people had 1.2 times the odds of using cannabis (OR_{model4}= 1.2; 95% CI: 1.1, 1.2). In a sensitivity analysis, I explored how trimester-specific morning sickness severity might be associated with prenatal cannabis use (Figure 3.2). After adjustment for potential confounders, pregnant people had 1.1 times the odds of using cannabis during the first trimester of pregnancy with each one-point increase in the PUQE score (OR_{model4}= 1.1; 95% CI: 1.01, 1.2; n= 554 first trimester participants, n= 61 used cannabis). Pregnant people in the combined second and third trimester had 1.2 times the odds of using cannabis with each one-point increase in PUQE score (OR_{model4}= 1.2; 95% CI: 1.1, 1.4; n= 272 second and third trimester participants, n= 51 used cannabis).

Table 3.2. Results from Multiple Logistic Regression Models Estimating the Association Between Morning Sickness Severity and Prenatal Cannabis Use, MARCH (n= 826)

Increasing Morning Sickness Severity & Prenatal Cannabis Use Odds Ratio (95% Confidence Interval)				
	Model 1[a]	**Model 2[b]**	**Model 3[c]**	**Model 4[d]**
Prenatal Cannabis Use	1.2* (1.1, 1.3)	1.2* (1.1, 1.2)	1.2* (1.1, 1.2)	1.2* (1.1, 1.2)

*Indicates statistical significance at 0.05 level.
[a] Model 1: Unadjusted.
[b] Model 2: Adjusted for maternal age.
[c] Model 3: Adjusted for maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, pre-pregnancy BMI, and trimester of survey completion.
[d] Model 4: Adjusted for maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, pre-pregnancy BMI, trimester of survey completion, tobacco smoking, and alcohol drinking.

Figure 3.2. Results from Multiple Logistic Regression Models Estimating the Trimester-Specific Association Between Morning Sickness Severity and Prenatal Cannabis Use, MARCH (n= 826)



Diamond represents first trimester estimates. Triangle represents the combined second and third trimester estimates.
Model 1: Unadjusted.
Model 2: Adjusted for maternal age.
Model 3: Adjusted for maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, and pre-pregnancy BMI.
Model 4: Adjusted for maternal age, recruitment site, US census-based race/ethnicity, education level, health insurance, pre-pregnancy BMI, alcohol drinking, and tobacco smoking.

In a second sensitivity analysis, I investigated the relationship between prenatal cannabis use and morning sickness severity. Here, prenatal cannabis use was the independent variable and morning sickness severity was the dependent variable, analyzed via Poisson regression. While morning sickness might influence the odds of using cannabis, using cannabis during pregnancy may also be associated with the degree to which morning sickness is experienced. After full model adjustment for potential confounders, the expected log count for each unit increase in PUQE score among pregnant people who use cannabis, compared to those who do not, is 0.2 units ($beta_{model4}$= 0.2; 95% CI: 0.1, 0.2).

In a third sensitivity analysis, I restricted cannabis use to participants who had used cannabis in the three months prior to pregnancy and first trimester morning sickness severity. The total sample size was n= 554, of which n= 255 participants had used cannabis in the three months before becoming pregnant. After full model adjustment, the expected log count for each unit increase in PUQE score among participants who used cannabis in the three months prior to pregnancy, compared to those who did not, was 0.1 units ($beta_{model4}$= 0.1; 95% CI: 0.003, 0.2).

3.4. Discussion

In the current study, I detected a modest association between morning sickness severity and prenatal cannabis use. A trimester-specific sensitivity analysis suggested increased odds of prenatal cannabis use with increasing NVP in the first trimester as well as in the combination of the second and third trimesters. Study findings are in agreement with the hypothesis that morning sickness severity is associated with prenatal cannabis use, and also in line with the few epidemiological studies on the NVP-cannabis association. Roberson et al. concluded that pregnant people who reported severe nausea, measured via the *International Classification of Disease* and diagnostic codes from electronic health records, were more likely to report using

cannabis than those who did not report severe NVP (PR= 1.63; 95% CI: 1.08, 2.44).[71] Young-Wolff et al. found that pregnant people with severe and mild NVP, measured by a single survey item, had 3.8 times the odds (95% CI: 3.19, 4.52) and 2.4 times the odds (95% CI: 2.17-2.59), respectively, of using cannabis.[72] Study findings are consistent with the idea that individuals who experience morning sickness are more likely to use cannabis to self-medicate nausea and vomiting. Results from the current study along with the findings from past epidemiological studies indicate the importance of the need for more research on NVP and prenatal cannabis use.

Qualitative studies explored healthcare providers' responses to pregnant patients who ask for information on prenatal cannabis use. Findings suggest that healthcare providers are unsure of how to address questions surrounding prenatal cannabis use due to a lack of causal evidence. Physicians feel that current research is not suggestive of strong associations between prenatal cannabis use and health effects on the developing fetus. On the other hand, physicians feel confident discussing the harmful effects of other drug use, such as opioids and cocaine. Because healthcare providers feel unable to effectively discuss the effects cannabis may have on the fetus, they may advise against cannabis use during pregnancy without an explanation outlining the consequences of use; some providers may avoid counseling the patient on prenatal cannabis use altogether. Pregnant patients report feeling that prenatal cannabis use must not be harmful given the lack of emphasis on the effects of cannabis use.[146,147,148] Further, one study explored provider opinions surrounding the safety of prenatal cannabis use. Results indicated that while over half of providers viewed cannabis as harmful to use in pregnancy, the remaining ~44% of providers either viewed cannabis as safe, had mixed feelings, or avoided addressing safety of cannabis use in pregnancy, the majority being in the latter category.[148] Therefore, future research is justified to

better understand the health effects of using cannabis during pregnancy so that providers can properly counsel pregnant patients who use or who are considering using cannabis.

It is worth highlighting the sensitivity analyses on the association between prenatal and pre-pregnancy cannabis use and morning sickness severity. Findings suggest that prenatal cannabis use is modestly associated with more severe morning sickness. However, limitations of this analysis should be addressed. The prenatal cannabis use survey item was not time-specific with the exception of participants who completed the survey within the first trimester of pregnancy. Moreover, the PUQE scale captured NVP in the 24 hours prior to survey assessment. As a result, it is possible that the analysis is capturing cannabis use earlier in pregnancy than the trimester the survey was completed. In addition, although morning sickness severity was time-specific, it may not have matched the timeframe in which cannabis was used. It is possible that the 24-hour assessment of morning sickness does not reflect the trimester as a whole. In an effort to address these issues, another sensitivity was restricted to cannabis use within the three months prior to pregnancy and assessment of NVP in the first trimester only. The objective of this analysis was to predict whether pre-pregnancy cannabis use was associated with severity of morning sickness in the first trimester. Findings are suggestive of a modest, statistically significant relationship which is in line with a recent epidemiological study that sought to explore this relationship.[73] Metz et al. measured cannabis use via urine immunoassay and liquid chromatography with tandem mass spectrometry to detect THC. NVP was assessed via the PUQE tool. Authors found that cannabis use was associated with nausea and vomiting during pregnancy and that individuals who used cannabis reported a higher frequency and NVP severity. [73] Moreover, cannabinoid hyperemesis syndrome (CHS), a term coined in 2004,[63] is increasingly seen in clinical literature. CHS is defined by recurrent episodes of nausea, vomiting,

and dehydration, frequent emergency department visits, and compulsive hot showers for symptom relief. The syndrome is often seen in young adults with a history of chronic and heavy cannabis use, and discontinuation of cannabis resolves nausea and vomiting.[61,63,64] Results of the current study suggest that both pre-pregnancy and prenatal cannabis use are associated with increasing morning sickness severity, justifying the need for future studies to investigate how chronic, heavy pre-pregnancy or prenatal cannabis use might influence morning sickness. Future research should capture data on frequency of cannabis use as well as length of time cannabis was used. Specifically, epidemiological studies are warranted for the investigation of CHS in pregnancy, as the few studies available are clinical case reports.[149,150,151]

3.4.1. Limitations

The current study is not without limitations. First, cannabis use was measured via self-report, a subjective measure that may introduce social desirability bias. Skelton et al. conducted a scoping review and concluded that concordance between self-reported cannabis use and biological samples was poor.[123] Objective measures of cannabis use would improve study validity. Moreover, because MARCH was not restricted to first trimester recruitment into the study, the sample size was small and led to imprecise estimation. As previously stated, MARCH recruited only 554 of the 826 participants in their first trimester. Small cell sizes of prenatal cannabis users (n= 61 in first trimester, n= 43 in second trimester, and n= 8 in third trimester) likely reduced statistical power. Despite the prospective nature of MARCH, the PUQE tool was only asked once, in prenatal survey one. This limited the ability to analyze morning sickness severity across trimesters within the same participant. Further, the prenatal cannabis use survey item was not specific to the timing of use; while it was certain that participants in their first trimester of pregnancy who answered ‘yes’ to cannabis use, reliably used cannabis in the first

trimester, those who answered 'yes' to the cannabis survey item and who were in their second or third trimester of pregnancy could not have been assumed to necessarily have used cannabis during that timeframe, as the question asked about cannabis use 'at all during pregnancy.' Therefore, although MARCH was prospective in design, analyses were cross-sectional. Furthermore, the survey did not ask participants about frequency of cannabis use or mode of administration. Such information would be useful in analyzing dose-response effects of cannabis use as well as how smoking cannabis may have unique effects compared to using edibles, for example.

3.4.2. Strengths

A strength of this study was the use of a validated tool to measure morning sickness. The PUQE scoring system was developed specifically to quantify NVP, opposed to tools used previously which were designed to assess nausea and vomiting among cancer patients. Prior studies have relied on diagnostic codes found in medical records or a single binary question to assess NVP. These methods may underestimate the prevalence of NVP and do not capture the full continuum of symptoms. Another strength of the study was that the prospective design allowed for real-time data collection and reduced recall bias.

3.4.3. Conclusions

More research on the association between morning sickness severity and prenatal cannabis use are warranted. Future studies should ask more detailed prenatal cannabis use questions to adequately capture trimester-specific use. Further, asking questions regarding quantity and frequency of prenatal cannabis use will provide the opportunity to assess dose-response effects. Due to the lack of epidemiological studies on the association, the relationship between increasing NVP and prenatal cannabis use has not been clearly established. Future

research should explore the temporality of the association, as some studies suggest that using cannabis early in pregnancy may be linked to increased nausea and vomiting. People who are pregnant or thinking of becoming pregnant might consider refraining from cannabis use during pregnancy until more evidence becomes available.

Lastly, it is imperative to comment on the link between Aim 1 and Aim 2 results. In Aim 1, I observed that compared to non-users, pregnant people who used cannabis delivered neonates with lower birth size z-scores. In Aim 2, the main analysis indicated an association between morning sickness severity and higher odds of prenatal cannabis use. Sensitivity analyses detected (1) an association in the opposite direction, between prenatal cannabis use and morning sickness severity and (2) pre-pregnancy cannabis use and increased first trimester morning sickness severity.

CHAPTER 4. DESIGNING A FEASIBILITY STUDY TO ASSESS THE RECRUITMENT AND RETENTION OF PREGNANT PEOPLE WHO REGULARLY USE CANNABIS

4.1. Background

The rising prevalence of cannabis use during pregnancy[2] indicates the need for more research on the health effects of prenatal cannabis use. Qualitative surveys suggest that using cannabis is perceived as low risk among pregnant people.[66,68,153] The widespread legalization of cannabis in many states across the US has contributed to the liberalization of using cannabis in both the general adult population and among pregnant people. However, research findings on the potential risks associated with prenatal cannabis use remain unclear. The majority of prior studies use retrospective recall and are cross-sectional in nature. Further, many studies use medical chart abstraction for data collection and in consequence, data are oftentimes incomplete and non-specific. Confounding by polysubstance use is also a common issue among studies on prenatal cannabis use, as tobacco is often used concurrently with cannabis. The lack of trimester-specific data further contributes to the limitations of prior research, as it is imperative to understand the trimester(s) during which cannabis might have an effect on maternal and infant health. Lastly, the majority of prior studies do not assess the recency and frequency of prenatal cannabis use. This information would aid in an improved understanding of a possible dose-response effect of prenatal cannabis use.

While some research findings suggest modest associations between prenatal cannabis use and birth outcomes,[36,37,38] others are null.[33,34,35] The American College of Obstetricians and Gynecologists (ACOG) recommends against the use of cannabis during pregnancy; however, the lack of evidence makes it difficult for pregnant people as well health professionals to understand how cannabis use might influence maternal and neonatal health outcomes. High quality

prospective studies are needed to assess the health effects of prenatal cannabis use trimester-by-trimester, with restriction on polysubstance use to eliminate confounding from other drug use. Moreover, such a study should be designed to specifically address cannabis use during pregnancy, capturing data on recency of use, frequency of use, mode of use, and motivation for use. Here, we designed a prospective feasibility study, Cannabis Legalization in Michigan-Maternal & Infant Health (CLM-MIH) to assess the recruitment and retention of pregnant people who regularly use cannabis.

4.2. Methods

CLM-MIH is a prospective feasibility study of pregnant people who used cannabis regularly, defined as using four or more times during the 30 days prior to survey assessment. CLM-MIH is a convenience sample that includes four timepoints: first trimester, second trimester, third trimester, and postpartum. CLM-MIH recruited participants from Women's Health and Family Medicine Residency clinics at Sparrow Hospital, located in Lansing, Michigan. The study began on October 9, 2020, and continued until mid-November 2020, when the study was paused by the Michigan State University Institutional Review Board due to the statewide COVID-19 Executive Order. The pause was lifted on February 1, 2021, and recruitment efforts resumed. To be eligible for the study, patients must have been pregnant, 21-35 years old, and initiating a prenatal care visit. The restricted age group accounted for advanced maternal age and ensured that participants were of legal age to use cannabis (21 years old). Here, to initiate prenatal care means that a patient was attending their first or second prenatal visit. The first prenatal appointment was a nurse intake, in which nurses collect health information on the patient. The second prenatal appointment was the patient's first meeting with a physician. The timing of prenatal care initiation was restricted to capture people very early in pregnancy. At

each clinic, medical staff, which included nurses, medical assistants, physician assistants, nurse practitioners, and residents, were educated on study eligibility criteria. Medical staff provided CLM-MIH study staff with eligible patient schedules for each week, excluding all personal identifiers (*i.e.,* only patient appointment days and times were shared). Additionally, the study was advertised through flyers at the clinics; study contact information was listed on the flyers and those interested in participation could contact study staff.

Study recruitment took place during or immediately after a scheduled initial prenatal care appointment. Medical staff advertised the study to eligible patients during prenatal care appointments. CLM-MIH study staff educated all medical staff on the study recruitment process, including how to approach an eligible patient for recruitment into the study. If the patient was interested, they were directed to CLM-MIH study staff in the clinic. The study staff then consented the participant by describing the study protocol. If the participant was still interested in participation, they selected a random envelope; each envelope contained a copy of the informed consent sheet, a CLM-MIH study business card, and a sheet of labels with randomly generated unique identification (ID) numbers. The participant was given a study tablet, from which they self-administered a Qualtrics survey using the unique ID from the randomly selected envelope. The survey inquired about topics such as general health, substance use, and demographic information. No personal identifying information was collected. This screening survey determined eligibility for prospective follow-up: 1) first trimester of pregnancy, 2) never or regular cannabis user 3) no active tobacco use, 4) no or light alcohol drinking (defined as drinking no more than one alcoholic beverage per day in the past 30 days), and 5) no active use of other drugs including cocaine, heroin, methadone, methamphetamine, benzodiazepines, or extramedical prescriptions. Participants who were not eligible for prospective follow-up received

a $10 gift card as a token of appreciation. The purpose of the screening survey was two-fold: it determined prospective recruitment as well as collected a series of data on all survey participants. As the goal of CLM-MIH was to recruit n= 15 prospective participants, we used this 'baseline' sample to better understand the characteristics of clinic patients.

CLM-MIH enrolled participants who regularly used cannabis as well as those who had never used cannabis in their lifetime. Participants who had never used cannabis were recruited so that study staff was unable to distinguish pregnant people who used cannabis from those who did not to maintain privacy. Among those who used cannabis, participants who used cannabis in the 30 days prior to the assessment for at least four of the past 30 days were considered regular cannabis users. If determined to be eligible for the prospective study, participants were asked to provide a urine sample for drug screening to determine drug use status. Participants labeled urine samples with their unique ID. Next, participants completed a second survey, containing only two questions. These questions pertained to scheduling a follow-up interview and asked the participant to provide contact information and the date of an upcoming appointment for a future CLM study interview if known. CLM-MIH hired a third-party administrative assistant to handle the study email and all communication with participants. The purpose of the administrative assistant was to protect the identity of participants from study staff. The administrative assistant emailed study staff participant schedules for follow-up interviews at the clinic. Scheduling information could not be linked to survey data. Follow-up interviews were conducted during the participant's next obstetric appointment to make the study interview process as convenient as possible for the participants. In total, the prospective study consisted of four interviews. A $25 gift card was given after each interview for prospective participants, totaling up to $100 for study participation. The post-delivery survey, which asked about birth outcomes, was administered via

an electronic link and was completed by the participant within one month of delivery, and a gift card was sent electronically (*i.e.*, participants did not meet with study staff in the clinic for the postpartum interview and no urine sample was needed). During the third trimester assessment, CLM-MIH study staff gave participants an information sheet and explained the post-delivery survey assessment in advance. The sheet contained spaces to fill in information such as the baby's birth weight and 1-minute and 5-minute Apgar scores. The study staff explained that participants should place the information sheet in their purse or overnight bag for their hospital stay during delivery so that a nurse could help them locate all information needed, as some information (such as Apgar score) will not be obvious to the participant. Participants were instructed to complete the post-delivery survey within one month postpartum. Some participant interviews were affected by the COVID-19 pandemic. Participants who needed to complete a follow-up survey during the COVID-19 Executive Order pause in research were emailed a link to the study survey. Urine sample collection was not possible during this time, however. Electronic gift cards were emailed to participants after survey completion.

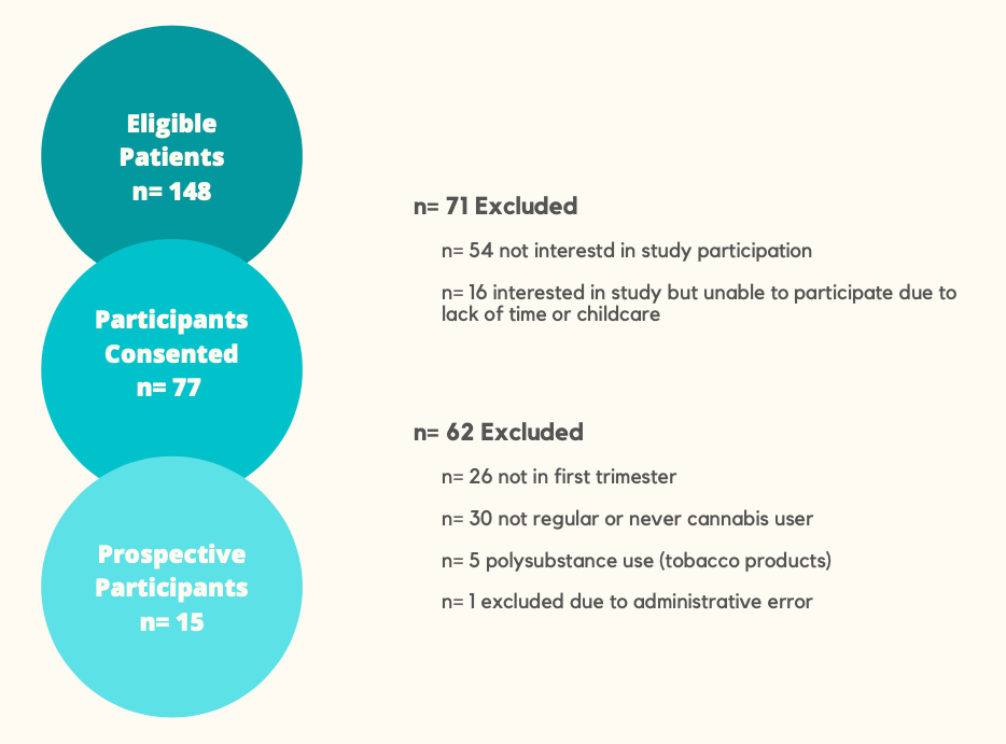
4.3. Results

4.3.1. Study Recruitment

Between October 2020 and August 2021, a total of n= 294 patients were on the participant recruitment schedule provided by medical staff at both clinics. Although the study period appears to be ten months, the COVID-19 Executive Order research pause lasted nearly three months, placing a temporary hold on recruitment between November 2020 and February 2021. Of the patients on the recruitment schedule, n= 146 were not approached by CLM-MIH study staff for various reasons. Specifically, n= 15 patients were not told about the study by medical staff; n= 3 patients were missed by CLM-MIH study staff; n= 1 patient switched

prenatal practices; n= 9 patients were duplicates; n= 37 patients were mistakenly placed on the schedule (*i.e.*, patients did not meet eligibility criteria); n= 10 patients did not speak or read English; n= 16 patients switched an in-person appointment to telehealth due to the pandemic; n= 13 patients canceled an appointment; n= 42 patients did not show up to an appointment without cancellation (*i.e.*, 'no show'). As depicted in Figure 4.1, n= 148 pregnant patients were approached for recruitment into CLM-MIH. Of these patients, n= 54 said they were uninterested in participation; n= 16 said they had an interest in the study but were unable to participate; n= 1 patient could not be interviewed due to the research pause (*i.e.*, the patient had contacted CLM-MIH directly via email while study staff were unable to be present in the clinic). The primary reason for non-participation among patients who expressed interest in the study was lack of time; the majority of patients reported that although they would like to participate in the study, they were unable to do so for reasons such as childcare and dependency on a ride from the clinic. A total of n= 77 pregnant patients consented to the study and completed the recruitment survey. As described in the Methods section, all consented participants took the recruitment survey, which also served as a screening tool for prospective follow-up. Participants who were ineligible for prospective follow-up did not complete the entire survey; only individuals who were eligible for follow-up (*i.e.*, first trimester, never or regular cannabis user, and no polysubstance use) were administered the full survey. CLM-MIH study staff recruited a total of n= 77 pregnant people between the ages of 21 and 35 years old who were initiating prenatal care at either the Women's Health clinic (n= 74) or the Family Medicine Residency clinic (n= 3) at Sparrow Hospital. Table 4.1 illustrates the maternal characteristics of the sample by cannabis use status.

Figure 4.1. Cannabis Legalization in Michigan-Maternal & Infant Health Eligibility Flowchart



4.3.2. Baseline Characteristics of Prenatal Cannabis Users

Table 4.1 categorizes cannabis use status into three groups: never user, past user, and recent user. There is an additional column for the n= 1 participant missing on cannabis. 'Never user' was defined as a participant who had never used cannabis in their lifetime. 'Past user' was defined as a participant who had used cannabis in the past but not within the 30 days prior to survey assessment. 'Recent user' was defined as a participant who had used cannabis in the 30 days prior to survey assessment (*i.e.*, prenatal cannabis user). Sixty-six percent of pregnant people in the sample were recruited during their first trimester of pregnancy. Forty-two percent of the sample used cannabis while pregnant, of which 87% were cannabis-only users. The percentage of prenatal cannabis users in the current study is significantly higher than that of other published studies. For example, prior research has reported prenatal cannabis use

prevalence between 2.6% and 5.8%.[72,131,71,144,34,154,73] Further, the prevalence of past-month cannabis use in US pregnant people is 6.3% according to the National Surveys on Drug Use and Health.[1] Moreover, 50% of study participants used cannabis for all 30 days of the month prior to survey assessment and 75% used cannabis two or more times per day; 97% reported that cannabis use was not recommended by a physician. The vast majority of participants reported smoking cannabis, either in a joint or blunt, when asked about mode of use.

Furthermore, 82% of participants who had reported ever using cannabis were asked about use in the three months prior to the current pregnancy. Almost every participant who had reported prenatal cannabis use also indicated using before pregnancy (only one participant reported no use in the three months prior). The mean age of people who used cannabis during pregnancy was 26 years old. The majority of prenatal cannabis users were non-Hispanic White, had a high school diploma, had an annual household income less than $25,000, and were insured under a government health plan. About 21% of the sample used tobacco during pregnancy, while about 13% of the sample used cannabis and tobacco products concurrently. Only 3% of the sample used alcohol; however, those who reported alcohol use during pregnancy were 'light' drinkers, as they consumed less than one alcoholic beverage per day during the 30 days prior to survey assessment.

Table 4.1. Prenatal Cannabis Use by Maternal Characteristics, CLM-MIH (n= 77)

	Cannabis Use Status			
	Missing	**Never user[a]**	**Past user[b]**	**Recent user[c]**
	n= 1	n= 6	n= 38	n= 32
	n (column %)[¶] or mean (standard error)			
Trimester				
1	1 (100.0)	5 (83.3)	23 (60.5)	22 (68.8)
2	0	0	11 (29.0)	8 (25.0)
3	0	0	4 (10.5)	2 (6.3)
Missing	0	1 (16.7)	0	0
Mean Maternal Age, Years	21(0.0)	27 (2.0)	27 (0.6)	26 (0.7)
US Census-Based Race/Ethnicity				
Non-Hispanic White	0	1 (16.7)	14 (36.8)	15 (46.9)
Non-Hispanic Black	0	2 (33.3)	16 (42.1)	9 (28.1)
Hispanic	0	3 (50.0)	5 (13.2)	5 (15.6)
Multiracial	1 (100.0)	0	3 (7.9)	3 (9.4)
Education Level				
No high school diploma	1 (100%)	0	5 (13.2)	5 (15.6)
High school diploma/GED/ some college	0	4 (66.7)	26 (68.4)	24 (75.0)
College or graduate degree	0	2 (33.3)	7 (18.4)	3 (9.4)
Household Income				
<$25,000	1 (100.0)	3 (50.0)	20 (52.6)	23 (71.9)
$25,000-$49,999	0	1 (16.7)	14 (36.8)	7 (21.9)
$50,000-$74,999	0	1 (16.7)	2 (5.3)	2 (6.3)
≥$75,000	0	1 (16.7)	2 (5.3)	0
Health Insurance				
Government plan	1 (100.0)	4 (66.7)	28 (73.7)	26 (81.3)
Private plan	0	2 (33.3)	7 (18.4)	6 (18.8)
None	0	0	2 (5.3)	0
Unsure	0	0	1 (2.6)	0
Marital Status				
Married	1 (100.0)	4 (66.7)	10 (26.3)	7 (21.9)
Never married	0	2 (33.3)	19 (50.0)	17 (53.1)
Other	0	0	9 (23.7)	8 (25.0)
Pre-pregnancy BMI				
Obese	0	2 (33.3)	17 (44.7)	12 (37.5)
Not obese	1 (100.0)	4 (66.7)	21 (55.3)	20 (62.5)

Table 4.1. (cont'd)

Gravidity[*]				
1-4 pregnancies	1 (100.0)	5 (83.3)	30 (79.0)	23 (71.9)
5+ pregnancies	0	1 (16.7)	8 (21.1)	9 (28.1)

[¶] Percentages may not add to 100% due to rounding.
[a] Never used cannabis in lifetime.
[b] Used cannabis in the past but not in the past 30 days.
[c] Used cannabis in the past 30 days.
[*] Number of times pregnant including current pregnancy.

4.3.3. Baseline Perceived Harm of Cannabis Use

Participants were asked to share their opinions about the risk of using cannabis. They were surveyed about how much they thought people risk harming themselves, physically and in other ways when they use cannabis once per month and twice per week. Next, they were asked how much they thought pregnant people risk harming themselves when they use cannabis. Participants were also asked about the risk of harming the baby when using cannabis, and also about how using cannabis while breastfeeding might be harmful. Survey questions measured risk perception as 'no risk,' 'slight risk,' 'moderate risk,' 'great risk,' 'I do not know,' or 'I do not wish to answer this question.' Among the full sample, regardless of cannabis use status (Table 4.2), over half the participants felt that people, in general, did not risk harming themselves if they used cannabis once a month or twice a week. Nearly half the participants felt that pregnant people did not risk harming themselves if they used cannabis. Over half the participants reported no risk or slight risk of harm to the baby when people used cannabis once a month or twice a week, and over a quarter of participants reported that they were unsure of the risk. Trends were similar when asked about the risk of using cannabis while breastfeeding.

Table 4.2. Perceived Risk of Cannabis Use Among Study Sample (n= 77)

	No Risk	Slight Risk	Moderate Risk	Great Risk	Unsure/ Refused
General Risk					
Once a month	43 (56%)	15 (19%)	5 (6%)	1 (1%)	13 (17%)
Twice a week	42 (55%)	18 (23%)	6 (8%)	0	11 (14%)
Pregnancy Risk					
Once a month	35 (45%)	22 (29%)	4 (5%)	3 (4%)	13 (17%)
Twice a week	34 (44%)	21 (27%)	5 (6%)	4 (5%)	13 (17%)
Baby Risk					
Once a month	25 (32%)	23 (30%)	4 (5%)	4 (6%)	20 (26%)
Twice a week	23 (30%)	17 (22%)	10 (13%)	6 (8%)	21 (27%)
Breastfeeding Risk	18 (23%)	20 (26%)	9 (12%)	11 (14%)	19 (25%)

Among participants who used cannabis in the month prior to survey assessment, 72% reported that people do not risk harming themselves when they use cannabis once a month or twice a week; over half the participants reported that pregnant people do not put themselves at risk when using cannabis once per month or twice per week. When asked about how cannabis use once a month might put the baby at risk, over one-third said there was no risk or a slight risk. When asked about how using cannabis twice a week might affect the baby, over one-third reported no risk while 25% reported slight risk. Further, a nearly equal proportion (25%) of participants reported no risk, slight risk, and moderate risk of harming the baby while breastfeeding.

4.3.4. Recruitment and Retention of the Prospective Sample

The prospective study sample included n= 15 participants. Exclusion criteria were as follows: n= 26 pregnant people were not in their first trimester; n= 30 were not eligible based on cannabis use criteria; n= 5 actively used tobacco products during pregnancy; no participants used other drugs including cocaine, heroin, methadone, methamphetamine, benzodiazepines,

extramedical prescriptions, or alcohol. One participant who completed the recruitment survey early in the study and who reported never cannabis use, was not included in the prospective sample although eligibility criteria were met. CLM-MIH initially oversampled cannabis users as to ensure recruitment into the prospective sample before opening the survey to never cannabis users as well. Study retention was 80%; briefly, of n= 15 first-trimester participants, n= 3 were lost-to-follow-up. Of the remaining 12 participants, 83% had complete data across all four timepoints.

4.3.5. Self-Reported Cannabis Use and Urinalysis Concordance

A urine sample was collected to confirm cannabis use status and measure agreement between self-report and urinalysis. All first-trimester participants supplied a urine sample, with 100% concordance between self-reported prenatal cannabis use and urine detection of THC. Moreover, there was 73% concordance between self-reported prenatal tobacco use and urine detection of cotinine for tobacco use during pregnancy. Ten second-trimester urine samples were collected, as n= 2 participants were missing a sample due to the COVID-19 Executive Order pause in research. These participants were able to complete the study via an online link to the survey. Three participants were missing the survey assessment and therefore, were also missing a urine sample. Concordance between self-reported prenatal cannabis use and urinalysis was 100% at the second trimester while concordance between self-reported tobacco use and urine detection of cotinine was 80%. During the third trimester, urine was collected from n= 12 participants. Agreement between self-reported cannabis use and urinalysis was 92% while agreement between self-reported tobacco and urinalysis was only 67%. No participants self-reported other drug use which matched urinalysis results across all trimesters.

4.3.6. Characteristics of Prospective Prenatal Cannabis Users

Among first trimester participants, four had never used cannabis in their lifetime while 11 participants were regularly (*i.e.,* at least four days of the 30 days prior to survey assessment) using cannabis during pregnancy. The mean age of participants who regularly used cannabis during pregnancy was 26 years old. The distribution of non-Hispanic White, non-Hispanic Black, and Hispanic people in the sample was nearly equal. The majority of the prospective sample had a high school diploma (55%), had an annual household income less than $25,000 (82%), was insured under a government health plan (81%), and was obese (73%). Eight of the 11 participants (73%) who regularly used cannabis during the first trimester of pregnancy reported using cannabis for 21-30 days of the past 30 days. The majority of first-trimester regular cannabis users reported using cannabis 1-2 times per day (64%), although the remainder of the sample reported using cannabis three or more times in a day.

The second trimester follow-up survey was completed by n= 12 pregnant people, of whom 7 reported prenatal cannabis use within the past 30 days. Forty-three percent reported using cannabis for 21-30 days of the month prior to survey assessment. The majority of the sample (86%) reported using cannabis 1-2 times per day. Further, of participants who reported no cannabis (THC) use during the second trimester of pregnancy, one participant reported CBD use for 1-10 of the past 30 days, and of participants who reported cannabis use, one also reported CBD use but for 21-30 days of the prior month. Among cannabis users, one participant reported concurrently using smokeless tobacco and another reported use of a tobacco product other than cigarettes or smokeless tobacco (e.g., hookah, e-cigarettes) and used at a frequency of 21-30 days.

The third trimester follow-up survey was completed by n= 12 participants, of whom 6 reported using cannabis in the past 30 days. Half the sample used cannabis for 11-20 days of the prior month while 33% of the sample used 21-30 days. Sixty-seven percent of the sample used cannabis 1-2 times per day while the remainder of participants used more often. One participant reported cannabis use concurrently with CBD and used for 21-30 days of the prior month.

4.3.7. Morning Sickness in the Prospective Sample

Nausea and vomiting of pregnancy (NVP), also known as morning sickness, was assessed across all three trimesters of pregnancy using the 24-hour Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) tool. The tool measured severity of morning sickness through three questions that asked about nausea, vomiting, and dry heaving over a 24-hour period. A total PUQE score of ≤6 is classified as mild morning sickness; a score between 7 and 12 is classified as moderate morning sickness; a score ≥13 is severe morning sickness. The average PUQE score among first trimester participants was 8.1; the second trimester mean PUQE score decreased to 4.8; finally, the mean PUQE score among participants in their third trimester was 4.0. More simply, on average, moderate NVP was experienced during the first trimester of pregnancy and reduced to mild NVP by the second trimester.

4.3.8. Motivation for Prenatal Cannabis Use in the Prospective Sample

Participants who used cannabis during pregnancy were asked about their reasons for use. Throughout all three trimesters of pregnancy, the majority of participants reported using cannabis to relive stress and anxiety (*i.e.*, 82%, 86%, and 100%, respectively). Still, motivations including to relieve symptoms of a chronic condition and pain relief were reported by over half of prenatal cannabis user across trimesters. Moreover, during the first trimester, 73% of pregnant people reported using cannabis to relieve nausea and vomiting. During the second and third

trimesters, however, the proportion of participants who reported using cannabis for symptom relief of morning sickness decreased to 43% and 33% respectively. Finally, around half the participants reported using cannabis to relax or for fun during the first and third trimesters, but a much smaller proportion said they used cannabis for this reason during the second trimester.

4.3.9. Perceived Risk of Cannabis Use Across Each Trimester of Pregnancy

Roughly half of first-trimester participants felt that people did not put themselves at risk when they used cannabis either in general or while pregnant, whether use was once a month or twice per week. Risk perception changed when first-trimester participants were asked about whether using cannabis during pregnancy harmed the baby; about one-quarter of the sample reported no risk or slight risk, while 33% were unsure of the risk. When asked about risk associated with breastfeeding, almost one-quarter of participants felt that using cannabis while breastfeeding presented no risk.

Trends in risk decreased with duration of pregnancy. Nearly 60% of second-trimester participants reported no risk of using cannabis in general or during pregnancy, whether use was once a month or twice per week. Over 40% of the sample reported no risk of cannabis on the baby once a month or twice per week. Half the sample reported no risk of using cannabis while breastfeeding.

Risk decreased further in the third trimester of pregnancy; nearly 70% of third-trimester participants reported no risk of using cannabis in general. Almost 60% of participants reported no risk associated with using cannabis during pregnancy. Half of third-trimester participants felt that there was no risk on the baby when pregnant people used cannabis, while nearly 60% of participants reported no risk of using cannabis while breastfeeding.

4.3.10. Post-Delivery Findings

Twelve participants completed the post-delivery survey, of which ten had complete data. One participant had indicated that their delivery did not result in a live birth and therefore, birth outcome data was not collected. It appears that the remaining participant with missing data did not complete her survey before it was submitted. Moreover, one participant had reported that she had a live birth, however, the baby was no longer living within one month postpartum.

Of the twelve participants with birth data, n= 7 had used cannabis in the 30 days prior to assessment, of whom 43% used for 27-30 days at a frequency of one to two times per day. One participant reported concurrent CBD for all 30 days prior to survey assessment. Additionally, two participants reported light alcohol use in the 30 days prior to assessment, concurrently with cannabis use.

Ninety percent of the sample delivered a neonate who was at least 2500 grams; 92% delivered between 37- and 41-weeks' gestation; 60% delivered a neonate with a 1-minute Apgar score greater than or equal to seven, while the remainder reported that they did not know the Apgar score. Further, 60% delivered a neonate with a 5-minute Apgar score equal to nine while the remainder did not know their child's score.

4.4. Discussion

The CLM-MIH study was designed to assess the feasibility of recruitment and retention of pregnant people who regularly used cannabis. The majority of previous studies were flawed by confounding from polysubstance use, maternal age, and non-restriction of the study sample to people in the first trimester of pregnancy. The CLM-MIH study only recruited pregnant people in their first trimester who did not use substances other than cannabis. The study also captured

people who used cannabis at a frequency of at least four times a month to tease out those who only occasionally used cannabis.

First trimester recruitment of pregnant people was a challenge given that only 66% were in their first trimester at initiation of prenatal care. One prior research study performed a secondary analysis on a prospective cohort of pregnant people who completed a substance use questionnaire during a prenatal care appointment. Nearly 80% of participants were in their first trimester of pregnancy,[72] suggesting that initiation of prenatal care during the first trimester in the current study sample may be low.

It took roughly seven months to recruit n= 15 participants for the prospective sample based on exclusion criteria, highlighting the difficulties associated with capturing pregnant people between 21-35 years old, who initiated prenatal care within the first three months of pregnancy and who did not use substances other than cannabis. Nonetheless, the study design and methods implemented by CLM-MIH are critical in understanding the effects of prenatal cannabis use on maternal health as well as birth outcomes. Because THC crosses the placental barrier early in pregnancy, when the effects of drug use are most detrimental to the developing fetus,[155] it is imperative to study pregnant people as early in pregnancy as possible.

It is worth noting that acetaminophen was used by half of the participants within the 30 days prior to post-delivery survey assessment. Acetaminophen was also used during all three trimesters of pregnancy but by a small proportion of the sample. A recent study that investigated acetaminophen use in pregnancy suggested a potential link with fetal development (e.g., neurodevelopmental, urogenital effects, and reproductive effects). This publication was a Consensus Statement written by a group of clinicians, epidemiologists, and basic scientists. Briefly, the consensus stated that pregnant people should take acetaminophen with caution. With

limited alternative medications deemed safe for use in pregnancy, the it was suggested that acetaminophen should only be used an absolutely necessary as low doses for a short period of time.[156]

CLM-MIH retained 80% of participants, indicating that pregnant people were interested and dedicated to the success of the study. The gift card incentives for participation may have aided in retention, as prospective participants had the opportunity to receive up to $100 as a token of appreciation. Further, study staff made follow-up assessments as convenient as possible for participants; follow-up meetings were always scheduled during the participant's already-scheduled prenatal appointment. Medical staff directed patients to study staff within the clinic immediately following the patient's appointment. Sometimes, study staff met with participants during an appointment, in the exam room while waiting for the physician. This method of survey administration provided an efficient way for the participant to complete the assessment. One theme which emerged was that many pregnant people who agreed to participate in CLM-MIH expressed the importance of the research and felt more studies were needed to investigate the safety of using cannabis during pregnancy. Some participants were unsure of the effects of prenatal cannabis use and were eager to learn more. The high agreement between self-reported cannabis and other substance use and urinalysis displayed a willingness to participate. One limitation of CLM-MIH might be that study staff were unable to recruit pregnant people who used cannabis but who did not initiate prenatal care at all, or initiated care later in pregnancy, due to the characteristics of patients at the Sparrow clinics.

Another limitation of the study was the collection of data on the 1- and 5-minute Apgar scores. Although CLM-MIH study staff instructed each participant to ask their nurse for help completing the information sheet, which contained space for Apgar scores, a large proportion of

participants reported that they were unsure of their child's Apgar score on the post-delivery survey. CLM-MIH did not have access to medical records of the participant or the neonate, making it difficult to retrieve data that was not self-reported by the participant.

Although study staff successfully met participants in the clinic, it was challenging for study staff to initiate follow-up after the prenatal appointment. This is because successful follow-up relied on the participant to remember to mention the study to their nurse. However, there were multiple instances in which the patient forgot to do so. A potential solution was for medical staff to include a reminder note about the study in medical charts of enrolled patients. That way, the nurse could easily direct the patient to study staff without the participant having to remember. However, this method was not pursued, as study staff was informed of the possibility of insurance companies noticing the note. If the note mentioned drug use, there was a fear that insurers would no longer be willing to provide coverage.

4.4.1. Implications for Future Research

The CLM-MIH study has numerous implications for future research. CLM-MIH successfully assessed the feasibility of recruiting pregnant people who regularly used cannabis, and followed participants throughout pregnancy and postpartum. Retention was high, demonstrating that participants were willing to participate in a study exploring prenatal cannabis use. Agreement between self-reported substance use and urinalysis was also high, signifying truthful responses. Among pregnant people in our sample, the stigma surrounding cannabis use in pregnancy was not apparent. It is possible that the liberalization of cannabis use in Michigan played a role in risk perception. CLM-MIH demonstrated the capability to restrict recruitment to the first trimester of pregnancy to capture cannabis use as early as possible. Participants were willing to answer questions not only about general prenatal cannabis use, but also disclosed the

number of days they used cannabis in addition to the frequency of use each day. Participants also disclosed how they used cannabis and supplied information on their motivation to use cannabis while pregnant, whether it be to relieve symptoms of morning sickness or to self-medicate anxiety. CLM-MIH attests to the willingness of pregnant people to be involved in such research, and so larger future studies should assess statistical associations between prenatal cannabis use and birth outcomes as well as maternal health. For example, current literature on the topic is cross-sectional in nature, relies on retrospective recall, and/or does not inquire on fine-grained detail of prenatal cannabis use. CLM-MIH should motivate future studies to design an adequately-powered prospective cohort study in which pregnant people are recruited in their first trimester of pregnancy and who do not concurrently use substances other than cannabis to better understand the health effects of prenatal cannabis use on the developing fetus as well as maternal health.

CHAPTER 5. DISCUSSION & CONCLUSIONS

5.1. Summary of Findings

AIM 1 estimated the association between prenatal cannabis exposure and birth outcomes including birth size, gestational age, 5-minute Apgar score, and NICU admission. The average age of prenatal cannabis users was 26 years old; the majority of participants who used cannabis during pregnancy were non-Hispanic Black, had a high school diploma, and were insured under a government health plan. After adjustment for confounding variables, findings suggested a modest but statistically significant association between exposure to cannabis during pregnancy and birth size. Specifically, compared to neonates who were not exposed to cannabis during pregnancy, birth size was smaller in neonates exposed to cannabis.

AIM 2 estimated how the severity of morning sickness might be associated with the odds of using cannabis during pregnancy. Estimates of morning sickness severity were measured using the 24-hour PUQE scoring system, a standardized tool designed specifically for the assessment of NVP. The mean age of people who used cannabis during pregnancy was 27 years old. The majority of participants had received a high school diploma and were insured under a government health plan. However, there was a similar proportion of non-Hispanic Black and White participants in the sample. After adjustment for confounding variables, findings suggested higher odds of prenatal cannabis use with increased morning sickness severity.

Aim 2 also estimated the trimester-specific association between morning sickness severity and prenatal cannabis use. After covariate adjustment, participants had higher odds of using cannabis during the first trimester of pregnancy with each one-point increase in PUQE score. Odds of cannabis use were similar but slightly increased, during the second and third

trimesters of pregnancy. Sensitivity analyses also determined an association between pre-pregnancy and prenatal cannabis use and increased morning severity.

AIM 3 assessed the recruitment and retention of pregnant people who regularly used cannabis via the design and launch of a prospective feasibility study in two Lansing, Michigan clinics. Of n= 77 participants recruited to the study, 66% were in their first trimester of pregnancy. One participant did not provide information on her cannabis use status. The mean age of participants who used cannabis in the 30 days prior to assessment was 26 years old. The majority of participants were non-Hispanic White, had a high school diploma, had an annual household income of less than $25,000, and were insured under a government health plan. Ninety-three percent reported using cannabis in their lifetime. Forty-two percent of participants reported using cannabis within the 30 days prior to assessment. Of prenatal cannabis users, 87% reported using only cannabis and no other substances during pregnancy. The recruitment survey captured baseline data on all participants and also screened for prospective participants for study follow-up.

Study retention among prospective participants was 80%; two participants were loss-to-follow-up after first trimester recruitment, and one participant completed only the first and third trimester assessments but was loss-to-follow-up for the post-delivery survey assessment. No study participants refused to supply a urine sample, however, among second trimester participants, two were missing due to the COVID-19 pandemic Executive Order research pause. The concordance between self-reported cannabis use and urinalysis was 100% during trimester one, 100% during trimester two, and 92% during trimester three.

Finally, NVP was assessed across all three trimesters using the 24-hour PUQE scoring system. The mean PUQE score in trimester one was 8.1, translating to moderate morning

sickness severity, while the PUQE scores in trimesters two and three were categorized as mild morning sickness severity with PUQE scores of 4.8 and 4.0, respectively. Moreover, NVP was assessed among prenatal cannabis users and never users. The mean PUQE score during the first trimester among regular prenatal cannabis users was 9.0 (moderate severity) and 5.5 (mild severity) among never cannabis users. During the second trimester, prenatal cannabis users had a mean PUQE score of 6.0 (mild severity) while never users had a score of 5.3 (mild severity). Lastly, both prenatal cannabis users and never users had mild morning sickness severity during the third trimester, with PUQE scores of 5.8 and 4.3, respectively.

5.2. Strengths and Limitations

5.2.1. Strengths of the MARCH Study

Aims 1 and 2 of this dissertation analyzed data for the MARCH cohort. A strength of MARCH is its prospective design. The majority of prior research on the topic of prenatal cannabis use and birth outcomes was cross-sectional in nature. Prospective studies are the best design for observational studies; they allow for real-time data collection and reduce recall bias. Further, self-reported survey responses are more reliable than medical chart data abstraction, which can be incomplete and non-specific. On the other hand, birth outcome data were collected from state-archived birth records, which provided information on variables including Apgar score, which might be unknown to the participant if asked to self-report. Another major strength of MARCH was its utilization of the PUQE tool to assess morning sickness severity. Much prior research measured morning sickness via medical diagnostic codes or with a single survey question. The PUQE tool was designed specifically to assess nausea and vomiting in pregnancy.

5.2.2. Limitations of the MARCH Study

No study is without its limitations. Although self-report of cannabis use was advantageous relative to abstraction from medical records, self-report is a subjective measure and could be subject to social desirability bias. Objective measures of cannabis use would have contributed to the validity of the study. Although MARCH used a prospective design, it did not assess participants during each trimester of pregnancy and so analyzes were akin to a cross-sectional study. MARCH did not restrict study recruitment to the first trimester thus decreasing the cell size of participants with available first trimester data. It is important to collect substance use information early in pregnancy, as drug use can be detrimental to the developing fetus as early as the first trimester. Each participant had up to two timepoints of survey data during varying trimesters. Because recruitment was not restricted, some participants completed prenatal survey one during the third trimester of pregnancy. This made it difficult to assess cannabis use trimester-by-trimester. Moreover, the cannabis use survey items were not specific. Participants were asked if they had used cannabis at all during pregnancy, and not within the past month, for example. By not capturing recency of use, it was impossible to determine cannabis use during the second and third trimesters. Only first-trimester cannabis use could be assessed; however, the small sample size presented an issue given that many participants did not complete the survey during the first trimester of pregnancy. On the topic of prenatal cannabis use, MARCH also did not capture data on the frequency, dose, or mode of use. This type of data would allow investigators to better understand any dose-response effect of cannabis use during pregnancy and how the mode of use might impact outcomes. Lastly, although MARCH used a standardized tool to assess NVP, morning sickness severity was only measured in prenatal survey one. Measuring

NVP in prenatal survey two would have been beneficial in evaluating the change in morning sickness severity throughout pregnancy.

5.2.3. Strengths of the CLM-MIH Study

The CLM-MIH study was designed specifically to assess pregnant people who regularly used cannabis, therefore providing fine-grained detail, including recency of use, frequency of use, and the mode in which cannabis was used. Further, CLM-MIH collected data on the perceived risk of cannabis use as well as motivations for using cannabis during pregnancy. Moreover, CLM-MIH restricted recruitment to the first trimester of pregnancy for prospective follow-up, and collected data on participants once during the first trimester, once during the second trimester, once again during the third trimester, and finally within one month postpartum. This allowed for the real-time collection of data during each stage of pregnancy. Participants were instructed to complete the post-delivery survey within one month of birth to reduce potential bias from recall. Additionally, urine samples were collected during each trimester at the time of survey completion to accurately confirm self-reported substance use.

CLM-MIH was able to assess the feasibility of recruiting and retaining pregnant people by measuring willingness to participate and complete the recruitment/screening assessment, providing the proportion of participants who regularly used cannabis, the ability to follow-up participants throughout pregnancy, collecting urine samples throughout pregnancy for confirmation of self-reported substance use, measuring pregnant participants who used cannabis only (no polysubstance use).

5.2.4. Limitations of the CLM-MIH Study

One limitation of the CLM-MIH study was its reliance on self-reported birth outcomes. Because study staff did not have access to medical records, outcomes were not able to be

retrieved from birth records. Of particular importance was Apgar score data; many participants were unsure of their new baby's 1-minute and 5-minute Apgar score, even though study staff instructed all participants to ask medical staff at delivery for such information.

Another limitation of the CLM-MIH study was that it was a convenience sample, and the proportion of cannabis users was far higher than cannabis prevalence reported in prior research as well as nationally. The clinics in which participants were recruited consisted primarily of patients with a low socioeconomic status. Therefore, study findings are not generalizable nationally nor at the state level.

5.3. Public Health Implications & Conclusions

Findings from this dissertation suggest that pregnant people who use cannabis are willing to participate in a study that explores the health effects of prenatal cannabis use on neonatal outcomes as well as maternal health. Stigma centered around using cannabis during pregnancy seems to have declined over the years, given the increased prevalence in use and the perception that prenatal cannabis use is not a great risk.

Large, well-powered prospective studies are warranted to longitudinally measure the association of prenatal cannabis use and fetal growth and development, and also to investigate the temporal sequence of cannabis use and severity of nausea and vomiting during pregnancy. With the growing clinical literature on CHS, understanding the temporality of the cannabis-NVP association would aid in a better understanding of the relationship.

This dissertation detected a significant association between prenatal cannabis use and lower birth size. Moreover, this study identified a relationship between heightened morning sickness severity and higher odds of using cannabis during pregnancy. Findings also suggested that pre-pregnancy and prenatal cannabis use are associated with increasing morning sickness

severity. Given that cannabis may decrease size at birth, pregnant people, and especially those who report morning sickness, should be cautioned against using cannabis during pregnancy until more studies are conducted to establish causality between cannabis use during pregnancy and maternal and infant health outcomes.

REFERENCES

REFERENCES

1. United States. Substance Abuse and Mental Health Data Archive. National Survey on Drug Use and Health. https://rdas.samhsa.gov/#/.

2. Volkow ND, Han B, Compton W, McCance-Katz EF. Self-reported Medical and Nonmedical Cannabis Use Among Pregnant Women in the United States. *JAMA - J Am Med Assoc*. 2019;321(6):607-609. doi:10.1001/jama.2018.20391

3. UNODC. *Drug Market Trends:Cannabis*; 2021. https://www.unodc.org/res/wdr2021/field/WDR21_Booklet_4.pdf%0Ahttps://www.unodc.org/res/wdr2021/field/WDR21_Booklet_3.pdf.

4. National Institute on Drug Abuse. Marijuana Potency. https://www.drugabuse.gov/drug-topics/marijuana/marijuana-potency. Published 2020.

5. Long T, Wagner M, Demske D, Leipe C, Tarasov PE. Cannabis in Eurasia: origin of human use and Bronze Age trans-continental connections. *Veg Hist Archaeobot*. 2017;26(2):245-258. doi:10.1007/s00334-016-0579-6

6. Klimkiewicz A, Jasinska A. *The Health Effects of Cannabis and Cannabinoids*. Vol 15.; 2018. doi:10.17226/24625

7. Lawler A. Oldest evidence of marijuana use discovered in 2500-year-old cemetery in peaks of western China. Science. https://www.science.org/content/article/oldest-evidence-marijuana-use-discovered-2500-year-old-cemetery-peaks-western-china. Published 2019.

8. Zuardi AW. History of cannabis as a medicine: A review. *Rev Bras Psiquiatr*. 2006;28(2):153-157. doi:10.1590/S1516-44462006000200015

9. Russo EB. History of Cannabis as Medicine: Nineteenth Century Irish Physicians and Correlations of Their Observations to Modern Research. In: Chandra S, Lata H, ElSohly MA, eds. *Cannabis Sativa L. - Botany and Biotechnology*. Springer; 2017:63-78.

10. Bridgeman MB, Abazia DT. Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. *Pharmacol Ther*. 2017;42(3):180-188.

11. Pertwee RG. Cannabinoid pharmacology: The first 66 years. *Br J Pharmacol*. 2006;147(SUPPL. 1). doi:10.1038/sj.bjp.0706406

12. Howlett AC, Bidaut-Russell M, Devane WA, Melvin LS, Johnson MR, Herkenham M. The cannabinoid receptor: biochemical, anatomical and behavioral characterization. *Trends Neurosci*. 1990;13(10):420-423. doi:10.1016/0166-2236(90)90124-S

13. Holt S. What is the Endocannabinoid System? 2021. https://www.pbs.org/wgbh/nova/video/endocannabinoid-system/.

14. NOVA. What is the Endocannabinoid System? 2021.

15. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. *Int J Mol Sci*. 2018;19(3). doi:10.3390/ijms19030833

16. Grinspoon P. The Endocannabinoid System: Essential and Mysterious. Harvard Health Publishing. https://www.health.harvard.edu/blog/the-endocannabinoid-system-essential-and-mysterious-202108112569. Published 2021.

17. Dong C, Chen J, Harrington A, Vinod KY, Hegde ML, Hegde VL. Cannabinoid exposure during pregnancy and its impact on immune function. *Cell Mol Life Sci*. 2019;76(4):729-743. doi:10.1007/s00018-018-2955-0

18. Paneth NS. The problem of low birth weight. *Future Child*. 1995;5(1):19-34. doi:10.2307/1602505

19. Centers for Disease Control and Prevention. Preterm Birth. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm. Published 2021.

20. Children's Hospital of Philadelphia. Low Birthweight. https://www.chop.edu/conditions-diseases/low-birthweight. Published 2022.

21. Lubchenco LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated. *Pediatrics*. 1963;32(5):793-800.

22. Hutcheon JA, Zhang X, Cnattingius S, Kramer MS, Platt RW. Customised birthweight percentiles: Does adjusting for maternal characteristics matter? *BJOG An Int J Obstet Gynaecol*. 2008;115(11):1397-1404. doi:10.1111/j.1471-0528.2008.01870.x

23. Talge NM, Mudd LM, Sikorskii A, Basso O. United states birth weight reference corrected for implausible gestational age estimates. *Pediatrics*. 2014;133(5):844-853. doi:10.1542/peds.2013-3285

24. Apgar V. A proposal for a new method of evaluation of the newborn infant. *Anesth Analg*. 2015;120(5):1056-1059. doi:10.1213/ANE.0b013e31829bdc5c

25. The American College of Obstetricians and Gynocologists. Committee Opinion: The Apgar Score. *Obstet Gynecol*. 2015;4(126):1-4. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2015/10/the-apgar-score.

26. Watterberg KL, Aucott S, Benitz WE, et al. The apgar score. *Pediatrics*. 2015;136(4):819-

822. doi:10.1542/peds.2015-2651

27. Apgar V. The newborn (Apgar) scoring system. Reflections and advice. *Pediatr Clin North Am*. 1966;13(3):645-650. doi:10.1016/S0031-3955(16)31874-0

28. Gartner LM, Gartner CB, Gluck L, et al. The care of premature infants: Historical perspectives. *Neonatal Intensive Care A Hist Perspect*. 1992:1-40. http://www.nichd.nih.gov/publications/pubs/neonatal/nic.htm.

29. Rasmussen KM. The "fetal origins" hypothesis: Challenges and opportunities for maternal and child nutrition. *Annu Rev Nutr*. 2001;21(February 2001):73-95. doi:10.1146/annurev.nutr.21.1.73

30. Calkins K, Devaskar S. Fetal origin of adult disease. *Curr Probl Pediatr Adolesc Heal Care*. 2011;41(6):158-176. doi:10.1016/j.cppeds.2011.01.001

31. The American College of Obstetricians and Gynocologists. Marijuana use during pregnancy and lactation. *Obstet Gynecol*. 2017;130(4):e210.

32. Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: A review of the evidence. *Am J Obstet Gynecol*. 2015;213(6):761-778. doi:10.1016/j.ajog.2015.05.025

33. Chabarria KC, Racusin DA, Antony KM, et al. Marijuana use and its effects in pregnancy. *Am J Obstet Gynecol*. 2016;215(4):506.e1-506.e7. doi:10.1016/j.ajog.2016.05.044

34. Ko JY, Tong VT, Bombard JM, Hayes DK, Davy J, Perham-Hester KA. Marijuana use during and after pregnancy and association of prenatal use on birth outcomes: A population-based study. *Drug Alcohol Depend*. 2018;187(November 2017):72-78. doi:10.1016/j.drugalcdep.2018.02.017

35. Klebanoff MA, Wilkins DG, Keim SA. Marijuana Use during Pregnancy and Preterm Birth: A Prospective Cohort Study. *Am J Perinatol*. 2020;1(212). doi:10.1055/s-0040-1708802

36. Crume TL, Juhl AL, Brooks-Russell A, Hall KE, Wymore E, Borgelt LM. Cannabis Use During the Perinatal Period in a State With Legalized Recreational and Medical Marijuana: The Association Between Maternal Characteristics, Breastfeeding Patterns, and Neonatal Outcomes. *J Pediatr*. 2018;197:90-96. doi:10.1016/j.jpeds.2018.02.005

37. El Marroun H, Tiemeier H, Steegers EAP, et al. Intrauterine Cannabis Exposure Affects Fetal Growth Trajectories: The Generation R Study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(12):1173-1181. doi:10.1097/CHI.0b013e3181bfa8ee

38. Corsi DJ, Walsh L, Weiss D, et al. Association between Self-reported Prenatal Cannabis Use and Maternal, Perinatal, and Neonatal Outcomes. *JAMA - J Am Med Assoc*. 2019;322(2):145-152. doi:10.1001/jama.2019.8734

39. Nguyen VH, Harley KG. Prenatal Cannabis Use and Infant Birth Outcomes in the Pregnancy Risk Assessment Monitoring System. *J Pediatr*. 2021:1-7. doi:10.1016/j.jpeds.2021.08.088

40. Kharbanda EO, Vazquez-Benitez G, Kunin-Batson A, Nordin J, Olsen A, Romitti PA. Birth and early developmental screening outcomes associated with cannabis exposure during pregnancy. *J Perinatol*. 2020;40(3):473-480. doi:10.1038/s41372-019-0576-6.

41. Michalski CA, Hung RJ, Seeto RA, et al. Association between maternal cannabis use and birth outcomes: an observational study. *BMC Pregnancy Childbirth*. 2020;20(1):1-9. doi:10.1186/s12884-020-03371-3

42. Lee NM, Saha S. Nausea and Vomiting of Pregnancy. *Gastroenterol Clin North Am*. 2011;40(2):309-334. doi:10.1016/j.gtc.2011.03.009

43. Einarson TR, Piwko C, Koren G. Prevalence of nausea and vomiting of pregnancy in the USA: A meta-analysis. *J Popul Ther Clin Pharmacol*. 2013;20(2):163-170.

44. Bottone-post C. *Nausea and Vomiting of Pregnancy*. Vol 13. Elsevier Inc.; 1966. doi:10.1016/b978-0-12-818902-3.00013-0

45. Body C, Christie JA. Gastrointestinal Diseases in Pregnancy. Nausea, Vomiting, Hyperemesis Gravidarum, Gastroesophageal Reflux Disease, Constipation, and Diarrhea. *Gastroenterol Clin North Am*. 2016;45(2):267-283. doi:10.1016/j.gtc.2016.02.005

46. Bustos M, Venkataramanan R, Caritis S. Nausea and vomiting of pregnancy - What's new? *Auton Neurosci Basic Clin*. 2017;202:62-72. doi:10.1016/j.autneu.2016.05.002

47. Colodro-Conde L, Cross SM, Lind PA, et al. Cohort profile: Nausea and vomiting during pregnancy genetics consortium (NVP Genetics Consortium). *Int J Epidemiol*. 2017;46(2). doi:10.1093/ije/dyv360

48. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: A burden of early pregnancy. *Aust New Zeal J Obstet Gynaecol*. 2000;40(4):397-401. doi:10.1111/j.1479-828X.2000.tb01167.x

49. Mazzotta P, Maltepe C, Navioz Y, Magee LA, Koren G. Attitudes, management and consequences of nausea and vomiting of pregnancy in the United States and Canada. *Int J Gynecol Obstet*. 2000;70(3):359-365. doi:10.1016/S0020-7292(00)00255-1

50. O'Brien B, Naber S. Nausea and Vomiting During Pregnancy: Effects on the Quality of Women's Lives. *Birth*. 1992;19(3):138-143. doi:10.1111/j.1523-536X.1992.tb00671.x

51. Weigel M, Weigel R. Nausea and vomiting of early pregnancy and pregnancy outcome. An epidemiological study. *Br J Obstet Gynaecol*. 1989;96:1304-1311.

52. Tierson F, Olsen C, Hook E. Nausea and Vomiting of Pregnancy and Association with Pregnancy Outcome. *Am J Obstet Gynecol*. 1986;155(5):1017-1022.

53. American Pregnancy Association. What is HCG? 2021. https://americanpregnancy.org/getting-pregnant/hcg-levels/.

54. Goodwin TM, Montoro M, Mestman JH, Perkary AE, Hershman JM. The Role of Chorionic Gonadotropin in Transient Hyperthyroidism of Hyperesmesis Gravidarum. *Trans Assoc Am Physicians*. 1991:233-237.

55. Staneva A, Bogossian F, Pritchard M, Wittkowski A. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review. *Women and Birth*. 2015;28(3):179-193. doi:10.1016/j.wombi.2015.02.003

56. McManis PG, Talley NJ. Nausea and vomiting associated with selective serotonin reuptake inhibitors: Incidence, mechanisms and management. *CNS Drugs*. 1997;8(5):394-401. doi:10.2165/00023210-199708050-00005

57. MacDuffie KE, Kleinhans NM, Stout K, Wilfond BS. Protection versus progress: The challenge of research on cannabis use during pregnancy. *Pediatrics*. 2020;146(August 2020):S93-S98. doi:10.1542/peds.2020-0818R

58. Abalo R, Vera G, López-Pérez AE, Martnez-Villaluenga M, Martín-Fontelles MI. The gastrointestinal pharmacology of cannabinoids: Focus on motility. *Pharmacology*. 2012;90(1-2):1-10. doi:10.1159/000339072

59. Sharkey KA, Darmani NA, Parker LA. Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system. *Eur J Pharmacol*. 2014;722(1):134-146. doi:10.1016/j.ejphar.2013.09.068

60. Izzo AA, Camilleri M. Emerging role of cannabinoids in gastrointestinal and liver diseases: Basic and clinical aspects. *Gut*. 2008;57(8):1140-1155. doi:10.1136/gut.2008.148791

61. Galli JA, Sawaya RA, Friedenberg FK. Cannabinoid Hyperemesis Syndrome. *Curr Drug Abus Rev*. 2011;4(4):241-249.

62. United States Food and Drug Administration. FDA and Cannabis: Research and Drug Approval Process. https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process. Published 2020.

63. Allen JH, De Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: Cyclical hyperemesis in association with chronic cannabis abuse. *Gut*. 2004;53(11):1566-1570. doi:10.1136/gut.2003.036350

64. Creedon ES, Maloy MK, DelloStritto RA. Cannabinoid hyperemesis syndrome: A case

study and discussion. *J Am Assoc Nurse Pract*. 2020;32(3):269-276. doi:10.1097/JXX.0000000000000215

65. Heard K, Marlin MB, Nappe T, Hoyte CO. Common marijuana-related cases encountered in the emergency department. *Am J Heal Pharm*. 2017;74(22):1904-1908. doi:10.2146/ajhp160715

66. Barbosa-Leiker C, Burduli E, Smith CL, Brooks O, Orr M, Gartstein M. Daily Cannabis Use During Pregnancy and Postpartum in a State With Legalized Recreational Cannabis. *J Addict Med*. 2020;00(00):1. doi:10.1097/adm.0000000000000625

67. Chang JC, Tarr JA, Holland CL, et al. Beliefs and attitudes regarding prenatal marijuana use: Perspectives of pregnant women who report use. *Drug Alcohol Depend*. 2019;196(May 2018):14-20. doi:10.1016/j.drugalcdep.2018.11.028

68. Mark K, Gryczynski J, Axenfeld E, Schwartz RP, Terplan M. Pregnant Women's Current and Intended Cannabis Use in Relation to Their Views Toward Legalization and Knowledge of Potential Harm. *J Addict Med*. 2017;11(3):211-216. doi:10.1097/ADM.0000000000000299

69. The American College of Obstetricians and Gynocologists. Nausea and Vomiting of Pregnancy. *Obstet Gynecol*. 2018;131(1):190-193.

70. Westfall RE, Janssen PA, Lucas P, Capler R. Survey of medicinal cannabis use among childbearing women. *Complement Ther Clin Pract*. 2006;12(1):27-33. doi:10.1016/j.ctcp.2005.09.006

71. Roberson EK, Patrick WK, Hurwitz EL. Marijuana use and maternal experiences of severe nausea during pregnancy in Hawai'i. *Hawaii J Med Public Health*. 2014;73(9):283-287.

72. Young-Wolff KC, Sarovar V, Tucker L-Y, Avalos LA, Armstrong MA, Goler N. Association of Nausea and Vomiting in Pregnancy With Prenatal Marijuana Use. *JAMA Intern Med*. 2018;178(10):1423-1424.

73. Metz TD, Allshouse AA, McMillin GA, Silver RM, Jarlenski MP. Association of Marijuana Use with Nausea and Vomiting of Pregnancy. *Am J Obstet Gynecol*. 2022;226(1):S22-S23. doi:10.1016/j.ajog.2021.11.082

74. Ko JY, Coy KC, Haight SC, et al. Characteristics of Marijuana Use During Pregnancy — Eight States, Pregnancy Risk Assessment Monitoring System, 2017. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1058-1063. doi:10.15585/mmwr.mm6932a2

75. Nashed MG, Hardy DB, Laviolette SR. Prenatal Cannabinoid Exposure: Emerging Evidence of Physiological and Neuropsychiatric Abnormalities. *Front Psychiatry*. 2021;11(January):1-10. doi:10.3389/fpsyt.2020.624275

76. Congressional Research Service. The Evolution of Marijuana as a Controlled Substance and the Federal-State Policy Gap. 2022. https://crsreports.congress.gov.

77. Friedrich J, Khatib D, Parsa K, Santopietro A, Gallicano GI. The grass isn't always greener: The effects of cannabis on embryological development. *BMC Pharmacol Toxicol*. 2016;17(1):1-13. doi:10.1186/s40360-016-0085-6

78. Sosinsky A. The Effects of Marijuana on Fetal Development. MGH Center for Women's Mental Health. https://womensmentalhealth.org/posts/effects-marijuana-embryo-development/. Published 2017.

79. Alshaarawy O, Anthony JC. Cannabis use among women of reproductive age in the United States: 2002–2017. *Addict Behav*. 2019;99(May):106082. doi:10.1016/j.addbeh.2019.106082

80. Biegon A, Kerman IA. Autoradiographic study of pre- and postnatal distribution of cannabinoid receptors in human Brain. *Neuroimage*. 2001;14(6):1463-1468. doi:10.1006/nimg.2001.0939

81. Pereira PP da S, Da Mata FAF, Figueiredo ACG, de Andrade KRC, Pereira MG. Maternal active smoking during pregnancy and low birth weight in the americas: A systematic review and meta-analysis. *Nicotine Tob Res*. 2017;19(5):497-505. doi:10.1093/ntr/ntw228

82. Solomon L, Oncken C. Maternal Smoking and Its Association With Birth Weight Related papers Nicot ine Gum for Pregnant Smokers A Randomized Cont rolled Trial. 2005.

83. Murin S, Rafii R, Bilello K. Smoking and Smoking Cessation in Pregnancy. *Clin Chest Med*. 2011;32(1):75-91. doi:10.1016/j.ccm.2010.11.004

84. Massachusetts Department of Public Health. Smoking and Pregnancy. *N Engl J Med*. 1978;298(6):2020.

85. Nykjaer C, Alwan NA, Greenwood DC, et al. Maternal alcohol intake prior to and during pregnancy and risk of adverse birth outcomes: Evidence from a british cohort. *J Epidemiol Community Health*. 2014;68(6):542-549. doi:10.1136/jech-2013-202934

86. Virji SK. The relationship between alcohol consumption during pregnancy and infant birthweight: An epidemiologic study. *Acta Obstet Gynecol Scand*. 1991;70(4-5):303-308. doi:10.3109/00016349109007877

87. Child Health Advances from Research with Mothers. About CHARM. 2020. https://www.epi.msu.edu/charmstudy/about.

88. Sauzet O, Ofuya M, Peacock JL. Dichotomisation using a distributional approach when the outcome is skewed. *BMC Med Res Methodol*. 2015;15(1). doi:10.1186/s12874-015-0028-8

89. Sauzet O, Peacock JL. Binomial outcomes in dataset with some clusters of size two: Can the dependence of twins be accounted for? A simulation study comparing the reliability of statistical methods based on a dataset of preterm infants. *BMC Med Res Methodol*. 2017;17(1):1-13. doi:10.1186/s12874-017-0369-6

90. Schreiber-Gregory D, Bader K. Logistic and Linear Regression Assumptions: Violation Recognition and Control. *Midwest SAS User Gr*. 2018;(May):1-21. https://www.lexjansen.com/wuss/2018/130_Final_Paper_PDF.pdf.

91. Weng YH, Yang CY, Chiu YW. Risk assessment of adverse birth outcomes in relation to maternal age. *PLoS One*. 2014;9(12):1-16. doi:10.1371/journal.pone.0114843

92. Cleary-Goldman J, Malone FD, Vidaver J, et al. Impact of maternal age on obstetric outcome. *Obstet Gynecol*. 2005;105(5):983-990. doi:10.1097/01.AOG.0000158118.75532.51

93. Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH. Maternal age and adverse pregnancy outcome: A cohort study. *Ultrasound Obstet Gynecol*. 2013;42(6):634-643. doi:10.1002/uog.12494

94. Da Silva AAM, Simões VMF, Barbieri MA, et al. Young maternal age and preterm birth. *Paediatr Perinat Epidemiol*. 2003;17(4):332-339. doi:10.1046/j.1365-3016.2003.00515.x

95. Campbell EE, Gilliland J, Dworatzek PDN, De Vrijer B, Penava D, Seabrook JA. Socioeconomic status and adverse birth outcomes: A population-based Canadian sample. *J Biosoc Sci*. 2018;50(1):102-113. doi:10.1017/S0021932017000062

96. Luo ZC, Wilkins R, Kramer MS. Effect of neighbourhood income and maternal education on birth outcomes: A population-based study. *Cmaj*. 2006;174(10):1415-1420. doi:10.1503/cmaj.051096

97. Cantarutti A, Franchi M, Monzio Compagnoni M, Merlino L, Corrao G. Mother's education and the risk of several neonatal outcomes: An evidence from an Italian population-based study. *BMC Pregnancy Childbirth*. 2017;17(1):1-10. doi:10.1186/s12884-017-1418-1

98. Dominguez TP. Race, racism, and racial disparities in adverse birth outcomes. *Clin Obstet Gynecol*. 2008;51(2):360-370. doi:10.1097/GRF.0b013e31816f28de

99. Ely DM, Driscoll AK. Infant mortality in the United States, 2018: Data from the period linked birth/infant death file. *Natl Vital Stat Reports*. 2020;69(7):1-17.

100. Slaughter-Acey JC, Sealy-Jefferson S, Helmkamp L, et al. Racism in the form of micro aggressions and the risk of preterm birth among black women. *Ann Epidemiol*. 2016;26(1):7-13. doi:10.1016/j.annepidem.2015.10.005

101. Kothari CL, Paul R, Dormitorio B, et al. The interplay of race, socioeconomic status and neighborhood residence upon birth outcomes in a high black infant mortality community. *SSM - Popul Heal*. 2016;2(April):859-867. doi:10.1016/j.ssmph.2016.09.011

102. Bower KM, Geller RJ, Perrin NA, Alhusen J. Experiences of Racism and Preterm Birth: Findings from a Pregnancy Risk Assessment Monitoring System, 2004 through 2012. *Women's Heal Issues*. 2018;28(6):495-501. doi:10.1016/j.whi.2018.06.002

103. SAMSHA. Racial / Ethnic Differences in Substance Use , Substance Use Disorders , and Substance Use Treatment Utilization among People Aged 12 or Older. 2021.

104. Shapiro C, Sutija VG, Bush J. Effect of maternal weight gain on infant birth weight. *J Perinat Med*. 2000;28(6):428-431. doi:10.1515/JPM.2000.056

105. Li N, Liu E, Guo J, et al. Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes. *PLoS One*. 2013;8(12). doi:10.1371/journal.pone.0082310

106. Lima RJCP, Batista RFL, Ribeiro MRC, et al. Prepregnancy body mass index, gestational weight gain, and birth weight in the BRISA cohort. *Rev Saude Publica*. 2018;52:1-10. doi:10.11606/S1518-8787.2018052000125

107. Alshaarawy O, Anthony JC. Are cannabis users less likely to gain weight? Results from a national 3-year prospective study. *Int J Epidemiol*. 2019;48(5):1695-1700. doi:10.1093/ije/dyz044

108. Hayatbakhsh MR, O'Callaghan MJ, Mamun AA, Williams GM, Clavarino A, Najman JM. Cannabis use and obesity and young adults. *Am J Drug Alcohol Abuse*. 2010;36(6):350-356. doi:10.3109/00952990.2010.500438

109. Windham GC, Hopkins B, Fenster L, Swan SH. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. *Epidemiology*. 2000;11(4):427-433. doi:10.1097/00001648-200007000-00011

110. Bernstein IM, Mongeon JA, Badger GJ, Solomon L, Heil SH, Higgins ST. Maternal smoking and its association with birth weight. *Obstet Gynecol*. 2005;106(5):986-991. doi:10.1097/01.AOG.0000182580.78402.d2

111. NIDA. Marijuana drug use increasing during pregnancy. National Institute on Drug Abuse. https://nida.nih.gov/news-events/science-highlight/marijuana-drug-use-increasing-during-pregnancy. Published 2018.

112. Passey ME, Sanson-Fisher RW, D'Este CA, Stirling JM. Tobacco, alcohol and cannabis use during pregnancy: Clustering of risks. *Drug Alcohol Depend*. 2014;134(1):44-50. doi:10.1016/j.drugalcdep.2013.09.008

113. Ramo DE, Delucchi KL, Hall SM, Liu H, Prochaska JJ. Marijuana and tobacco co-use in

young adults: Patterns and thoughts about use. *J Stud Alcohol Drugs*. 2013;74(2):301-310. doi:10.15288/jsad.2013.74.301

114. Koto P, Allen VM, Fahey J, Kuhle S. Maternal cannabis use during pregnancy and maternal and neonatal outcomes: A retrospective cohort study. *BJOG An Int J Obstet Gynaecol*. 2022;(January):1-8. doi:10.1111/1471-0528.17114

115. Sturrock S, Williams E, Ambulkar H, Dassios T, Greenough A. Maternal smoking and cannabis use during pregnancy and infant outcomes. *J Perinat Med*. 2020;48(2):168-172. doi:10.1515/jpm-2019-0422

116. Malik S, Cleves MA, Zhao W, Correa A, Hobbs, Charlotte A. Association Between Congenital Heart Defects and Small for Gestational Age. *Pediatrics119*. 2007:e976-e982.

117. Nordman H, Jääskeläinen J, Voutilainen R. Birth Size as a Determinant of Cardiometabolic Risk Factors in Children. *Horm Res Paediatr*. 2020;93(3):144-153. doi:10.1159/000509932

118. Lundgren EM, Tuvemo T. Effects of being born small for gestational age on long-term intellectual performance. *Best Pract Res Clin Endocrinol Metab*. 2008;22(3):477-488. doi:10.1016/j.beem.2008.01.014

119. Day N, Cornelius M, Goldschmidt L, Richardson G, Robles N, Taylor P. The effects of prenatal tobacco and marijuana use on offspring growth from birth through 3 years of age. *Neurotoxicol Teratol*. 1992;14(6):407-414. doi:10.1016/0892-0362(92)90051-B

120. Wilcox AJ. On the importance-and the unimportance-of birthweight. *Int J Epidemiol*. 2001;30(6):1233-1241. doi:10.1093/ije/30.6.1233

121. Altman DG, Royston P. The cost of dichotomising continuous variables. *Br Med J*. 2006;332(7549):1080. doi:10.1136/bmj.332.7549.1080

122. Ethical considerations for including women as research participants. *Obstet Gynecol*. 2015;126(5):e100-e107. doi:10.1542/peds.2015-3990

123. Skelton KR, Donahue E, Benjamin-Neelon SE. Validity of self-report measures of cannabis use compared to biological samples among women of reproductive age: a scoping review. *BMC Pregnancy Childbirth*. 2022;22(1):1-16. doi:10.1186/s12884-022-04677-0

124. Reeves S, Bernstein I. Effects of maternal tobacco-smoke exposure on fetal growth and neonatal size. *Expert Rev Obstet Gynecol*. 2008;3(6):719-730. doi:10.1586/17474108.3.6.719

125. Dickson B, Mansfield C, Guiahi M, et al. Recommendations from cannabis dispensaries about first-trimester cannabis use. *Obstet Gynecol*. 2018;131(6):1031-1038.

doi:10.1097/AOG.0000000000002619

126. Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk - PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. *Am J Obstet Gynecol*. 2002;186(5):228-231. doi:10.1067/mob.2002.123054

127. Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and Vomiting of Pregnancy: Using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) Scale. *J Obstet Gynaecol Canada*. 2009;31(9):803-807. doi:10.1016/S1701-2163(16)34298-0

128. Lacasse A, Rey E, Ferreira E, Morin C, Bérard A. Epidemiology of nausea and vomiting of pregnancy: Prevalence, severity, determinants, and the importance of race/ethnicity. *BMC Pregnancy Childbirth*. 2009;9:1-9. doi:10.1186/1471-2393-9-26

129. Louik C, Hernandez-Diaz S, Werler MM, Mitchell AA. Nausea and vomiting in pregnancy: Maternal characteristics and risk factors. *Paediatr Perinat Epidemiol*. 2006;20(4):270-278. doi:10.1111/j.1365-3016.2006.00723.x

130. Weigel MM, Weigel RM. The association of reproductive history, demographic factors, and alcohol and tobacco consumption with the risk of developing nausea and vomiting in early pregnancy. *Am J Epidemiol*. 1988;127(3):562-570. doi:10.1093/oxfordjournals.aje.a114831

131. Young-Wolff KC, Sarovar V, Tucker LY, et al. Trends in marijuana use among pregnant women with and without nausea and vomiting in pregnancy, 2009–2016. *Drug Alcohol Depend*. 2019;196(October 2018):66-70. doi:10.1016/j.drugalcdep.2018.12.009

132. Chan RL, Olshan AF, Savitz DA, et al. Maternal Influences on Nausea and Vomiting in Early Pregnancy. *Matern Child Heal J*. 2011;15(1):122-127.

133. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: A prospective study of its frequency, intensity, and patterns of change. *Am J Obstet Gynecol*. 2000;182(4):931-937. doi:10.1016/S0002-9378(00)70349-8

134. Coronado PJ, Fasero M, Álvarez-Sánchez Á, Rey E. Prevalence and persistence of nausea and vomiting along the pregnancy. *Rev Esp Enfermedades Dig*. 2014;106(5):318-324.

135. Hasin DS, Shmulewitz D, Sarvet AL. Time trends in US cannabis use and cannabis use disorders overall and by sociodemographic subgroups: a narrative review and new findings. *Am J Drug Alcohol Abuse*. 2019;45(6):623-643. doi:10.1080/00952990.2019.1569668

136. Ben-aroya Z, Lurie S, Segal D. Association of nausea and vomiting in pregnancy with lower body mass index. 2005;118:196-198. doi:10.1016/j.ejogrb.2004.04.026

137. Källen B, Lundberg G, Åberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. *Acta Obstet Gynecol Scand*. 2003;82(10):916-920. doi:10.1034/j.1600-0412.2003.00307.x

138. Little RE, Hook EB. Maternal alcohol and tobacco consumption and their association with nausea and vomiting during pregnancy. *Acta Obstet Gynecol Scand*. 1979;58(1):15-17. doi:10.3109/00016347909154905

139. Society for Endocrinology. Link found between morning sickness, smoking and healthy pregnancies.

140. Agrawal A, Budney AJ, Lynskey MT. The Co-occurring Use and Misuse of Cannabis and Tobacco: A Review. *Addiction*. 2012;107(7):1221-1233.

141. Tucker JS, Pedersen ER, Seelam R, Dunbar MS, Shih RA, D'Amico EJ. Types of Cannabis and Tobacco/Nicotine Co-Use and Associated Outcomes in Young Adulthood. *Psychol Addict Behav*. 2019;33(4):401-411. doi:10.1037/adb0000464

142. Akbar SA, Tomko RL, Salazar CA, Squeglia LM, McClure EA. Tobacco and cannabis co-use and interrelatedness among adults. *Addict Behav*. 2019;(90):354-361.

143. Coleman-Cowger VH, Oga EA, Peters EN, Mark K. Prevalence and associated birth outcomes of co-use of Cannabis and tobacco cigarettes during pregnancy. *Neurotoxicol Teratol*. 2018;68(June):84-90. doi:10.1016/j.ntt.2018.06.001

144. Crume TL, Juhl AL, Brooks-Russell A, Hall KE, Wymore E, Borgelt LM. Cannabis Use During the Perinatal Period in a State With Legalized Recreational and Medical Marijuana: The Association Between Maternal Characteristics, Breastfeeding Patterns, and Neonatal Outcomes. *J Pediatr*. 2018;197:90-96. doi:10.1016/j.jpeds.2018.02.005

145. Gunn JKL, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open*. 2016;6(4):1-8. doi:10.1136/bmjopen-2015-009986

146. Jarlenski M, Tarr JA, Holland CL, Farrell D, Chang JC, Sciences R. Pregnant women's access to information about perinatal marijuana use: A qualitative study. *Womens Heal Issues*. 2016;26(4):452-459. doi:10.1016/j.whi.2016.03.010

147. Holland CL, Nkumsah MA, Morrison P, et al. "Anything above marijuana takes priority": Obstetric providers' attitudes and counseling strategies regarding perinatal marijuana use. *Patient Educ Couns*. 2016;99(9):1446-1451. doi:10.1016/j.pec.2016.06.003

148. Young-Wolff KC, Gali K, Sarovar V, Rutledge GW, Prochaska JJ. Women's Questions about Perinatal Cannabis Use and Health Care Providers' Responses. *J Women's Heal*. 2020;29(7):919-926. doi:10.1089/jwh.2019.8112

149. Tram Anh H N, Melissa C P. Cannabinoid Hyperemesis Syndrome in Pregnancy: A Case Report and Treatment Overview. *J Clin Gastroenterol Treat*. 2019;5(2):1-6. doi:10.23937/2469-584x/1510069

150. Kim HG, Moon J, Dixon H, Tullar P. Recurrent Nausea and Vomiting in a Pregnant Woman with Chronic Marijuana Use. *Case Rep Obstet Gynecol*. 2018;2018(Iv):1-3. doi:10.1155/2018/9746062

151. Alaniz VI, Liss J, Metz TD, Stickrath E. Cannabinoid hyperemesis syndrome: A cause of refractory nausea and vomiting in pregnancy. *Obstet Gynecol*. 2015;125(6):1484-1486. doi:10.1097/AOG.0000000000000595

152. Health U. In Utero Exposure to Extreme Morning Sickness May Harm Offspring. U Magazine. https://www.uclahealth.org/u-magazine/in-utero-exposure-to-extreme-morning-sickness-may-harm-offspring. Published 2015.

153. Ng JH, Rice KK, Ananth C V., Brandt JS. Attitudes about marijuana use, potential risks, and legalization: a single-center survey of pregnant women. *J Matern Neonatal Med*. 2020;0(0):1-9. doi:10.1080/14767058.2020.1858279

154. Metz TD, Allshouse AA, Hogue CJ, et al. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. *Am J Obstet Gynecol*. 2017;217(4):478.e1-478.e8. doi:10.1016/j.ajog.2017.05.050

155. Volkow ND, Compton WM, Wargo EM. The risks of marijuana use during pregnancy. *JAMA*. 2017;317(2):129-130.

156. Bauer AZ, Swan SH, Kriebel D, et al. Paracetamol use during pregnancy — a call for precautionary action. *Nat Rev Endocrinol*. 2021;17(12):757-766. doi:10.1038/s41574-021-00553-7