THE EFFECT OF PRENATAL MARIJUANA EXPOSURE ON OFFSPRING MARIJUANA USE AND CANNABIS USE DISORDER IN YOUNG ADULTHOOD

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ABSTRACT

Marijuana is the most commonly-used illicit substance among pregnant women. Few studies have been conducted on the long-term effects of prenatal marijuana exposure (PME) on offspring. This dissertation examines the association between PME and offspring marijuana use and cannabis use disorder (CUD) in young adulthood.

First, the association between PME and offspring frequency of marijuana use at 22 years of age was evaluated. PME was defined as a continuous measure of the average daily joints and frequency of use by the offspring was defined as no use, using less than three times per week, and using three times per week or more. An ordinal logistic regression model was used. Results showed that PME was initially significant but this association was attenuated to non-significance after adjusting for covariates. Childhood maltreatment, but not race or gender, moderated the association between PME and offspring use. PME was associated with offspring frequency of use at low levels of childhood maltreatment, but not at high levels of childhood maltreatment.

Second, a path analysis was used to evaluate pathways from PME to frequency of marijuana use in offspring. Results showed a significant indirect path through early initiation of marijuana. There was also a significant indirect path through depressive symptoms and early initiation of marijuana. In addition, PME predicted early marijuana initiation but maternal marijuana use during the offspring's childhood did not.

Third, a path analysis was used to evaluate pathways from PME to CUD. Results showed a significant indirect path of PME on CUD through early initiation of marijuana. There was also a significant indirect path of PME on CUD through depressive symptoms in childhood and early initiation of marijuana.

In summary, PME may create a biologic vulnerability in offspring. In addition, aspects of the offspring's environment also contribute to marijuana use and CUD in young adulthood. The findings of this dissertation are significant to public health. Healthcare professionals should encourage pregnant women to abstain from marijuana and public health programs should target youth to delay marijuana initiation.

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PREFACE

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1.0 INTRODUCTION

1.1 OVERVIEW OF CANNABIS AND ITS EFFECTS ON DEVELOPMENT

1.1.1 Cannabis and its consumption

Cannabis is an illicit substance made from the *Cannabis sativa* plant (Leung, 2011). There are several types of preparations, with most derived from the female plant (Hall & Solowij, 1998). The herbal form, marijuana, is a dried mixture of the stems, seeds, leaves, and flowers of the plant (National Institute on Drug Abuse [NIDA], 2012b). Hashish or hash is a resin created from pressing the resin glands from unfertilized buds of the plant (United Nations Office on Drugs and Crime [UNODC], 2012). Finally, cannabis and hash oils are the concentrated extract of the plant in liquid or semi-liquid form (Mehmedic et al., 2010; UNODC, 2012).

Cannabis is most commonly smoked in a cigarette, pipe, or blunt (Hazekamp, Bastola, Rashidi, Bender, & Verpoorte, 2007; NIDA, 2012b). It can also be consumed by inhaling a vaporized preparation, drinking it as a brewed tea, or eating it in prepared food (Hazekamp et al., 2007; NIDA, 2012b).

1.1.2 Prevalence of cannabis use

Cannabis is the most commonly used illicit substance in the world (UNODC, 2012). Annual prevalence estimates from the World Health Organization (WHO) demonstrate that among those 15-64 years of age there are between 119-224 million cannabis users, representing 2.5%-5% of the world's population (UNODC, 2012). In the US, the Substance Abuse and Mental Health Services Administration (SAMHSA) collects annual prevalence estimates about cannabis use through the National Survey on Drug Use and Health (NSDUH). In 2011, approximately 18.1 million people, or 7% of the US population ages 12 years and older, reported using marijuana in the past month (Substance Abuse and Mental Health Services Administration [SAMHSA], 2012a).

1.1.3 Definition and prevalence of Cannabis Use Disorder

Cannabis Use Disorder (CUD) is defined using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (WHO, 2012; American Psychiatric Association [APA], 2000). The DSM-IV-TR makes a distinction between substance abuse and dependence and these definitions are mutually exclusive (Appendix, Table 9). To be diagnosed with abuse, individuals must have experienced at least one of the criteria from the DSM-IV-TR within the past 12 months, and they cannot have met the criteria for dependence in the past (APA, 2000). To be diagnosed with dependence, individuals must have experienced at least three of the criteria from the DSM-IV-TR within the past 12 months (APA, 2000).

US national surveys provide estimates about the prevalence of CUD. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) conducted from 2001-2002 demonstrated that the past-year prevalence of CUD was 1.5%, with 1.1% experiencing abuse and 0.4% experiencing dependence (Stinson, Ruan, Pickering, & Grant, 2006). The National Survey on Drug Use and Health (NSDUH) provides a past-year CUD estimate that combines abuse and dependence. For nearly a decade, CUD rates have remained relatively stable. The past-year prevalence rate in 2012 was 1.7%, representing 4.3 million people (SAMHSA, 2013).

Survey findings on lifetime history of CUD are sparse. The National Comorbidity Survey conducted from 1990-1992 demonstrated that 4.2% had a lifetime diagnosis of cannabis dependence (Anthony, Warner, & Kessler, 1994). Ten years later, the NESARC data demonstrated that 8.5% had lifetime CUD, with 7.2% experiencing abuse and 1.3% experiencing dependence (Stinson, Ruan, Pickering, & Grant, 2006).

1.2 FACTORS ASSOCIATED WITH CANNABIS USE AND CANNABIS USE DISORDER

Many factors are associated with cannabis initiation, use, and CUD. This section summarizes demographic and risks factors identified in the literature.

1.2.1 Demographic factors

Age, gender, socioeconomic status (SES), and race are used to describe individuals who initiate and continue to use marijuana and have a CUD diagnosis. According to the 2012 NSDUH findings, the average age of first use among recent initiates ages 12-49 was 17.9 years (SAMHSA, 2013). This age of marijuana initiation has remained relatively stable over the past ten years (SAMSHA, 2013). Marijuana use is highest between ages 15-30 and use declines after that time (Sundram, 2006). Age of initiation is a risk factor for cannabis dependence (Chen, O'Brien, & Anthony, 2005). Those who initiate cannabis at an early age are more likely to be diagnosed with a CUD later in life. Additionally, CUD onset is more likely to occur among individuals less than 30 years of age (Stinson, Ruan, Pickering, & Grant, 2006).

The literature offers conflicting evidence about gender differences in marijuana initiation. Some studies report that males initiate earlier and others report no significant difference between the sexes (Day, Goldschmidt, & Thomas, 2006; D. B. Kandel & Chen, 2000; Korhonen et al., 2008; Porath & Fried, 2005; Richardson, Larkby, Goldschmidt & Day, 2013). Marijuana use estimates are higher for men compared to women. Recent findings from the NSDUH indicate that among persons aged 12-17, the percentage of users is higher for males compared to females but the gap is narrowing (SAMSHA, 2013). Both the US National Longitudinal Alcohol Epidemiologic Survey (NLAES) conducted from 1991-1992 and NESARC surveys indicate a difference in sex with males having higher rates of CUDs than women. The estimates for abuse were 1.9% for males and 0.6% for females in the NLAES, and 2.2% for males and 0.8% for females in the NESARC (Compton et al., 2004). Further, male gender was a significant predictor of use and CUD in longitudinal studies (Hayatbakhsh, Najman, Bor, O'Callaghan, & Williams, 2009; Perkonigg et al., 2008; von Sydow et al., 2001).

Studies evaluating socioeconomic status (SES) as a predictor of marijuana initiation, use, and CUD also offer conflicting results. In a recent review article, Hanson and Chen (2007) evaluated 25 studies of Western samples of youth and concluded that SES was not related to use during adolescence. Chen and colleagues (2005) and Stinson and colleagues (2006) found that low SES was associated with CUD when analyzing data from US populations. However, authors evaluating data from an Australian birth cohort concluded that SES in adolescence was not associated with use and CUD in young adulthood (Hayatbakhsh et al., 2009).

Race was not identified as a significant predictor of marijuana initiation in two US birth cohorts (Day et al., 2006; Richardson et al., 2013). However, racial and ethnic differences have been reported with marijuana use. In an analysis of the Monitoring the Future (MTF) data, a study of middle and high school student use, Wallace and colleagues (2003) found use was highest among Native Americans, followed by Hispanics, whites, and blacks. Use was lowest among Asian-Americans. Racial and ethnic differences associated with CUD have been changing. Results from the NLAES conducted from 1991-1992 showed that whites had the highest prevalence of CUD, followed by blacks, and then Hispanics at 0.6% (Compton et al., 2004). In the US National Household Survey on Drug Abuse conducted in 2000-2001, Chen and colleagues (2005) concluded there were no differences by race. Findings from the NESARC indicate that blacks had the highest prevalence of CUD, followed by whites, and then Hispanics (Compton et al., 2004). Most recently, analyses of survey data from the NSDUH also suggest that CUD is more common among African-Americans (Pacek, Malcolm, & Martins, 2012). Therefore, surveys from the past several years indicated that CUD diagnosis among minority populations is on the rise.

1.2.2 Risk factors

Numerous risk factors for marijuana initiation, use, and CUD have been identified in cross-sectional and longitudinal studies. Here we have categorized findings according to psychosocial factors, influences from the home environment, the influence of peers, the use of licit and illicit substances, genetics and family history, and prenatal substance exposure.

Psychosocial characteristics are associated with marijuana initiation, use, and CUD. Predictors of initiation include antisocial behavior, depressive symptoms, and aggression in childhood, as well as having low school aspirations (Coffey, Lynskey, Wolfe, & Patton, 2000; Miller & Miller, 1997; Day et al., 2006; Hayatbakhsh et al., 2008). Factors associated with use included having antisocial personality diagnosis, low self-competence, distressing life events, a history of sexual abuse, having a high number of symptoms of depression and anxiety, aggressive and delinquent behavior, and breaking rules at school (Hayatbakhsh et al., 2009; Perkonigg et al., 2008). Factors associated with CUD included a history of sexual abuse, self-reported below-average school performance, aggressive and delinquent behavior, breaking rules at school, having frequent arguments with a partner, psychological symptoms, having violence directed toward the individual, and expressing violence toward others (Brook, Lee, Finch, Koppel, & Brook, 2011; Hayatbakhsh et al., 2009).

Parental supervision and control predicted marijuana initiation in adolescence (Hayatbakhsh et al., 2008; Richardson et al., 2013). Being born to a teenage mother was also identified as a risk factor (Hayatbakhsh et al., 2008). Factors associated with marijuana use include leaving the family home before the age of 18, family conflict, change in mother's marital status, and maternal smoking when the offspring was an adolescent (Day et al., 2006; Hayatbakhsh et al., 2008; Hayatbakhsh et al., 2009; von Sydow, Lieb, Pfister, Hofler, &

Wittchen, 2002). Further, maternal use of marijuana when the offspring were adolescents predicted frequency of offspring marijuana use (Day et al., 2006). In addition to the change in mother's marital status and maternal smoking when the offspring was an adolescent, parental death before the age of 15 is a risk factor for cannabis dependence (Hayatbakhsh et al., 2009; von Sydow et al., 2002).

Cannabis use school-wide and peer use are predictors of marijuana initiation (Coffey et al., 2000; Miller & Miller, 1997). Individuals who report that they have more than one peer who used marijuana are more likely to use marijuana (Perkonigg et al., 2008). Individuals with a CUD are more likely to report associating with peers who display deviant behavior and peers who used drugs (Brook et al., 2011).

Historically, the initiation of tobacco and alcohol has been shown to occur before the initiation of marijuana (D. Kandel & Faust, 1975). Recent studies on adolescents and adults have supported that the use of other substances often precedes marijuana initiation. For example, alcohol consumption and daily cigarette smoking predict marijuana initiation (Coffey et al., 2000). Smoking cigarettes and alcohol use by age 14 are predictors of marijuana use and CUD (Hayatbakhsh et al., 2009). Finally, the use of other illicit substances has been shown to significantly predict cannabis dependence (von Sydow et al., 2002).

A family history of drug and alcohol problems is associated with marijuana initiation (Day et al., 2006; Richardson et al., 2013). Parental history of substance use and problematic substance use are associated with marijuana use (von Sydow et al., 2002). Self-reported family history measures are often seen in the literature because published findings on genetic influences are limited. The heritability is between 0.13 and 0.72 for cannabis initiation (Vink, Wolters, Neale, & Boomsma, 2010), between 0.17 to 0.67 for cannabis use, and between 0.45 to 0.78 for

CUD (Agrawal & Lynskey, 2006). Considering the wide range of these heritability estimates, additional research is needed to clarify genetic and environmental influences.

Finally, few studies have published findings on prenatal exposures as predictors of offspring cannabis initiation, use, and CUD. Prenatal marijuana exposure (PME) predicted offspring initiation of marijuana and frequency of marijuana use in adolescent offspring (Day et al., 2006; Porath & Fried, 2005). Prenatal exposure to tobacco also predicted offspring initiation of marijuana in two US birth cohorts (Day et al., 2006; Richardson et al., 2013). To date, there are no published findings on PME as a predictor of CUD.

In summary, many factors are associated with marijuana initiation, use, and CUD. The variability of factors identified in the literature suggests that there are many pathways to substance use and disordered use that are important to evaluate in this dissertation.

1.3 OVERVIEW OF THE ENDOGENOUS CANNABINOID SYSTEM

There are nearly 60 cannabinoids in the *Cannabis sativa* plant (Gomez-Ruiz, Hernandez, de Miguel, & Ramos, 2007). The cannabinoid Delta-9-tetrahydrocannabinol (THC) is the main psychoactive ingredient in marijuana (National Institute on Drug Abuse, 2012c). When marijuana is consumed, THC enters the blood stream and interacts with the endocannabinoid system (ECS).

The ECS is a lipid signaling system located throughout the body (Rodriguez de Fonseca et al., 2005). This signaling system has several main roles: stress response and recovery in which endocannabinoids return the body to a level of homeostasis by working through the endocrine and nervous systems; control of energy by regulating food intake and how it is used in

the body; immune regulation and inflammatory responses; and reproduction (Castillo, Younts, Chavez, & Hashimotodani, 2012; Fride, 2004; Hillard, Weinlander, & Stuhr, 2012; Tasker, 2004). Here we describe two main components of the ECS: endocannabinoids and cannabinoid receptors (Fride, 2008; Gomez-Ruiz et al., 2007).

To date, five endocannabinoids or endogenous ligands have been identified as part of the ECS. These are: arachidonoyl ethanol amide (anandamide or AEA), 2-arachidonoyl glycerol (2-AG), noladin ether (2-arachidonyl glycerol ether), arachidonoyl dopamine (NADA), and virodhamine (Gomez-Ruiz et al., 2007; Jutras-Aswad, DiNieri, Harkany, & Hurd, 2009).

AEA and 2-AG were the first endocannabinoids identified and have been studied in greater detail than the others (Fride, 2002; Gomez-Ruiz et al., 2007). They are produced by the body and released on demand, but the mechanism for how this is done is not fully understood (Pazos, Nunez, Benito, Tolon, & Romero, 2005). AEA release is initiated by rises in Ca2+ (calcium ion) or by the activation of neurotransmitter receptors, specifically dopamine (Freund, Katona, & Piomelli, 2003).

When endocannabinoids are released, they activate the cannabinoid receptors. To date, two cannabinoid receptors have been identified: CB1 and CB2 (Jutras-Aswad et al., 2009). CB1 receptors are present in the reproductive, immune, and digestive systems and are abundant in the brain (Fride, 2004; Jutras-Aswad et al., 2009). There is a high concentration of CB1 receptors in the hippocampus, basal ganglia, and cerebellum, which are associated with learning and forming memories, affect, and generating and controlling movement (Fride, 2002; Jutras-Aswad et al., 2009; Strick, Dum, & Fiez, 2009; Sundram, 2006). There is a moderate concentration of CB1 receptors in the cerebral cortex and nucleus accumbens, which are associated with cognition, attention, and reward and effort-based functions (Jutras-Aswad et al., 2009; Salamone, Correa,

Farrer, & Mingote, 2007; Sundram, 2006). Low concentrations of CB1 receptors are found in the hypothalamus and brain stem, which manage signals regarding homeostasis such as body temperature, blood pressure, sleep, and energy (Rolls, Schaich Borg, & de Lecea, 2010; Sundram, 2006; Suzuki, Jayasena, & Bloom, 2012). Although CB2 receptors are found in the brain, they are predominately located throughout other systems of the body (e.g., immune system) (Gomez-Ruiz et al., 2007).

THC mimics the endogenous cannabinoids (Gomez-Ruiz et al., 2007). When cannabis is consumed, there is an overstimulation of the ECS, which can alter the strength and efficacy of synaptic activity in the brain (Malenka, 2002).

1.4 CANNABIS AND THE DEVELOPING CENTRAL NERVOUS SYSTEM

Exposure to cannabis has implications for human reproduction. THC is an agonist at the cannabinoid receptors CB1 and CB2 and can mimic the endogenous cannabinoids (Gomez-Ruiz et al., 2007). Animal models demonstrate that one-third of the THC in maternal plasma crosses the placenta (Sundram, 2006). Thus, a pregnant woman can expose her offspring to cannabis during gestation. The brain begins to develop shortly after fertilization and exogenous cannabis can affect the ECS, opioidergic, serotoninergic, and dopaminergic systems.

1.4.1 Endogenous cannabinoid system

Immediately following conception, the ECS is involved in progenitor cell migration and differentiation, neuronal migration, and development of axonal pathways (Gaffuri, Ladarre, &

Lenkei, 2012; Wu, Jew, & Lu, 2011). In the second trimester, the ECS is implicated in creating functional synapses (Gaffuri et al., 2012). Postmortem fetal samples have identified active cannabinoid receptors as early as 14, 19, and 33 weeks gestation (Biegon & Kerman, 2001; Glass, Dragunow, & Faull, 1997; Mato, Del Olmo, & Pazos, 2003). This demonstrates that very early in development, the ECS is implicated in making the appropriate cells for neuronal development, migrating neurons to the right places, and beginning to have synapses firing between neurons.

Cannabis can also affect the CNS after the prenatal period. THC is excreted in breast milk, although no long-term studies have evaluated its effects (Djulus, Moretti & Koren, 2005). Further, youth who choose to use cannabis may put themselves at risk for CNS changes. The CNS continues to develop through adolescence into young adulthood, and ECS functionality changes (Lebel & Beaulieu, 2011; Malone, Hill, & Rubino, 2010). There is a spike in AEA in mid-adolescence in the nucleus accumbens and AEA increases in the prefrontal cortex during adolescence (Malone et al., 2010). During this time, 2-AG declines in the nucleus accumbens and prefrontal cortex (Malone et al., 2010). Other structural and functional CNS changes take place from birth through adolescence. Synapses continue to develop, CB1 receptors change in their distribution with increases in the frontal cortex, striatum, and hippocampus, and there is growth in the volume of brain structures such as the hippocampus and prefrontal cortex (Malone et al., 2010).

1.4.2 Opioidergic system

CB1 and opioid receptors are present in the same structures of the CNS; thus, an interaction between the cannabinoid and opioid systems may exist (Maldonado, Valverde, & Berrendero,

2006). Opioid receptors are present in the fetal brain by mid-gestation, and there is evidence that PME results in increased mu-opioid receptor expression in the amygdala (Jutras-Aswad et al., 2009). Further, the interaction between the two systems is associated with the regulation of reward (Navarro et al., 2001). Thus, a disruption to these systems during fetal development may have implications for emotion regulation, memory, and addiction later in life.

1.4.3 Serotoninergic system

Animal studies demonstrate that exposure to THC in the prenatal period affects serotonergic transmission (Jutras-Aswad, 2009). The raphe nuclei are the main source of serotonin, and THC causes a decrease in serotonin levels in the raphe nuclei as well as the hippocampus (Jutras-Aswad, 2009). Therefore, it is believed that this disruption of the normal development of the serotoninergic system may put offspring at risk for mood disorders (Jutras-Aswad, 2009).

1.4.4 Dopaminergic system

Prenatal exposure to THC can also alter the development of the dopaminergic system. THC used during fetal development can lead to a decrease in the neurotransmitter D2 mRNA levels in the amygdala (Jutras-Aswad et al., 2009). This also may affect emotion regulation and memory later in life.

In summary, disruption of brain development and function can occur early in the prenatal period as a result of THC exposure. Because the CNS continues to develop through adolescence, insults from marijuana use during this time can also disrupt brain development and function.

Collectively, these insults can be functional abnormalities manifested as behavior problems as the offspring ages.

1.5 THE EFFECTS OF PRENATAL CANNABIS EXPOSURE ON OFFSPRING

1.5.1 Marijuana use during pregnancy

Marijuana is commonly used during pregnancy. The National Pregnancy and Health Survey, conducted by NIDA in 1992-1993, sampled women who had live-born infants from the 48 contiguous states. The findings were that 2.9% or 119,000 women used marijuana at some point during their pregnancies (NIDA, 1996). More recently, findings from the NSDUH from 2002-2007 suggest a slightly higher prevalence of use. In this nationally representative sample, pregnant women ages 18-44 were asked about their marijuana use in the past month. About 4.6% reported use in the first trimester, 2.9% in the second trimester, and 1.4% in the third trimester (SAMHSA, 2009). However, because these data are only for women at least 18 years of age, these rates may be underestimates due to use in pregnant teens (SAMHSA, 2009).

Pregnant women who use marijuana tend to be: non-white, lower SES, less educated, younger, single, and to use other substances such as alcohol (Behnke & Eyler, 1993). In the Maternal Health Practices and Child Development (MHPCD) cohort, women who smoked at least one joint per day were more likely to be African American, unmarried, and to drink more alcohol compared to nonusers (Chandler, Richardson, Gallagher, & Day, 1996).

1.5.2 Prenatal marijuana exposure and offspring birth outcomes

Few studies have published findings on the effects of prenatal marijuana exposure on birth outcomes. In the MHPCD cohort, PME was not significantly associated with length of gestation, preterm birth, birth weight, head circumference, chest circumference, or small for gestational age status, or morphologic abnormalities (Day & Richardson, 1991). However, PME was significantly associated with shorter length at birth (Day & Richardson, 1991).

In comparison, the Ottawa Prenatal Prospective Study (OPPS) found a reduced length of gestation of about one week among women who smoked 6 or more times per week (Fried, Watkinson, & Willan, 1984). There were no differences in PME and non-PME exposed neonates in regard to major physical anomalies (Fried, 1982). However, the OPPS study found anomalies of true ocular hypertelorism and severe epicanthus that were not seen in the MHPCD cohort (N. Day et al., 1992; O'Connell & Fried, 1984).

More recently, the Generation R study, currently underway in the Netherlands, found that women who used cannabis throughout pregnancy were more likely to have a fetus with growth restriction, defined as a lower fetal weight and smaller head circumference measured by ultrasound, compared to the fetuses of women who did not use cannabis during pregnancy (El Marroun et al., 2009). At birth, infants born to nonusers had a higher birth weight than infants born to users (El Marroun et al., 2009). The authors did not observe a difference in gestational age (El Marroun et al., 2009).

1.5.3 Prenatal marijuana exposure and offspring behavior

In the neonatal period, offspring in the OPPS cohort were assessed within 8 days of birth using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS; Brazelton, 1973). Those offspring exposed to marijuana prenatally had more tremors and startles and poorer habituation to light (Fried, 1980; Fried & Makin, 1987). Offspring in the MHPCD cohort were assessed at 48 hours after birth using the BNBAS but there was no relationship between PME and behavior (Richardson, Day, & Taylor, 1989). In addition, a subsample of 55 neonates in the MHPCD cohort completed an EEG sleep study. Offspring exposed to ≥1 joints per day displayed more body movements and spent less time in total quiet sleep and trace alternant quiet sleep than unexposed offspring (Scher et al., 1988).

Offspring in the MHPCD cohort were evaluated at 8 and 18 months using the Bayley Scales of Infant Development (BSID; 1969). Richardson and colleagues (1995) concluded that at 8 months, PME did not predict lower scores on the Psychomotor Development Index (PDI). Third trimester PME, however, predicted lower scores on the Mental Development Index (MDI). Offspring exposed to ≥1 joints per day during the third trimester had scores about 10 points lower compared to women who smoked less than this amount or none at all. At 18 months, PME did not predict scores on either the MDI or PDI. Exposed and unexposed offspring in the OPPS cohort did not have significantly different PDI or MDI scores at 12 or 24 months of age (Fried & Watkinson, 1988).

Chandler and colleagues (1996) found that PME did not significantly predict deficits in gross motor skills at age 3 in the MHPCD cohort. However, PME predicted lower scores on the short-term memory and verbal reasoning scales of the Stanford-Binet Intelligence Scale in the MHPCD cohort (Thorndike, Hagen, & Sattler, 1986; Day et al., 1994). PME also affected sleep

at age 3 in this cohort. An EEG sleep study demonstrated that PME was associated with lower sleep efficiency (percent of recorded time spent asleep), more minutes awake after sleep onset, and more arousals after sleep onset (Dahl, Scher, Williamson, Robles, & Day, 1995).

At age 4, the McCarthy Scales of Children's Abilities (McCarthy, 1972) were administered to individuals in the OPPS cohort. Offspring exposed to ≥5 joints per week had lower verbal and memory scores (Fried & Watkinson, 1990). At 5-6 years, PME was not associated with any of the scales on the McCarthy Scales of Children's Abilities (Fried et al., 1992). Additionally, in the OPPS cohort, children with PME did not differ from unexposed children on language and cognition at ages 5 and 6 (Fried, O'Connell, & Watkinson, 1992).

At age 6, offspring in the MHPCD cohort with PME had deficits in attention as evaluated by a Continuous Performance Test (CPT) (Leech, Richardson, Goldschmidt, & Day, 1999). Impulsivity and inattention were reported more often for those with PME (Leech et al., 1999). Similarly in the OPPS cohort, offspring of mothers who used ≥5 joints per week during pregnancy had deficits in sustained attention on a vigilance task compared to offspring exposed to less than that amount or not at all (Fried, Watkinson, & Gray, 1992). In this paper, mothers who used ≥5 joints per week during pregnancy rated their 6-year-old offspring as more impulsive/hyperactive on the Conners' Parent Questionnaire (Conners, 1989) compared to offspring exposed to less than that amount or not at all (Fried, Watkinson, & Gray, 1992).

At age 10 in the MHPCD cohort, PME in the first and third trimesters significantly predicted depressive symptoms measured by the Children's Depression Inventory (CDI; Kovacs, 1992; Gray, Day, Leech, & Richardson, 2005). Offspring behavior was assessed using the Swanson, Noland, and Pelham (SNAP; Pelham & Bender, 1982) measure and PME significantly predicted symptoms of hyperactivity, impulsivity, and inattention (Goldschmidt, Day, &

Richardson, 2000). In this same paper, mothers and teachers evaluated offspring behavior using the Child Behavior Checklist (CBCL; Achenbach, 1991a) and the Teacher's Report Form (TRF; Achenbach, 1991b), respectively. Offspring exposed to ≥1 joints per day in the first trimester had higher scores on the CBCL delinquency subscale compared to those exposed to less than that amount or not at all. Offspring exposed to ≥3 joints per week in the second and third trimesters had higher scores on the TRF delinquency subscale compared to those exposed to less than that amount or not at all. The association between PME and delinquency was mediated by inattention (Goldschmidt et al., 2000).

Neuropsychological outcomes were evaluated in the MHPCD cohort at age 10. Richardson and colleagues (2002) concluded that offspring exposed to ≥1 joints per day in the first trimester had lower memory scores on the Wide Range Assessment of Memory and Learning (WRAML; Sheslow & Adams, 1990) than those exposed to <1 joint per day. Second trimester PME expressed as a continuous measure of the average daily joints used also predicted more errors of commission on a CPT suggesting impulsivity (Richardson et al., 2002). Academic achievement was also evaluated in the MHPCD cohort at age 10. Goldschmidt and colleagues (2004) determined that heavy PME (≥1 joints per day) in the first trimester predicted lower reading and spelling scores on the Wide Range Achievement Test-Revised (WRAT-R; Jastak & Wilkinson, 1984) compared to those offspring exposed to less than that amount or not at all. In addition, first trimester heavy PME was also associated with offspring anxiety as measured by the Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds and Richmond, 1978; Goldschmidt et al., 2004).

In the OPPS cohort, PME was associated with deficits in attention at ages 13-16 (Fried & Watkinson, 2001). Day and colleagues (2011) found that PME was associated with delinquency

in offspring at age 14 in the MHPCD cohort and that this association was mediated by attention problems and depressive symptoms. Findings from the MHPCD cohort demonstrated that PME was also associated with deficits in academic achievement at age 14 as measured by the Wechsler Individual Achievement Test (WIAT) Screener (Psychological Corporation, 1992; Goldschmidt, Richardson, Willford, Severtson, & Day, 2012). PME predicted poorer reading scores and the composite scores (reading, math, and spelling) on the WIAT but the effect was mediated by intelligence score, attention, depressive symptoms, and early initiation of marijuana (Goldschmidt et al., 2012).

At age 16, a subsample of 320 offspring of the MHPCD cohort completed a bimanual coordination test, and the results showed third trimester PME was associated with decreased processing speed and interhemispheric coordination (Willford, Chandler, Goldschmidt, & Day, 2010). At ages 18-22, Smith and colleagues (2004) reported findings from an fMRI study conducted on the OPPS cohort and concluded that offspring with PME committed more errors of commission on a blocked design Go/No-Go task than those unexposed offspring, suggesting impulsivity.

In conclusion, the findings of these two cohort studies demonstrate that PME affects offspring behavior from birth through adolescence.

1.5.4 Prenatal marijuana exposure and offspring marijuana use

To date, the MHPCD and OPPS cohorts are the only studies to evaluate whether PME is a significant predictor of offspring marijuana use. Findings from the MHPCD cohort demonstrated that PME, defined as a continuous value of self-reported average number of daily joints, significantly predicted the age of initiation of marijuana in the offspring at age 14 (HR=1.14), as

well as the frequency of marijuana use (OR=1.30) (Day et al., 2006). In the OPPS cohort, PME, defined as a dichotomous variable indicating whether women used marijuana or abstained, predicted initiation of marijuana (OR=2.76, 95% CI: 1.11-6.86) but did not predict marijuana use in offspring between the ages of 16 and 21 years (OR=0.79, 95% CI: 0.33-1.90) (Porath & Fried, 2005). Additionally, there was an interaction by gender in the OPPS cohort: males initiated marijuana at a faster rate compared to females (Porath & Fried, 2005). This interaction was not evaluated in the MHPCD cohort (Day et al., 2006). The association between PME and offspring use in young adulthood has not yet been evaluated.

1.6 SUMMARY

In summary, PME affects the CNS of the developing offspring, changing cognition, emotion regulation, and behavior. Prior studies determined that PME was associated with offspring age of marijuana initiation, frequency of marijuana use, behavior problems, and neurocognitive function. By young adulthood, marijuana initiation is likely to have occurred and use is most frequent. Therefore, young adulthood is a significant time point to evaluate the effects of PME. In this dissertation, we evaluate the effects of PME on offspring frequency of marijuana use and CUD at 22 years. We also examined pathways from PME to frequency of marijuana use and CUD using intervening variables identified in prior studies. To date, there are no published findings on this topic, making the papers presented here unique contributions to the literature.

1.7 SPECIFIC AIMS AND HYPOTHESES

The goal of this dissertation was to examine the effect of prenatal marijuana exposure on offspring frequency of marijuana use and CUD in young adulthood. The specific aims and hypotheses for each paper are described below.

1.7.1 Prenatal marijuana exposure as a predictor of offspring marijuana use in young adulthood

The first aim of this paper was to evaluate the association between PME and offspring frequency of marijuana use in young adulthood. The hypothesis was that PME would significantly predict offspring frequency of use in young adulthood. The second aim was to determine whether the gender, race, or history of childhood maltreatment moderated the association between PME and offspring frequency of marijuana use in young adulthood. The second hypothesis was that this finding would remain significant after adjusting for covariates. A third hypothesis was that gender, race, and history of childhood maltreatment moderated the association between PME and offspring frequency of marijuana use in young adulthood.

At 22 years, a sample of 589 individuals was available for analysis, representing 77% of the birth cohort. PME was defined as a continuous variable, average daily joints used by the mother during the first trimester. Offspring marijuana use was ascertained for the past year and the categories were defined as: no use, using less than three times per week, and using at least three times per week. A simple ordinal logistic regression model was used to test the significance of the first hypothesis. The second hypothesis was tested using a multivariable ordinal logistic regression model. Covariates were selected based on a search of the literature, prior experience

with this dataset, and the statistical significance with the exposure and outcome. The hypotheses about moderation were tested separately using the multivariable ordinal logistic regression model. A separate interaction term was created between PME and each moderator.

1.7.2 From prenatal marijuana exposure to offspring frequency of marijuana use in young adulthood: A path analysis

The aim of this paper was to examine pathways from PME to offspring frequency of marijuana use in young adulthood. We hypothesized that there would be a significant direct effect from PME to offspring frequency of marijuana use. We also hypothesized that we would observe significant indirect effects of PME on offspring frequency of marijuana use through the following intervening variables: offspring depressive symptoms, anxiety, attention, delinquent behavior at 10 years of age, and parental authoritativeness at age 16, as well as early onset of marijuana use. Early initiation of marijuana was defined as never used, first use ≥16 years, and first use <16 years. A path analysis was conducted to determine the significance of individual paths and the overall indirect effect of PME on use through the intervening variables.

1.7.3 From prenatal marijuana exposure to offspring cannabis use disorder in young adulthood: A path analysis

The aim of this paper was to examine the role of offspring depressive symptoms and early initiation of marijuana as variables in the pathway from PME to CUD. We hypothesized that there would be a significant direct effect of PME on CUD. We also hypothesized that there would be a significant indirect effect of PME on CUD through the intervening variables of

offspring depressive symptoms and early initiation of marijuana. Offspring depressive symptoms were self-reported at age 10 and early initiation of marijuana was defined as first use before age 16, first use at age 16 or older, and never used. Offspring CUD was determined from a structured interview. A path analysis was conducted to determine the significance of individual paths and the overall indirect effect of PME on CUD through the intervening variables.

2.0 PRENATAL MARIJUANA EXPOSURE AS A PREDICTOR OF MARIJUANA USE IN OFFSPRING IN YOUNG ADULTHOOD

Manuscript in preparation

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2.1 ABSTRACT

Background. Prenatal marijuana exposure (PME) affects the developing CNS, which may affect offspring behavior. Prior studies have shown that PME is a significant predictor of marijuana initiation and frequency of marijuana use during adolescence, after controlling for other prenatal exposures and current environment. The objective of this study was to determine whether this finding was observed in young adulthood.

Methods. The present study evaluated the effect of PME on frequency of marijuana use in offspring at 22 years of age and tested variables that may moderate this association. Women were recruited from a prenatal clinic in Pittsburgh, Pennsylvania from 1982-1985 when they were in their fourth month of pregnancy. At 22 years, frequency of offspring marijuana use was defined as no use, using less than three times per week, and using three or more times per week. Using an ordinal logistic regression model, analyses were performed on 589 mother-offspring pairs, representing 77% of the birth cohort.

Results. PME significantly predicted frequency of marijuana use in offspring at 22 years, suggesting that the odds of higher frequency of use increased as PME increased. These findings remained significant controlling for prenatal alcohol exposure and offspring demographic characteristics. However, this finding was no longer significant after controlling for the home environment, maternal marijuana use during offspring childhood, and the offspring's self-reported history of childhood maltreatment. The association between PME and offspring use was moderated by a history of childhood maltreatment, but not by race or gender.

Conclusions. The initial association between PME and frequency of marijuana use in young adulthood was not significant after controlling for environmental and psychosocial influences. The interaction between PME and offspring childhood maltreatment suggested that

PME was associated with offspring frequency of use at low levels of childhood maltreatment, but not at high levels of childhood maltreatment. Future directions of this research include examining pathways from PME to offspring frequency of marijuana use.

2.2 INTRODUCTION

Marijuana is the most widely used illicit substance in the world, with recent estimates from the United Nations Office on Drugs and Crime indicating that 2.5%-5% of the world's population reported using cannabis in the past year (Danovitch & Gorelick, 2012; United Nations Office on Drugs and Crime [UNODC], 2012). In the US, the average age of marijuana initiation is 17.5 years (Substance Abuse and Mental Health Services Administration [SAMHSA], 2012). Use is highest between the ages of 15-30 and typically declines after that time (Sundram, 2006). Males typically have higher rates of use than females, but this gender gap may be narrowing (Perkonigg et al., 2008; SAMHSA, 2012; von Sydow et al., 2001; Wallace et al., 2003). In addition, national survey data of middle and high school students indicate that use is highest among Native Americans, followed by Hispanics, whites, blacks, and Asian-Americans (Wallace et al., 2003).

Other influences have been shown to play a role in marijuana initiation and use. The effects of genetics on marijuana use have been demonstrated using twin studies and family histories of substance use problems (Agrawal & Lynskey, 2006; von Sydow, Lieb, Pfister, Hofler, & Wittchen, 2002). Environmental factors associated with use include leaving the family home before the age of 18, family conflict, change in mother's marital status, maternal smoking and marijuana use when the offspring was an adolescent, parental supervision and control, and peer marijuana use (Day, Goldschmidt, & Thomas, 2006; Hayatbakhsh et al., 2008;

Hayatbakhsh, Najman, Bor, O'Callaghan, & Williams, 2009; Perkonigg et al., 2008; Richardson, Larkby, Goldschmidt, & Day, 2013; von Sydow et al., 2002).

Psychosocial factors associated with use include having an antisocial personality diagnosis, low self-competence, distressing life events, having a high number of symptoms of depression and anxiety, aggressive and delinquent behavior, and a history of childhood maltreatment, particularly sexual and physical abuse (Hayatbakhsh et al., 2009; Hussey, Chang, & Kotch, 2006; Kilpatrick et al., 2000; Lo & Cheng, 2007; Perkonigg et al., 2008).

One understudied factor is how prenatal marijuana exposure (PME) is associated with offspring marijuana use. Marijuana is a commonly-used illicit substance during pregnancy. Findings from the National Pregnancy and Health Survey conducted in 1992-1993 indicate that 2.9% of women used marijuana at some point during pregnancy (National Institute on Drug Abuse [NIDA], 1996). Use during pregnancy has the potential to disrupt the endogenous cannabinoid system (ECS) of the developing fetus. When marijuana is consumed, the main psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), enters the mother's bloodstream and crosses the placenta (Sundram, 2006). These exogenous cannabinoids bind to receptors in the developing ECS. The ECS is important in the development of the CNS and is associated with progenitor cell migration and differentiation, neuronal migration, development of axonal pathways, and the creation of functional synapses (Gaffuri, Ladarre, & Lenkei, 2012; Wu, Jew, & Lu, 2011). Animal models also demonstrate that PME affects the endogenous opioid, dopamine, and serotonin systems (Jutras-Aswad, DiNieri, Harkany, & Hurd, 2009). Taken together, these changes may put offspring at risk for problems with emotion regulation, memory, depression, and addiction later in life (Jutras-Aswad et al., 2009).

There are two birth cohorts with published findings on long-term outcomes of PME: the Maternal Health Practices and Child Development (MHPCD) Study and the Ottawa Prenatal Prospective Study (OPPS). These studies have found that PME predicted deficits in memory and attention, increases in impulsivity and hyperactivity; symptoms of anxiety and depression, and delinquent behavior (Day, Leech, & Goldschmidt, 2011; Day et al., 1994; Fried, Watkinson, & Gray, 1992; Fried & Watkinson, 1990; Fried & Watkinson, 2001; Goldschmidt, Day, & Richardson, 2000; Goldschmidt, Richardson, Cornelius, & Day, 2004; Gray, Day, Leech, & Richardson, 2005; Leech, Richardson, Goldschmidt, & Day, 1999). Some of these effects of PME have also been shown to be associated with marijuana use as described above.

Earlier findings published on the MHPCD cohort demonstrated that PME predicted early onset of use, defined as initiation of marijuana in the offspring by age 14 (HR=1.14), as well as the frequency of marijuana use (OR=1.30) (Day et al., 2006). In the OPPS cohort, PME predicted age of initiation of marijuana (OR=2.76, 95% CI: 1.11-6.86), but did not predict frequency of marijuana use in offspring between the ages of 16 and 21 years (OR=0.79, 95% CI: 0.33-1.90) (Porath & Fried, 2005). Additionally, an interaction was found with gender. The results suggested that males initiated marijuana at a faster rate than females (Porath & Fried, 2005). This interaction was not assessed in the MHPCD cohort (Day et al., 2006).

Race and childhood maltreatment are other factors that may interact with PME and affect offspring marijuana use, but these findings have not been reported in either cohort. This interaction between race and PME was not reported in the OPPS cohort (Porath & Fried, 2005). This was likely because it could not be tested, as the cohort was predominately composed of Caucasian women. This interaction was not reported in the MHPCD cohort at 14 years but it can be tested due to the racial heterogeneity of the sample (Day et al., 2006). To date, childhood

maltreatment findings have not been reported in the OPPS cohort and its association with PME has not yet been evaluated in the MHPCD cohort. Prenatal substance use has been associated with an increased risk of offspring childhood maltreatment (Jaudes, Ekwo, & Van Voorhis, 1995; Smith, Johnson, Pears, Fisher, & DeGarmo, 2007). Further, childhood maltreatment has been associated with substance use later in life (Hussey et al., 2006; Kilpatrick et al., 2000; Lo & Cheng, 2007). Therefore, evaluating this interaction represents a novel and meaningful contribution to the literature.

In summary, few studies involving longitudinal data have been conducted to evaluate the effects of PME on offspring marijuana use. To date, the published findings of this association were found when the offspring were 14 years on average in the MHPCD cohort and ranged from 16-21 years in OPPS cohort. There have been no publications from birth cohorts evaluating the association between PME and offspring use in young adulthood. It is important to evaluate this association for two reasons. One, the average age of marijuana initiation has consistently been reported to be in the teenage years (SAMSHA, 2012). Thus, initiation is likely to have occurred by young adulthood. Two, levels of substance use are highest during young adulthood, suggesting it is developmentally appropriate to evaluate the effect of PME on offspring marijuana at this time point (Spoth, Trudeau, Guyll, Shin, & Redmond, 2009). This paper also offers insight about the relationship between PME and offspring marijuana use in young adulthood in a low socioeconomic, racially diverse sample.

In this paper, we aim to determine the association between PME and marijuana use in early adulthood. We hypothesize that: 1) PME will predict offspring use of marijuana in early adulthood, 2) the association between PME and offspring use will remain significant after

controlling for covariates, and 3) the effects of PME on marijuana use in offspring in early adulthood will be moderated by offspring gender, race, and childhood maltreatment.

2.3 METHODS

2.3.1 Sample description

The data for this study come from the Maternal Health Practices and Child Development (MHPCD) study at the University of Pittsburgh. This is a longitudinal study of the effects of prenatal exposure to alcohol and marijuana on offspring development. The participants were recruited from a prenatal clinic at Magee-Womens Hospital in Pittsburgh, PA. Recruitment took place from 1982-1985. Eligible women had to speak English, be at least 18 years of age, and be in their fourth or fifth gestational month. There was a 15% refusal rate. There were 1,360 women who completed an initial interview about substance use in the first trimester. These substances were alcohol, tobacco, marijuana, and other illicit drugs.

The initial interview was administered to select two cohorts. One cohort was composed of women who drank three or more alcoholic drinks per week in the first trimester and a random sample of one-third of those women who drank less than this amount or not at all. The second cohort was composed of women who used marijuana at least two times per month in the first trimester and a random sample of one-third of those women who reported they used less marijuana or none at all. Sampling was done with replacement allowing women to be eligible for both cohorts. Participants followed the same protocols, which allowed the study cohorts to be combined for analysis. The combined cohort was composed of 829 women with 60% overlap

between the alcohol and marijuana cohorts. Informed consent was obtained from the women and this study was approved by Magee-Womens Hospital and the Institutional Review Board of the University of Pittsburgh.

The women enrolled in the MHPCD study were interviewed again in their 7th gestational month. Subsequent assessments of mothers and offspring were conducted after the offspring's birth, 8 and 18 months, and 3, 6, 10, 14, 16, and 22 years of age. At each phase of data collection, information was gathered about maternal psychological, social, and environmental factors, demographic status, and substance use, and the children's cognitive, behavioral, psychological, and physical development.

The birth cohort consisted of 763 live singleton infants. The reasons for the loss of participants at birth were that 8 individuals refused the delivery assessment, 16 women were lost to follow-up, and 21 women moved out of the area. Other exclusions included 18 offspring due to early fetal death, two offspring due to multiple gestation birth, and one offspring was placed for adoption and could not be followed. Only those mother-child pairs who completed the assessment at birth were selected for follow-up.

At the 22-year phase, 608 offspring participated in an interview, representing 80% of the birth cohort. Among the 155 who did not participate, 30 individuals refused, 3 had been adopted and could not be located, 18 were institutionalized in either jail or a rehabilitation facility, 56 were lost to follow-up, 29 had moved out of the area, 11 had died, and 8 could not participate due to low cognitive functioning. Fourteen individuals did not complete the instrument about childhood maltreatment used in this analysis, and five individuals were excluded because they reported that they had not used marijuana but tested positive for the substance on a urine screen. This resulted in a final sample size of 589, representing 77% of the birth cohort. Those who were

included in the analysis (n=589) did not differ from those who were not included in the analysis (n=174) based on maternal characteristics assessed at the first trimester visit including age, race, education, marital status, household income, and substance use (Appendix, Table 10).

2.3.2 Measures

2.3.2.1 Prenatal marijuana exposure

The mothers provided information about the pattern of their marijuana use at each assessment. A series of questions developed for the MHPCD study measured usual, maximum, and minimum quantity and frequency (Day & Robles, 1989). The same questions were asked about use of hashish and sinsemilla. Conversions of hashish and sinsemilla were done to account for the higher THC content in those substances. One joint of sinsemilla was equal to two joints of marijuana, one joint or bowl of hashish was equal to three joints of marijuana (Gold, 1989; Hawks, 1986; Julien, 1988). A blunt was scored as the self-reported number of joints in the blunt. If the participant did not report the number of joints in the blunt, then it was coded as four joints. Marijuana use was calculated as the average daily joints (ADJ). The ADJ formula is: (number of joints/week x 4 weeks/month)/31 days/month. An ADJ of 0.4 is equivalent to using three joints per week and an ADJ of 0.89 is equivalent to using one joint per day. A bogus pipeline was used to encourage accurate reporting of substance use at the first phase (Jones & Sigall, 1979).

2.3.2.2 Offspring frequency of marijuana use

Marijuana use among the offspring was measured with the same questions and conversions described above. The frequency categories were collapsed to no use, use <3 times per week, and use ≥3 times per week to be consistent with a prior analysis using this data set (Day et al., 2006).

2.3.2.3 Covariates

We considered covariates identified in the literature and based on prior findings of this cohort. We evaluated the following maternal demographic covariates assessed at the first interview: age, race, years of education, and household income. We considered the psychological factors of depressive symptoms, anxiety, and hostility. The mothers completed the Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977) to provide an assessment of depressive symptoms. This is a 20-item self- report questionnaire in which respondents indicate their symptoms on a Likert scale. They completed the State-Trait Anxiety Inventory (Spielberger, 1970), which assessed anxiety and hostility. This questionnaire is also a self-reported measure of symptoms using a Likert scale. Finally, we considered use of alcohol, cigarettes, and other illicit drugs during the first trimester. Alcohol use was defined as the average number of drinks (Average Daily Volume [ADV]) consumed per day using the same formula described above for ADJ. Cigarette use was expressed as the number of cigarettes smoked per day. The use of cocaine and other illicit drugs were dichotomized due to the low frequency of use in this sample.

When the offspring were 10 years of age, the mothers provided information about their own substance use using the same procedure described above. They also reported information about the home environment in which the offspring were being raised. The Home Observation

for Measurement of the Environment-Short Form (HOME; Baker & Mott, 1989) was used to measure the home environment in regard to cognitive stimulation and emotional support.

At 16 years of age, the offspring reported the number of friends they had who used alcohol, cigarettes, and marijuana. These variables were collapsed into dichotomous variables to indicate whether they had friends who used these substances. Parenting was assessed using the My Parents (Steinberg, Lamborn, Dornbusch, & Darling, 1992) tool. The offspring completed this questionnaire and scores were ascertained for scales related to parental acceptance/involvement, supervision/strictness, and psychological autonomy granting. These subscales are used to create a composite of an overall score of authoritativeness. A score above the median on a subscale is coded as one and the sum is added for a maximum of three. The 16-year phase for the peer and parenting variables was chosen because we wanted to look at influences during adolescence based on the literature search.

At 22 years, the offspring reported whether their mothers, fathers, or siblings had a history of problems with alcohol or drugs. A dichotomous variable for family history of problematic use was created to represent whether the offspring had a first degree relative with such problems. Offspring also provided information about demographic characteristics and their own use of other substances during the interview.

2.3.2.4 Moderators

Interaction terms were created to test whether the effects of PME differed by offspring gender, race, and childhood maltreatment. Gender was ascertained during the assessment that took place at birth. Offspring race was self-reported during the 22-year assessment. Offspring child maltreatment was assessed at 22 years of age using the Child Trauma Questionnaire (CTQ; Bernstein & Fink, 1998). The CTQ contains 25 items that assess whether an individual

experienced the following five types of abuse: emotional abuse, physical abuse, sexual abuse, emotional neglect, or physical neglect when they were growing up. Respondents use a 5 point Likert scale ranging from never true to very often true. The scores for the subscales range from 5 to 25. The subscales were dichotomized to indicate whether an offspring had experienced moderate to severe abuse using the following suggested cut points: ≥13 for emotional abuse, ≥10 for physical abuse, ≥8 for sexual abuse, ≥15 for emotional neglect, and ≥10 for physical neglect (Bernstein & Fink, 1998). A sum of the five dichotomous scales was used in this analysis.

2.3.3 Analysis plan

Analyses were performed on the combined cohort. We restricted our analysis to the first trimester for two reasons. First, fewer women participated in the second study visit. Approximately 10% of the participants did not complete the interview for the second trimester. Second, marijuana use declined during pregnancy. While 41% of the women reported marijuana use during the first trimester, only 18% reported use by the third trimester (Figure 1). Therefore, analyzing the data based on the first trimester only allowed us to maximize the sample size. Table 11 of the Appendix displays the sample sizes and marijuana use of the mothers across gestation.

The covariates considered for the analysis were based on a review of the literature and prior analyses performed on this data set. There were covariates with missing data and the range of missing was 0.2%-16%. Values were calculated using multiple imputation by chained equations (MICE). MICE can perform imputation of continuous, dichotomous, and ordinal variables (Royston & White, 2011). Ten data sets were imputed to ensure the efficiency of the

estimates was above 95% (Rubin, 1987). Our efficiency with 16% missing was 98%. The final analysis was done using the pooled estimates of the imputed datasets.

The distributions of marijuana and alcohol variables were examined. Out of range values for marijuana were set to 10.0 joints per day and the out of range values for alcohol use were set to 8.0 drinks per day.

Descriptive statistics were generated to explore the associations between the variables considered for this analysis. We looked at the correlations and performed t-tests or analysis of variance (ANOVA) to evaluate continuous variables. For those continuous variables that were not normally distributed, we used the Mann-Whitney U test or the Kruskal-Wallis test. We performed Chi-square tests to evaluate the association between dichotomous variables. Cohen's d and Cramer's V were calculated to assess effect size. The effect size is a statistic used to quantify the differences between the groups.

To assess the first hypothesis evaluating the association between PME and offspring use, we performed a univariable ordinal logistic regression model. The second hypothesis was that the association between PME and offspring use would remain significant after controlling for covariates. To test this hypothesis, variables significantly associated with the exposure and the outcome at $p<.05$ were identified. Our final model included these significant variables and those relevant from the literature. We also hypothesized that the association between PME and offspring use would be moderated by gender, race, and childhood maltreatment. An interaction term was created between PME and each moderator. Moderation was tested separately for each term to avoid oversaturation of the final model.

2.4 RESULTS

Characteristics of the sample for this analysis are displayed in the Appendix, Table 12. During the first prenatal visit, the women recruited for this study were 23 years of age, on average, and ranged from 18-42 years. Fifty-one percent of the women were African American and 32% were married. The women completed 11.8 years of education and 25% were in school and/or working outside the home. The sample was composed predominantly of low income women with 61% reporting a monthly household income of less than $400. Maternal substance use in the first trimester is also reported. Forty-one percent of the women reported using marijuana and the average daily joints was 0.37, indicating use occurred about three times per week. Sixty-four percent of women reported using any alcohol with average daily volume of 0.55, and 53% reported smoking cigarettes. Four percent of the mothers reported using cocaine and 9% reported using other illicit drugs such as heroin or LSD.

At birth, 47% of the offspring were male. On average, the offspring were born at about 40 weeks gestation with 8% born preterm (before 37 weeks). The average birth weight was 3.20 kg and 10% were of low birth weight (<2500g).

At 10 years, the average score was 12.7 (range: 3-18) on the HOME measure. This is the total of the cognitive stimulation and emotional support scales with a higher score indicating a more stimulating and supportive environment. Maternal substance use was reported at this time. Twenty-one percent reported using marijuana, 78% reported using alcohol, 59% reported using cigarettes, and 8% reported using other illicit drugs.

At 16 years, mean scores for the acceptance/involvement, psychological autonomy, and strictness/supervision subscales on the My Parents instrument were 30 (range: 15-36), 24 (range: 9-36), and 19 (range: 8-30), respectively. Higher scores indicate that offspring believe their

parents are more loving and involved, allow offspring to express individuality, and monitor offspring and set limits (Steinberg et al., 1992). The overall authoritativeness score was 1.42, demonstrating parenting is considered to be between somewhat nonauthoritative to somewhat authoritative (Steinberg et al., 1992). Over 70% of offspring reported that they had at least one friend who used alcohol, tobacco, or marijuana.

At the 22-year assessment, the offspring were 22.8 years old, on average, and 56% identified their race as African American. The average number of years of education completed was 12.8 and 87% of the offspring had completed high school. Sixty-one percent were working and/or in school and the median monthly personal income was $800. Thirty-five percent were living with their mother or caregiver. Only 6% of the offspring were married and 36% had at least one child. Over 80% had initiated cigarettes and marijuana and 99% had initiated alcohol. Past-year cigarette use was reported by 43% of respondents. Fifty percent of the offspring used marijuana in the past year and 93% reported using alcohol in the past year. Forty-seven percent of the offspring reported that a first degree relative had problems with alcohol or drugs. Twenty-nine percent reported experiencing moderate, severe, or extreme child maltreatment. The mean child maltreatment score was 2.43 (range: 1-5).

Table 1 presents characteristics of the sample according to maternal marijuana use in the first trimester. For descriptive purposes, categories were created representing women who did not use marijuana during the first trimester, those who used less than one joint per day (light to moderate use), and those who used one or more joints per day (heavy use). Mothers who were using marijuana during the first trimester were more likely to be African American, unmarried, not working outside the home or in school, report a lower monthly household income, and use other substances. There were no significant differences by offspring gender, gestational age, or

birth weight. When the offspring were 10 years of age, the mean HOME scores were not significantly different for the categories of marijuana use. Mothers who used marijuana during the first trimester had higher percentages or mean quantities of licit and illicit substances when their offspring were 10 years of age. When the offspring were 16 years of age, there were no significant differences on any of the My Parents subscales. Those with PME were not more likely to have peers who used cigarettes and alcohol, but there was a marginally significant difference for peer marijuana use. Those with PME reported a higher percentage of peers who used marijuana, compared to those without PME.

At 22 years, those without PME were older than those with PME. African American offspring were more likely to have PME than those who were Caucasian. There no significant differences by years of education, personal income, percent working or in school, marital status, living with a mother or caregiver, or having at least one child. Those in the heavy PME group had a marginally significant higher mean score on the CTQ than those with light to moderate PME and those unexposed. There were no differences according to a family history of drug or alcohol problems. There were no significant differences in initiation or past-year use of alcohol or cigarettes. There were differences in marijuana initiation and frequency of use. Offspring across all levels of PME had a higher percentage of marijuana initiation and a higher frequency of marijuana use compared to those without PME. There were no significant differences in past-year use of cocaine or other illicit drugs.

Among the non-users at 22 years, 66% had no PME, 24% had light to moderate exposure, and 10% had heavy exposure (Table 2). This is in contrast to the most frequent users at 22 years, where 44% had no PME exposure, 36% had light to moderate exposure, and 20% had heavy

exposure. This relation between PME and offspring use was statistically significant with a p-value of 0.001.

Model 1 tested the crude association between PME and offspring use (Table 3). The association was significant (p = 0.003; OR = 1.28 (95% CI: 1.09-1.51)). As PME increased by one joint per day, the odds of the offspring being in a higher category of use increased by 1.28. In Model 2, first trimester prenatal alcohol exposure and offspring race, gender, and age at the 22-year assessment were added. PME remained a significant predictor of offspring use with a p-value of 0.019. Adjusting for these covariates, a one unit increase in PME increased the odds of being in a higher category of use by 1.22.

Model 3 built on the prior model by adjusting for maternal marijuana use at 10 years, the home environment at 10 years, and the offspring's self-reported history of childhood maltreatment. In this model, PME was no longer a significant predictor of offspring use (p= 0.182) after adjusting for selected covariates in the full model. Although maternal marijuana use at 10 years and the offspring's home environment at 10 years were not significant factors in the adjusted model, the remaining covariates were significant. The results of this model indicated that the odds of being in a higher category of use were higher for males (OR = 1.98 (95% CI: 1.44-2.73)) and lower for Caucasians (OR = 0.70 (95% CI: 0.50-0.98)). The odds of being in a higher category of use increased as prenatal alcohol exposure (OR = 1.18 (95% CI: 1.03-1.35)) and childhood maltreatment scores (OR = 1.23 (95% CI: 1.07-1.42)) increased. However, the odds decreased as age at the time of the 22-year assessment increased (OR = 0.77 (95% CI: 0.61-0.97)), indicating that the younger offspring were more likely to be in a higher category of use.

The last aim of this paper was to evaluate whether gender, race, and a history of child maltreatment moderated the association between PME and offspring use at 22 years (Table 4). In

Model 4, the interaction term created for PME and gender was not significant. After adjusting for the covariates in the model, the p-value of the interaction term was 0.228 and the odds ratio was 1.25 (95% CI: 0.087-1.81). In Model 5, the interaction term created for PME and race was not significant with a p-value of 0.404 and an odds ratio of 1.21 (95% CI: 0.78-1.87). Neither gender nor race was a significant moderator of the association between PME and offspring frequency of marijuana use at 22 years.

The interaction between PME and childhood maltreatment was significant (p= 0.004; OR = 0.85 (95% CI: 0.75-0.95)). In the absence of PME (ADJ=0), the probability of using marijuana at 22 years was higher as the childhood maltreatment scores increased (Figure 2). In the presence of PME, offspring with a low childhood maltreatment score increased the likelihood of marijuana use at 22 years at a faster rate than offspring with a high childhood maltreatment score. This suggests that in the absence of moderate, severe, or extreme childhood maltreatment, PME contributed to the prediction of frequency of marijuana use in the young adult offspring. However, when offspring experienced high levels of childhood maltreatment and had higher PME, then PME was not as influential in the prediction of offspring frequency of marijuana use at 22 years.

2.5 DISCUSSION

The aim of this study was to evaluate whether PME was a significant predictor of offspring marijuana use in young adulthood. The crude association between these variables was significant, and the finding remained significant after controlling for prenatal alcohol exposure, offspring race, offspring gender, and offspring age. However, this finding was not significant

when controlling for the offspring's home environment, maternal marijuana use when offspring were 10 years of age, and the offspring's history of childhood maltreatment. Further, we determined that gender and race did not moderate the association between PME and offspring marijuana use at 22 years. The interaction between PME and offspring child maltreatment suggested that PME was associated with offspring frequency of use at low levels of childhood maltreatment, but not at high levels of childhood maltreatment.

The findings of this paper build on prior reports of this study. When the offspring were 14 years old, PME was a significant predictor of use after adjusting for several confounders including the home environment, parenting, peer use, offspring behavior, and current offspring use of other substances (Day et al., 2006). In contrast, we did not find a significant association at age 22 after we adjusted for similar factors. One reason for this may be because of the significance of childhood maltreatment in our model. Childhood maltreatment had not been assessed in earlier phases of the MHPCD study. Thus, it could not be accounted for in the analyses until this 22-year assessment.

Although Porath and Fried (2005) did not find that gender modified the association between PME and offspring frequency of marijuana use in that sample, this was tested in our analysis because of the preponderance of male users. Our findings confirm the reports from the OPPS that PME does not affect offspring frequency of marijuana use differently for males and females. We also concluded that, although marijuana use was more common among African American mothers, race did not moderate the association between PME and offspring frequency of marijuana use. This is an important contribution to the literature as this hypothesis was not tested in the OPPS cohort, presumably due to the racially homogenous sample (Porath & Fried, 2005).

The observed interaction between PME and offspring childhood maltreatment was surprising in that the effect of PME was stronger for those who reported less childhood maltreatment. A theory as to why this may occur is that those who experience childhood maltreatment are already at risk for substance use in adulthood, thus PME had no additional influence to contribute (Lo & Cheng, 2007). By contrast, PME was an additional risk factor for the offspring who did not experience such childhood maltreatment. In light of this speculation, this finding needs further investigation in future studies.

This study has several strengths. The study had a large sample size of 589 individuals and excellent follow-up rates: 77% of the birth cohort was seen at age 22. Second, this study recruited approximately equal numbers of African American and Caucasian women during the early 1980s, allowing for an analysis of a racially heterogeneous sample. Third, the data for this study were obtained prospectively, which minimizes recall bias.

There are some notable limitations to this analysis. This sample is composed of predominately low income women, and the results may not be generalizable to women in higher socioeconomic groups. Additionally, marijuana use was ascertained by self-report. However, a bogus pipeline procedure was used to encourage honest reporting from mothers at the first prenatal visit. In addition, a urine screen was part of the study protocol for the offspring at the 22-year visit. Among those who reported they did not use marijuana, only 2% screened positive. Among those who reported that they used marijuana in the past year, 64% had positive results on the urine screen. While the results of the urine screen can only offer insight about recent marijuana use, they do suggest that participants are being honest about their use. Further, the staff members who interviewed the participants were comfortable asking questions about the sensitive topics (e.g., substance use, psychosocial factors) and followed an established protocol

for the sequence of questioning. In addition, a National Institutes of Health Certificate of Confidentiality was obtained for this study because of the sensitive nature of topics discussed. This provides research participants with a sense of confidentiality and privacy because it offers protection from the release of identifying information when requested through court order or subpoena (National Institutes of Health).

In summary, the findings of this analysis suggest that PME predicted offspring marijuana use in young adulthood, but this finding was no longer significant after controlling for environmental and psychosocial factors. A future direction of this research will be to examine variables in the pathway from PME to offspring frequency marijuana use in young adulthood, including depressive symptoms and early initiation of marijuana.

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2.7 TABLES AND FIGURES

Table 1. Sample characteristics by category of first trimester marijuana use

	Maternal Marijuana Use				
	No use[a] (n=347)	Light to moderate use[b] (n=165)	Heavy use[c] (n=77)	p-value[d]	Effect size[e]
Maternal Characteristics at the First Trimester Visit					
Age (mean years)	23.32	22.61	22.84	0.161	0.006
Race (% African American)	45.53	52.73	75.32	<0.001	0.196
Education (mean years)	11.85	11.84	11.72	0.760	0.001
Marital status (% married)	37.46	27.27	18.18	0.001	0.150
Employment status (% in school or working outside the home)	25.36	30.91	14.29	0.022	0.114
Household income (%<US$400/month)[f]	57.10	64.63	73.33	0.020	0.117
Depression (mean CES-D score)[g]	20.83	21.10	21.26	0.894	<0.001
Anxiety (mean STPI score)[h]	17.58	17.93	18.01	0.627	0.002
Hostility (mean STPI score)[h]	18.30	19.11	19.83	0.063	0.009
Any alcohol use (%)	55.33	78.18	74.03	<0.001	0.222
Average daily volume of alcohol	0.40	0.75	0.78	<0.001	0.027
Any cigarette use (%)	47.26	60.00	64.94	0.002	0.144
Average daily cigarettes	7.68	8.65	9.38	0.410	0.003
Any cocaine use (%)	1.73	5.45	9.09	0.003	0.139
Any other drug use (%)	6.92	9.70	15.58	0.047	0.102
Offspring Characteristics at Birth					
Gender (% male)	47.84	47.27	44.16	0.842	0.024
Gestational age (mean weeks)	39.71	39.96	39.84	0.460	0.003
Preterm birth (% <37 weeks)	8.36	8.48	6.49	0.849	0.024
Birthweight (mean kg)	3.21	3.22	3.08	0.172	0.006
Low birth weight (%<2500g)	9.51	10.91	10.39	0.880	0.021
Characteristics at 10 Years					
Home environment score[i]	12.89	12.50	12.37	0.186	0.007
Maternal average daily joints[j]	0.02	0.08	0.26	<0.001	0.083
Any maternal marijuana use (%)[j]	7.97	34.90	48.57	<0.001	0.392
Maternal average daily volume of alcohol[j]	0.69	1.19	1.28	<0.001	0.027
Any maternal alcohol use (%)[j]	73.09	87.25	81.43	0.002	0.153
Maternal average daily cigarettes[j]	8.48	10.13	10.03	0.247	0.005

Table 1 Continued

Any maternal cigarette use (%)[j]	50.83	67.11	74.29	<0.001	0.191
Any maternal other illicit drug use (%)[j]	4.65	12.08	15.71	0.001	0.159
Characteristics at 16 Years					
Parental acceptance/involvement score[k]	30.19	30.30	30.07	0.936	<0.001
Parental psychological autonomy score[k]	24.54	23.72	23.72	0.170	0.007
Parental strictness/supervision score[l]	19.00	18.70	18.72	0.717	0.001
Parental authoritativeness overall score[l]	1.50	1.32	1.33	0.138	0.008
Offspring has peers who use cigarettes (%)[m]	80.76	76.39	80.88	0.544	0.049
Offspring has peers who drink alcohol (%)[n]	79.45	79.02	79.41	0.994	0.005
Offspring has peers who smoke marijuana (%)[o]	72.41	74.31	85.29	0.088	0.098
Offspring Characteristics at 22 Years					
Age (mean years)	22.98	22.78	22.70	0.020	0.013
Race (% African American)	51.59	55.15	79.22	<0.001	0.183
Education (mean years)	12.82	12.92	12.39	0.056	0.010
Personal income (mean US$/month)	1006.07	969.70	800.43	0.308	0.006
Work status (% working or in school)	61.96	63.64	51.95	0.195	0.075
Marital status (% married)	5.48	7.88	3.90	0.403	0.056
Lives with mother or caregiver (%)	37.18	30.30	33.77	0.306	0.063
Has at least one child (%)	36.02	34.55	45.45	0.231	0.071
Child maltreatment score (mean)	2.35	2.53	2.61	0.072	0.009
Experienced moderate, severe, or extreme child maltreatment (%)	26.51	30.91	37.66	0.128	0.084
Family history of alcohol or drug problems (%)	45.38	46.34	54.55	0.341	0.061
Initiated cigarettes (%)	80.40	83.03	84.42	0.618	0.040
Past-year cigarette use (%)	41.21	43.64	53.25	0.156	0.080
Average daily cigarettes	4.00	4.61	5.47	0.138	0.005
Initiated alcohol (%)	98.85	100.00	98.70	0.372	0.058
Past-year alcohol use (%)	92.22	93.33	92.21	0.898	0.019
Average daily volume of alcohol	1.48	1.82	1.59	0.124	0.005
Initiated marijuana (%)	79.25	87.27	90.91	0.011	0.124
Past-year marijuana use (%)	44.09	56.97	62.34	0.002	0.147
Average daily joints of marijuana	0.70	0.67	1.70	<0.001	0.028
Past-year cocaine use (%)	5.48	7.88	9.09	0.383	0.057
Past-year other illicit drug use (%)	12.10	14.55	19.48	0.222	0.072

[a] Zero joints per day
[b] Less than one joint per day
[c] One or more joints per day
[d] ANOVA for continuous variables, Kruskal-Wallis test for skewed variables, χ^2 test for dichotomous variables
[e] Eta^2 for continuous variables, Cramer's V for dichotomous variables; absolute value reported
[f] Sample size: 331, 164, 75

Table 1 Continued

[g] Sample size: 344, 164, 77
[h] Sample size: 346, 165, 77
[i] Sample size: 297, 149, 68
[j] Sample size: 301, 149, 70
[k] Sample size: 288, 143, 68
[l] Sample size: 284, 142, 67
[m] Sample size: 291, 144, 68
[n] Sample size: 292, 143, 68
[o] Sample size: 290, 144, 68

Table 2. First trimester marijuana exposure by offspring frequency of marijuana use at 22 years

	Offspring Frequency of Marijuana Use				
First Trimester Maternal Marijuana Use	No Use (n=294)	Using less than three times per week (n=173)	Using three times per week or more (n=122)	**p-value**[d]	**Effect size**[e]
None[a] (n, %)	194 (65.99)	99 (57.23)	54 (44.26)		
Light to moderate[b] (n, %)	71 (24.15)	50 (28.90)	44 (36.07)	0.001	0.123
Heavy[c] (n, %)	29 (9.86)	24 (13.87)	24 (19.67)		

[a] Zero joints per day
[b] Less than one joint per day
[c] One or more joints per day
[d] χ^2 test
[e] Cramer's V

Table 3. Ordinal logistic regression models evaluating the association between prenatal marijuana exposure and offspring frequency of marijuana use

	Model 1 (McFadden's R^2=0.001)			**Model 2** (McFadden's R^2=0.033)			**Model 3** (McFadden's R^2=0.044)		
Variable	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**
Prenatal marijuana exposure	0.003	1.28	1.09-1.51	0.019	1.22	1.03-1.44	0.182	1.13	0.94-1.36
Prenatal alcohol exposure				0.010	1.19	1.04-1.36	0.017	1.18	1.03-1.35
Offspring race				0.013	0.66	0.48-0.92	0.037	0.70	0.50-0.98
Offspring gender				0.000	1.91	1.39-2.62	0.000	1.98	1.44-2.73
Offspring age at assessment				0.030	0.77	0.61-0.97	0.028	0.77	0.61-0.97
Maternal marijuana use at 10 years							0.164	1.52	0.84-2.73
Home environment at 10 years							0.313	0.97	0.90-1.03
Child maltreatment							0.004	1.23	1.07-1.42

Table 4. Ordinal logistic regression models testing moderation of prenatal marijuana exposure and offspring frequency of marijuana use

	Model 4 (McFadden's R^2=0.045)			**Model 5** (McFadden's R^2=0.044)			**Model 6** (McFadden's R^2=0.050)		
Variable	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**
Prenatal marijuana exposure	0.679	1.05	0.84-1.31	0.388	1.09	0.89-1.34	0.002	1.95	1.28-2.97
Prenatal alcohol exposure	0.017	1.18	1.03-1.35	0.020	1.17	1.03-1.35	0.039	1.15	1.01-1.32
Offspring race	0.039	0.70	0.50-0.98	0.025	0.66	0.46-0.95	0.046	0.71	0.51-0.99
Offspring gender	0.001	1.83	1.30-2.58	0.000	1.99	1.45-2.73	0.000	2.03	1.47-2.79
Offspring age at assessment	0.026	0.77	0.60-0.97	0.032	0.77	0.61-0.98	0.025	0.76	0.60-0.97
Maternal marijuana use at 10 years	0.221	1.45	0.80-2.63	0.148	1.54	0.86-2.77	0.216	1.45	0.80-2.62
Home environment at 10 years	0.322	0.97	0.90-1.03	0.306	0.97	0.90-1.03	0.359	0.97	0.91-1.04
Child maltreatment	0.005	1.23	1.07-1.42	0.005	1.23	1.07-1.42	0.000	1.34	1.15-1.57
PME x gender	0.228	1.25	0.87-1.81						
PME x race				0.404	1.21	0.78-1.87			
PME x child maltreatment							0.004	0.85	0.75-0.95

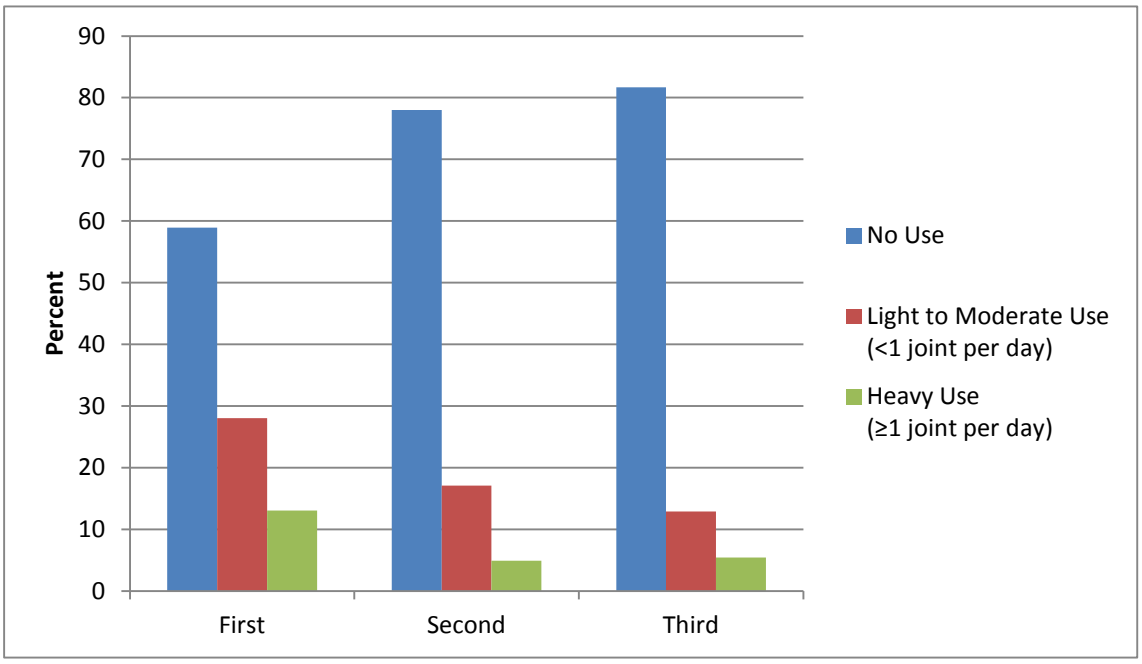

Figure 1. Maternal marijuana use by trimester

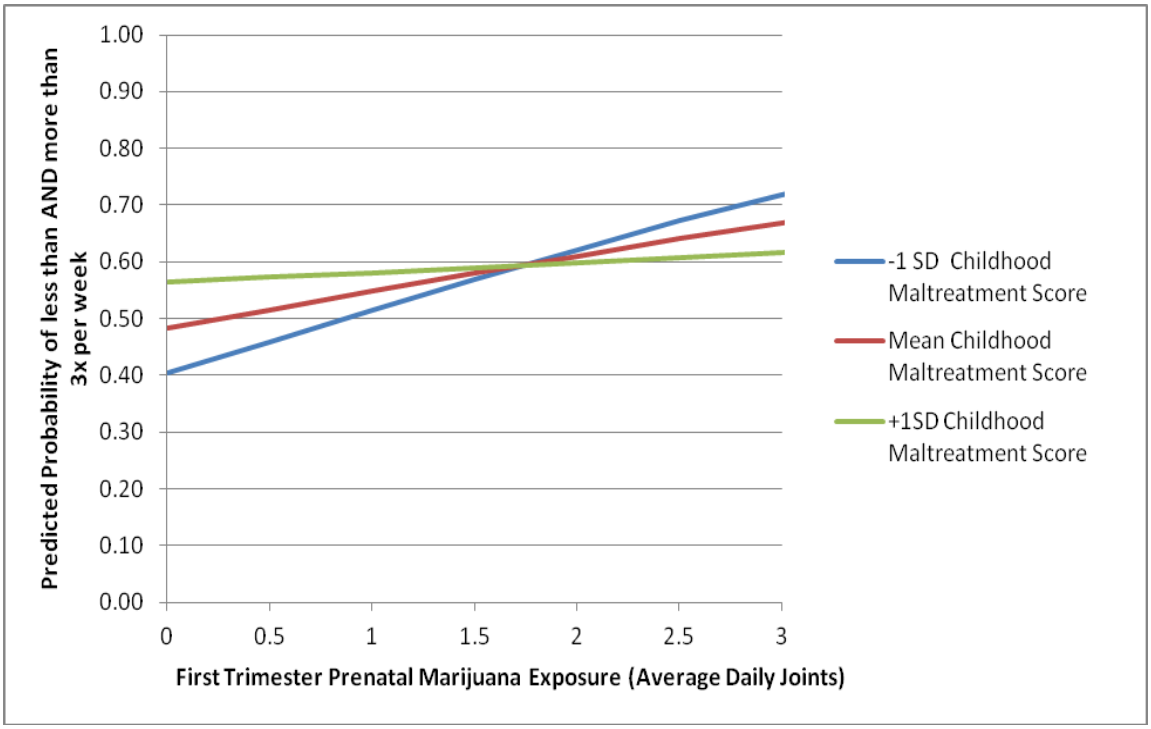

Figure 2. Predicted probability of offspring frequency of marijuana use

3.0 FROM PRENATAL MARIJUANA EXPOSURE TO OFFSPRING FREQUENCY OF MARIJUANA USE IN YOUNG ADULTHOOD: A PATH ANALYSIS

Manuscript in preparation

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3.1 ABSTRACT

Background. Prenatal marijuana exposure (PME) affects the development of the CNS of the fetus. Prior studies demonstrate that PME predicts offspring behavior in childhood and marijuana initiation and frequency of use in adolescence. The aim of this study was to evaluate pathways from PME to frequency of offspring marijuana use in young adulthood through offspring behavior and the age of marijuana initiation.

Methods. Path analyses were conducted to examine potential pathways from PME to offspring frequency of marijuana use at 22 years of age. Women were recruited from a prenatal clinic in Pittsburgh, Pennsylvania from 1982-1985 when they were in their fourth month of pregnancy. At 22 years, offspring marijuana use was defined as no use, use <3 times per week, and use ≥3 times per week. Analyses were performed on 585 mother-offspring pairs, representing 77% of the birth cohort. We tested the significance of the indirect paths from PME to young adult offspring marijuana use through offspring depressive symptoms, anxiety, attention, delinquent behavior at 10 years of age, and parental authoritativeness at age 16, as well as early initiation of marijuana use. Early initiation of marijuana was defined as never used, first use ≥16 years, or first use <16 years;

Results. There was not a significant direct relationship between PME and offspring frequency of marijuana use in young adulthood after adjusting for prenatal alcohol exposure, the home environment, maternal marijuana use when the offspring were 10 years of age, and offspring age, gender, race, and history of childhood maltreatment. However, there was a significant indirect path between PME and offspring frequency of use through early initiation of marijuana (p=0.025). There was a significant indirect path of PME on offspring frequency of use through depressive symptoms and early initiation of marijuana (p=0.043). PME predicted

initiation of marijuana use, although maternal marijuana use when the offspring were 10 years of age did not predict initiation. We did not find significant indirect pathways from PME to offspring frequency of marijuana use through offspring anxiety, attention, and delinquent behavior at age 10 or parental authoritativeness at age 16.

Conclusions. PME had an indirect effect on offspring frequency of marijuana use in young adulthood. These findings demonstrate that PME in conjunction with early age of initiation and depression create a vulnerability to marijuana use in offspring. The implications of this research are that there are several time points for public health intervention: women should be counseled to abstain from using marijuana during pregnancy, healthcare providers should screen for depressive symptoms in children, and public health efforts should focus on programs to delay the initiation of marijuana among youth.

3.2 INTRODUCTION

Marijuana is the most widely-used illicit substance in the world (Danovitch & Gorelick, 2012). The United Nations Office on Drugs and Crime (UNODC) estimates that the annual prevalence of use may be as high as 5% (United Nations Office on Drugs and Crime, 2012). Marijuana use typically begins in adolescence and peaks in young adulthood (Copeland, Rooke, & Swift, 2013). In the US, the average age of marijuana initiation is 17.5 years (Substance Abuse and Mental Health Services Administration [SAMSHA], 2012). Males have higher rates of use than females, but this gender gap may be narrowing (Perkonigg et al., 2008; von Sydow et al., 2001; SAMSHA, 2012; Wallace et al., 2003). In addition, national survey data of middle and high

school students indicate that use is highest among Native Americans, followed by Hispanics, whites, blacks, and Asian-Americans (Wallace et al., 2003).

Other influences also play a role in marijuana initiation and use. The effects of genetics on marijuana use have been demonstrated using twin studies (Agrawal & Lynskey, 2006) and family histories of substance use problems (Agrawal & Lynskey, 2006; von Sydow, Lieb, Pfister, Hofler, & Wittchen, 2002). Environmental factors include leaving the family home before the age of 18, family conflict, change in mother's marital status, maternal smoking and marijuana use when the offspring was an adolescent, parental supervision and control, and peer marijuana use (Day, Goldschmidt, & Thomas, 2006; M. R. Hayatbakhsh et al., 2008; M. R. Hayatbakhsh, Najman, Bor, O'Callaghan, & Williams, 2009; Perkonigg et al., 2008; Richardson, Larkby, Goldschmidt, & Day, 2013; von Sydow et al., 2002). Psychosocial factors include having an antisocial personality diagnosis, low self-competence, distressing life events, having a high number of symptoms of depression and anxiety, aggressive and delinquent behavior, and a history of childhood maltreatment, particularly sexual and physical abuse (Day et al., 1994; M. R. Hayatbakhsh et al., 2009; Kilpatrick et al., 2000; Lo & Cheng, 2007; Perkonigg et al., 2008).

One understudied factor is whether prenatal marijuana exposure (PME) is associated with offspring marijuana use. Marijuana is a commonly-used illicit substance during pregnancy. Findings from the National Pregnancy and Health Survey conducted in 1992-1993 demonstrate that 2.9% of women used marijuana at some point during pregnancy (National Institute on Drug Abuse [NIDA], 1996). When marijuana is consumed, delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient, enters the mother's bloodstream and crosses the placenta (Sundram, 2006). These exogenous cannabinoids bind to receptors in the developing ECS, which is important in progenitor cell migration and differentiation, neuronal migration, development of

axonal pathways, and the creation of functional synapses (Gaffuri, Ladarre, & Lenkei, 2012; Wu, Jew, & Lu, 2011). Animal models also demonstrate that PME affects the endogenous opioid, dopamine, and serotonin systems, which puts offspring at risk for problems with emotion regulation, memory, depression, and addiction later in life (Jutras-Aswad, DiNieri, Harkany, & Hurd, 2009).

Two birth cohorts have published findings on long-term behavioral outcomes of PME: the Maternal Health Practices and Child Development (MHPCD) study and the Ottawa Prenatal Prospective Study (OPPS). PME predicted deficits in memory and attention, increases in impulsivity and hyperactivity, symptoms of anxiety and depression, delinquent behavior, age of initiation of marijuana, and offspring frequency of marijuana use in adolescence (Day et al., 2006; Day, Leech, & Goldschmidt, 2011; Day et al., 1994; Fried & Watkinson, 1990; Fried, Watkinson, & Gray, 1992; Goldschmidt, Day, & Richardson, 2000; Goldschmidt, Richardson, Cornelius, & Day, 2004; Gray, Day, Leech, & Richardson, 2005; Leech, Richardson, Goldschmidt, & Day, 1999; Porath & Fried, 2005). All of these consequences of PME are also associated with marijuana use and serve as the rationale for our path analysis.

To date, no published findings exist on pathways from PME to offspring frequency of marijuana use in young adulthood. In this paper, we conducted path analyses to evaluate significant direct and indirect pathways to offspring frequency of marijuana use through offspring behavior. We hypothesized that: 1) PME would predict offspring frequency of marijuana use at 22 years, 2) PME would predict offspring depressive symptoms, anxiety, attention, and delinquent behavior at 10 years of age, early initiation of marijuana, and parental authoritativeness at age 16, 3) offspring depressive symptoms, anxiety, attention, and delinquent behavior at 10 years of age and parental authoritativeness at age 16 would predict early initiation

of marijuana, and 4) depressive symptoms, anxiety, attention, and delinquent behavior at 10 years of age, early initiation of marijuana, and parental authoritativeness at age 16 would predict offspring frequency of use at 22 years.

3.3 METHODS

3.3.1 Sample description

The data for this study come from the MHPCD study at the University of Pittsburgh. This is a longitudinal study evaluating the effects of prenatal exposure to alcohol and marijuana on offspring development. Study participants were recruited from a prenatal clinic at Magee Women's Hospital in Pittsburgh, PA from 1982-1985. To be eligible, participants had to speak English, be at least 18 years of age, and in their fourth or fifth gestational month. There was a 15% refusal rate. An initial interview about substance use (alcohol, tobacco, marijuana, and other illicit drugs) in the first trimester was completed by 1,360 women.

This initial interview was used to select two cohorts. One cohort was composed of women who drank three or more alcoholic drinks per week in the first trimester and a random sample of one-third of those women who drank less than this amount or not at all. The second cohort was composed of women who used marijuana at least two times per month in the first trimester and a random sample of one-third of those women who reported they used less marijuana or none at all. Sampling was done with replacement allowing women to eligible for both cohorts. Both studies had the same protocols and personnel, allowing the cohorts to be combined for analyses. The combined cohort was 829 women and there was 60% overlap

between the cohorts. This study was approved by the Institutional Review Board of the University of Pittsburgh and Magee-Womens Hospital, and informed consent was obtained from the women at each phase.

The women enrolled in the MHPCD study were interviewed again in their 7th gestational month. Subsequent assessments of mothers and offspring were conducted after the offspring's birth, 8 and 18 months, and 3, 6, 10, 14, 16, and 22 years of age. At each phase of data collection, information was gathered about maternal psychological, social, and environmental factors, demographic status, and substance use, and the children's cognitive, behavioral, psychological, and physical development.

The birth cohort consisted of 763 live singleton infants. Eight individuals refused the delivery assessment, 16 women were lost to follow-up, and 21 women moved out of the area. Other exclusions included 18 offspring due to fetal or perinatal death, one infant was placed for adoption and could not be followed, and two sets of twins. Only mother-child pairs who completed the assessment at birth were selected for follow-up.

At the 22-year phase, 608 offspring participated in an interview, 80% of the birth cohort. Among those 155 who did not participate, 30 individuals refused, 3 had been adopted, 18 were institutionalized, 56 were lost to follow up, 29 had moved out of the area, 11 had died, and 8 could not participate due to low cognitive functioning. Twenty-three individuals were excluded from the analyses: 14 did not complete the instrument about child maltreatment used in this analysis, five reported that they did not use marijuana but had positive results on a urine screen, and four initiated marijuana prior to the assessment of depressive symptoms at age 10. The final sample size was 585 individuals representing 77% of the birth cohort. Those who were included in the analyses (n=585) did not differ from those who were excluded from the analyses (n=178)

based on characteristics assessed at the first trimester visit. There were no differences by age, race, education, marital status, household income, and substance use (Appendix, Table 13).

3.3.2 Measures

3.3.2.1 Prenatal marijuana exposure

The mothers provided information about the pattern of their marijuana use at each assessment. A series of questions developed for the MHPCD study measured usual, maximum, and minimum quantity and frequency (Day & Robles, 1989). The same questions were asked about use of hashish and sinsemilla. Conversions of hashish and sinsemilla were done to account for the higher THC content in those substances. One joint of sinsemilla was equal to two joints of marijuana, one joint or bowl of hashish was equal to three joints of marijuana (Gold, 1989; Hawks, 1986; Julien, 1988). A blunt was scored as the self-reported number of joints in the blunt. If the participant did not report the number of joints in the blunt, then it was coded as four joints. Marijuana use was calculated as the average daily joints (ADJ). The ADJ formula is: (number of joints/week x 4 weeks/month)/31 days/month. An ADJ of 0.4 is equivalent to using three joints per week and an ADJ of 0.89 is equivalent to using one joint per day. A bogus pipeline was used to encourage accurate reporting of substance use at the first phase (Jones & Sigall, 1979).

3.3.2.2 Offspring frequency of marijuana use

Marijuana use among the offspring was measured with the same questions and conversions described above. The frequency categories were collapsed to no use, use <3 times per week, and use ≥3 times per week to be consistent with a prior analysis using this data set (Day et al., 2006).

3.3.2.3 Intervening variables and covariates

The variables considered for the analyses were based on a review of the literature and prior experience with this data set. The intervening variables were: offspring depressive symptoms, anxiety, attention, and delinquent behavior at age 10; early initiation of marijuana; and parenting at age 16.

At 10 years of age, the offspring completed the Children's Depression Inventory (CDI; Kovacs, 1992) that asks children about depressive symptoms experienced during the past two weeks. The instrument has 27 questions in which a 0 indicates not experiencing a symptom, a 1 indicates experiencing a mild symptom, and a 2 indicates experiencing the symptom. The responses were totaled and a continuous T-score was used in the analyses. Depressive symptoms at this phase were chosen for this analysis because PME predicted depressive symptoms at age 10 in this cohort and this assessment occurred before the majority of offspring initiated marijuana (Gray et al., 2005).

The Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds & Richmond, 1978) was used to assess offspring anxiety. This 28-item questionnaire assesses anxiety on subscales of physiological anxiety, worry/oversensitivity, and fear/concentration. The total score is the sum of the offspring's affirmative responses.

Offspring attention was assessed using the Swanson, Noland, and Pelham (SNAP; Pelham & Bender, 1982) questionnaire. The SNAP is made up of 25 questions that correspond with the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-3) definition of Attention Deficit Disorder with Hyperactivity. The responses of never, sometimes, often, and all the time are reported on a Likert scale ranging from 1-4. We used the attention

subscale in the analyses, which is the sum of four questions. The SNAP questionnaire was completed by the mothers.

Offspring delinquent behavior was assessed using the Child Behavior Checklist (CBCL; Achenbach; 1991). The mothers completed 113 questions about the offspring's behavior at 10 years. The responses are summed to create scores for total problems, internalizing problems, externalizing problems, and eight subscales. The delinquent behavior subscale T-score was used in these analyses.

At the 10-year assessment, the offspring were asked to report whether they had used alcohol or drugs and the age at which they first tried each substance (Jessor, Donovan, & Costa, 1989). These questions were also asked at the 14, 16, and 22-year study visits. Where there were differences, the youngest reported age of initiation was used in these analyses. Early initiation was defined at use <16 years of age. A categorical variable was created: never used marijuana, first use ≥16 years, or first use <16 years. The age used to define early initiation of substances varies in the literature (R. Hayatbakhsh, Williams, Bor, & Najman, 2013; Kokkevi, Nic Gabhainn, Spyropoulou, & Risk Behaviour Focus Group of the HBSC, 2006; Lynskey et al., 2003). We selected 16 because it is below the average age of marijuana initiation in the US (SAMSHA, 2012).

At 16 years of age, parenting was assessed using the My Parents (Steinberg, Lamborn, Dornbusch, & Darling, 1992) tool. The offspring completed this questionnaire and scores were ascertained for three subscales related to parental acceptance/involvement, supervision/strictness, and psychological autonomy granting. These subscales were used to create a composite of an overall score of authoritativeness used for the analyses (Steinberg et al., 1992). A subscale score

above the median was coded as a 1, otherwise it was coded as 0. The sum is added for a maximum of three.

The covariates for which we adjusted were first trimester maternal alcohol use, the home environment, maternal marijuana use when the offspring were 10 years of age, and the offspring's gender, age, race, and history of childhood maltreatment. We adjusted for maternal alcohol use because the analyses were conducted on the combined alcohol and marijuana cohorts. We adjusted for the home environment at age 10 as assessed by the mother's reports on the Home Observation for Measurement of the Environment-Short Form (HOME; Baker & Mott, 1989), a measure of the cognitive stimulation and emotional support that the child receives. The mothers reported their substance use when their offspring were 10 years of age. We chose to use the ADJ at this time point because of its potential influence on offspring use. The offspring's gender was ascertained from the birth assessment and age was calculated from the birth date. We adjusted for gender because males have a higher rate of marijuana use and age because offspring were 21-26 years old when completing this data collection phase. We also adjusted for race because African American mothers were more likely to use marijuana than Caucasian mothers in this sample. Lastly, we adjusted for offspring childhood maltreatment, which was assessed at 22 years of age using the Child Trauma Questionnaire (CTQ; Bernstein & Fink, 1998). The CTQ contains 25 items that assess whether an individual experienced the following five types of abuse: emotional abuse, physical abuse, sexual abuse, emotional neglect, or physical neglect when they were growing up. Respondents use a 5 point Likert scale ranging from never true to very often true. The scores for the subscales range from 5 to 25. The subscales were dichotomized to indicate whether an offspring had experienced moderate to severe abuse using the following suggested cut points for the five subscales: ≥13 for emotional abuse, ≥10 for

physical abuse, ≥8 for sexual abuse, ≥15 for emotional neglect, and ≥10 for physical neglect (Bernstein & Fink, 1998). A sum of the five dichotomous scales was used in the analyses.

3.3.3 Analysis plan

Analyses were performed on the combined marijuana and alcohol cohorts. We restricted our analyses to the first trimester for two reasons. First, approximately 10% of the participants did not complete the interview for the second trimester. Second, marijuana use declined during pregnancy. While 41% of the sample reported marijuana use during the first trimester, only 18% of the sample reported use by the third trimester (Figure 3). Sample sizes in the second and third trimesters were not large enough to analyze patterns of exposure. Table 14 of the Appendix displays the sample sizes and marijuana use of the mothers across gestation.

The distributions of marijuana and alcohol variables were examined. Out of range values for marijuana were set to 10.0 joints per day and the out of range values for alcohol use were set to 8.0 drinks per day.

Descriptive statistics were generated to explore the associations between variables. We looked at the correlations and performed t-tests or analysis of variance (ANOVA) to evaluate continuous variables. For those continuous variables that were not normally distributed, we used the Mann-Whitney U or the Kruskal-Wallis test. We performed Chi-square tests to evaluate the associations between dichotomous variables. Cohen's d and Cramer's V were calculated to assess effect size.

Path analyses were performed using Mplus version 5.2 (Muthén & Muthén, 2008). The mean and variance adjusted weighted least square (WLSMV) adjusted estimation method was used due to the categorical dependent variables in this analysis. The fit of the path model was

assessed using several indices. A value over 0.95 is considered good for the comparative fit index (CFI; Hu & Bentler, 1999). For the Tucker-Lewis Index (TLI), over .90 is considered a good fit, the Root Mean Square Error of Approximation (RMSEA) value of less than .06 is considered a good fit, and a Weighted Root Mean Square Residual (WRMR) of less than .90 is considered a good fit (Hu & Bentler, 1999; Yu, 2002).

3.4 RESULTS

Table 15 of the Appendix displays characteristics of the sample. At the first trimester visit, the average age of the mothers was 23 years (range: 18-42), 52% were African American, and 32% were married. The women had completed 11.8 years of education, 26% were in school or worked outside the home, and 61% had a household monthly income of less than $400. Sixty-four percent used alcohol, 41% used marijuana, 53% smoked cigarettes, 4% used cocaine, and 9% used other illicit drugs. At birth, 47% of the offspring were male. The average gestational age was 40 weeks and the average birth weight was 3.2kg. At 10 years of age, the offspring had an average CDI T-score of 45.94 (range: 35-77), with a higher score indicating more depressive symptoms. The average anxiety score was 10.06 (range: 0-29), the average attention score was 8.84 (range: 5-20), and the average delinquent behavior CBCL subscale T-score was 55.98 (50-94). The average parenting score for authoritativeness was 1.43, indicating parenting was somewhat nonauthoritative. By age 16, 51% of the offspring had tried marijuana. At the 22-year assessment, the average age was 22.8 years and 56% of the offspring were African American. They had completed 12.8 years of education and 61% were working and/or in school. The median monthly income was $800. Thirty-five percent were living with their mother or a

caregiver, 6% were married, and 37% had at least one child. Twenty-nine percent experienced moderate, severe, or extreme childhood maltreatment. The average childhood maltreatment score was 2.42 (range: 1-5) with a higher score indicating a higher level of childhood maltreatment. In the past year, 43% of the offspring used cigarettes, 92% used alcohol, 7% used cocaine, and 14% used other illicit drugs. Fifty percent of offspring did not use marijuana, 29% used marijuana <3 times per week, and 20% used marijuana ≥3 times per week in the past year.

Table 5 displays sample characteristics by maternal first trimester marijuana use. For descriptive purposes, categories were created representing women who did not use marijuana during the first trimester, light to moderate users (<1 joint/day), and heavy users (≥1 joint/day). As the category of PME increased, there was an increase in the percent of African American women, household income less than $400, average daily volume of alcohol, cigarette use, cocaine use, and use of other illicit drugs. As the level of PME increased, the percent of women who were married decreased. Women with PME in the light to moderate categories had the highest percent of women who reported any alcohol use. There were no differences in PME by maternal age, years of education completed, or average daily cigarettes smoked. PME was associated with maternal marijuana use when the offspring were 10 years of age. The mean ADJ increased as PME increased. At birth, offspring did not differ by gender, gestational age, or birth weight. At 10 years, offspring depressive symptoms, anxiety, and attention problems increased as PME increased. There were no differences by PME in delinquent behavior or the home environment at age 10 or parental authoritativeness at age 16. At 22 years, the offspring with PME were slightly younger and more likely to be African American. There were no differences by years of education completed, whether they were working and/or in school, personal monthly income, marital status, living with a mother or caregiver, having at least one child, or history of

childhood maltreatment. Those offspring with PME were more likely to initiate marijuana and to initiate marijuana early compared to those offspring without PME. The percent of offspring who reported any marijuana use in the past year increased as PME increased. There were no differences according to past-year use of alcohol, cigarette, cocaine, or other illicit drugs.

Table 16 of the Appendix displays sample characteristics according to offspring frequency of marijuana use at 22 years. There were no differences according to the maternal age, education, working outside the home and/or in school, or household income. Offspring who did not use marijuana were more likely to have white mothers and those who used were more likely to have African American mothers. The percent of mothers who were married at the first trimester visit decreased as the offspring frequency of use category increased. There were no significant differences by maternal use of alcohol, cigarettes, cocaine, or other illicit drugs. Maternal use during the first trimester increased as offspring frequency of use increased. At birth, there were no differences by gestational age. Birth weight was inversely proportional to the frequency of marijuana use. The percent of males significantly increased as frequency of marijuana use increased. Home environment scores decreased as frequency of offspring marijuana use increased, demonstrating lower emotional support and cognitive stimulation among those who became frequent marijuana users. Maternal mean ADJ, depressive symptoms, anxiety, attention problems, and delinquency scores increased as offspring frequency of offspring marijuana use increased. At age 16, there were no differences by parental authoritativeness. At 22 years, there were significant demographic differences. As the frequency of use increased, the percent of African Americans in each category increased. Younger offspring used marijuana at lower rates, and the percent of offspring who were married and working and/or in school decreased as offspring frequency of marijuana use increased. Offspring

median income also decreased as frequency of marijuana use category increased. Having at least one child or living with a mother or caregiver did not differentiate use patterns. There was a difference by childhood maltreatment: Nonusers had the lowest average childhood maltreatment scores compared to marijuana users, although those who used at a higher rate (<3x per week) reported more childhood maltreatment compared to heavier users. Marijuana initiation differed according to offspring frequency of use. Those using most frequently were more likely to initiate marijuana before age 16. Marijuana users were also more likely to report using alcohol, cigarettes, cocaine, and other illicit drugs.

Path analyses were used to test our hypotheses. First, we fit a model with depressive symptoms at age 10 and early initiation of marijuana as the hypothesized intervening variables, adjusting for prenatal alcohol exposure, the home environment, maternal marijuana use when the offspring were 10 years of age, and offspring age, gender, race, and history of childhood maltreatment. Although we hypothesized that PME would have a significant direct effect on offspring frequency of marijuana use, the results did not support this hypothesis (p=0.841) (Appendix, Table 17, Model 1). In a second model, we removed this path. In model 2, we observed that the path from depressive symptoms to offspring frequency of use was non-significant (p=0.502). We removed this path (Model 3) and observed that the covariate of maternal marijuana use at 10 years was not a significant predictor of offspring age of initiation. We further evaluated this relationship by using it as an intervening variable instead of a covariate (Model 4). The model fit was good. There was no significant difference between the observed and model covariance matrices, $\chi^2(3) = 0.969$, p = 0.809, CFI = 1.000, TLI = 1.054, RMSEA = 0.000, WRMR = 0.085. We used this as our base model for adding other intervening variables.

We hypothesized that there would be a significant indirect effect from PME to offspring frequency of marijuana use through anxiety, attention, and delinquent behavior at age 10 and parenting at age 16. We tested the effect of each intervening variable separately. PME did not significantly predict anxiety, attention, delinquent behavior, or parenting. There were no significant indirect effects and none of these intervening variables are included in our final model. Thus, these hypotheses were not supported. Thus, Model 4 was retained as the final model.

The final results are displayed in Table 6 and Figure 4. PME predicted depressive symptoms at age 10 ($\beta = 0.140$; $p<0.001$) as did prenatal alcohol exposure ($\beta = 0.080$; $p=0.041$), the home environment score ($\beta = -0.107$; $p=0.016$), and childhood maltreatment ($\beta = 0.158$; $p<0.001$). Overall, 9% of the variance of depressive symptoms was explained by PME and the covariates. PME also predicted maternal marijuana use at 10 years ($\beta = 0.141$; $p<0.001$). Overall, 12% of the variance of maternal marijuana use at the 10-year assessment was explained by PME and the covariates.

PME significantly predicted early initiation of marijuana use in the offspring. Offspring were 14% more likely to initiate marijuana early for a one standard deviation increase in PME.

Offspring were 13% more likely to initiate marijuana early for one standard deviation increase in depressive symptoms. Male offspring were 15% more likely to initiate marijuana earlier than females. Twelve percent of the variance of early initiation of marijuana was explained by PME, depressive symptoms, maternal marijuana use at the 10-year assessment, and the covariates. Offspring who initiated use earlier were 73% more likely to be in a higher frequency of use category. Thirty-eight percent of the variance of offspring frequency of use was explained by marijuana initiation and the covariates.

Overall, there was a significant indirect effect of PME on offspring frequency of marijuana use at age 22 through early initiation of marijuana (p=0.025). There was a significant indirect effect of PME on offspring frequency of marijuana use at age 22 through two intervening variables, depressive symptoms and early initiation of marijuana (p=0.043).

3.5 DISCUSSION

The aim of this paper was to describe the direct and indirect pathways from PME to offspring frequency of marijuana use in young adulthood. Although PME predicted offspring frequency of marijuana use at 22 years in bivariate analyses, the association was not significant after adjusting for prenatal alcohol exposure, the home environment, maternal marijuana use when the offspring were 10 years of age, and the offspring's age, gender, race, and history of childhood maltreatment. We found a significant indirect path from PME to offspring frequency of marijuana use through early initiation of marijuana. We found a second significant indirect path of PME on offspring frequency of marijuana use through depressive symptoms and early initiation of marijuana.

Although PME predicted offspring marijuana initiation, maternal marijuana use at 10 years did not, suggesting a biological association between PME and offspring frequency of marijuana use rather than an environmental influence. Although PME predicted attention, anxiety, and delinquent behavior at age 10 in prior analyses of this dataset, we did not see significant paths in our model (Goldschmidt et al., 2000; Goldschmidt et al., 2004). One reason may be that we controlled for childhood maltreatment in these analyses but not in earlier ones.

This study has several strengths. The study had a large sample size of 585 individuals and excellent follow-up rates with 77% of the birth cohort available for this analysis. Second, this study recruited approximately equal numbers of African American and Caucasian women, allowing a racially heterogeneous sample. Third, the data for this study were obtained prospectively, which avoids recall bias.

There are some limitations of this analysis. This sample is composed of predominately low income women, and the results may not be generalizable to women in higher socioeconomic groups. Additionally, marijuana use was ascertained by self-report. However, a bogus pipeline procedure was used to encourage accurate reporting from mothers at the first prenatal visit. At the 22-year visit, a urine screen was part of the study protocol for the offspring. Among those who reported they did not use marijuana, only 2% screened positive. Among those who reported that they used marijuana in the past year, 64% had positive results on the urine screen. While the results of the urine screen can only offer information on recent marijuana use, they do suggest that participants are being honest about their use. Further, staff members who interviewed the participants were comfortable asking questions about the sensitive topics (e.g., substance use, psychosocial factors) and followed an established protocol for the sequence of questioning. In addition, a NIH Certificate of Confidentiality allowed us to reassure the participants that their data were confidential.

In summary, this analysis identified significant indirect paths from PME to offspring frequency of marijuana use in young adulthood. Marijuana use has health and psychosocial consequences. Chronic smoking of marijuana affects the respiratory system (Taylor et al., 2002). Marijuana use is associated with an increased risk of schizophrenia symptoms and 9% of users become dependent (Andreasson, Allebeck, Engstrom, & Rydberg, 1987; Anthony, Warner, &

Kessler, 1994; Arseneault et al., 2002). Other adverse factors associated with marijuana use include lower educational achievement and income, unemployment, and risky sexual behavior, which can lead to unintended pregnancy or sexually transmitted infections (Fergusson & Boden, 2008; Staton et al., 1999). In the MHPCD sample, 29% of those using ≥3 times per week had a history of a lifetime Cannabis Use Disorder diagnosis compared to 17% of those using <3 times per week and 6% of non-users in the past year. The most frequent users in young adulthood had a higher rate of licit and illicit substance use, less formal education, were less likely to be working and/or in school, were less likely to be married, had a lower personal monthly income, and were more likely to be arrested. Thus, the adverse consequences of cannabis use are numerous but preventable.

Our conclusions offer several time points for public health intervention. First, pregnancy is a time of frequent contact with a healthcare provider and pregnant women should be encouraged to abstain from using marijuana. Second, healthcare providers could screen for depressive symptoms in children. Third, public health could focus interventions to delay marijuana initiation because it is a strong predictor of marijuana use in young adulthood.

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3.7 TABLES AND FIGURES

Table 5. Sample characteristics by category of first trimester marijuana use

	Maternal Marijuana Use				
	No use[a] (n=344)	Light to moderate use[b] (n=164)	Heavy use[c] (n=77)	**p-value[d]**	**Effect size[e]**
Maternal Characteristics at the First Trimester					
Age (mean years)	23.34	22.62	22.84	0.151	0.007
Race (% African American)	45.64	53.05	75.32	<0.001	0.196
Marital status (% married)	37.21	27.44	18.18	0.002	0.147
Education (mean years)	11.87	11.84	11.73	0.700	0.001
Employment status (% working outside the home and/or in school)	25.58	31.10	14.29	0.021	0.115
Household income (%<US$400/month)[f]	57.01	64.42	73.33	0.020	0.117
Alcohol use (%)	55.23	78.05	74.03	<0.001	0.222
Average daily volume of alcohol	0.40	0.75	0.78	<0.001	0.027
Cigarette use (%)	47.09	60.37	64.94	0.002	0.148
Average daily cigarettes	7.58	8.70	9.38	0.339	0.004
Cocaine use (%)	1.74	5.49	9.09	0.004	0.139
Other illicit drug use (%)	6.98	9.76	15.58	0.051	0.101
Offspring Characteristics at Birth					
Gender (% male)	47.38	47.56	44.16	0.856	0.022
Gestational age (mean weeks)	39.70	39.96	39.84	0.403	0.003
Birth weight (mean kg)	3.21	3.22	3.08	0.183	0.006
Characteristics at 10 Years					
Home environment[g] (mean score)	12.88	12.50	12.37	0.200	0.006
Depressive symptoms[h] (mean score)	45.25	45.82	49.04	0.003	0.023
Anxiety symptoms[i] (mean score)	9.65	10.15	11.65	0.033	0.012
Attention[j] (mean score)	8.58	8.97	9.70	0.004	0.017
Delinquent behavior[j] (mean score)	55.54	56.18	57.45	0.173	0.008
Maternal average daily joints[k]	0.02	0.07	0.26	<0.001	0.083
Characteristics at 16 Years					
Parental authoritativeness overall score[l]	1.50	1.33	1.33	0.137	0.008
Offspring Characteristics at 22 Years					
Age (mean years)	22.90	22.78	22.70	0.030	0.012
Race (% African American)	51.74	55.49	79.22	<0.001	0.182
Education (mean years)	12.82	12.91	12.39	0.058	0.010

Table 5 Continued

Work status (% working and/or in school)	62.21	64.02	51.95	0.176	0.077
Median personal income (US$/month)[m]	1006	972	803	0.291	0.006
Marital status (% married)	5.23	7.93	3.90	0.356	0.059
Lives with mother or caregiver (%)	37.21	30.49	33.77	0.324	0.062
Has at least one child (%)	35.76	34.76	45.45	0.230	0.071
Child maltreatment (mean score)	2.34	2.51	2.61	0.144	0.009
Past-year cigarette use (%)	40.70	43.29	53.25	0.132	0.083
Average daily cigarettes	3.94	4.61	5.47	0.186	0.006
Past-year alcohol use (%)	92.15	93.29	92.21	0.897	0.019
Average daily volume of alcohol	1.48	1.83	1.59	0.102	0.005
Marijuana initiation (%)					
>16 years	47.67	51.22	62.34	0.022	0.099
≥16 years	31.40	35.98	28.57		
Never	20.93	12.80	9.09		
Past-year marijuana use (%)	43.60	56.71	62.34	0.001	0.151
Average daily joints of marijuana	0.69	0.68	1.70	<0.001	0.028
Frequency of marijuana use (%)					
No use	56.40	43.29	37.66	0.001	0.126
Use <3 times per week	28.49	30.49	31.17		
Use ≥3 times per week	15.12	26.22	31.17		
Past-year cocaine use in past year (%)	5.52	7.93	9.09	0.393	0.057
Past-year other illicit drug use (%)	11.63	14.63	19.48	0.168	0.078

[a] Zero joints per day
[b] Less than one joint per day
[c] One or more joints per day
[d] ANOVA for continuous variables, Kruskal-Wallis test for skewed variables, χ^2 test for dichotomous variables
[e] Eta^2 for continuous variables, Cramer's V for dichotomous variables; absolute value reported
[f] Sample size: 328, 163, 75
[g] Sample size: 294, 148, 68
[h] Sample size: 294, 146, 70
[i] Sample size: 293, 147, 69
[j] Sample size: 298, 148, 69
[k] Sample size: 298, 148, 70
[l] Sample size: 282, 141, 67
[m] Sample size: 336, 159, 75

Table 6. Path results for final model

	B	β	z	p	R^2
Depressive Symptoms ← PME					0.092
Prenatal marijuana exposure	1.256	0.140	3.535	<0.001	
Prenatal alcohol exposure	0.618	0.080	2.048	0.041	
Offspring gender	-1.407	-0.084	-1.958	0.050	
Offspring age	-0.158	-0.013	-0.290	0.772	
Offspring race	-0.016	-0.001	-0.020	0.984	
Home environment	-0.334	-0.107	-2.403	0.016	
Childhood maltreatment	1.224	0.158	3.638	<0.001	
Maternal Use ← PME					0.116
Prenatal marijuana exposure	0.096	0.319	14.977	<0.001	
Prenatal alcohol exposure	-0.002	-0.007	-0.145	0.884	
Offspring gender	0.008	0.015	0.364	0.716	
Offspring age	0.003	0.007	0.284	0.776	
Offspring race	-0.028	-0.050	-0.617	0.537	
Home environment	-0.008	-0.075	-1.778	0.075	
Childhood maltreatment	-0.016	-0.062	-1.382	0.167	
Early Initiation ← PME, Depressive Symptoms, and Maternal Use					0.122
Prenatal marijuana exposure	0.156	0.135	2.651	0.021	
Depressive symptoms	0.016	0.125	2.651	0.008	
Maternal use	0.079	0.021	0.391	0.696	
Prenatal alcohol exposure	0.071	0.072	1.416	0.157	
Offspring gender	0.298	0.139	3.028	0.002	
Offspring age	-0.162	-0.106	-2.380	0.017	
Offspring race	0.207	0.096	1.928	0.054	
Home environment	-0.040	-0.102	-1.928	0.054	
Childhood maltreatment	0.118	0.120	2.398	0.016	
Offspring Use ← Early Initiation					0.382
Early initiation	0.655	0.550	8.665	<0.001	
Prenatal alcohol exposure	0.075	0.063	1.246	0.213	
Offspring gender	0.317	0.124	2.888	0.004	
Offspring age	-0.088	-0.049	-1.147	0.251	
Offspring race	-0.418	-0.163	-3.413	0.001	
Home environment	-0.010	-0.022	-0.422	0.673	
Childhood maltreatment	0.040	0.034	0.694	0.488	

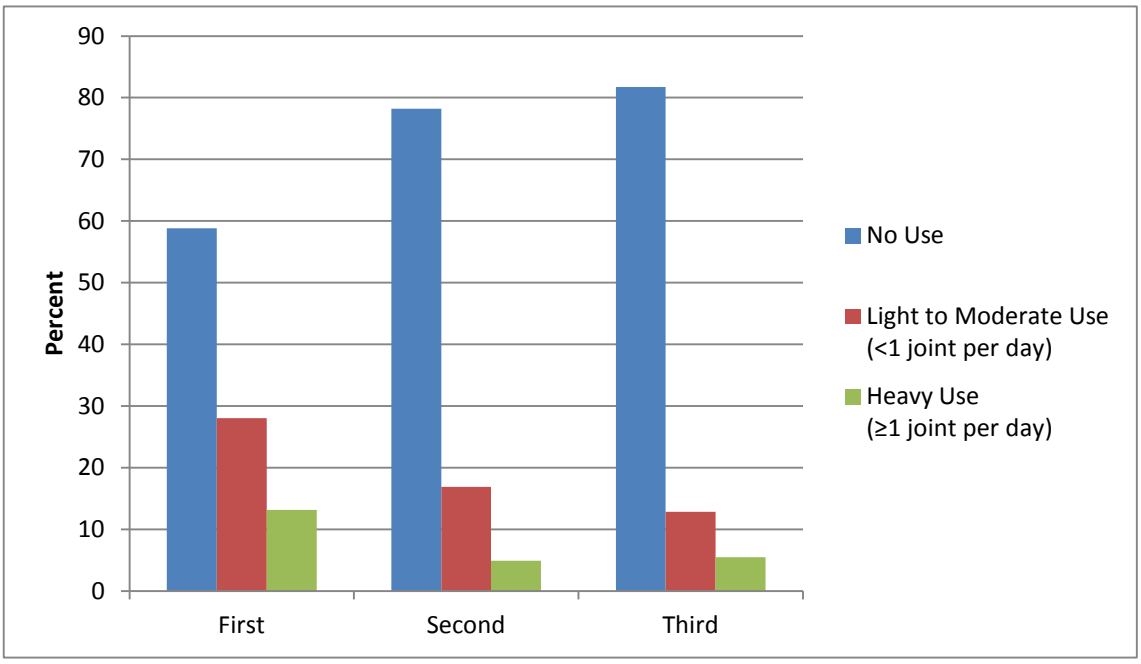
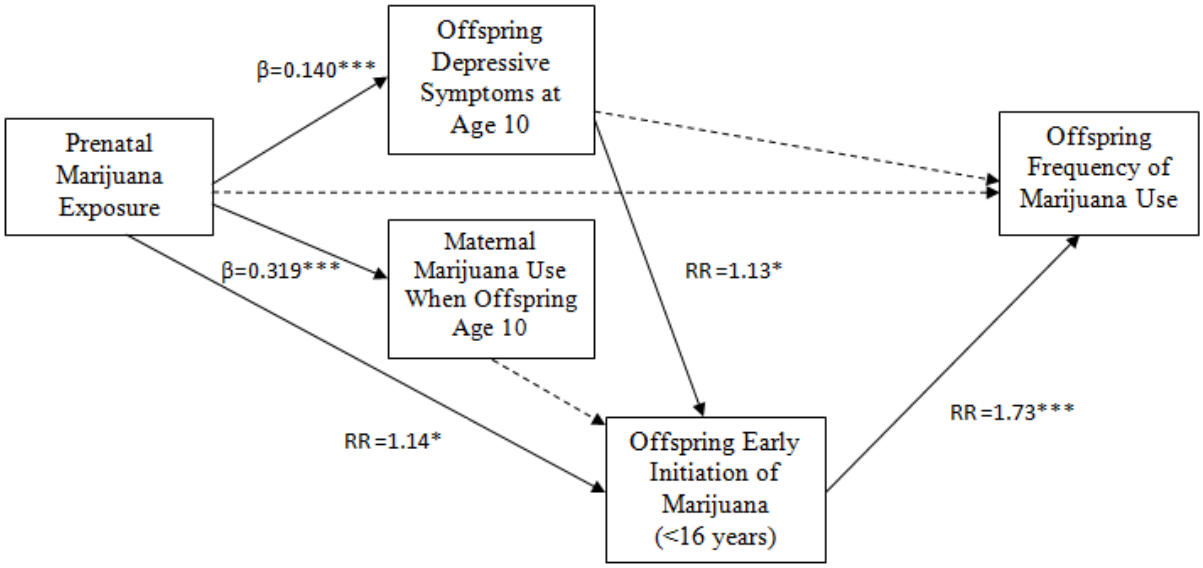


Figure 3. Maternal marijuana use by trimester



*p<.05, **p<.01, ***p<.001

Adjusted for prenatal alcohol exposure, home environment, and offspring age, sex, and race, and history of childhood maltreatment

Figure 4. Final path model

4.0 FROM PRENATAL MARIJUANA EXPOSURE TO OFFSPRING CANNABIS USE DISORDER IN YOUNG ADULTHOOD: A PATH ANALYSIS

Manuscript in preparation

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4.1 ABSTRACT

Background. Prenatal marijuana exposure (PME) affects the CNS of the developing offspring, changing behavior, emotional status, and cognition. Prior studies have demonstrated that PME predicts offspring depressive symptoms, initiation of marijuana, and frequency of marijuana use. No published findings have evaluated pathways from PME to Cannabis Use Disorder (CUD) diagnosis in offspring. In this paper, we will evaluate whether PME predicts CUD, and whether offspring depressive symptoms and early initiation of marijuana are in the pathway from PME to CUD diagnosis in young adulthood.

Methods. A path analysis was conducted to examine potential pathways from PME to CUD in offspring at 22 years of age. Women were recruited from a prenatal clinic in Pittsburgh, Pennsylvania from 1982-1985 when they were in their fourth month of pregnancy. At 22 years, the offspring completed the Diagnostic Interview Schedule-IV (DIS-IV). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria were used to determine a diagnosis of cannabis abuse or dependence. Analyses were performed on 590 mother-offspring pairs, representing 77% of the birth cohort. Using structural equation modeling, we tested the significance of the indirect paths of PME to CUD through offspring depressive symptoms at age 10 and early initiation of marijuana, defined as first use before age 16, first use after age 16, or never used marijuana.

Results. At 22 years of age, 80 offspring (14%) had a CUD diagnosis. While there was not a significant pathway from PME to CUD after adjusting for prenatal alcohol exposure and the offspring's age, gender, and race, there was a significant indirect path from PME to CUD through early initiation of marijuana ($p=0.013$). There was also a significant indirect path of PME to CUD through depressive symptoms and early initiation of marijuana ($p=0.023$).

Conclusions. Although PME did not directly predict CUD, it was associated with a significant indirect pathway through depressive symptoms and early initiation of marijuana to CUD. The implications of this research are that there are several time points for public health intervention prior to the development of CUD: women should be counseled to abstain from using marijuana during pregnancy, healthcare providers should screen for depressive symptoms in children, and public health efforts should focus on programs to delay the initiation of marijuana among youth.

4.2 INTRODUCTION

Marijuana is the most widely-used illicit substance in the world (Danovitch & Gorelick, 2012). The United Nations Office on Drugs and Crime (UNODC) estimates that the annual prevalence of use may be as high as 5% (United Nations Office on Drugs and Crime, 2012). Marijuana is typically initiated in adolescence and used most often until young adulthood (Copeland, Rooke, & Swift, 2013).

Cannabis use disorder (CUD) is a diagnosis of cannabis dependence or cannabis abuse defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; APA, 2000). US national survey data demonstrate that the lifetime prevalence of CUD in the US is 8.5% (Stinson, Ruan, Pickering, & Grant, 2006). Further, CUD is often a co-morbid psychopathological condition. Those with a CUD diagnosis are also likely to have a diagnosis of an alcohol use disorder, mood disorder, anxiety disorder, or personality disorder (Stinson et al., 2006).

Prior research has identified demographic and risk factors for CUD. Demographic factors include male gender, African American race, and age, as those affected are often adolescents or young adults (Compton, Grant, Colliver, Glantz, & Stinson, 2004; Pacek, Malcolm, & Martins, 2012). Risk factors identified in the literature include family history and genetic heritability of CUD, aggressive or delinquent behavior, symptoms of depression and anxiety, exposure to violence, use of other licit or illicit substances, early initiation of cannabis use, and a history of sexual abuse in childhood (Agrawal & Lynskey, 2006; Brook, Lee, Finch, Koppel, & Brook, 2011; Chen, O'Brien, & Anthony, 2005; M. R. Hayatbakhsh, Najman, Bor, O'Callaghan, & Williams, 2009; von Sydow, Lieb, Pfister, Hofler, & Wittchen, 2002).

No study has considered the effects of prenatal marijuana exposure (PME). When marijuana is consumed by a pregnant woman, the main psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), enters her bloodstream and crosses the placenta (Sundram, 2006). These exogenous cannabinoids bind to receptors in the developing ECS, which has an important role in progenitor cell migration and differentiation, neuronal migration, development of axonal pathways, and the creation of functional synapses in the CNS (Gaffuri, Ladarre, & Lenkei, 2012; C. S. Wu, Jew, & Lu, 2011). Animal models also demonstrate that PME can affect the endogenous opioid, dopamine, and serotonin systems (Jutras-Aswad, DiNieri, Harkany, & Hurd, 2009). These changes put offspring at risk for problems with emotion regulation, memory, depression, and addiction later in life.

Two birth cohort studies have evaluated the long-term effects of PME in human populations: the Maternal Health Practices and Child Development (MHPCD) study and the Ottawa Prenatal Prospective Study (OPPS). In the MHPCD study, PME predicted depressive symptoms in offspring as well as age of marijuana initiation (HR=1.14) and frequency of

marijuana use (OR=1.30) at age 14 (Day, Goldschmidt, & Thomas, 2006; Gray, Day, Leech, & Richardson, 2005). In the OPPS cohort, PME predicted age of marijuana initiation (OR=2.76, 95% CI: 1.11-6.86) but not frequency of marijuana use between ages 16-21 (OR=0.79, 95% CI: 0.33-1.90) (Porath & Fried, 2005).

By young adulthood, initiation of marijuana has largely occurred and marijuana use is most frequent. To date, there have been no findings published on pathways from PME to offspring diagnosis of CUD in young adulthood. In this paper, we identified the direct and indirect effects of PME on offspring CUD diagnosis at 22 years of age. We hypothesized that: 1) PME predicts CUD, 2) depressive symptoms at age 10 predict a CUD diagnosis at age 22, 3) PME predicts depressive symptoms at age 10, 4) PME predicts early initiation of marijuana, 5) depressive symptoms at age 10 predict early initiation of marijuana, and 6) early initiation of marijuana predicts a CUD diagnosis at age 22.

4.3 METHODS

4.3.1 Sample description

The data for this study come from the MHPCD study at the University of Pittsburgh. This is a longitudinal study designed to evaluate the effects of prenatal exposure to alcohol and marijuana on offspring development. Participants were recruited from a prenatal clinic at Magee-Womens Hospital in Pittsburgh, PA. The recruitment took place from 1982-1985. To be eligible, participants had to speak English, be at least 18 years of age, and in their fourth or fifth gestational month. The refusal rate was 15%. There were 1,360 women who completed an initial

interview about substance use in the first trimester. These substances were alcohol, tobacco, marijuana, cocaine, and other illicit drugs.

The initial interview was conducted to select two cohorts. One cohort was composed of women who drank three or more alcoholic drinks per week in the first trimester and a random sample of one-third of those women who drank less than this amount or not at all. The second cohort was composed of women who used marijuana at least two times per month in the first trimester and a random sample of one-third of those women who reported they used less marijuana or none at all. Sampling was done with replacement allowing women to be eligible for both cohorts. All participants followed the same protocols, which allowed the cohorts to be combined for analyses. The combined cohort was composed of 829 women with 60% overlap. Informed consent was obtained from the women and this study was approved by the Institutional Review Boards of the University of Pittsburgh and Magee-Womens Hospital.

The women in the MHPCD cohorts were interviewed again in their 7th gestational month. Subsequent assessments of mothers and offspring were conducted after the offspring's birth, 8 and 18 months, and 3, 6, 10, 14, 16, and 22 years of age. At each phase of data collection, information was gathered about maternal psychological, social, and environmental factors, demographic status, and substance use, and the children's cognitive, behavioral, psychological, and physical development.

The birth cohort consisted of 763 live singleton infants. Eight individuals refused the delivery assessment, 16 women were lost to follow-up, and 21 women moved out of the area. Other exclusions included 18 offspring due to fetal or perinatal death, one child who was placed for adoption and could not be followed, and two sets of twins. Only those mother-child pairs who completed the assessment at birth were followed-up.

At the 22-year phase, 608 offspring participated in an interview, representing 80% of the birth cohort. Among those 155 individuals who did not participate, 30 refused the assessment, 3 had been adopted and could not be followed, 18 were institutionalized in jail or a rehabilitation facility, 56 were lost to follow-up, 29 had moved out of the area, 11 died, and 8 could not participate due to low cognitive functioning. Eighteen individuals were excluded for the purposes of this analysis: 14 did not complete the instrument used to assess CUD and four initiated marijuana prior to the assessment of depressive symptoms at age 10. The final sample size was 590 offspring, representing 77% of the birth cohort. Those included in the analysis (n=590) did not differ from those excluded from the analysis (n=173) based on maternal age, race, education, marital status, household income, and substance use assessed at the first trimester interview (Appendix, Table 18).

4.3.2 Measures

4.3.2.1 Prenatal marijuana exposure

The mothers provided information about their patterns of marijuana use at each assessment. A series of questions developed for the MHPCD study was administered to assess usual, maximum, and minimum use and quantity (Day & Robles, 1989). The same questions were asked to ascertain use of hashish and sinsemilla. Conversions of hashish and sinsemilla amounts were done to account for the higher THC content in those substances. One joint of sinsemilla was equal to two joints of marijuana, one joint or bowl of hashish was equal to three joints of marijuana (Gold, 1989; Hawks, 1986; Julien, 1988). A blunt was scored as the self-reported number of joints in the blunt. If the participant did not report the number of joints in the blunt, then it was coded as four joints. Marijuana use was calculated as the average daily joints (ADJ).

The ADJ formula is: (number of joints/week x 4 weeks/month)/31 days/month. An ADJ of 0.4 is equivalent to using three joints per week and an ADJ of 0.89 is equivalent to using one joint per day. A bogus pipeline procedure was used initially to encourage accurate reporting of substance use (Jones & Sigall, 1971).

4.3.2.2 Cannabis Use Disorder

At the 22-year assessment, the offspring completed the Diagnostic Interview Schedule-IV (DIS-IV; Robins, et al., 1994). The DIS-IV is a structured interview that can be administered by non-clinicians. The DIS-IV aligns with the criteria of the DSM-IV (APA, 2000). Current (past 12 months) and lifetime diagnoses of cannabis abuse and dependence were assessed. The interviews were audiotaped and a trained clinician listened to a random sample of de-identified tapes to ensure the study protocol was followed. If a deviation from protocol was observed, then staff members received additional training.

4.3.2.3 Intervening variables and covariates

The variables considered for these analyses were based on a review of the literature and prior experience with this data set. At 10 years of age, the offspring completed the Children's Depression Inventory (CDI; Kovacs, 1992), which asks children to report depressive symptoms experienced during the past two weeks. The offspring completed 27 questions in which a 0 indicates not experiencing a symptom, a 1 indicates experiencing a mild symptom, and a 2 indicates experiencing the symptom. The responses were totaled and a continuous T-score was used in the analyses. Depressive symptoms at this phase were used because PME predicted depressive symptoms at age 10 in the cohort and the assessment occurred before the overwhelming majority of offspring initiated marijuana (Gray et al., 2005).

At the 10-year assessment, offspring were asked to report whether they had used alcohol, marijuana, or other illicit drugs. They completed a series of questions in the study protocol to ascertain patterns of substance use, including a question about the age at which they first tried marijuana (Jessor, Donovan, & Costa, 1989). These questions were also asked at the 14, 16, and 22-year study visits. Where there were differences, the youngest reported age of initiation was used in these analyses. Early initiation was defined as use <16 years of age. A categorical variable was created: marijuana use before age 16, marijuana use at or after age 16, and never using marijuana. The age used to define early initiation of substances varies in the literature (R. Hayatbakhsh, Williams, Bor, & Najman, 2013; Kokkevi, Nic Gabhainn, Spyropoulou, & Risk Behaviour Focus Group of the HBSC, 2006; Lynskey et al., 2003). We selected 16 because it is below the average age of marijuana initiation in the US (Substance Abuse and Mental Health Services Administration [SAMSHA], 2012).

The covariates in these analyses were maternal alcohol use during the first trimester and the offspring's gender, age, and race. Maternal alcohol use during the first trimester was ascertained from questions about substance use patterns designed for the MHPCD study (Day & Robles, 1989). We adjusted for this variable because the analyses were conducted on the combined alcohol and marijuana cohorts. The offspring's gender was ascertained from the birth assessment and age was calculated from the birth date. We adjusted for gender because males have a higher rate of CUD and age because there was variability at the 22-year assessment. We also adjusted for race because African American mothers were more likely to use marijuana than Caucasian mothers in this sample. Although the home environment at age 10 was assessed using the Home Observation for Measurement of the Environment-Short Form (HOME; Baker & Mott, 1989) and offspring child maltreatment was assessed at 22 years of age using the Child

Trauma Questionnaire (CTQ; Bernstein & Fink, 1998), neither variable was associated with the exposure and outcome in bivariate analyses. Therefore, these variables were not included as covariates in the final model.

4.3.3 Analysis plan

Analyses were performed on the combined marijuana and alcohol cohorts. We restricted our analyses to the first trimester for two reasons. First, approximately 9% of the participants did not complete the second trimester interview. Second, marijuana use declined during pregnancy. While 41% of the sample reported marijuana use during the first trimester, only 18% of the sample reported use by the third trimester (Figure 5). As a result, sample sizes in the second and third trimesters were not large enough to analyze patterns of exposure. Table 19 of the Appendix displays the sample sizes and marijuana use of the mothers across gestation.

The distributions of marijuana and alcohol variables were examined. Out of range values for marijuana were set to 10.0 joints per day and the out of range values for alcohol use were set to 8.0 drinks per day.

Descriptive statistics were generated to explore the associations between the variables considered for this analysis. We looked at the correlations and performed t-tests or analysis of variance (ANOVA) to evaluate continuous variables. For continuous variables that were not normally distributed, we used the Mann-Whitney U test or the Kruskal-Wallis test. We performed Chi-square tests to evaluate the association between dichotomous variables. Cohen's d and Cramer's V were calculated to assess effect size.

Path analyses were performed with the Mplus version 5.2 (Muthén & Muthén, 2008). The mean and variance adjusted weighted least square (WLSMV) estimation method was used due to

the categorical dependent variables in this analysis. The fit of the path model was assessed using several indices. A value over 0.95 is considered good for the comparative fit index (CFI; Hu & Bentler, 1999). For the Tucker-Lewis Index (TLI), over .90 is considered a good fit, a Root Mean Square Error of Approximation (RMSEA) value of less than .06 is considered a good fit, and a Weighted Root Mean Square Residual (WRMR) of less than .90 is considered a good fit (Hu & Bentler, 1999; Yu, 2002).

4.4 RESULTS

Table 20 of the Appendix displays characteristics of the sample. At the initial visit, the average age of the mothers was 23 years (range: 18-42), 52% were African American, and 31% were married. The women completed an average of 11.8 years of education, 25% were in school or worked outside the home, and 61% had a household monthly income of less than $400 in 1982-1985. Forty-one percent used marijuana and the average ADJ was 0.38, demonstrating a mean use of three times per week. Sixty-four percent of the mothers drank alcohol, 53% smoked cigarettes, 4% used cocaine, and 9% used other illicit drugs.

At birth, 47% of the offspring were male. The average gestational age was 40 weeks and the average birth weight was 3.2kg. At 10 years of age, the offspring had an average CDI T-score of 45.99 (range: 35-79), with a higher score indicating more depressive symptoms. Fifty-one percent of the offspring used marijuana before age 16. At the 22-year assessment, the average age was 22.8 years and 57% of the offspring were African American. They had completed an average of 12.8 years of education, and 61% were working and/or in school. Their median monthly income was $800, 35% were living with their mother or a caregiver, 6% were married,

and 37% had at least one child. Forty-three percent reported smoking cigarettes, 92% reported drinking alcohol, 6% used cocaine, and 13% used other illicit drugs. Although 82% had used by the 22-year study phase, only 49% of offspring reported using marijuana in the past year. The prevalence of CUD was 14% in the total cohort and 16% among those who used marijuana.

Table 7 displays sample characteristics by maternal first trimester marijuana use. For descriptive purposes, categories were created representing women who did not use marijuana during the first trimester, light to moderate users (<1 joint/day), and heavy users (≥1 joint/day). As the amount of PME increased, there was an increase in the percent of African American women, a household income less than $400, average daily volume of alcohol consumed, any use of tobacco, cocaine, or other drugs, and a decrease in the proportion of women who were married. There were no differences by maternal age, years of education completed, or average daily cigarettes. At birth, there were no significant differences in offspring gender, weight, or gestational age by PME category. At 10 years, offspring depressive symptoms increased as PME increased. At the 22-year assessment, the offspring with PME were slightly younger and more likely to be African American. There were no differences between those with PME and those without by years of education completed, whether they were working and/or in school, personal monthly income, marital status, or the percent living with a mother or caregiver. There were no differences according to past-year use of alcohol, cigarette, cocaine, or other illicit drugs. There was, however, a significant difference with marijuana use. The percent of those who reported past-year marijuana use increased as PME increased. Offspring ADJ also increased as PME increased. Although the rate CUD diagnoses increased as PME increased, this observation was not statistically significant.

Table 21 of the Appendix displays sample characteristics according to CUD diagnosis of the offspring. There were no differences between those with and without CUD, according to maternal demographic characteristics or maternal substance use. The offspring did not differ by gestational age or birth weight. There was a difference by gender. Among those with a CUD diagnosis, 74% were male compared to 43% among those without a CUD diagnosis. The number of depressive symptoms at age 10 did not differ by CUD status. On average, those without a CUD diagnosis completed one more year of education than those with a CUD diagnosis. There were no other significant demographic differences. While there was no difference in the proportion of past-year alcohol users, offspring with a CUD diagnosis consumed a higher ADV of alcohol and more often used other illicit substances.

Hypothesis 1 was that PME would predict CUD. Although CUD diagnoses increased as PME increased, the association was not statistically significant in the bivariate analyses.

Path models were used to test the remaining hypotheses. First, we fit the conceptual model (Appendix, Figure 8) and evaluated the pathways for significance. Depressive symptoms at age 10 did not predict CUD at age 22 ($p=0.738$). Thus, Hypothesis 2 was not supported. This path was removed to create a final parsimonious model. The overall fit for this model was good. There was no significant difference between the observed and model covariance matrices, $\chi^2(2) = 0.161$, $p = 0.923$, CFI = 1.000, TLI = 1.134, RMSEA = 0.000, WRMR = 0.079 (Appendix, Table 22). Table 8 displays the path results for this final model.

Hypothesis 3 was that PME would predict depressive symptoms. This hypothesis was supported. We observed a significant positive prediction of depressive symptoms at age 10 by PME ($\beta = 0.141$; $p<0.001$). There was also a significant positive prediction of depressive symptoms at age 10 by prenatal alcohol exposure and gender, where male offspring had

significantly fewer depressive symptoms than females. Overall, 5% of the variance of depressive symptoms was explained by PME and covariates.

Hypotheses 4 and 5 were that PME and depressive symptoms at age 10 would predict early initiation of marijuana, respectively. These hypotheses were supported. Offspring were 16% more likely to initiate marijuana early for a one standard deviation increase in PME. A one standard deviation increase in depressive symptoms increased the likelihood of earlier marijuana initiation by 18%. Male offspring were 32% more likely to initiate marijuana earlier than females. For every one year increase in age, offspring were 15% less likely to initiate marijuana early. Overall, 9% of the variance of marijuana initiation was explained by PME, depressive symptoms, and the covariates.

Hypothesis 6 was that early initiation of marijuana would predict CUD at age 22. This hypothesis was supported. Offspring who initiated marijuana early were 61% more likely be diagnosed with CUD. Male offspring were two times more likely to be diagnosed with CUD than females. Prenatal alcohol exposure, age, and race were not associated with CUD. Thirty-four percent of the variability of CUD was explained by marijuana initiation and the covariates.

Our sample includes offspring who did not initiate marijuana as well as those who did. To assess the effects of this, we ran our models excluding those who did not initiate marijuana and observed a 12% reduction in the R^2 of initiation predicting CUD diagnosis. The implications of this are that we may be overestimating the influence of initiation because CUD is a conditional diagnosis. However, in both samples, initiation was still the strongest contributor in the path to CUD.

We considered whether these findings were specific to CUD diagnosis as opposed to any Substance Use Disorder (SUD). We excluded offspring with a CUD diagnosis and evaluated the

association between PME and any offspring SUD. SUD diagnosis did not increase as PME increased and the relationship was not significant in bivariate analyses (p=0.169). We also ran the path models with this reduced sample. The pathway from PME to SUD through early initiation of marijuana was marginally significant (p=0.090). The pathway from PME to SUD through depressive symptoms and early initiation of marijuana was also marginally significant (p=0.071). These results suggest that PME may be specific to CUD outcome but this should be evaluated in future studies.

In conclusion, although the direct effect was not significant, there were two significant pathways representing the indirect effects of PME on CUD at age 22. The first was through early initiation of marijuana (p=0.013), and the second was through two intervening variables, depressive symptoms and early initiation of marijuana (p=0.023).

4.5 DISCUSSION

The goal of these analyses was to evaluate whether PME predicted offspring CUD in young adulthood, and whether depressive symptoms and early initiation of marijuana were in the pathway from PME to offspring CUD in young adulthood. The direct pathway from PME to CUD was not significant. However, we found a significant indirect path of PME to CUD through early initiation of marijuana. We also found a significant indirect path of PME to CUD through depressive symptoms and early initiation of marijuana.

In our sample, the lifetime prevalence of CUD was 16% among those who used marijuana. Our rate is higher than the 8.5% listed by Stinson et al. (2006). Our cohort is composed of offspring of predominantly low-income women who used substances during

pregnancy, which may explain the differences. This is because our sample may be at a higher risk of CUD compared to the US national sample reported by Stinson et al. (2006).

This analysis offers insight about the relationship between depressive symptoms, marijuana initiation, and CUD. Although marijuana use and CUD have been associated with depression and depressive symptoms, the relationship is unclear (Brook et al., 2011; Degenhardt, Hall, & Lynskey, 2003; Fergusson & Horwood, 1997). Depressive symptoms did not predict CUD in this study. However, the longitudinal nature of the study allowed us to assess depressive symptoms before marijuana initiation and demonstrate that depressive symptoms predicted early initiation, which in turn predicted CUD. This is consistent with recent findings on 12 to 17-year-old participants from the National Survey on Drug Use and Health (NSDUH; SAMSHA, 2007). Subjects who reported a major depressive episode in the past were more likely to initiate marijuana use than were those who did not experience a major depressive episode. Further, depressive symptoms have been shown to be associated with the initiation of other substances (P. Wu et al., 2006). This topic needs further exploration in data sets that can establish a temporal relationship of depressive symptoms, marijuana use, and Substance Use Disorders.

This study had several limitations. Although self-report of substance use may be considered a limitation, efforts were made to encourage accurate reporting. At the first prenatal visit, a bogus pipeline procedure was used for the mothers and a urine screen was part of the study protocol for the offsprings' reports of substance use. Further, the staff members who interviewed the participants were comfortable asking questions about the sensitive topics (e.g., substance use, psychosocial factors) and followed an established protocol for the sequence of questioning. In addition, a NIH Certificate of Confidentiality allowed us to reassure the clients that their data were confidential.

This study had several strengths. First, this sample is heterogeneous with 52% of the mothers being African American and 48% Caucasian. Second, there was excellent follow-up with 80% of the birth cohort interviewed at age 22. Third, the large sample size allowed us to use a path analysis to test our hypotheses. Lastly, the prospective nature of the data collection allowed use to minimize recall bias and establish a temporal sequence of events to evaluate pathways from PME to CUD.

In conclusion, to the best of our knowledge, this is the first study to evaluate potential pathways from PME to CUD in young adulthood. Our findings are important because CUD is a preventable public health problem and there are currently no approved medications to treat CUD (Danovitch & Gorelick, 2012). While behavioral therapy has been shown to be effective, the success rates are poor to modest with about 9-29% of individuals treated reporting abstinence after one year (Budney, Roffman, Stephens, & Walker, 2007). Thus, we need to develop methods to prevent the development of CUD.

Our results identify several time points for intervention. Pregnancy is a time when women have frequent contact with healthcare providers and should be encouraged to abstain from marijuana. Depressive symptoms are a risk factor for marijuana initiation. This knowledge is important for parents and healthcare providers because children can easily be screened for depressive symptoms and offered treatment. Finally, public health efforts should be targeted toward delaying initiation of marijuana as this is a risk factor for CUD. This will be particularly salient as states continue to adopt policies permitting medical and recreational marijuana use.

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4.7 TABLES AND FIGURES

Table 7. Sample characteristics by category of first trimester marijuana use

	None[a] (n=350)	Light to Moderate[b] (n=161)	Heavy[c] (n=79)	p-value[d]	Effect Size[e]
Maternal Characteristics at the First Trimester Visit					
Age (mean years)	23.29	22.57	22.87	0.161	0.006
Education (mean years)	11.89	11.84	11.70	0.522	0.002
Race (% African American)	46.86	52.17	75.95	<0.001	0.193
Marital status (% married)	36.57	26.09	17.72	0.001	0.150
Employment status (% in school or worked outside the home)	25.43	30.43	15.19	0.039	0.105
Household income <US$400/month (%)[f]	56.89	64.38	72.73	0.022	0.115
Alcohol use (%)	55.14	77.02	74.68	<0.001	0.216
Average daily volume of alcohol	0.40	0.75	0.86	<0.001	0.031
Cigarette use (%)	46.57	60.25	67.09	0.001	0.162
Average daily cigarettes	7.40	8.80	9.53	0.195	0.006
Cocaine use (%)	1.43	5.59	8.86	0.001	0.149
Other illicit drug use (%)	6.86	9.32	15.19	0.055	0.099
Offspring Characteristics at Birth					
Gender (% male)	47.14	47.83	45.57	0.947	0.014
Birth weight	3.21	3.23	3.09	0.180	0.006
Gestational age	39.70	39.93	39.86	0.486	0.002
Offspring Characteristics at 10 Years					
Children's Depression Inventory T-Score (mean)[g]	45.36	45.70	49.19	0.005	0.023
Marijuana initiation Before age 16 (%) Between ages 16-22 Never	 47.71 30.57 21.71	 50.31 36.65 13.04	 63.29 27.85 8.86	0.009	0.107
Offspring Characteristics at 22 Years					
Age (years)	22.89	22.77	22.69	0.029	0.012
Race (% African American)	52.86	54.66	79.75	<0.001	0.182
Employed or in school (%)	61.71	63.98	51.90	0.180	0.076
Education (years)	12.82	12.95	12.42	0.054	0.001
Personal income (median US$/month)[h]	800	800	650	0.257	0.006
Lives with mother or caregiver (%)	37.71	31.06	32.91	0.307	0.063

Table 7 Continued

Marital status (% married)	5.14	7.45	3.80	0.433	0.053
Past-year alcohol use (%)	92.00	93.17	92.41	0.899	0.019
Average daily volume of alcohol	1.44	1.85	1.62	0.044	0.007
Past-year cigarette use (%)	40.00	44.72	51.90	0.133	0.083
Average daily cigarettes	3.80	4.81	5.28	0.120	0.007
Past-year marijuana use (%)	43.14	55.28	62.03	0.002	0.147
Average daily joints	0.67	0.69	1.70	<0.001	0.028
Past-year cocaine use (%)	4.86	8.70	8.86	0.167	0.078
Past-year other illicit drug use (%)	11.43	14.91	18.99	0.164	0.078
Cannabis Use Disorder (%)	12.86	14.29	15.19	0.819	0.026
Cannabis Use Disorder among lifetime marijuana users (%)	16.42	16.43	16.67	0.999	0.002

[a] Zero joints per day
[b] Less than 1 joint per day
[c] One or more joints per day
[d] ANOVA for continuous variables, Kruskal-Wallis test for skewed variables, χ^2 test for dichotomous variables
[e] Eta^2 for continuous variables, Cramer's V for dichotomous variables; absolute value reported
[f] Sample sizes: 334, 160, 77
[g] Sample sizes: 301, 145, 72
[h] Sample sizes: 341, 157, 77

Table 8. Path results for final model

	B	β	z	p	R^2
Depressive Symptoms ← PME					0.049
Prenatal marijuana exposure	1.374	0.152	3.734	<0.001	
Prenatal alcohol exposure	0.603	0078	2.102	0.036	
Offspring gender	-1.838	-0.108	-2.469	0.014	
Offspring age	-0.250	-0.021	-0.430	0.667	
Offspring race	-0.580	-0.034	-0.746	0.456	
Early Initiation ← Depressive Symptoms and PME					0.092
Depressive symptoms	0.020	0.165	3.497	<0.001	
Prenatal marijuana exposure	0.163	0.146	2.543	0.011	
Prenatal alcohol exposure	0.070	0.074	1.538	0.124	
Offspring gender	0.284	0.135	2.880	0.004	
Offspring age	-0.162	-0.108	-2.335	0.020	
Offspring race	0.120	0.057	1.219	0.223	
CUD ← Early Initiation					0.341
Early Initiation	0.562	0.479	4.957	<0.001	
Prenatal alcohol exposure	0.016	0.014	0.272	0.786	
Offspring gender	0.700	0.284	4.430	<0.001	
Offspring age	-0.050	-0.028	-0.480	0.631	
Offspring race	-0.091	-0.037	-0.569	0.569	

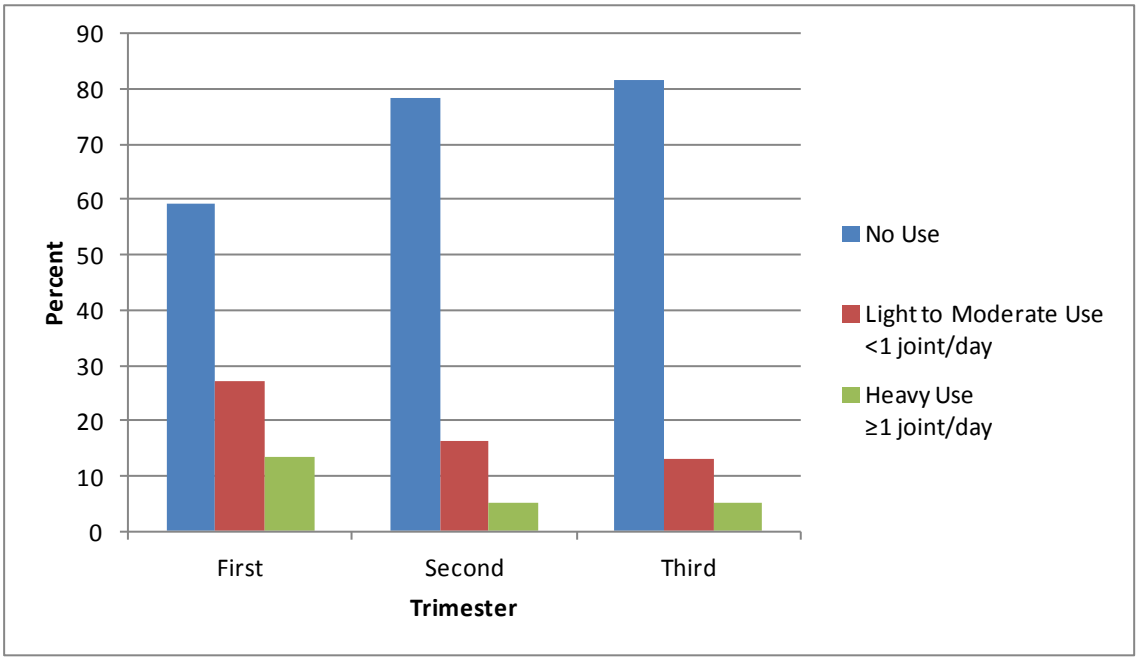
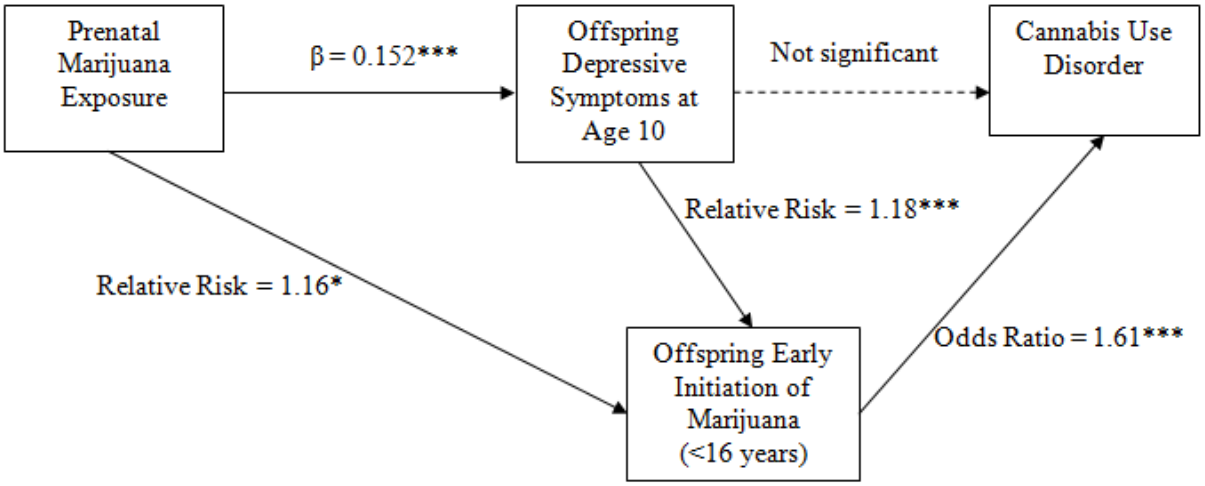


Figure 5. Maternal marijuana use by trimester



*p<.05, **p<.01, ***p<.001

Adjusted for prenatal alcohol exposure and offspring age, gender, and race

Figure 6. Final path model

5.0 DISCUSSION AND CONCLUSIONS

5.1 OVERVIEW OF FINDINGS

The goal of this dissertation was to evaluate the effects of PME on frequency of offspring marijuana use and CUD in offspring in young adulthood. The main findings and a summary of each paper are presented.

In Paper 1, we evaluated the association between PME and frequency of offspring marijuana use in young adulthood. Using a simple ordinal logistic regression model, PME significantly predicted frequency of offspring marijuana use at 22 years. This finding was attenuated to non-significance after adjusting for prenatal alcohol exposure, the home environment and maternal marijuana use at the 10-year assessment, and the offspring's race, gender, age, and history of childhood maltreatment. The association between PME and frequency of offspring use was moderated by a history of childhood maltreatment, but not by race or gender. The interaction between PME and offspring childhood maltreatment suggested that PME was associated with frequency of offspring use at low levels of childhood maltreatment, but not at high levels of childhood maltreatment.

In Paper 2, we examined the role of several intervening variables in the pathway from PME to offspring frequency of use in young adulthood. We did not find significant pathways when considering aggression, anxiety, attention or delinquent behavior at age 10. We did observe

significant indirect paths when considering offspring depressive symptoms and early initiation of marijuana. Offspring depressive symptoms were self-reported at age 10 and early initiation of marijuana defined as first use before age 16, first use at age 16 or older, and never used. After adjusting for prenatal alcohol exposure, the home environment, and the offspring's age, gender, race, and history of childhood maltreatment, there was a significant indirect path of PME on offspring frequency of use through early initiation of marijuana. There was also a significant indirect path of PME on offspring frequency of use through depressive symptoms and early initiation of marijuana. Further, we found that PME was a significant path to initiation, but maternal marijuana use when the offspring were 10 years of age did not predict initiation.

In Paper 3, we examined the role of offspring depressive symptoms and early initiation of marijuana as variables in the pathway from PME to CUD. Offspring depressive symptoms were self-reported at age 10 and early initiation of marijuana was defined as first use before age 16, first use at age 16 or older, and never used. After adjusting for prenatal alcohol exposure and the offspring's age, gender, and race, there was a significant indirect path of PME on CUD through early initiation of marijuana. There was also a significant indirect path of PME on CUD through depressive symptoms and early initiation of marijuana.

5.2 STRENGTHS AND LIMITATIONS

The strengths of the MHPCD study make these dissertation papers important contributions to the literature. First, this data set is unique because it has assessments of the patterns of substance use during pregnancy and the offspring who were followed through young adulthood. There are few data sets in the world that have such data about prenatal marijuana exposure and offspring

substance use. Second, the study population was a racially heterogeneous sample. About half of the women recruited for the study were African American and the other half were Caucasian. This allowed us to test for interactions by race, and broadly report information about offspring marijuana use and CUD in the cohort by race. Third, the retention rate of the sample is outstanding. The efforts made to track the mothers and their offspring have resulted in 80% of the birth cohort being available for analysis at the 22 year period.

Despite these noted strengths, there are a few limitations to this dissertation. This sample is composed of predominately low income women, and the results may not be generalizable to women in higher socioeconomic groups. Additionally, marijuana use was ascertained by self-report. However, a bogus pipeline procedure was used to encourage honest reporting from mothers at the first prenatal visit. In addition, a urine screen was part of the study protocol for the offspring. Further, the staff members who interviewed the participants were comfortable asking questions about the sensitive topics (e.g., substance use, psychosocial factors) and followed an established protocol for the sequence of questioning. In addition, a National Institutes of Health Certificate of Confidentiality was obtained for this study because of the sensitive nature of topics discussed. This provides research participants with a sense of confidentiality and privacy because it offers protection from the release of identifying information when requested through court order or subpoena.

5.3 PUBLIC HEALTH SIGNIFICANCE

The findings of this dissertation are significant to public health. Marijuana is the most widely-used illicit substance during pregnancy. Findings from the National Pregnancy and Health

Survey conducted in 1992-1993 indicate that 2.9% of women used marijuana at some point during pregnancy (NIDA, 1996). And, while animal and human models do not suggest that PME is associated with physical defects seen at birth, the findings of this dissertation contribute to the body of literature on the long-term behavioral effects on offspring. Further, the THC content in marijuana has doubled since the 1980s when the women were recruited for this study (UNODC, 2012). Therefore, our results may underestimate the effects we would see in a cohort recruited today.

Public health intervention can take many forms. First, pregnancy is a time of frequent contact with a healthcare provider. Providers can educate women about the potential risks of marijuana use and encourage them to abstain during pregnancy. Second, our results demonstrated that child depressive symptoms predicted early initiation of marijuana. Parents and healthcare providers should be educated about this risk. If depressive symptoms are suspected, then a pediatrician can administer a screening tool during an office visit. The results of the screening tool can be used to determine whether the child should be referred elsewhere for possible treatment. Third, educational programs about the consequences of marijuana use should continue to be targeted toward youth. Programs could focus on refraining from using marijuana; however, delaying initiation of marijuana would also be a desirable outcome. This is especially important now that states have authorized the legal use of marijuana for medical purposes and recreational use.

5.4 FUTURE DIRECTIONS OF RESEARCH

The findings of this dissertation suggest that PME may create a vulnerability for offspring. Future work in this sample could include following this cohort for a longer period of time, as the offspring in the sample are now about the age of 30. It would be interesting to evaluate the patterns of marijuana use at this age, as well as the lifetime prevalence of CUD in this high-risk sample.

Another opportunity for research would be to repeat this study in another sample. The findings would be an important contribution to the literature, as the results could be compared to those of the OPPS and MHPCD study. Further, because the THC content of marijuana has doubled since this study began, it is plausible that the effects of the MHPCD study underestimate what would be seen in a cohort recruited today. Finally, with the recent introduction of synthetic marijuana, there is an opportunity to look at the long-term effects of prenatal exposure to this substance as well. Little is known about synthetic marijuana use patterns, and researchers do not yet know if the effects are the same as marijuana.

5.5 CONCLUSIONS

The goal of this dissertation was to evaluate the effects of PME on offspring frequency of marijuana use and CUD at 22 years. While PME was not a significant predictor of offspring frequency of use at 22 years after adjusting for environmental and psychosocial variables, there were significant indirect pathways from PME to frequency of use. We also demonstrated significant pathways from PME to CUD.

The results of this dissertation suggest that PME may create a vulnerability for offspring, and this is an important contribution to the literature. These findings support the need to focus public health efforts on the prevention of marijuana use and educating the public about the potential risks of using this substance. Our findings are particularly relevant to pregnant women, who should be encouraged to abstain from marijuana.

APPENDIX: ADDITIONAL TABLES AND FIGURES

Table 9. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, criteria for Cannabis Use Disorder

Abuse	A maladaptive pattern of cannabis use leading to clinically significant impairment or distress, as manifested by **one or more** of the following, during a 12 month period: 1. Recurrent cannabis use that interferes with major role obligations at work, school, or home. Examples include frequent absences, poor performance, suspensions, job loss or expulsion from school, neglect of children or household. 2. Recurrent cannabis use in situations in which it is physically hazardous. Examples include driving or operating machinery when intoxicated. 3. Recurrent legal problems related to cannabis use. 4. Persistent cannabis use despite continued social or interpersonal problems caused or exacerbated by the effects of cannabis, such as arguments with a spouse about the consequences of intoxication. The symptoms have never met criteria for cannabis dependence.
Dependence	A maladaptive pattern of cannabis use resulting in clinically significant impairment or distress, as indicated by **three or more** of the following at any time during the same 12 month period: 1. Tolerance, defined by either of the following: a. Using markedly increased amounts of cannabis to achieve the desired effect or intoxication. b. Markedly diminished effect with continued use of the same amount of cannabis. 1. Cannabis is often taken in larger amounts or over a longer period than was intended. 2. There is a persistent desire or there are unsuccessful efforts to cut down or control cannabis use. 3. A great deal of time is spent obtaining cannabis, using it, or recovering from its effects. 4. Important social, occupational, or recreational activities are

Table 9 Continued

	neglected because of cannabis use. Persistent cannabis use despite knowledge of having a recurrent or ongoing physical or psychological problem that is probably caused or exacerbated by cannabis, such as a chronic cough related to smoking or a decrease in goal related activities.

Table 10. Chapter 2: First trimester maternal characteristics of offspring included in and excluded from the analyses

Maternal Characteristics First Trimester	**Included in Analyses (n=589)**	**Excluded from Analyses (n=174)**	**p-value[a]**	**Effect Size[b]**
Age (mean years)	23.06	22.95	0.752	0.027
Race (% African American)	51.44	51.72	0.948	0.002
Education (mean years)	11.83	11.91	0.532	0.054
Marital status (% married)	32.09	35.06	0.463	0.027
Household income (mean US$/mo)	300-399[c]	300-399[d]	0.407	0.073
Average daily volume of alcohol	0.55	0.77	0.137	0.164
Any alcohol use (%)	64.18	67.24	0.457	0.030
Average daily joints of marijuana	0.37	0.43	0.931	0.057
Any marijuana use (%)	41.09	38.51	0.542	0.022
Average daily cigarettes	8.17	8.89	0.471	0.062
Any cigarette use (%)	53.14	58.05	0.254	0.041
Any cocaine use (%)	3.74	4.02	0.862	0.006
Any other illicit drug use (%)	8.83	9.20	0.881	0.005

[a]t-test for continuous variables, Mann Whitney test for skewed variables, χ^2 test for dichotomous variables

[b]Cohen's d for continuous variables, Cramer's V for dichotomous variables; absolute value reported

[c]sample size 570

[d]sample size 166

Table 11. Chapter 2: Maternal marijuana use by trimester

	First Trimester N = 589	Second Trimester N = 532	Third Trimester N = 589
No use[a] (n, %)	347 (58.91)	415 (78.01)	481 (81.66)
Light to moderate use[b] (n, %)	165 (28.01)	91 (17.11)	76 (12.90)
Heavy use[c] (n, %)	77 (13.07)	26 (4.89)	32 (5.43)

[a] Zero joints per day
[b] Less than one joint per day
[c] One or more joints per day

Table 12. Chapter 2: Sample characteristics

	Total N	Mean or n	Standard deviation or %	Range
Maternal Characteristics at the First Trimester Visit				
Age (mean years)	589	23.06	4.04	18-42
Race (n, % African American)	589	303	51.44	
Education (mean years)	589	11.83	1.36	7-18
Marital status (n, % married)	589	189	32.09	
Employment status (n, % in school and/or working outside the home)	589	150	25.47	
Household income (n, %<US$400/month)	589	350	61.40	0-1000+
Depression (mean CES-D score)	585	20.96	8.59	1-51
Anxiety (mean STPI score)	588	17.74	4.65	10-39
Hostility (mean STPI score)	588	18.73	5.75	10-40
Any alcohol use (n, %)	589	378	64.13	
Average daily volume of alcohol among cohort	589	0.55	1.07	0-8
Average daily volume of alcohol among users	382	0.85	1.24	0.0057-8
Any marijuana use (n, %)	589	242	41.09	
Average daily joints of marijuana among cohort	589	0.37	0.93	0-7.4
Average daily joints of marijuana among users	242	0.91	1.27	0.0011-7.4
Any cigarette use (n, %)	589	313	53.14	
Average daily cigarettes among cohort	589	8.17	11.37	0-50
Average daily cigarettes among users	313	15.38	11.50	0.5-50
Any cocaine use (n, %)	589	22	3.74	
Any other illicit drug use (n, %)	589	52	8.83	
Offspring Characteristics at Birth				
Gender, % male)	589	278	47.20	
Gestational age (mean weeks)	589	39.80	2.19	28-44
Preterm birth (n, % <37 weeks)	589	48	8.15	
Birthweight (mean kg)	589	3.20	0.57	1.04-4.99
Low birth weight (n, %<2500g)	589	59	10.02	

Table 12 Continued

Characteristics at 10 Years				
Home environment score (mean)	514	12.71	2.69	3-18
Maternal average daily joints among cohort	520	0.07	0.28	0-2.6
Maternal average daily joints among users	110	0.37	0.54	0.0015-2.6
Any maternal marijuana use (n, %)	520	110	21.15	
Maternal average daily volume of alcohol among cohort	520	0.91	1.59	0-8
Maternal average daily volume of alcohol among alcohol users	407	1.16	1.71	0.0075-8
Any maternal alcohol use (n, %)	520	407	78.27	
Maternal average daily cigarettes among cohort	520	9.16	10.85	0-50
Maternal average daily cigarettes among cigarette smokers	305	15.62	10.00	.5-50
Any maternal cigarette use (n, %)	520	305	58.65	
Any maternal other illicit drug use (n, %)	520	43	8.27	
Characteristics at 16 Years				
Parental acceptance/involvement score (mean)	499	30.21	4.38	15-36
Parental psychological autonomy score (mean)	499	24.19	4.83	9-36
Parental strictness/supervision score (mean)	493	18.88	3.97	8-30
Parental authoritativeness overall score (mean)	493	1.42	0.94	0-3
Offspring has peers who use cigarettes (n, %)	503	400	79.52	
Offspring has peers who drink alcohol (n, %)	503	399	79.32	
Offspring has peers who smoke marijuana (n, %)	502	375	74.70	
Offspring Characteristics at 22 Years				
Age (mean years)	589	22.84	0.70	21.16-26.09
Race (n, % African American)	589	331	56.20	
Education (mean years)	589	12.79	1.63	8-18
Completed high school (n, %)	589	510	86.59	
Personal income (mean US$/month)	574	969.46	861.10	0-5000
Median personal income (US$/month)	574	800		0-5000
Work status (n, % working and/or in school)	589	360	61.12	
Marital status (n, % married)	589	35	5.94	
Lives with mother or caregiver (n, %)	589	205	34.80	
Has at least one child (n, %)	589	217	36.04	
Child maltreatment score (mean)	589	2.43	1.08	1-5
Experienced moderate, severe, or extreme child maltreatment (n, %)	589	172	29.20	
Family history of alcohol or drug problems (n, %)	587	275	46.85	
Initiated cigarettes (n, %)	589	481	81.66	
Past-year cigarette smoker (n, %)	589	256	43.46	
Average daily cigarettes among cohort	589	4.36	7.01	0-50
Average daily cigarettes among cigarette smokers	256	10.03	7.50	0.5-50
Initiated alcohol (n, %)	589	584	99.15	
Past-year alcohol user (n, %)	589	545	92.53	
Average daily volume of alcohol among cohort	589	1.58	2.18	0-8

Table 12 Continued

Average daily volume of alcohol among alcohol users	545	1.72	2.21	0.01-8
Initiated marijuana (n, %)	589	489	83.02	
Past-year marijuana user (n, %)	589	295	50.08	
Average daily joints of marijuana among cohort	589	0.82	2.06	0-10
Average daily joints of marijuana among marijuana users	295	1.65	2.67	0.0025-10
Any cocaine use in past year (n, %)	589	39	6.62	
Any other illicit drug use in past year (n, %)	589	81	13.75	

Table 13. Chapter 3: First trimester maternal characteristics of offspring included in and excluded from the analyses

Maternal Characteristics Assessed at the First Trimester	**Included in Analyses (n=585)**	**Excluded from Analyses (n=178)**	**p-value[a]**	**Effect Size[b]**
Age (mean years)	23.04	22.90	0.611	0.044
Race (% African American)	51.62	51.12	0.907	0.004
Education (mean years)	11.84	11.87	0.824	0.019
Marital status (% married)	31.97	35.39	0.394	0.031
Household income (mean US$/mo)[c]	300-399	300-399	0.479	0.062
Average daily volume of alcohol	0.55	0.77	0.125	0.199
Alcohol use (%)	64.10	67.42	0.417	0.029
Average daily joints of marijuana	0.38	0.42	0.813	0.045
Marijuana use (%)	41.20	38.20	0.476	0.026
Average daily cigarettes	8.13	9.02	0.266	0.079
Cigarette use (%)	53.16	57.87	0.270	0.040
Cocaine use (%)	3.76	3.93	0.916	0.004
Other illicit drug use (%)	8.89	8.99	0.967	0.002

[a]t-test for continuous variables, Mann Whitney test for skewed variables, χ^2 test for dichotomous variables

[b]Cohen's d for continuous variables, Cramer's V for dichotomous variables; absolute value reported

[c]sample size 566, 170

Table 14. Chapter 3: Maternal marijuana use by trimester

	First Trimester N = 585	Second Trimester N = 528	Third Trimester N = 585
No use[a] (n, %)	344 (58.80)	413 (78.22)	478 (81.71)
Light to moderate use[b] (n, %)	164 (28.03)	89 (16.86)	75 (12.82)
Heavy use[c] (n, %)	77 (13.16)	26 (4.92)	32 (5.47)

[a]Zero joints per day
[b]Less than one joint per day
[c]One or more joints per day

Table 15. Chapter 3: Sample characteristics

	Total N	Mean or n	Standard Deviation or %	Range
Maternal Characteristics at the First Trimester Visit				
Age (mean years)	585	23.07	4.05	18-42
Race (n, % African American)	585	302	51.62	
Education (mean years)	585	11.84	1.35	7-18
Marital status (n, % married)	585	187	31.97	
Work status (n, % working outside the home and/or in school)	585	150	25.64	
Household income (n, %<US$400/month)	566	347	61.31	0-1000+
Alcohol use (n, %)	585	375	64.10	
Average daily volume of alcohol	585	0.55	1.08	0-8
Marijuana use (n, %)	585	241	41.20	
Average daily joints of marijuana	585	0.38	0.93	0-7.4
Cigarette use (n, %)	585	311	53.16	
Average daily cigarettes	585	8.13	11.33	0-50
Cocaine use (n, %)	585	22	3.76	
Other illicit drug use (n, %)	585	52	8.89	
Offspring Characteristics at Birth				
Gender (n, % male)	585	275	47.01	
Gestational age (mean weeks)	585	39.79	2.19	28-44
Birth weight (mean kg)	585	3.19	0.57	1.04-4.99
Characteristics at 10 Years				
Home environment (mean score)	510	12.70	2.69	3-18
Depressive symptoms (mean T-score)	510	45.94	8.37	35-77
Anxiety (mean score)	509	10.06	6.23	0-28
Attention (mean score)	515	8.84	2.95	5-20
Delinquent behavior (mean T-score)	515	55.98	6.99	50-94

Table 15 Continued

Maternal average daily joints	516	0.07	0.28	0-2.6
Characteristics at 16 Years				
Parenting authoritativeness (mean score)	490	1.43	0.94	0-3
Offspring Characteristics at 22 Years				
Age (mean years)	585	22.84	0.70	21.16-26.09
Race (n, % African American)	585	330	56.41	
Education (mean years)	585	12.79	1.64	8-18
Employment status (n, % working and/or in school)	585	359	61.37	
Median personal income (US$/month)	570	800		0-5000
Lives with mother or caregiver (n, %)	585	204	34.87	
Marital status (n, % married)	585	34	5.81	
Has at least one child (n, %)	585	215	36.75	
Child maltreatment (mean score)	585	2.42	1.08	1-5
Experienced moderate, severe, or extreme child maltreatment (n, %)	585	168	28.72	
Past-year cigarette use (n, %)	585	252	43.08	
Average daily cigarettes	585	4.33	7.02	0-50
Past-year alcohol use (n, %)	585	541	92.48	
Average daily volume of alcohol	585	1.59	2.18	0-8
Marijuana initiation (n, %)	585			
Initiated <16 years		296	50.60	
Initiated ≥16 years		189	32.31	
Never initiated		100	17.09	
Past-year marijuana use (n, %)	585	291	49.74	
Average daily joints of marijuana	585	0.82	2.06	0-10
Frequency of marijuana use (%)	585			
No use		294	50.26	
Use <3 times per week		172	29.40	
Use ≥3 times per week		119	20.34	
Past-year cocaine use (n, %)	585	39	6.67	
Past-year other illicit drug use (n, %)	585	79	13.50	

Table 16. Chapter 3: Characteristics by offspring frequency of marijuana use

	Offspring Frequency of Marijuana Use				
	No Use (n=294)	Use <3 times per week (n=172)	Use ≥3 times per week (n=119)	**p-value[d]**	**Effect size[e]**
Maternal Characteristics First Trimester					
Age (mean years)	22.97	23.13	23.24	0.658	0.001
Race (% African American)	46.60	49.42	67.23	<0.001	0.160
Education (mean years)	11.95	11.70	11.80	0.141	0.007
Marital status (% married)	37.76	27.33	24.37	0.009	0.127
Employment status (% working outside the home and/or in school)	24.15	27.33	26.89	0.706	0.035
Household income (%<US$400/month)[f]	58.36	64.88	63.25	0.347	0.061
Alcohol use (%)	61.90	63.95	69.75	0.322	0.062
Average daily volume of alcohol	0.41	0.70	0.65	0.062	0.015
Cigarette use (%)	50.68	54.65	57.14	0.441	0.053
Average daily cigarettes	7.46	9.79	7.39	0.272	0.009
Marijuana use (%)	34.01	43.02	56.30	<0.001	0.174
Average daily joints of marijuana	0.27	0.41	0.59	<0.001	0.018
Cocaine use (%)	3.40	5.23	2.52	0.440	0.053
Other illicit drug use (%)	7.82	10.47	9.24	0.619	0.041
Offspring Characteristics at Birth					
Gender (% male)	40.82	48.84	59.66	0.002	0.146
Gestational age (mean weeks)	40.00	39.62	39.54	0.297	0.009
Birth weight (mean kg)	3.25	3.15	3.11	0.039	0.011
Characteristics at 10 years					
Home environment[g] (mean score)	13.04	12.43	12.28	0.034	0.016
Depressive symptoms[i] (mean score)	45.25	45.51	48.22	0.008	0.019
Anxiety[j] (mean score)	9.62	10.19	10.95	0.007	0.117
Attention[k] (mean score)	8.38	8.97	9.78	<0.001	0.033
Delinquent behavior[k] (mean score)	55.33	56.54	56.72	0.075	0.009
Maternal average daily joints[h]	0.04	0.08	0.10	0.049	0.007
Characteristics at 16 years					
Parental authoritativeness[l]	1.44	1.47	1.34	0.588	0.002
Offspring Characteristics at 22 years					
Age (mean years)	22.92	22.75	22.78	0.030	0.012
Race (% African American)	52.04	54.65	69.75	0.004	0.138
Education (mean years)	13.08	12.71	12.19	<0.001	0.044
Work status (% working and/or in school)	68.03	56.98	51.26	0.002	0.143
Median personal income (US$/month)[m]	937	800	672	<0.001	0.037
Marital status (% married)	9.18	2.91	1.68	0.002	0.146

Table 16 Continued

Lives with mother or caregiver (%)	37.07	35.47	28.57	0.255	0.068
Has at least one child (%)	32.99	37.79	44.54	0.083	0.092
Childhood maltreatment (mean score)	2.27	2.62	2.53	0.003	0.023
Marijuana initiation (%) >16 years ≥16 years Never	 35.03 30.95 34.01	 60.47 39.53 0.00	 74.79 25.21 0.00	<0.001	0.340
Past-year cigarette use (%)	27.55	55.81	63.03	<0.001	0.319
Average daily cigarettes	2.84	5.62	6.13	<0.001	0.046
Past-year alcohol use (%)	87.76	97.67	96.64	<0.001	0.181
Average daily volume of alcohol	1.00	1.93	2.58	<0.001	0.087
Past-year cocaine use (%)	1.70	15.12	6.72	<0.001	0.214
Past-year other illicit drug use (%)	3.40	19.77	29.41	<0.001	0.313
Lifetime history of Cannabis Use Disorder (%)[n]	6.19	16.67	28.70	<0.001	0.254
Arrested ≥1 times (%)	24.49	43.02	63.03	<0.001	0.310

[a] Zero joints per day
[b] Less than one joint per day
[c] One or more joints per day
[d] ANOVA for continuous variables, Kruskal-Wallis test for skewed variables, χ^2 test for dichotomous variables
[e] Eta^2 for continuous variables, Cramer's V for dichotomous variables; absolute value reported
[f] Sample size: 281, 168, 117
[g] Sample size: 252, 155, 103
[h] Sample size: 255, 156, 105
[i] Sample size: 252, 154, 104
[j] Sample size: 249, 156, 104
[k] Sample size: 255, 156, 104
[l] Sample size: 248, 149, 93
[m] Sample size: 286, 168, 116
[n] Sample size: 291, 168, 115

Table 17. Chapter 3: Fit indices for models tested during model identification

Model	**χ2**	**df**	**p**	**CFI**	**TLI**	**RMSEA**	**WRMR**
1 – Conceptual model	0.000	0	0.000	1.000	1.000	0.000	1.000
2 – Removed Offspring Use ← PME	0.041	1	0.840	1.000	1.076	0.000	0.017
3 – Removed Offspring Use ← Depressive symptoms	0.424	2	0.809	1.000	1.063	0.000	0.055
4 – Added paths: Maternal Use ← PME Early Initiation ← Maternal Use	0.969	3	0.809	1.000	1.054	0.000	0.085

CFI=Comparative Fit Index (cut-off >.95), TLI= Tucker Lewis Index (cut-off >.90),
RMSEA = Root Mean Square Error of Approximate (cut-off <.06), WRMR = Weighted Root Mean Square Residual (cut-off <.90)

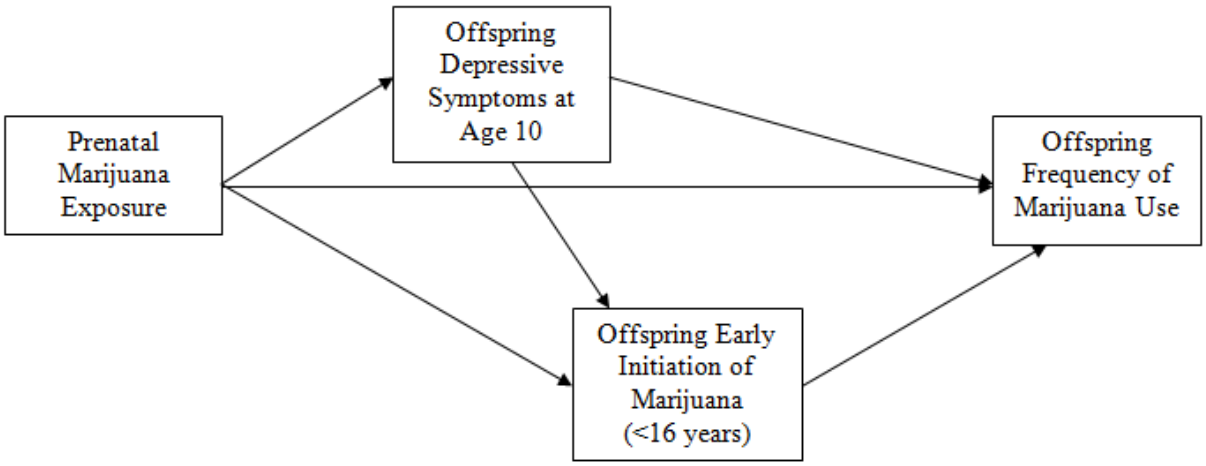


Figure 7. Chapter 3: Conceptual path model

Table 18. Chapter 4: First trimester maternal characteristics of offspring included in and excluded from the analyses

Maternal Characteristics Assessed at the First Trimester	Included in Analyses (n=590)	Excluded from Analyses (n=173)	p-value[a]	Effect Size[b]
Age (mean years)	23.03	23.03	0.989	0.001
Race (% black)	52.20	49.13	0.477	0.026
Education (mean years)	11.85	11.85	0.992	0.001
Marital status (% married)	31.19	38.15	0.086	0.062
Household income (mean US$/mo)	300-399[c]	300-399[d]	0.794	0.008
Average daily volume of alcohol	0.55	0.75	0.073	0.166
Alcohol use (%)	63.73	68.79	0.220	0.044
Average daily joints of marijuana	0.38	0.41	0.829	0.035
Marijuana use (%)	40.68	39.88	0.852	0.007
Average daily cigarettes	8.07	9.25	0.214	0.104
Cigarette use (%)	53.05	58.38	0.216	0.045
Cocaine use (%)	3.56	4.62	0.519	0.023
Other illicit drug use (%)	8.64	9.83	0.631	0.017

[a]t-test for continuous variables, Mann Whitney test for skewed variables, χ^2 test for dichotomous variables
[b]Cohen's d for continuous variables, Cramer's V for dichotomous variables; absolute value reported
[c]sample size 571
[d]sample size 165

Table 19. Chapter 4: Maternal marijuana use by trimester

	First N = 590	Second N = 534	Third N = 590
None[a] (n, %)	350 (59.32)	419 (78.46)	482 (81.69)
Light to moderate[b] (n, %)	161 (27.29)	88 (16.48)	77 (13.05)
Heavy users[c] (n, %)	79 (13.39)	27 (5.06)	31 (5.25)

[a] Zero joints per day
[b] Less than 1 joint per day
[c] One or more joints per day

Table 20. Chapter 4: Sample characteristics

	n	Mean (SD) or n (percent)	Range
Maternal Characteristics at the First Trimester Visit			
Age (years)	590	23.03 (4.04)	18-42
Race (% African American)	590	308 (52.20)	
Marital status (% married)	590	184 (31.19)	
Education (years)	590	11.85 (1.36)	7-18
Employment status (% in school and/or worked outside the home)	590	150 (25.42)	
Household income (n, %<US$400/month)	571	349 (61.12)	0-1000+
Marijuana use (%)	590	240 (40.68)	
Average daily joints of marijuana	590	0.38 (0.94)	0-7.4
Alcohol use (%)	590	376 (63.73)	
Average daily volume of alcohol	590	0.55 (1.10)	0-8
Cigarette use (%)	590	313 (53.05)	
Average daily cigarettes	590	8.07 (11.17)	0-50
Cocaine use (%)	590	21 (3.56)	
Other illicit drug use (%)	594	51 (8.64)	
Offspring Characteristics at Birth			
Gender (% male)	590	278 (47.12)	
Gestational age (weeks)	590	39.79 (2.19)	28-44
Birth weight (kg)	590	3.20 (0.56)	1.04-4.99
Offspring Characteristics at Age 10			
Children's Depression Inventory T-Score	518	45.99 (8.50)	35-79
Offspring Characteristics at Age 22			
Initiated marijuana before age 16 (%)	590	298 (50.51)	
Age (years)	590	22.83 (0.70)	21.16-26.09
Race (% African American)	590	336 (56.95)	
Education (years)	590	12.80 (1.62)	8-18
Employment status (% working and/ or in school)	590	360 (61.02)	
Median personal income (US$/month)	575	800	0-5000
Lives with mother or caregiver (%)	590	208 (35.25)	
Marital status (% married)	590	33 (5.59)	
Has at least one child (%)	590	217 (36.78)	
Past-year cigarette use (%)	594	253 (42.88)	
Average daily cigarettes	590	4.27 (6.97)	0-50
Past-year alcohol use (%)	590	545 (92.37)	
Average daily volume of alcohol	590	1.58 (2.16)	0-8
Lifetime marijuana use (%)	590	486 (82.37)	
Past-year marijuana use (%)	590	289 (48.98)	
Average daily joints of marijuana	590	0.81 (2.06)	0-10
Past-year cocaine use (%)	590	38 (6.44)	
Past-year use of other illicit drugs (%)	590	79 (13.39)	

Table 20 Continued

Cannabis Use Disorder diagnosis (%)	590	80 (13.56)	
Cannabis Use Disorder diagnosis among lifetime marijuana users (%)	486	80 (16.46)	

Table 21. Chapter 4: Sample characteristics by Cannabis Use Disorder diagnosis

	No CUD Diagnosis (n=510)	**CUD Diagnosis (n=80)**	**p-value[a]**	**Effect Size[b]**
Maternal Characteristics at the First Trimester Visit				
Age (years)	22.99	23.29	0.546	0.073
Race (% black)	51.76	55.00	0.590	0.022
Education (years)	11.85	11.85	0.995	0.001
Marital status (% married)	31.18	31.25	0.989	0.001
Employment status (% in school and/or worked outside the home)	25.69	23.75	0.712	0.015
Household income (%<US$400/month)[c]	61.05	61.54	0.935	0.003
Any alcohol use (%)	64.51	58.75	0.319	0.041
Average daily volume of alcohol	0.53	0.68	0.968	0.133
Any cigarette use (%)	53.53	50.00	0.556	0.024
Average daily cigarettes	8.05	8.21	0.905	0.014
Any marijuana use (%)	40.20	43.75	0.547	0.025
Average daily joints	0.36	0.51	0.329	0.161
Any cocaine use (%)	3.53	3.75	0.921	0.004
Any other illicit drug use (%)	8.43	10.00	0.643	0.019
Offspring Characteristics at Birth				
Gender (% male)	42.94	73.75	<0.001	0.211
Gestational age (weeks)	39.84	39.48	0.421	0.165
Birth weight (kg)	3.20	3.15	0.422	0.097
Offspring Characteristics at Age 10				
Children's Depression Inventory T-Score (mean)[d]	45.89	46.61	0.315	0.085
Offspring Characteristics at Age 22				
Marijuana initiation Before age 16 (%) Between ages 16-22 Never	 45.69 33.92 20.39	 81.25 18.75 0.00	<0.001	0.256
Age (years)	22.84	22.77	0.403	0.101
Race (% African American)	56.86	57.50	0.915	0.004
Education (years)	12.88	12.29	0.002	0.371
Personal income (median US$/month)[e]	800.00	750.00	0.371	0.081
Employed or in school (%)	61.57	57.50	0.488	0.029
Marital status (% married)	5.69	5.00	0.804	0.010
Lives with mother or caregiver (%)	35.69	32.50	0.579	0.023

Table 21 Continued

Has at least one child (%)	36.47	38.75	0.694	0.016
Past-year alcohol use (%)	92.55	91.25	0.684	0.017
Average daily volume of alcohol	1.37	2.92	<0.001	0.738
Past-year cigarette use (%)	39.22	66.25	<0.001	0.187
Average daily cigarettes	3.81	7.21	<0.001	0.496
Past-year marijuana use (%)	44.51	77.50	<0.001	0.226
Average daily joints of marijuana	0.59	2.23	<0.001	0.823
Past-year cocaine use (%)	4.90	16.25	<0.001	0.158
Past-year other illicit drug use (%)	10.20	33.75	<0.001	0.237

[a]t-test for continuous variables, Mann Whitney test for skewed variables, χ^2 test for dichotomous variables
[b]Cohen's d for continuous variables, Cramer's V for dichotomous variables; absolute value reported
[c]sample sizes: 493, 78
[d]sample sizes: 446, 72
[e]sample sizes: 498, 77

Table 22. Chapter 4: Fit indices for models tested during model identification

Model	**χ2**	**df**	**p**	**CFI**	**TLI**	**RMSEA**	**WRMR**
1 - Conceptual model	0.056	1	0.814	1.000	1.138	0.000	0.049
2 – Removing CUD ← Depressive Symptoms	0.161	2	0.923	1.000	1.134	0.000	0.079

CFI=Comparative Fit Index (cut-off >.95), TLI= Tucker Lewis Index (cut-off >.90), RMSEA = Root Mean Square Error of Approximate (cut-off <.06), WRMR = Weighted Root Mean Square Residual (cut-off <.90)

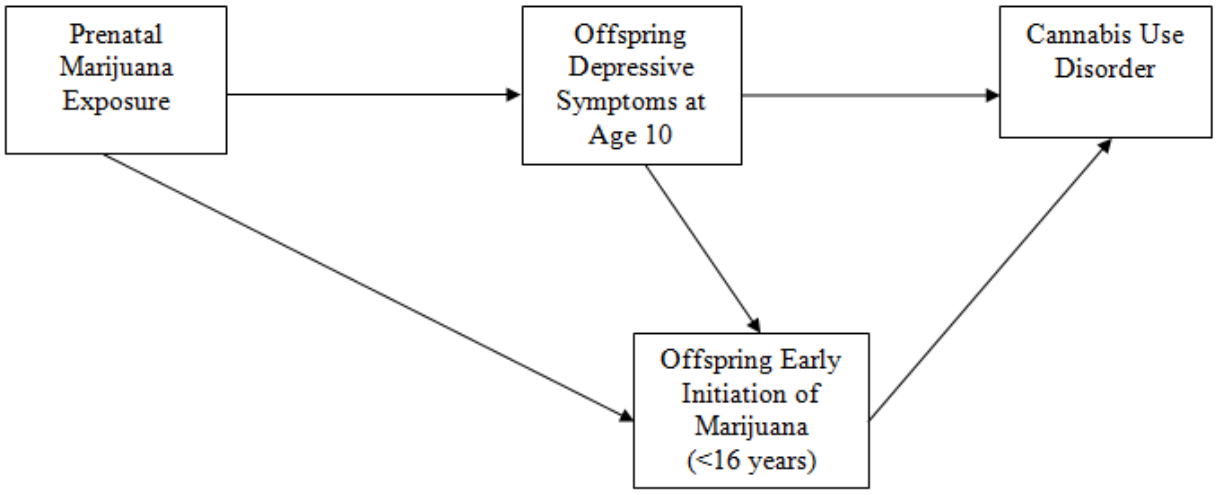


Figure 8. Chapter 4: Conceptual path model

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