Maternal cannabis use and associations with Autism Spectrum Disorder diagnosis in Californian children using data from CHARGE

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Abstract

The California Department of Developmental Services (DDS) (2003) reported that children with Autism Spectrum Disorder (ASD) are being recognized at accelerated rates. These increases in prevalence cannot be fully attributed to changes in diagnostic criteria, improvements in detection, or population increases. Maternal substance use is one area of environmental risk under study. Of these substances, cannabis remains one of the most used by pregnant mothers. Cannabis, referring to the component of the plant *cannabis sativa* that contains >0.3% delta-9-tetrahydrocannabinol (THC), has been identified as a developmental toxicant. The psychoactive cannabinoid–THC–can be passed from mother to fetus via the placenta or to the child through breastfeeding. THC has been implicated in affecting a child's developing endocannabinoid system, and ultimately affects a child's neurodevelopment. This is concerning as the THC content of cannabis products has increased with increased legalization and evolving markets. This study sought to examine the association between maternal cannabis use before or during pregnancy and the odds of ASD diagnosis in 1,152 children from the Childhood Autism Risk from Genetics and the Environment (CHARGE) study, a large population-based case-control study with data from over 20 counties. The crude model indicated an association in the direction of increased risk with low precision (OR=1.28; 95%CI=0.81-2.01). After adjustment for mother's age at delivery, maternal experience of stress, family history of ADHD, maternal intake of folic acid supplements during pregnancy, presence of any smokers in the house before or during pregnancy,

protective socioeconomic factors, maternal use of non-cannabis recreational drugs and tobacco products, and year of birth, the effect was moved toward the null (OR=1.20; 95%CI=0.68, 2.12). However, the lack of significant results does not confirm that maternal cannabis use does not increase odds of ASD. Further studies are needed on more recent cohorts given the increased THC potency, accessibility of cannabis products, and changing attitudes toward use during pregnancy.

Introduction

In the latest report by the Autism and Developmental Disabilities Monitoring (ADDM) Network, the Centers for Disease Control and Prevention (CDC) reported 23.0 cases of Autism Spectrum Disorder (ASD) per 1,000 8-year-old children, which is a significant increase from prevalence estimates of 6.7 per 1,000 8-year-old children in 2002 (Maenner et al., 2021). This increase is a trend previously noted in a report on changes in California's caseload for ASD. The California Department of Developmental Services (2003) reported that children with ASD are recognized at accelerated rates. Such numbers are concerning as ASD is a lifelong disability with which individuals require a broad spectrum of support (Rogge & Janssen, 2019; Burscher, 2014; Ganz, 2007). These increases in prevalence cannot be entirely attributed to changes in diagnostic criteria (such as the changes from the DSM-IV to DSM-V), improvements in detection, or population increases (Nevison et al., 2018; Hertz-Picciotto & Delwiche, 2009; Byrd, 2002). As such, there remains a need to understand what the causes of ASD might be and how they might be leading to increases in prevalence. This knowledge will allow interventions that can decrease the odds of ASD diagnosis. While evidence has pointed

to genetic and environmental factors, much remains to be known (Lyall et al., 2014). Maternal use of substances during pregnancy is one area of maternal lifestyle factors identified to increase the odds of ASD. Of these substances, alcohol and smoked tobacco products are the better-known developmental or reproductive toxicants.

In 2020, the California Office of Environmental Health Hazard Assessment concluded that cannabis smoke exposure was a developmental toxicant. However, due to the legal and ethical challenges, studies using animal models are the primary source of information on the mechanistic pathways for neurotoxicity due to maternal cannabis exposure (Wu & Lu, 2011; Campbell et al., 2019). Studies in humans have identified that delta-9-tetrahydrocannabinol (THC), the primary psychoactive cannabinoid in cannabis products, can cross the placenta and be passed to the infant through breastmilk (Campbell et al., 2019). While the endocannabinoid system in the developing brain plays a vital role in neurodevelopment, the exact ways these signaling pathways change a child's development and neurobehavior are still under study (Campbell et al., 2019). THC can activate the cannabinoid receptors present early in the developing brain, which affects processes like neuronal migration, proliferation, and differentiation (Richardson et al., 2016; Fride et al., 2009; Huizink, 2014). Other proposed effects include modulation of other neurotransmitter systems or changing gene expression due to epigenetic modifications (Richardson et al.; 2016, Fride et al.; Huizink, 2014). In addition, several factors ranging from having a family history of ADHD, maternal age, and maternal health and lifestyle have been identified as associated with increased

odds of ASD and maternal cannabis use and thus are likely to contribute to confounding (Ghirardi et al., 2018; Skoglund et al. 2015; Shelton et al., 2010; van Gelder et al., 2010; Lyall et al., 2014).

According to the DSM-V, ASD is a neurodevelopmental disorder characterized by social challenges, repetitive behaviors/interests, and may co-occur with language or intellectual impairments (American Psychiatric Association, 2013). Often, the term "spectrum" refers to how different autistic individuals experience challenges navigating a society that often creates barriers to their participation. The level of support an individual requires is often determined by cognitive resources/limitations and specific ASD symptoms (Jensen & Spannagel, 2011). Individuals that experience the most impairments may need a blend of "true interventions" which are geared to increase functioning and "management", which includes therapy and environmental modifications (Jensen & Spannagel, 2011). A 2019 review of 49 studies measured the financial resources needed to support people on the spectrum and found it ranged from $2.4 million to $3.2 million per lifetime (Rogge & Janssen, 2019). The broad diversity of individuals' characteristics and needs also contributes to difficulties in understanding what causes this complex disorder.

Regarding maternal substance use, cannabis remains one of the most used illicit substances (Substance Abuse and Mental Health Services Administration, 2020) during pregnancy. A 2017 study examining women aged 18-44 years old from the annual National Survey on Drug Use and Health found that the use of cannabis during

pregnancy has increased from 2.87% in 2002 to 3.85% in 2014 (Brown et al., 2017). This trend is expected to continue as greater legalization means more expanded markets and accessibility (Brown et al., 2017; Young-Wolff et al., 2022) which is especially concerning as more mothers perceive the substance to be safe even though the concentration of THC in most products has been sharply increasing (Young-Wolff et al., 2022; ElSohly, 2021; Barbosa-Leiker et al., 2020; Chang et al., 2019; Jarlenski et al., 2017). Despite official recommendations against the use of cannabis during pregnancy or breastfeeding (Ryan, 2018; California Cannabis Health Information Initiative, 2017), mothers are turning to the substance as a “safer” alternative to established treatments for ailments such as mood disorders or vomiting and nausea due to pregnancy (Barbosa-Leiker et al., 2020; Chang et al., 2019; Jarlenski et al., 2017). Unlike other substances with a more established history of study, such as alcohol or smoking, maternal cannabis use and associations with birth outcomes such as low birth weight and long-term neurodevelopmental effects such as ASD are still inconclusive (El Marroun et al., 2009, Chang, 2020, Lyall et al., 2014).

Literature Review

Several major prospective cohort studies have examined the effect of maternal cannabis exposure on various outcomes ranging from neonatal sleep patterns and neurological states to adolescent outcomes. These studies include the Norwegian Mother and Child Cohort Study, the Ottawa Prenatal Prospective Study (OPPS), the Maternal Health Practices and Child Development Study (MHPCD), and the Generation

R Study. The Ottawa Prenatal Prospective Study (OPPS) began in Canada in 1978 and recruited pregnant women in major hospitals in Ottawa, Canada. The study included approximately 300 white, middle-aged women who reported using at least six cannabis joints per week (heavy users) before and/or during pregnancy out of the about 700 mothers enrolled (Fried, 1980; Fried & Makin, 1987; Fried et al., 1987; Fried & Watkinson, 1988; Fried & Watkinson, 1990; Fried et al., 1992). Notably, Fried et al. considered these study participants “low-risk” for cannabis use because they were predominantly middle-class and Caucasian, yet they self-reported as heavy users. Thus, this study failed to consider many of the environmental covariates, such as socioeconomic status, that could play a role in the association between cannabis use and neurodevelopmental outcomes. In particular, the authors also reported that this study did not control for covariates because of its modest sample size.

The MHPCD study included approximately 763 live births of women who visited the Magee-Women's Hospital in their fourth prenatal month (Goldschmidt et al., 2008). This project combined the use of marijuana, hashish, and sinsemilla into a variable measuring joint use of marijuana based on THC amounts (Goldschmidt et al., 2008). This study’s strength is that a large sample size allowed for adequate statistical power while controlling for prenatal exposure to other substance use (including tobacco and alcohol) and various social or environmental factors. In addition, this project attempted to measure how the dosage of substance use may cause differences in effect.

The Generation R study, based in Rotterdam, the Netherlands, included 8,880 women and their children born between April 2002 and January 2006 (El Marroun et al., 2009). The strengths of this study lie in its large sample size and the ability to control for confounding factors ranging from lifestyle to socioeconomic factors. In addition, this study compared a group of pregnant cannabis users with a group of pregnant women who only used tobacco.

The Norwegian Mother and Child Cohort Study included 74,641 pregnancies for 65,412 mothers from 50 hospital sites for births from 1999 until 2006 (Gabrhelík et al., 2021). The major strength of this study is its sample size, but only 1% of respondents used cannabis. In addition, it was noted by study researchers that the population included is likely not to represent the general population of Norway in substance use or other health covariates. Finally, outcomes for this study were limited to those found in the birth record, and so were limited to birth outcomes.

Several studies have found different effects related to maternal cannabis use as early as just hours after birth. OPPS found that babies of mothers who used cannabis during pregnancy exhibited significantly more tremors, startles, and less visual habituation as early as four to 30 days old (Fried, 1980; Fried & Makin, 1987; Fried et al., 1987). A study examining the MHPCD cohort 24-36 hours after birth found that maternal cannabis use during any trimester of pregnancy was associated with several sleep outcomes, including increased body movements and decreased total quiet sleep (Scher

et al., 1988). The MDPCD study reexamined their participants again at three years old and found children whose mothers used cannabis tended to have more nocturnal arousals and lower sleep efficiency than control children. They found that maternal cannabis use in the first trimester was most associated with sleep disruptions. These findings suggest that maternal cannabis use may significantly affect children at a neurological level.

Other outcomes of neurodevelopment are less clear. MDPCD and OPPS both examined different aspects of neurodevelopment of participating children using a variety of scales such as the Bayley Scales of Infant Development (Fried & Watkinson, 1988), Reynell Developmental Language Scales (Fried & Watkinson, 1988), McCarthy Scales of Children's Abilities (Fried & Watkinson, 1990), and Stanford-Binet Intelligence Scale (Day et al., 1994). The OPPS study found no significant effect on global cognitive scores at two years on the Bayley Scales of Infant Development and no significant effect on the Reynell Language scores after controlling for the child's home environment (Fried & Watkinson, 1988). The OPPS study also used the McCarthy Scales of Children's Abilities and the Reynell Developmental Language scales to examine the children at age three and also found no association of maternal cannabis use with any global or subscale scores for either test (Fried & Watkinson, 1990). However, at four years old, they found significantly lower scores in verbal and memory domains for the same group of exposed children (Fried & Watkinson, 1990). The MDPCD also examined children at three years old and found that neither maternal cannabis use

during any trimester nor current maternal cannabis use affected the Stanford Binet composite score (Fried & Watkinson, 1990). The only significant finding was a marginal negative relationship between second-trimester maternal cannabis use and short-term memory (Fried & Watkinson, 1990). These studies suggest maternal cannabis use may affect higher-order cognition (such as memory or attention) after age three rather than cognitive and language abilities in early childhood.

Yet, when the MDPCD and OPPS examined their respective participating children again at six years old, they found several significant associations, suggesting higher-order cognition may be affected. Two different MHPCD projects found that not only did maternal exposure to cannabis have a significant effect on child outcomes, but these outcomes also differed by trimester of use (Leech et al., 1999; Goldschmidt et al., 2008). These studies found that first-trimester use was associated with significant differences in verbal reasoning. In contrast, use during the second trimester was associated with lower scores on short-term memory, quantitative reasoning subscales on the Stanford-Binet Intelligence Scale, and errors of omission, which are related to impulsive responding that researchers hypothesized were due to the effects of cannabis on the developing limbic system. Use during the third trimester was associated with significant differences in quantitative reasoning subscales (Leech et al., 1999). While Fried et al.'s study did not examine use by trimester, they also found that maternal cannabis use was associated with significantly increased omission errors for their 6-year-old participants, which suggests a lack of sustained attention and a higher rating

on the impulsivity/hyperactive scale (Fried et al.,1992). These findings further support a need for longitudinal observation of neurodevelopmental trajectories as children grow, as the results suggest higher-level cognitive effects.

Indeed, even results for the physical effects of maternal cannabis use are mixed. Many studies have found an association between maternal cannabis use and significant birth weight and length differences (Gabrhelík et al., 2021; El Marroun et al., 2009). However, projects from the OPPS study did not find a significant association between the child's weight and maternal cannabis use until 12 months of age or a significant association between the child's height and maternal cannabis use until 24 months of age (Fried & Watkinson, 1988). This lack of agreement could be due to the confounding by the period of use by the mother, as demonstrated by results from a Generation R cohort study. The results suggest that cannabis use before pregnancy is not significantly associated with differences in fetal growth in mid-and late pregnancy or at birth. This same group found evidence that specific periods of development were possibly more associated with affected growth because they found that mothers who used cannabis in early pregnancy had fetuses that showed reduced growth (El Marroun et al., 2009).

Some critiques of previous studies examining children after five years old include the exclusion of children who received a neurodevelopmental diagnosis, had a cognitive disability, or received medication for behavioral issues, and the omission of existing family histories of neurodevelopmental disorders (Leech et al., 1999; Fried et al., 1992).

The most likely reason for such exclusion was because outcome scales used by those studies have not been tested for accuracy in children with neurodevelopmental disorders. More recent studies are beginning to address this gap by using instruments validated explicitly for children with ASD and specifically examining cohorts of children with neurodevelopmental disorders such as ASD or developmental delay. Three studies examined maternal cannabis exposure and outcomes among children diagnosed with ASD and/or other neurodevelopmental disorders (DiGuiseppi et al., 2021, Pham et al., 2022, Corsi et al., 2020). These three studies are summarized in Table 1 and have been chosen with the same criteria as in Lyall (2014), with to act as an extension and update to that previously published literature review.

Corsi et. al examined a population-based cohort using a birth registry of individuals born between April 1, 2007 and March 31, 2012 in Ontario, Canada (Corsi et al., 2020). They found that individuals with in-utero cannabis exposure were more at risk for ASD diagnosis (Hazard ratio=1.54; 95% CI=1.17–2.03) after coarsened exact matching (maternal age, maternal education, preexisting maternal conditions, maternal psychiatric disorders, rurality, income quintiles) and controlling for parity, antenatal care, other substance use including tobacco, alcohol, or non-cannabis drugs. This study was uniquely strong in that there were a large number of cases at the 18-month follow-up at which these results were reported (n=7,125 (1.4%)) and a large number of mothers who used cannabis (CEM cohort n = 2,364). This study occurs in Canada, where universal public-funded healthcare is available (Government of Canada, 2023), and recreational

cannabis (legally referred to as marijuana in Canada) use has been legalized since 2018 (Butler, 2018). Such legalization could decrease participant bias due to reduced stigmatization and increased accessibility. However, such results may not be immediately applicable to populations that do not experience the same legalization due to differences in accessibility and stigmatization.

Indeed, different results were found in a birth cohort study in Australia, which also has universal public-funded healthcare but has legalized only medical cannabis and not recreational. Pham et al. conducted this study with data from 1074 mother-child pairs recruited from two Barwon region hospitals in Victoria, Australia, between June 2010 and June 2013 (Pham et al., 2022). Of these pairs, only 676 children completed the CBCL at two years old, and 11 were diagnosed with ASD at four years. While the study presents results for diagnosis at four years old, only one exposed case was in this group; thus, the study was too underpowered and insufficient to support a stable measure of association. Analysis at two years old showed no significant association between CBCL 1½–5 (preschool version) score and maternal cannabis use (ß=0.58; 95% CI=−0.58, 1.75), adjusted for only two variables: participant sex and age at the time of assessment.

To better situate the current research literature in the United States, DiGuiseppi et al. conducted a multi-site case-control study spanning catchment areas in California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania between September

2003 to August 2005 (SEED1) or January 2008 to December 2011 (SEED2) (DiGuiseppi et al., 2021). 1,428 case children were compared to two control groups, one of which was children from the general population (n=1,628) and the second children with non-ASD developmental delays/disorders (DD) (n=1,198). One strength of this study is that the Social Communication Questionnaire (SCQ) and Mullen Scales of Early Learning (MSEL) were used to screen all children for ASD regardless of enrollment group. In addition, maternal tobacco use was assessed as an effect modifier. Models were also adjusted for maternal education, alcohol, and tobacco use during peri-pregnancy (defined by the authors as the three months before conception until delivery) period, and the catchment area was included as a random effect due to the differing legal guidelines for cannabis use. DiGuiseppi et al. found that maternal cannabis use in peri-pregnancy, pre-conception only, or during pregnancy had no significant effect on risk of ASD diagnosis after adjustment for maternal education, and alcohol and tobacco use during peri-pregnancy when compared to DD and population control groups. However, because multiple states with differing cannabis legislation were involved in this study, a study situated entirely within a single region of legality (such as only states that legalized only medical use or states that legalized both recreational and medical use) could better account for residual confounding.

One of the main difficulties in comparing results across different studies is that the definition of “exposed to maternal cannabis use” differs greatly. One of the contributing factors is that cannabis products come in many different forms and products. The

Norwegian project examined predominantly women who used hashish, which is higher in THC content, whereas the majority of participants in the OPPS study smoked what is traditionally referred to as “marijuana” (Gabrhelík et al., 2021). The Generation R project included hashish and marijuana in their definition of cannabis (El Marroun et al., 2009). Another contribution to the difficulty of definition is that there are many possibilities for periods under examination. The Norway project examined previous use (cannabis use at any time before pregnancy in a lifetime), prolonged use (cannabis during at least two trimesters in pregnancy), and curtailed use (use in one period in the pregnancy). In contrast, the OPPS project looked at nonusers, irregular users (1 joint or less per week), moderate users (2-5 per week), and heavy users (more than 5 joints per week) in the year before pregnancy and throughout the trimesters of pregnancy (Gabrhelík et al., 2021; Fried, 1980; Fried et al., 1987; Fried & Watkinson, 1988). The Generation R cohort defined cannabis use into categories such as continued cannabis use (beginning in early pregnancy and throughout), cannabis use in early pregnancy, cannabis use only before pregnancy, and nonuse (no cannabis or tobacco use during pregnancy) (El Marroun et al., 2009). SEED examined maternal cannabis exposures at different points in time (before pregnancy, during pregnancy, and peri-pregnancy) and attempted to investigate per-trimester results, while Corsi and Pham only examined use during pregnancy (DiGuiseppi et al., 2021; Pham et al., 2022; Corsi et al., 2020).

This project

The Childhood Autism Risk from Genetics and the Environment (CHARGE) study is a large-scale, case-control study in California focused primarily on examining environmental exposures, and their interactions with genes, as possible causes for ASD. Due to the extensive questionnaires completed by a biological parent, information on a variety of covariates such as family history, demographics, child characteristics, and maternal health, is available to be considered for confounding. Through the recruitment of children diagnosed with Autism Spectrum Disorders and population controls matched on variables, such as year of birth, regional center, and sex, this project's subset includes a sample size of 1,152 participants with 685 cases (ASD) and 467 controls. As such, we can examine a variety of cofactors related to demographics, socioeconomics, and maternal lifestyle for possible confounding in exploring the association between maternal cannabis use and the odds of ASD diagnosis. Because past studies have indicated that factors such as maternal stress and other substance use are likely associated with maternal cannabis use or ASD diagnosis, this project examined the relationship between maternal cannabis use and the odds of ASD diagnosis by controlling for those factors. This project sought to investigate if maternal cannabis use was associated with an increased risk of ASD diagnosis after controlling for confounding such as socioeconomics or maternal use of other substances for California children aged 2-5 years old enrolled in the CHARGE study.

Methods

Study Population

This study was conducted using data from the Childhood Autism Risk from Genetics and the Environment (CHARGE) study, a large population-based case-control study with data from multiple catchment areas around Department of Developmental Services (DDS) regional centers in California. Full details of this study can be found elsewhere (Hertz-Picciotto et al., 2006). Recruitment into this study began in 2003 and is ongoing. Eligibility criteria included children between 24 and 60 months of age born in California, living with at least one biological parent who spoke English or Spanish, and residing in the catchment areas of a specified list of regional centers in California. Children included in this dataset were born between the years 1998 and 2017.

The study population was sampled from three strata: children with autism or autism spectrum disorder (ASD), children with developmental disorders (DD) but not autism, and children from the general population (TD). Children with ASD or DD were identified from regional centers that contract with the California Department of Developmental Services (DDS). The DDS does not restrict eligibility based on citizenship or financial status and, therefore, is used widely across socioeconomic and racial/ethnic groups. In a 2002 study, it was estimated that 75%-80% of the total population of diagnosed autistic children in the state were enrolled in the DDS system (Croen et. Al, 2002). As universal screening for ASD was recommended by the American Pediatric Association after the publication of those figures, the proportion enrolled in the DDS may have

increased markedly since then. Healthcare providers, schools, or other people in their lives referred the other CHARGE Study participants. Children from the general population were identified using state birth files and are frequency-matched to the age, sex, and broad geographic residential areas.

Outcomes

Two standardized clinical assessments confirmed diagnostic groups. The Autism Diagnostic Interview-Revised (ADI-R) is a standardized semi-structured 2- to 3-hour interview with the primary caregiver of an individual with autism and has interrater reliability kappa values between 0.62 and 0.89 (Le Couteur et al., 2003). The ADI-R provides summary scores for qualitative impairment in social interactions, communication, and repetitive behaviors. The Autism Diagnostic Observations Schedules, 2nd edition (ADOS-2) is also semi-structured and standardized. However, instead of an interview, the examiner interacts with and individual's social interactions for communication, play, and imaginative use of materials for about 30 minutes (Lord et al., 2003). There are five possible modules; an examiner chooses the one that best matches the child's expressive language level so a relatively low language ability does not impede accurate assessment. The ADOS measures four domains: reciprocal social interactions, communication, stereotypical behaviors, restricted interests, and play. Interrater reliability for the ADOS has kappa values > 0.60 (Lord et al., 2003). The ADI-R and ADOS-2 are considered the gold standard for assessing autism spectrum disorder.

Potential cases with ASD mainly were identified based on a DDS diagnosis of autism. Families of children diagnosed with autism who were not receiving services through the DDS system were also invited. The final definition of cases was children who met the criteria on communication, social, and repetitive behaviors for the ADI-R and scored at or above the total cutoff for ASD on the ADOS module 1 or 2. Only cases that completed diagnostic testing are included in this analysis (N=685 cases).

Potential controls were children selected randomly from birth records that are frequency matched to the age and catchment area distribution of cases and a 4:1 male-to-female ratio. Children who were initially enrolled from the general population were screened for evidence of autism symptoms using the Social Communication Questionnaire (SCQ), which was developed from the ADI-R (Rutter et al., 2003). Confirmed controls completed the SCQ and scored under 15. On the second visit, the ADI-R and ADOS were administered to participants who scored above the cutoff of 15 (indicating increased ASD risk) on the SCQ.

Exposures

Exposure data was collected through the maternal lifestyle portion of the telephone interview with a primary caregiver of the child (2003-2016) and through extraction from medical records. The interview took approximately 1 hour and 40 minutes to complete. During the maternal lifestyle portion of the interview, respondents were first asked, “During the index time [defined as the three months before pregnancy and through

pregnancy, including breastfeeding for those who did], did you use any recreational or street drugs?". Interviewers probed with a list of substances such as cannabinoids (including hashish and marijuana or cannabis) or depressants and hallucinogens. For each substance taken, respondents were asked which months they used the substance (beginning from the three months before pregnancy through the breastfeeding period) and how often they used it. Complete interview details can be found in Hertz-Picciotto, 2006 (Hertz-Picciotto, 2006). The lifestyle portion became a self-administered questionnaire beginning in 2017. Participants were considered exposed if their biological mother reported cannabis use within the period from the three months before pregnancy until the child's birth. Use status for the different periods of pregnancy was determined as the following: -3 to -1 months of pregnancy as before pregnancy use, 1-3 months of pregnancy as first-trimester use, 4-6 months as second-trimester use, and 7-9 months as third-trimester use.

The data for this study is a subset of the CHARGE data for those with completed maternal lifestyle forms. Only the primary child in each family from the ASD and typical developmental groups were considered for this study. In addition, only those with a confirmed diagnosis of ASD or typical development were included. As a result, 1152 participants were included in this study. Figure 2 describes how the eligibility requirements were applied to reach the final sample size. The CHARGE study protocol was approved by institutional review boards of the University of California in Davis and

Los Angeles and the State of California Committee for the Protection of Human Subjects.

Covariates

A directed acyclic graph (DAG) informed by existing literature was constructed to identify possible confounding covariates. This method of confounder identification allows the identification of pathways and requires assigning of directionality of potential causation in bivariate relationships, yielding insight as to which variables may compose a sufficient set to account for confounding between the exposure and outcome. While bivariate associations with the outcome and exposure were used to examine relationships between variables initially, such analysis does not consider how other variables affect the association between maternal cannabis use and the odds of ASD diagnosis. Thus, maternal age, maternal stress, family history of ADHD, race/ethnicity, maternal average daily folic acid intake, presence of another smoker in the household, protective SES factors, maternal use of non-cannabis recreational drugs and tobacco products, and year of birth were considered potential confounders. The child's regional center and sex were also considered for model building as they were matching variables for selecting controls.

All covariates were collected through telephone interviews, self-administered questionnaires, or medical records when appropriate. Covariates considered include a family history of ADHD (yes/no); demographic variables such as the race, sex of the child (female or male), year of birth (1998-2002, 2003-2006, 2007-1017), and age of the

mother at the time of delivery (continuous), whether anyone in the household had a college degree (yes/no), home ownership (yes/no), and payment type at delivery (no insurance or government insurance, or private insurance). Two additional variables were the timing when prenatal care began (during or after the 3rd month of pregnancy vs. before) and the amount of folic acid supplementation before or during pregnancy (greater than or equal to 500mcg/day, as described by (Schmidt et al., 2012). Mothers were also asked if they breastfed and if they experienced nausea or vomiting due to pregnancy. To measure maternal emotional stress, we combined responses to three questions such as: if the mother felt sad, empty, or depressed for more than 2 weeks before or during pregnancy, if the mother lost interest in things 2 weeks before or during pregnancy (yes/no), and if there were financial hardships in the period 3 months before pregnancy to the interview date (yes/no). Due to the high correlation of these variables, an indicator variable was created to examine the presence of maternal stress.

Finally, non-cannabis recreational drugs and tobacco product use were also collected in response to the same question as maternal cannabis use as follows: “At any time during the index time [and/or during the time you breastfed], did you take or use any recreational or street drugs such as those in List #11, of your packet, or any others?”. If participants responded yes, they were then asked to enter the names of up to three recreational or street drugs from list 11 or any not listed. Due to small cell sizes, a variable was created to record any non-cannabis recreational drug use and tobacco

smoke before or during pregnancy. Second-hand smoke exposure from other smokers in the household before or during pregnancy was obtained.

Statistical analysis

We began with univariate descriptive analysis to examine all variables for outliers, out-of-range values, and logical inconsistencies. Categorical variables were examined for low cell counts, leading to instability in statistical analyses. If a categorical variable had a cell count of less than 20 in bivariate analysis with outcome and exoposure, they were recategorized to prepare for model building. Indicator variables were created to incorporate information from several variables, such as maternal stress or individual socioeconomic status, as stated in the above section. A child's race or ethnicity was recategorized as a bivariate measure that compared white (non-Hispanic) participants to otherwise identified (including white Hispanic) groups to examine possible effects of belonging to a non-white race or ethnicity. A participant's regional center of origin was also recategorized to compare the group of participants from the largest group (Alta, Far Northern, and Redwood Coast) to participants from other regional centers. The month that prenatal care began was recategorized as a dichotomous variable to compare participants whose mothers began care before the third month to those whose mothers began in the third month or later. Year of birth was categorized into three levels (1998-2002, 2003-2006, 2007-2017), with about 30-33% of observations in each level due to the later years having sparse data.

Bivariate analysis was conducted to examine the association of each covariate with the outcome and exposure and each of the other covariates. While p-values were determined using Chi-Squre or Fisher's Exact two-sided tests, the magnitudes of associations from crude logistic regressions were used primarily. There is more information regarding the direction and magnitude of the effect (Greenland et al., 2016) from an odds ratios. Using logistic regression, continuous variables were examined for associations with the categorical outcome, exposure, or. Significant associations with the exposure and/or outcome were noted as part of the confounder assessment.

The DAG was used to determine a sufficient set of confounders that were used in model building. These covariates were omitted one at a time from an initial logistic regression model with all possible confounders, referred to as the "full" model. However, a DAG comprises a set of assumptions that may not be fully verifiable, so this project integrates two other methods of determining confounder inclusion in model fitting. The covariate was considered a possible confounder if removing the variable changed the beta coefficient or odds ratio for the exposure-outcome association by at least 5% (Maldonado & Greenland, 1993). The change-in-estimate for the beta coefficient and odds ratio from the full model was noted for each variable removed. These values were used to determine which covariates contributed more to the model and determined the sequence in which variables were omitted during the step-down process (smaller change-in-estimate was omitted first) (Weng et al., 2009).

The variables identified as confounders were maternal age, presence of maternal perceived stress, family history of ADHD, presence of another smoker in the household, protective SES factors, maternal non-cannabis recreational drug and tobacco product use, and year of birth. Variables that controls were matched on (regional center, sex of the child) were included in a separate model as they did not meet the minimum criteria for a confounder but were matched on between controls and cases. All analyses were done using SAS OnDemand for Academics (2023).

Results

1,152 participants completed the questions regarding maternal cannabis use and were included in this analysis. Of these, 88 (7.36%) participants had mothers who reported cannabis use before or during pregnancy, and 46 (3.99%) participants used cannabis for more than one time period (before pregnancy and trimesters of pregnancy). For those who used cannabis in only one period, use declined from 2.52% of participants who used cannabis before pregnancy to less than 1% of participants who used it during the second trimester. Zero participants only used cannabis in the third trimester. Mothers in the typical development group (controls) only used cannabis before pregnancy (n=17; 3.64% of TD) or in more than one period (n=10; 2.14% of TD). These results are presented in Table 3. As shown in Figure 3, only 18% of the variation in the percentage of participants exposed to maternal cannabis use is explained by year of birth.

Having experienced any maternal stress factors (OR=2.51; 95%CI=1.58-3.97, a family history of ADHD (OR=2.17; 95%CI=1.38- 3.42), presence of other smokers in the house (OR=4.70; 95%CI=2.96-7.75), maternal smoking of any tobacco product before or during pregnancy (OR=12.17; 95%CI=7.55-19.64), alcohol use before or during pregnancy (OR=5.23; 95%CI= 3.10-8.84) and non-cannabis polysubstance use (OR=14.60; 95%CI=9.05-23.57) were all associated with increased odds of maternal cannabis use. Only having three protective SES factors (OR=0.35; 95%CI=0.21-0.59) was associated with decreased odds of maternal cannabis use. All other variables did not differ by exposure group including, identifying as non-white or mixed race, having breastfed, regional center, vomiting or nausea due to pregnancy, and maternal age at delivery. These results can be viewed in Table 2.

As seen in Table 4, maternal cannabis use before or during pregnancy indicated an association in the direction of increased risk with low precision (OR=1.28; 95%CI=0.81-2.01). After adjusting for maternal age, presence of maternal perceived stress, family history of ADHD, presence of another smoker in the household, protective SES factors, maternal use of non-cannabis recreational drugs and tobacco products, and year of birth, children of mothers who used cannabis before or during pregnancy were not found to be at significantly increased odds of ASD diagnosis compared to children of mothers who did not use cannabis before or during pregnancy (OR=1.20; 95%CI=0.68-2.12). The same held when the variables that controls were matched on (sex of the child and regional center) were additionally controlled for (OR=1.20; 95%CI=0.68-2.12).

Discussion

This project examined if maternal cannabis use was associated with an increased risk of ASD diagnosis for California children aged 2-5 years old enrolled in the CHARGE study. We found no significant association between maternal cannabis use before or during pregnancy and the odds of ASD diagnosis. While crude and partially adjusted model odds ratios were above 1, confidence intervals were wide, and results were not significant. The odds ratio pushed toward null by only .08 once maternal age, presence of maternal perceived stress, family history of ADHD, presence of another smoker in the household, protective SES factors, maternal use of non-cannabis recreational drugs and tobacco products, and year of birth were adjusted for. No other confounders were identified in the relationship between maternal cannabis use and ASD diagnosis.

In this study, we also found that maternal cannabis use declined as pregnancies progressed from before pregnancy to the third trimester. We also examined if an increasing percentage of participants were exposed to maternal cannabis over the years of participants' conception. There was no linear trend; however, this may have been due to the decreased number of participants conceived in the later years of the study. While the results for this study were not significant, they are not indicative of null effect. As an emerging field of study, these results align with a lineage of studies explained in the literature review that have attempted to examine the association between maternal cannabis use and child neurodevelopment outcomes.

Only three studies before this study have examined maternal cannabis use and child neurodevelopmental outcomes in children with disorders. Only one of these studies has been conducted in the United States. These results are consistent with 2 of these existing studies (SEED and Barwon Infant Study) that did not find a causal relationship between maternal cannabis use and the odds of ASD diagnosis (DiGuiseppi et al., 2021; Pham et al., 2022). Contradicting the results of this study are those from a Dutch birth cohort study by Corsi et al. which found that children with maternal cannabis use were at higher risk for ASD diagnosis (Corsi et al., 2020 The differences in results between this study using CHARGE observations and the Dutch birth cohort may lie in how the cannabis market and legislation in the United States differ greatly from that of the Netherlands.

As a U.S.-based case-control study, this project's results agree with those reported by DiGuiseppi et al. but has the additional strength of being entirely situated within California, thereby eliminating residual confounding due to state-specific cultural factors such as historical perspective, social acceptability, legal changes, and healthcare practices toward cannabis that may affect the mother and/or child. For example, the reliability of maternal cannabis self-reporting was specifically examined amongst Northern California Kaiser Permanente members that suggested that maternal cannabis use is greatly underreported, whereas it has been reported as accurate in a different study in the Netherlands, indicating that accuracy of self-reporting may be highly dependent on the atmosphere around cannabis use (El Marroun et al., 2011; Young-

Wolff et al., 2022). While the study conducted by DiGuiseppi et al. also used the SCQ and MSEL to screen all children regardless of source population and confirmed diagnoses of cases through standard diagnostic assessments administered by trained, research-reliable clinicians, the study described in this analysis is the first to control for maternal stress and depression, family history of ADHD, presence of another smoker in the household, and multiple determinants of individual socioeconomic status when considering confounding due to greater socioeconomic disadvantage.

The biggest limitation of this project was the low percentage of mothers who endorsed cannabis use during pregnancy, which limited the power and scope of analysis. The presence of a college degree in the household, having private insurance at the time of delivery, someone in the household owning the house of residence, maternal experience of sadness, maternal loss of interest, maternal experience of financial hardship, maternal use of non-cannabis recreational drugs, and maternal use of tobacco products were all strongly associated with maternal cannabis use, which led to cell sizes that were too small for analysis. Thus, indicator variables for individual socioeconomic status, maternal stress, and maternal non-cannabis recreational drug and tobacco product use were created. However, the grouping of variables into indicator variables meant that we could only examine the net effect of a group of variables on the association between maternal cannabis use and odds of ASD diagnosis but could not examine the impact of each individual variable (such as the maternal tobacco use) separately on the model.

As cannabis has been observed to be the most used substance by pregnant women (Substance Abuse and Mental Health Services Administration, 2020), it is possible that underreporting may have occurred for this study since exposure was determined through retrospective self-report. It is important to note that cannabis' legal status and social attitudes toward people who use cannabis were still developing in the earlier stages of this study. The low percentage of individuals with mothers who used cannabis during pregnancy meant that we did not have enough variability in periods of pregnancy during which cannabis use occurred or in the duration of use to examine effects per trimester or dose-response effects. Finally, as most participants were conceived between the period after medical cannabis use was legalized and recreational cannabis use was legalized, products used at that time were not as controlled. There was far less diversity in the types of products used, and people did not purchase "brands" of products as they may now. A study with current or future observations may have more power due to increased legalization and less stigmatization, which likely would mean more participants with mothers who used cannabis during pregnancy and are willing to disclose their substance use. Future studies should also record information about types and/or strains of cannabis products used as there is much more variability.

With cannabis' changing legal status, there have been corresponding changes to THC content in cannabis products, their accessibility, and how pregnant users may be perceived. Children included in this dataset were born between 1998 and 2017 (years of conception: 1997-2016) but the number of children decreased in the latest years.

Pertinent Californian legislative changes occurred during these years regarding cannabis, including Proposition 215 (the Compassionate Use Act) which legalized medical cannabis use in 1996, Proposition 47 (the Safe Neighborhoods and Schools Act) which charged possession of cannabis as a misdemeanor instead of a felony in 2014, and Proposition 64 (Adult Use of Marijuana Act) which legalized cannabis for use by adults 21 and over in 2016 and legalized sale of recreational cannabis in California by January 1, 2018. As described above, the vast majority of children in this study were conceived during a period when the legal status of cannabis use remained stable, which creates more homogeneity when it comes to cannabis products and attitudes toward use. However, future analyses that compare the effects of maternal cannabis use before and after legislative changes could offer insight to how legislation may have changed the products or frequency that people use them.

Due to the limitations discussed, this project's lack of significant results should be interpreted carefully, as the effects of cannabis in relation to fetus development are still under study. More research is particularly critical due to dynamic changes in the potency of current forms of cannabis now on the market. Due to cannabis' complicated and changing legal status, animal studies have been the primary source for experimental trials. Rat models have yielded the most insight into the effects of cannabinoids on development. Several potential mechanisms have been identified. One possible pathway is that THC passes from mother to child via the placenta, enters the

fetus's bloodstream, and can cross the fetal blood-brain barrier. The biological plausibility of detrimental effects of maternal cannabis use cannot be overlooked.

Cannabis marketing strategies actively seek to misinform consumers about the safety and risks of their products (Shi & Pacula, 2021; Berg et al., 2023; Dickson et al., 2018). These advertisements along with the rise of easy-to-access, but not always correct information on the internet make it difficult for mothers to find accurate information regarding the safety of cannabis use. Advertisement regulations and policies regarding cannabis advertising are primarily designed for traditional advertising methods such as physical advertisements on billboards, store signs, or print (Department of Cannabis Control). Despite these policies, compliance varies greatly. A study of 700 Californian recreational dispensaries found that" 272 (38.9%) promoted [the] health benefits of cannabis" (Shi & Pacula, 2021). While there have been studies on the health benefits of cannabis use for symptoms associated with specific conditions such as cancer or stroke, there is limited data regarding any potential benefits or the safety of cannabis use during pregnancy. Despite that, a wider mystery-shopper-based study of 5 cities across the United States, including Los Angeles, 54.3% endorsed their cannabis products specifically for pregnancy-related nausea (Berg et al., 2023). A Colorado study employed research assistants to pose as 8-week pregnant experiencing morning sickness. They found that 69% of the 400 dispensaries recommended their cannabis products for "morning sickness" (Dickson et al., 2018). While the frequency of endorsing cannabis products for morning sickness differed by license type (medical 83.1%, retail

60.4%, both 61.7%, P,.001), the proportion of dispensaries that endorsed the safety of mothers using cannabis did not differ by dispensary type (medical 40.7%, retail 28.4%, and both 34.5%) (Dickson et al., 2018). The authors note that 81.5% of the dispensaries discussing cannabis use with a health provider (Dickson et al., 2018).

Advertisement policies, such as restricting unsupported claims of health benefits from using cannabis products, are supposed to apply to online advertisements (Department of Cannabis Control). However, with the rise of social media and brand presence through corporate accounts, distributors take advantage of ambiguity, and compliance varies greatly. Cannabis distributors have developed a growing presence in the vastly uncontrolled landscape of social media presence. Studies regarding young adults and youth have shown that liking or following posts by a cannabis business was associated with higher odds of past-year cannabis use (Whitehill et al., 2020). Social media is unique in its ability to reach an audience. In a study on social media (Twitter and Facebook), posts by 6 cannabis businesses in Washington examined 1,027 posts that got from 342 to 2915 followers (Moreno et al., 2018). This same study found that, despite Washington State Liquor Control Board Washington Administrative Code (WAC) 314-55-155's prior restrictions mentioning social media specifically, 13.3% promoted therapeutic benefits of cannabis product use, and only 10.7% of posts included all required WAC warnings (Moreno et al., 2018). A more encompassing study looked at 2,660 posts from 14 businesses across four states (Alaska, Colorado, Oregon, and Washington) between June 1, 2017, and May 31, 2018, and found that the frequency of

posts alleging health benefits of cannabis use ranged from 1.3% of posts from the business in Alaska to 13% across the Oregon businesses (Moreno et al., 2022N). A Twitter-specific study examined 17,238 tweets from December 1, 2019 to December 1, 2020 that contained cannabis- and pregnancy-related words and found that safe use during pregnancy was mentioned in 36% of the posts (Pang et al., 2021). As information-gathering increasingly moves online, it is essential to consider how pro-cannabis use messages, especially regarding use during pregnancy, can mislead expecting mothers into thinking these products have been proven safe.

Such messages are especially concerning as expectant mothers have reported dissatisfaction with the information or care they receive from their providers. A study of 26 pregnant women found that they were worried about the effect of substance use on their child but did not receive satisfactory information from health care providers (Stone, 2015). Most reported being threatened with child welfare services involvement if they did not stop use instead of being offered information on health ramifications or resources on stopping use. While the sample size was only 26, a strength of this study was that the majority of women interviewed identified as black. Thus, responses from this study cannot be ignored as this highlights the ramifications of still-existing discrimination within the exam room in the context of cannabis use.

Given the rising rates of cannabis use and increasingly permissive legislation, coupled with rising THC content and information-gathering via social media, it is pertinent that

consumers receive accurate information regarding the possible effects of maternal cannabis use. However, current studies are insufficient to establish the presence or absence of causal effects due to difficulties in measuring exposure and controlling confounding. More extensive and recent studies with more information regarding the types and branda of cannabis used and dosage are needed to understand better if and how the amount of THC exposure can affect child neurodevelopment, particularly in relation to ASD and other behavioral disorders. It is critical not to mistake a lack of significance in results as evidence of no effect, particularly in light of the very plausible mechanisms as to how maternal cannabis use may affect neurodevelopment, and much future work is needed to provide expectant mothers quality guidance when it comes to costs and benefits of cannabis use during pregnancy.

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Tables and Figures

Figure 1: Directed Acyclic Graph

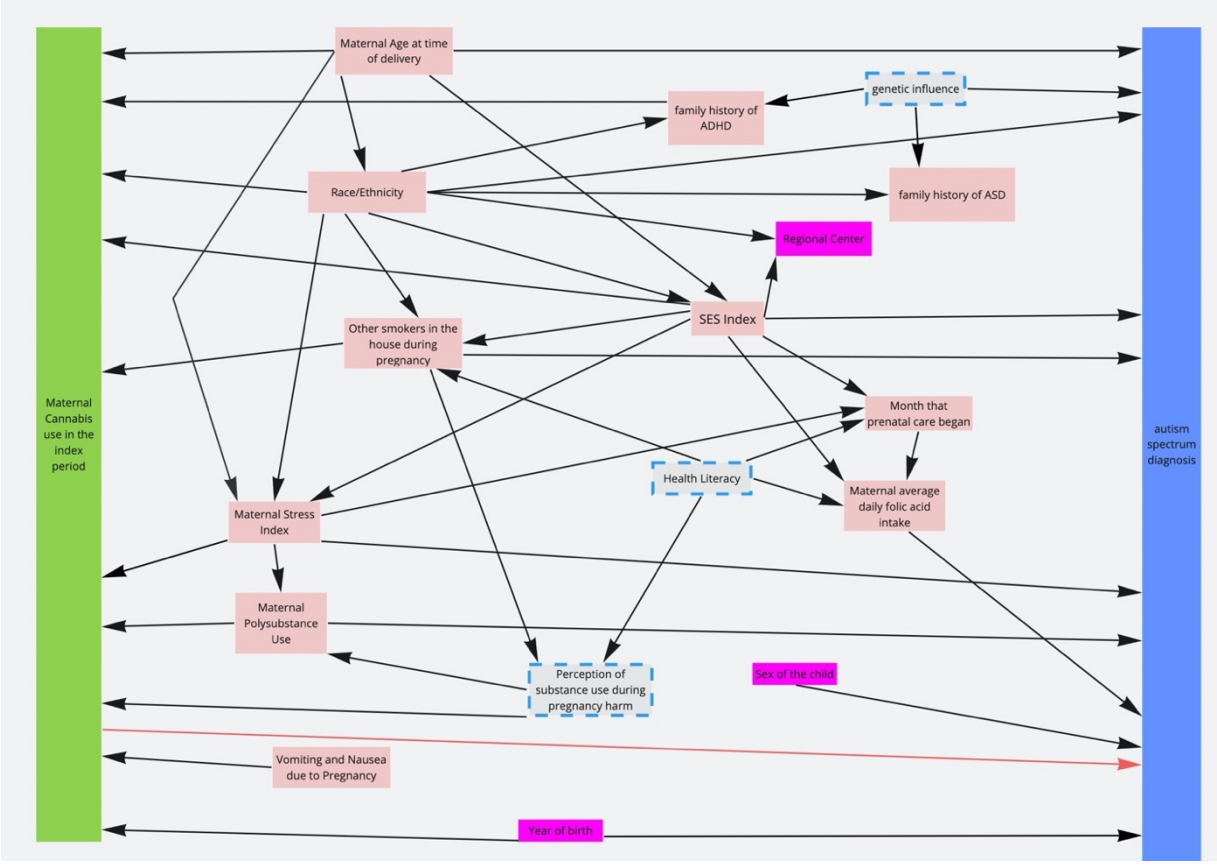

Figure 2: Sample Size changes

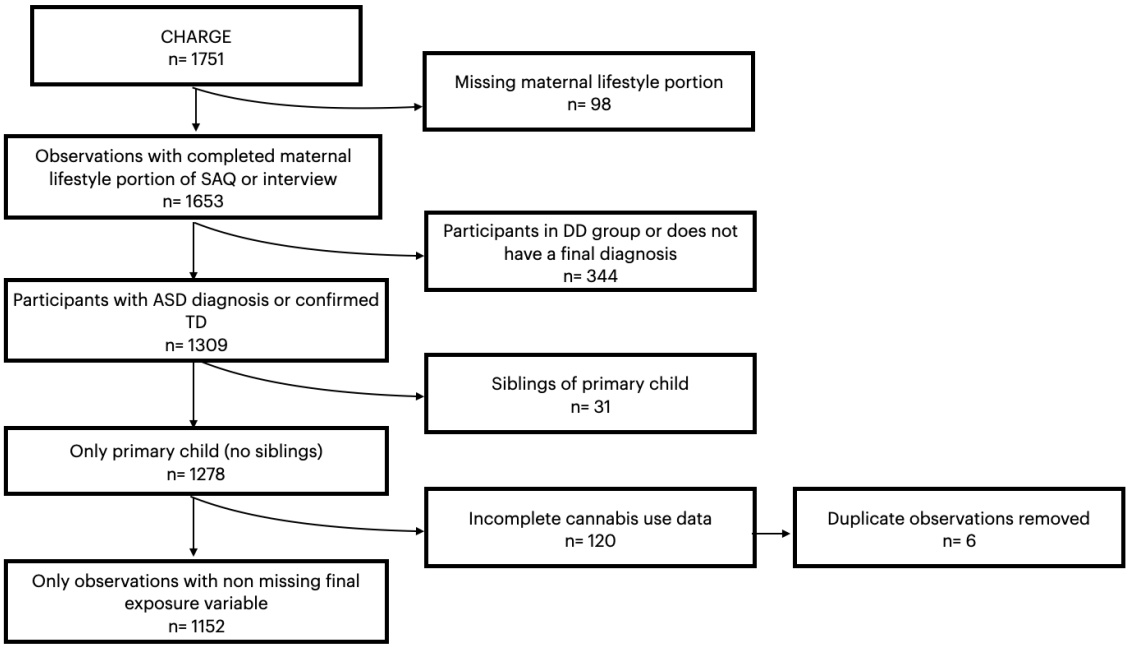

Figure 3– Percentage of mother reporting cannabis use by year of conception and percentage of included participants per year of conception

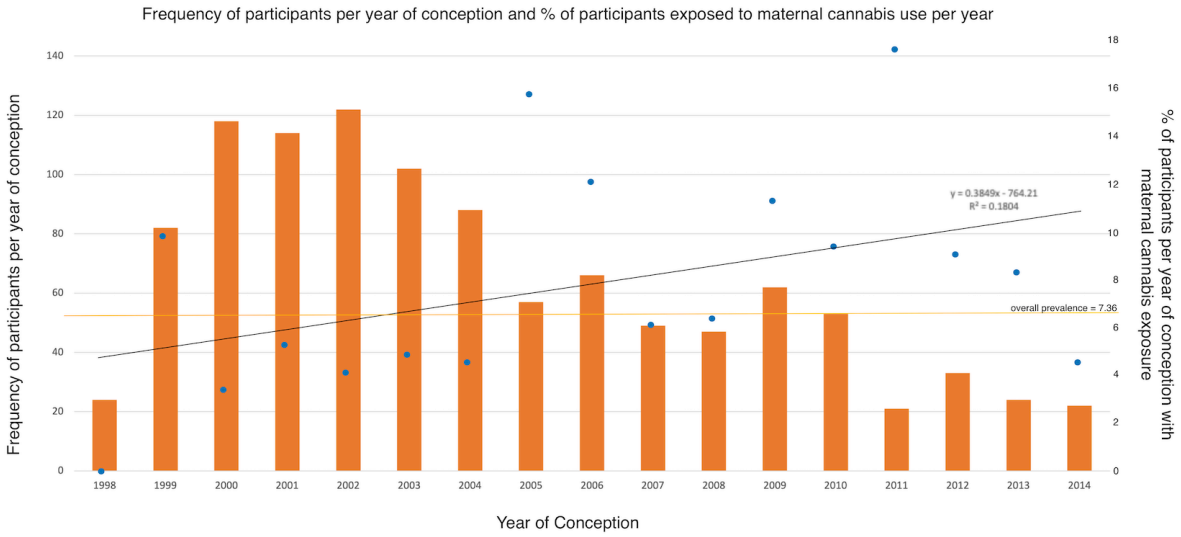

Table 1: Literature review summary of most relevant cannabis-ASD studies

References	Study Design	Sample Description	Exposure Assessment	Outcome Measure	Strengths	Limitations	Results
Corsi (2020)	Population-based cohort pulling data from birth registry between April 1, 2007 and March 31, 2012 in Ontario, Canada	503, 065 births including 7,125 diagnosed autism between 18 months and 10 years of age	Birth registry; abstracted from perinatal record which was completed for all pregnant women In Ontario by health professional. During first prenatal visit, women are asked about any substance use in the current pregnancy	Two or more outpatient diagnoses by either a pediatrician or psychiatrist or at least one diagnosis in hospital databases, or both between 18 months and 10 years old from	Large sample size; large numbers of children with ASD; parity, antenatal care, other substance use including tobacco, alcohol, or drug were adjusted for as confounders; coarsened exact matching (CEM) matching of cases and controls	small number of cannabis-only users but numbers not reported; cannabis use during current pregnancy is measured only as dichotomous yes/no; retrospective self-reporting of substance use, ASD diagnosis of children begins before 2 years old	Children with prenatal cannabis exposure were at higher risk for ASD diagnosis
DiGuiseppi (2021)	Multi-site case-control study that enrolled children born between September 2003 and august 2005 (SEED1) or January 2008 to December 2011 (SEED2) in a study catchment area in California, Colorado, Georgia, Maryland, North Carolina, or Pennsylvania	1428 case children were compared to two control groups, one group is children from general population (N=1628) and the second children with non-ASD developmental delays/disorders (DD) (N=1198)	Mother was interviewed about drug use during pregnancy. If they answered yes, follow-up questions were asked for each month in the three months before pregnancy through delivery, and then during breastfeeding	SCQ (Social Communication Questionnaire) and Mullen Scales of Early Learning (MSEL) were used to screen all children regardless of source population, and the Autism Diagnostic Observation-Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R) were used to confirm assessments.	Large number of cases, Developmental delay control group in addition to population controls, screening assessments to catch undiagnosed cases amongst controls, assessment of tobacco as an effect modifier, models adjusted for maternal education, alcohol, and tobacco use during peri-pregnancy period	Small, but statistically sound, number of exposed cases (N=76), inclusion of catchment area as a random effect may not be enough to account for confounding due to state of origin, no controlling for family history of disorders	Maternal cannabis use in per-pregnancy, pre-conception only, or during pregnancy had no significant effect on risk of ASD diagnosis after adjustment for maternal education, and alcohol and tobacco use during peri-pregnancy when compared to DD and population control groups
Pham (2022)	Population-based birth cohort - Barwon Infant Study of women and their child recruited from two Barwon region hospitals in Victoria, Australia between June 2010 and June 2013.	1074 mother-infant pairs, of which 676 completed the CBCL at 2 years old, 9 with diagnosed ASD at 4 years	Baseline self-administered questionnaires at gestation age; time periods and questions asked not specified	CBCL 1½–5 (preschool version), with focus on the DSM-oriented scale autism spectrum problems (ASP)	Validated measure for ASD symptoms appropriate for age	Not enough cases at 4-year-old follow up to evaluate association with diagnosis; only 1 of 9 ASD cases were exposed and the confidence interval was too wide to suggest a stable estimate (5.65, 237.75); only adjusted for child's sex and age at time of behavioral assessment for 2-year-old analysis	maternal cannabis use was not associated with ASD symptoms at 2 years using continuous ASP-raw

Table 2: Characteristics of Exposure and Outcome Groups

covariates	Children with confirmed typical development outcome (% Yes)	Children with confirmed ASD outcome (% Yes)	Unadjusted odds ratio (95% Confidence interval)	Mothers did not use cannabis in the before pregnancy and during pregnancy (% Yes)	Mothers used cannabis in the before pregnancy and during pregnancy (% Yes)	Unadjusted Odds ratio (95% CI)
Child Characteristics						
Year of Conception (Q1, mean, Q3)	2002, 2004, 2007	2000, 2003, 2009	0.3*	**2001, 2003, 2008**	**2002, 2006, 2010**	**0.0002***
Year of birth (Q1, Mean, Q3)	2003, 2005, 2008	2001, 2004, 2010	0.31*	2002, 2004, 2008.5	2003, 2007, 2011	**0.0003***
Child is female	81 (17)	110 (16)	0.91 (0.67, 1.25)	175 (16)	16 (18)	1.13 (0.64, 1.99)
Child's race was not white or they identified as multiracial	225 (48)	360 (52)	1.19 (0.94, 1.50)	539 (51)	46 (52)	1.06 (0.69, 1.65)
Child was breastfed	442 (95)	628 (93)	0.69 (0.41, 1.17)	992 (94)	78 (91)	0.58 (0.27, 1.26)
Regional Center			1.14 (0.90, 1.45)			0.74 (0.48, 1.15)
Alta , Far Northern, and Redwood Coast	211 (45)	287 (42)		454 (43)	44 (50)	
Other catchment areas	256 (55)	398 (58)		610 (57)	44 (50)	
Socioeconomic status						
Home owned by someone in household	384 (76)	487 (64)	**0.58 (0.44, 0.75)**	747 (71)	42 (48)	**0.38 (0.25, 0.59)**
Payment method at delivery was through private insurance	396 (86)	543 (80)	**0.68 (0.49, 0.93)**	884 (83)	55 (64)	**0.34 (0.21, 0.54)**
At least one household member with a college degree	288 (62)	402 (59)	0.88 (0.69, 1.12)	659 (62)	31 (35)	**0.33 (0.21, 0.53)**
All three protective Individual SES factors	242 (53)	279 (41)	**0.63 (0.50, 0.80)**	500 (48)	21 (24)	**0.35 (0.21, 0.59)**
Prenatal Care						

Mother felt sad, empty, or depressed for more than 2 weeks before or during pregnancy	18 (4)	71 (11)	**2.97 (1.75, 5.06)**	79 (8)	10 (12)	1.64 (0.81, 3.30)
Mother lost interest in most things for more than 2 weeks before or during pregnancy	12 (3)	43 (7)	**2.6 (1.36, 5.00)**	43 (4)	12 (14)	**3.66 (1.85, 7.23)**
Mother felt that between 3 months before pregnancy to the present hardship to pay for basic needs	71 (15)	134 (20)	**1.36 (0.99, 1.86)**	176 (17)	29 (33)	**2.47 (1.54, 3.97)**
Having any maternal stress indicator	83 (18)	181 (28)	**1.74 (1.30, 2.34)**	229 (23)	35 (42)	**2.51 (1.58, 3.97)**
Prenatal care began in the 3rd month or later	136 (29)	220 (33)	1.16 (0.90, 1.50)	317 (30)	39 (45)	**1.92 (1.23, 3.00)**
Vomiting or Nausea due to Pregnancy	344 (75)	514 (76)	1.10 (0.83, 1.45)	795 (76)	63 (72)	0.79 (0.49, 1.28)
Folic Acid (Categorized)						
Average daily folic acid supplement less than 500 mcg	81 (19)	148 (25)	ref	208 (22)	21 (27)	ref
Average daily folic acid supplement more than or equal to 500 mcg and less than 800 mcg	148 (35)	222 (37)	0.82 (0.58, 1.16)	338 (36)	32 (41)	0.94 (0.53, 1.67)
Average daily folic acid supplement less than or equal to 800 mcg	189 (45)	232 (39)	**0.67 (0.48, 0.94)**	395 (42)	26 (33)	0.65 (0.36, 1.18)
Family History						
Maternal age in years at delivery (Q1, Mean, Q3)	27, 31, 34	27, 31, 35	0.7*	27, 31, 35	23, 30, 33.5	**0.0009***
family history of ADHD	119 (23)	250 (33)	**1.59 (1.23, 2.05)**	296 (27)	37 (45)	**2.17 (1.38, 3.42)**
Family history of ASD	9 (2)	33 (6)	**2.78 (1.31, 5.86)**	37 (4)	5 (6)	1.63 (0.62, 4.28)
maternal substance use						
Other smokers in household before or during pregnancy	41 (9)	124 (18)	**2.30 (1.58, 3.35)**	130 (12)	35 (40)	**4.70 (2.96, 7.49)**
Mother smoked any tobacco product before or during pregnancy	36 (8)	84 (12)	**1.69 (1.12, 2.55)**	77 (7)	43 (49)	**12.17 (7.55, 19.64**)
Non-marijuana recreational drug use in 3 months before pregnancy and during	***	14 (2)	***	0 (0)	16 (18)	**

Alcohol use ever during or before pregnancy	205 (45)	282 (42)	0.90 (0.71, 1.14)	420 (40)	67 (79)	**5.23 (3.10, 8.84)**
Alcohol use ever during pregnancy	104 (23)	160 (24)	1.07 (0.81, 1.42)	367 (35)	59 (69)	**4.03 (2.51, 6.47)**
Alcohol use in the 3 months before pregnancy	184 (40)	242 (36)	0.84 (0.66, 1.07)	221 (21)	43 (50)	**3.72 (2.38, 5.83)**
non-cannabis polysubstance use before pregnancy	38 (8)	86 (13)	**1.64 (1.10, 2.45)**	77 (7)	47 (53)	**14.60 (9.05, 23.57)**

* p-values are presented for two sample t-tests. It there is no equality of variance, the Satterthwaite t-statistic is considered. Otherwise, the pooled t-statistic is presented.
**Due to the small cell sizes, this effect measure is unreliable and was omitted
*** due to small cell size, this number was omitted to protect participant anonymity

Table 3: Time Periods of use

	TD (N=467)	ASD (N=685)	Total (1152)
Mutually exclusive periods of use	(%)	(%)	(%)
No use before or during pregnancy	436 (93.36)	628 (91.68)	1064 (92.36)
Use before pregnancy	17 (3.64)	12 (1.75)	29 (2.52)
Use in first trimester	0 (0)	**	**
Use in second Trimester	0 (0)	**	**
Use in third trimester	0 (0)	0 (0)	0 (0)
Use in more than one period	10 (2.14)	36 (5.26)	46 (3.99)
Incomplete Information*	**	**	8 (0.69)
Total exposed	31 (6.64)	57 (8.32)	88 (7.64)

*Not enough information was provided to determine if a participant did not use cannabis during multiple time periods, but the participant had at least one period of use

**due to small cell size (under 5), this number was omitted to protect participant anonymity

Table 4: Model Results

		Crude Model+	All variables considered for model building	Model 1	Model 2	Fully Adjusted Model	Fully Adjusted Model with all matching replaced
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
exposure	Cannabis use before or during pregnancy	1.28 (0.81, 2.01)	1.21 (0.68, 2.14)	1.21 (0.69, 2.14)	1.21 (0.68, 2.13)	1.20 (0.68, 2.12)	1.20 (0.68, 2.12)
Confounders	Age of Mom (5 Year increments)	--	1.13 (0.99, 1.29)	1.13 (0.99, 1.29)	1.14 (0.99, 1.30)	1.13 (0.99, 1.29)	1.13 (0.99, 1.29)
	maternal stress^^^	--	1.26 (0.90, 1.76)	1.26 (0.90, 1.76)	1.26 (0.90, 1.77)	1.27 (0.91, 1.78)	1.27 (0.90, 1.77)
	family history of ADHD	--	1.17 (0.85, 1.62)	1.17 (0.85, 1.62)	1.17 (0.85, 1.62)	1.17 (0.85, 1.62)	1.17 (0.85, 1.62)
	Non-white or multi-race^	--	1.07 (0.82, 1.41)	1.07 (0.82, 1.41)	1.08 (0.83, 1.42)	--	--
	Maternal average daily folic acid intake greater than 500 mcg	--	0.71 (0.47, 1.07)	0.71 (0.47, 1.07)	0.72 (0.48, 1.08)	0.71 (0.47, 1.08)	0.71 (0.47, 1.07)
	Other smoker in the house	--	**1.96 (1.26, 3.05)****	**1.96 (1.26, 3.04)****	**1.95 (1.26, 3.03)****	**1.96 (1.26, 3.04)****	**1.96 (1.27, 3.05)****
	SES protective factors^^	--	**0.66 (0.49, 0.89)****	**1026 (0.90, 1.76)**	**0.65 (0.48, 0.88)****	**0.65 (0.48, 0.87)****	**0.65 (0.48, 0.88)****
	Non-cannabis recreational drug use and/or tobacco product used	--	1.07 (0.65, 1.79)	1.07 (0.65, 1.79)	1.08 (0.65, 1.79)	1.08 (0.65, 1.79)	1.07 (0.65, 1.78)
Matched Variables	Year of Birth						
	1998-2002	--	Ref	Ref	Ref	Ref	Ref
	2003-2006	--	**0.43 (0.31, 0.61)*****	**0.43 (0.31, 0.61)*****	**0.43 (0.31, 0.60)*****	**0.43 (0.31, 0.60)*****	**0.43 (0.31, 0.61)*****
	2007-2017	--	0.57 (0.65, 1.79)	**0.58 (0.41, 0.81)****	**0.56 (0.40, 0.78)*****	**0.56 (0.40, 0.78)****	**0.58 (0.41, 0.81)****
	Regional Center	--	1.13 (0.86, 1.49)	1.13 (0.86, 1.49)	--	--	1.14 (0.86, 1.50)
	Sex of the child	--	1.02 (0.72, 1.46)	--	--	--	1.02 (0.72, 1.46)
	BIC	--	1324.60	1317.75	1311.65	1305.12	1317.98

Boldfaced text signifies significance for the covariate (p<0.05*, p<0.01**, p<0.001 ***); ^ - Removal of the variable for child's race did not achieve 5% in OR and decreased model fit during model building, so it was omitted. ^^-defined as having private insurance at time of delivery, a college degree in the household, and someone in the household owns the primary house of residence; ^^^ - defined as experiencing financial difficulties for basic needs in the three months before pregnancy, mother felt sad, empty, or depressed for more than 2 weeks before or during pregnancy, and mother lost interest in most things for more than 2 weeks before or during pregnancy; +crude model includes participants which do not have Non-cannabis recreational drug use and/or tobacco product used information and includes

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