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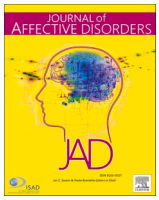

Research paper

Maternal perinatal cannabis use disorder and the risk of anxiety disorders in offspring: Insights from a longitudinal data-linkage cohort study

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ABSTRACT

Background: Cannabis use is increasing among pregnant women, but its effects on child mental health remain poorly understood. This study investigates whether maternal cannabis use disorder (CUD) during pregnancy and the postnatal period increases offspring risk of anxiety disorders.

Methods: We used linked administrative health data from New South Wales, Australia, covering 223,068 live births from January 2003 to December 2005. Maternal CUD and child anxiety disorders, including generalized anxiety disorder (GAD), phobic anxiety disorder (PAD), posttraumatic stress disorder (PTSD), separation and social anxiety disorders, were identified using ICD-10 codes. Generalized linear models (GLMs) with log-binomial regression estimated adjusted risk ratios (aRRs). Mediation and propensity score matching (PSM) analyses were also conducted to test the robustness of findings.

Results: After adjusting for covariates, offspring prenatally exposed to maternal CUD had a 79% increased risk of any anxiety disorder [adjusted risk ratio (aRR) = 1.79 (95 % CI 1.40, 2.26)]; specifically PTSD [aRR = 2.46 (95 % CI 1.78, 3.33)], GAD [aRR = 2.18 (95 % CI 1.03, 4.60)], and CADs [aRR = 1.91 (95 % CI 1.05, 4.60)], compared to non-exposed offspring. Postnatal CUD exposure was also associated with an increased risk of any anxiety disorder [aRR = 2.02 (95 % CI 1.22, 3.14)] and PTSD [aRR = 2.97 (95 % CI 1.56, 5.17)]. These associations remained significant in mediation and PSM analyses.

Conclusion: Maternal CUD during pregnancy and the postnatal period is associated with elevated risks of anxiety disorders in offspring. These findings highlight the need for targeted interventions, including perinatal counselling, to reduce anxiety risks in offspring.

1. Introduction

Anxiety disorders, including generalized anxiety disorder (GAD), phobic anxiety disorder (PAD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorders (OCD), and anxiety disorders specific to early childhood-onset such as separation anxiety and social anxiety disorder, are the most prevalent mental disorders diagnosed in school-age children (Barican et al., 2022; Koet et al., 2022; Mohammadi et al., 2020; Sanchez et al., 2022). For example, a 2022 meta-analysis reported that anxiety disorder is the most common childhood mental health disorder in high-income countries, with a prevalence of 5.2 % (95 % CI 3.2 % to 8.2 %) (Barican et al., 2022). In Australia, anxiety disorder in children and adolescents is the second most common mental disorder in children (7.0 %), preceded by ADHD (7.1 %) and followed by major depressive disorders (3.0 %) (ABS, 2024; AIHW, 2022). Risk factors contributing to anxiety disorder in children and adolescents are multifactorial, encompassing genetic predispositions, adverse neonatal health outcomes, substance use, maternal lifestyle-related factors, and exposure to environmental toxicants (Cabral and Patel, 2020; Pahl et al., 2012; Rapee et al., 2023; Warner and Strawn, 2023). Although research on in-utero exposure to cannabis and adverse maternal and neonatal health outcomes is expanding, the focus has largely been on short-term neonatal health outcomes (Koto et al., 2022; Lo et al., 2023b), leaving significant gaps in understanding how maternal cannabis use disorder may influence long-term child mental health outcomes, including anxiety disorders.

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Cannabis Use Disorder (CUD) is a severe form of cannabis use characterized by continued consumption despite awareness of a persistent or recurrent physical, mental, or psychological problem that is likely caused or worsened by cannabis use (APA, 2013). Globally, cannabis use and hospitalization due to cannabis use (CUD) during pregnancy have been notably increasing in prevalence in the last two decades (Bandoli et al., 2021; Q. L. Brown et al., 2023; Kobernik et al., 2024; Koto et al., 2022; Lo et al., 2023a; Washio et al., 2018; Wicken et al., 2022). In the United States, cannabis use during pregnancy contributed to 40.8 % of maternal hospitalizations due to substance use disorders (Washio et al., 2018). In Australia, between 0.3 % and 0.7 % of pregnant women are hospitalized due to CUD (Kim S. Betts et al., 2022; Oni et al., 2022). These figures underscore an emerging and significant public health issue related to cannabis use among pregnant women.

Emerging evidence suggests that Δ9-tetrahydrocannabinol (THC), the primary psychoactive ingredient of cannabis, can easily cross the placenta and is present in breast milk, exposing the fetus and breastfeeding newborn to its effects (Ayonrinde et al., 2021; Cermak and Stanford, 2023; El Marroun et al., 2010; Little and VanBeveren, 1996). THC can interfere with neuronal proliferation, differentiation, synaptogenesis, and changes in neurotransmitter systems like GABA and glutamate, potentially leading to altered neural circuitry associated with anxiety regulation and stress response mechanisms (El Marroun et al., 2010; Houston et al., 2014; Jutras-Aswad et al., 2009; Narouze, 2021; Navarrete et al., 2020; O'Donnell and Meaney, 2016; Thomason et al., 2021). Consequently, maternal cannabis use may increase the risk of anxiety disorder in offspring due to these neurobiological pathways. However, current empirical evidence on the relationship between maternal cannabis use and anxiety disorder in children is limited and inconsistent. Few studies suggest that cannabis exposure during the gestational period is linked to an increased risk of anxiety symptoms (Fine et al., 2019; Leech et al., 2006; Moore et al., 2023; Rompala et al., 2021) in children and adolescents. However, other studies have found no significant associations or mixed associations between maternal cannabis use and childhood anxiety disorder (El Marroun et al., 2019; Mensah et al., 2024; Murnan et al., 2021; Nomura et al., 2023; O'Connell and Fried, 1991). Notably, existing epidemiological studies examining the associations between maternal cannabis use and offspring anxiety symptoms have primarily relied on self-reported data and focused solely on in-utero exposure to cannabis, making them susceptible to underreporting and recall biases (Brener et al., 2003; J. Brown et al., 1992; Sujan et al., 2023; Sujan et al., 2022). These studies also involved relatively small sample sizes, limiting statistical power and the ability to adjust for key confounders (Mravčík et al., 2020). Additionally, to our knowledge, no previous study has examined the mediating role of adverse birth outcomes, including preterm birth, low birth weight, and small-for-gestational-age, in the association between maternal cannabis use and anxiety disorders in offspring. Further, no study was conducted using matching methods, such as propensity score matching techniques, to balance baseline characteristics of exposed and non-exposed groups by key confounding factors (Rubin, 1997; Steiner et al., 2011).

To close these gaps, this study aimed to examine the association between gestational and postnatal CUD and the risk of different types of anxiety disorders in offspring, using large linked administrative data with objectively measured exposure of interest, maternal CUD during antenatal and postnatal periods, and anxiety disorders in children as an outcome (Chiandetti et al., 2017; Shi et al., 2024).

We hypothesised that (i) exposure to gestational and postnatal CUD would increase the risk of different forms of anxiety disorders in offspring compared to non-exposed counterparts; (ii) adverse neonatal outcomes may mediate the associations between maternal CUD and anxiety disorder risks in offspring. The findings of this study could strengthen preventive strategies in health sector policies aimed at reducing the risk of anxiety disorders in children associated with maternal CUD.

2. Methods and materials

2.1. Study setting and study design

This population-based retrospective cohort study was conducted in New South Wales (NSW), Australia. NSW is the most populous state in Australia with a total population of 8,294,100 as of March 2023 (ABS, 2023).

2.2. The study participants and data sources

This study leveraged population-based linked administrative data from routinely collected health records in NSW. The birth cohort consisted of all live births between 1 January 2003 and 31 December 2005. We tracked mothers from pregnancy through their child's first year to identify hospital admissions due to CUD diagnoses during pregnancy and postnatal periods. Offspring were then followed from birth until December 2018 to capture hospital admissions and outpatient visits associated with anxiety disorder diagnoses in offspring. Birth records from the Perinatal Data Collection (PDC) were linked with the inpatients and outpatient records derived from admitted patient data collection (APDC) and ambulatory mental health data collection (MH-AMB-DC), respectively. These linked records captured both primary and secondary diagnoses of psychiatric admissions, including anxiety disorders in offspring and maternal CUD. The Centre for Health Record Linkage (CHeReL), overseen by the NSW Ministry of Health, carried out the data linkage. The details of this cohort profile are published elsewhere (Kim S. Betts et al., 2022; Tadesse et al., 2024).

As shown in Fig. 1, the final complete-case analysis included 222,706 mother-offspring pairs to assess the associations between maternal CUD and the risk of anxiety disorder in offspring (Fig. 1).

2.3. Measure

2.3.1. Outcome measure

The outcome variable, anxiety disorder, was derived from two main data sources: hospital admissions (APDC) and hospital outpatient visits (AMB-MH-DC). Different types of anxiety disorders in offspring were identified using the 10th edition International Classification of Diseases, Australia Modified (ICD-10-AM) criteria. The ICD diagnostic codes include phobic anxiety disorder (PAD) (F40.0-F40.9), generalized anxiety disorder (GAD) (F41.1), obsessive-compulsive disorder (OCD) (F42.0 - F42.9), panic and stress-related anxiety disorder [posttraumatic stress disorders (PTSD)] (F43.0 - F43.9), childhood-onset (separation and social) anxiety disorder (CAD) (F93.0 - F93.9), and others (unspecified) anxiety disorder (F41.2 - F41.9). Additionally, any anxiety disorder in offspring refers to the presence of any of the specific anxiety disorders listed above, including PAD, GAD, OCD, PTSD, or CAD, diagnosed during the follow-up periods.

2.3.2. Exposure measure

Maternal cannabis use disorders (CUDs) were identified from APDC data using ICD-10-AM codes (F12.0–F12.9), which align with mental and behavioural disorders due to cannabinoid use. CUD diagnoses were categorized as occurring during pregnancy or postnatal periods. Gestational CUD was defined as a diagnosis made between conception and delivery, with conception time estimated by subtracting gestational age from the delivery date in weeks (Kim S. Betts et al., 2022; Tadesse et al., 2024). Postnatal CUD was defined as occurring from birth to 12 months postpartum. Perinatal CUD exposure included any CUD diagnosis occurring either during pregnancy or the postnatal period.

2.3.3. Mediators

The mediators, adverse birth outcomes, were derived from the PDC dataset. Preterm birth was defined as all live births <37 completed weeks of gestation (yes/no). Low birth weight (LBW) and small-for-

gestational-age (SGA) were also defined as birth weight <2500 g (yes/no) and birth weight for gestational age z-scores less than 10th percentile (yes/no), respectively. Further, a 5-minute low APGAR score indicates an APGAR score of <7 (yes/no).

2.4. Covariates

Several epidemiological studies have highlighted factors associated with maternal CUD and anxiety disorder in offspring and adolescents. In our analyses, we accounted for key confounders, including maternal hospitalizations due to substance use-related diagnoses other than CUD such as maternal tobacco smoking (De Genna et al., 2021) and alcohol intake during pregnancy and postnatal periods (Meinhofer et al., 2022; Passey et al., 2014); maternal psychiatric admissions (Johnco et al., 2016; Mohammadi et al., 2020); socioeconomic status (SES) (Boden et al., 2010; Murray and Farrington, 2010); and maternal medical conditions, such as pre-existing and/or gestational diabetes and hypertension (Dachew et al., 2019; Meinhofer et al., 2022). The Australian Bureau of Statistics utilised the socioeconomic indexes for areas (SEIFA codes) to evaluate postcodes based on relative economic advantages and disadvantages. These were categorized into quartiles, with the 1st quartile representing the most disadvantaged areas and the 4th quartile representing the least disadvantaged areas (ABS, 2016). Additionally, we also adjusted for important child-related covariates, such as child sex, birth plurality, birth order, and admission to NICU. However, prematurity at birth (PTB), low birth weight (LBW), small-for-gestational-age (SGA), and 5-min APGAR scores (<7 scores) are thought to be in the causal pathway (Kim Steven Betts et al., 2013; SØMhovd et al., 2012; Ståhlberg et al., 2022). In this study, these covariates were sourced from three linked datasets: PDC, APDC, and MH-AMB-DC.

2.5. Statistical analysis

Using generalized linear models (GLMs) with a log-binomial regression, we estimated risk ratios (RRs) with 95 % confidence intervals (CIs) to examine the risks of anxiety disorder in offspring associated with exposure to maternal CUD, focusing on both antenatal and postnatal exposures. We fitted four separate models to examine the associations between maternal CUD and anxiety disorders in offspring. The first model was the analysis of crude associations between maternal CUD and different types of anxiety disorders in offspring (Model 1). Then, we adjusted for a wide range of maternal factors, including the socioeconomic index for areas (SEIFA quartiles), maternal substance use disorders during pregnancy and postnatal periods (tobacco use-, stimulant use-, opioids use-, and alcohol use- disorders), maternal psychiatric admissions during gestational and postnatal periods (i.e., schizophrenia-, depression-, bipolar-, and anxiety- disorders), maternal chronic medical conditions (i.e., diabetes and hypertension), and parity (Model 2). Additionally, we subsequently adjusted for child-related factors, including child sex, birth plurality, birth orders, and admission to NICU (Model 3). Finally, we conducted sensitivity analyses by maternal tobacco use to examine the independent effects of CUD on anxiety disorder in offspring. However, premature birth, low birth weight, small-for-gestational age, and lower APGAR scores at birth are thought to be on the causal path (Kim Steven Betts et al., 2013; SØMhovd et al., 2012).

Subsequently, we conducted a propensity score matching using nearest neighbour matching (NNM) with a calliper of 0.25 and a matching ratio of 4 to 1 using the MatchIt package (Stuart et al., 2011). This method paired each exposed subject with up to four unexposed subjects using propensity scores and a calliper to improve match quality (Rubin, 1997; Steiner et al., 2011). The matched data were then analyzed, adjusting for key covariates and incorporating weights for accurate variance estimation. Several diagnostic tests and graphical assessments were conducted to evaluate the balance achieved by propensity score matching. These included Standardized Mean Differences (SMDs), Covariate Balance Plots (CBPs), Variance Ratio (VR), and propensity score distribution plots, which were used to visualize the distribution of propensity scores between the treated and control groups.

We also carried out a mediation analysis to investigate the influence of adverse birth outcomes, such as preterm birth, low birth weight, small-for-gestational age, and low Apgar score, on the link between maternal antenatal cannabis use disorder and offspring anxiety disorders. This analysis was performed using the paramed package in Stata version 18 (Emsley and Liu, 2013). Initially, we established two statistical models: (1) the mediator model, which delineates the conditional distribution of adverse birth outcomes such as preterm birth, low birth weight, small-for-gestational age, or low Apgar score based on maternal antenatal cannabis use along with a specified set of covariates and confounders, and (2) the outcome model, which outlines the conditional distribution of childhood anxiety disorders in relation to maternal antenatal cannabis use disorder, mediators, and the same predetermined set of covariates and confounders. These fitted models were utilised as primary inputs to the mediate function, which calculates the estimated natural direct (NDE) and indirect (NIE) effects, along with marginal total effects (MTE) using standardized regression coefficients and 95 % confidence intervals derived by applying the bootstrap method. To determine the extent of mediation role, we calculated the proportion of the association mediated by each mediator using the formula: [(NDE × (NIE − 1)) / (NDE × NIE − 1)] (Duko et al., 2023; Vander Weele, 2016). The 95 % confidence intervals of the regression coefficients were generated from 1000 bootstrap replicates. The NDE represents the impact of maternal antenatal cannabis use disorder on offspring anxiety disorders, independent of any mediator variable. The Natural Indirect Effect (NIE) quantifies the influence of maternal antenatal cannabis use disorder on offspring anxiety disorders, which is mediated by each specific mediator variable. The Marginal Total Effect (MTE) is the sum of the NDE and NIE.

Finally, Stata version 18 and R version 4.3.2 were used for the analyses, with significance declared at a *P*-value of <0.05.

2.6. Ethics

Ethics approval was granted from the Cancer Institute NSW, the NSW Population and Health Service Research Ethics Committee (HREC/18/CIPHS/22), and Curtin University (HRE/2019/0601/01).

3. Results

3.1. Descriptive statistics of key findings

As presented in Fig. 2, of the total 222,706 offspring, 4543 (2.06 %) of offspring were diagnosed with any anxiety disorder, 1702 (0.76 %) were identified with PTSD, and 1596 (0.72 %) were diagnosed with other (unspecified) anxiety disorders (Fig. 2).

In this study, 1.6 % of offspring diagnosed with any anxiety disorder were exposed to CUD during the antenatal period, while 0.4 % were exposed to maternal CUD during the postnatal period. Among those diagnosed with anxiety disorder, 30.1 % were from the most disadvantaged socioeconomic backgrounds, 26.7 % were exposed to maternal smoking during pregnancy, 7.2 % were preterm births, 6.7 % had low birth weight, 3.0 % were admitted to NICUs, and 2.9 % were multiple births. Additionally, 2.2 % of offspring were exposed to maternal substance use disorders other than cannabis during pregnancy, and 5.3 % were exposed to maternal psychiatric admissions. Females were more frequently diagnosed with anxiety disorder than males (56.4 % vs. 43.6 %, $p < 0.001$) (Table 1).

3.2. Associations between maternal CUD and anxiety disorder in offspring

We conducted separate analyses to examine the risk of different types of anxiety disorders in offspring associated with exposure to both

maternal CUD during pregnancy and the postnatal periods, compared to non-exposed offspring.

After controlling for a range of key confounding factors in Model 3, our analyses revealed significant associations between maternal CUD exposure and increased risks of any anxiety disorder, GADs, PTSDs, and CADs in offspring compared to non-exposed counterparts. We found that maternal CUD during pregnancy was associated with a 79 % increased risk of any anxiety disorder in offspring [aRR = 1.79 (95 % CI 1.40, 2.26)], while postnatal CUD in mothers was linked to a 2-fold increased risk of any anxiety disorder in offspring [aRR = 2.02 (95 % CI 1.22, 3.14)] compared to non-exposed offspring.

We found an increased risk of PTSD associated with maternal CUD exposure during pregnancy and the postnatal period, with adjusted risk ratios of 2.46 (95 % CI 1.78, 3.33) and 2.97 (95 % CI 1.56, 5.17), respectively, while antenatal CUD exposure was also linked to an increased risk of GAD [aRR = 2.18 (95 % CI 1.03, 4.60)] and CAD [aRR = 1.91 (95 % CI 1.05, 3.21)] compared to non-exposed offspring. However, we did not observe statistically significant associations between maternal CUD during pregnancy and phobic and other anxiety disorders [aRR = 0.75 (95 % CI 0.22, 1.86) and aRR = 1.40 (95 % CI 0.81, 2.23)]. In our sensitivity analyses, we observed a slight increase in the risks of any anxiety disorder and PTSD in offspring associated with both antenatal and postnatal exposures to maternal CUD after excluding maternal CUD and tobacco use disorders comorbidities from the main analyses (Tables 2 & 3).

3.3. Propensity score matching

In our propensity score matching, we assessed the balance achievement using diagnostic tests and graphical assessments, we found Standardized Mean Differences (SMDs) below 0.1 after matching, a variance ratio close to 1, a covariate balance plot with a significant SMD reduction after matching, and an overlapped propensity score plot, suggesting adequate balance with successful matching (Figs. S1-S3). Thus, this matching process effectively addressed significant baseline differences between mothers with and without CUD. Finally, when the full cohort sample size was matched by antenatal, postnatal, and overall exposures to CUD, we found matched samples of 6326, 1312, and 7103 mothers of offspring, representing only 2.8 %, 0.59 %, and 3.2 % of the original cohort, respectively. This small proportion reflects the significant differences between mothers with and without CUD, indicating the importance of rigorous adjustments to address these disparities.

As summarized in Table 4, in the PSM analyses, after adjusting for a wide range of potential confounding factors, offspring of mothers with antenatal, postnatal, or overall perinatal cannabis use disorder exhibited more than a 41 % and 76 % increased risk of developing any anxiety disorders and PTSD, respectively (Table 4).

3.4. Mediation role of adverse birth outcomes

Fig. 3 and Table S1 show how adverse neonatal outcomes, including preterm birth, low birth weight, small-for-gestational-age, and 5-minute low Apgar scores, mediate the link between maternal antenatal cannabis use disorder and anxiety disorders in offspring.

As shown in Fig. 3, maternal antenatal cannabis use disorder was associated with an increased likelihood of preterm birth [β = 1.19 (95 % CI 1.03–1.36)], low birth weight [β = 1.74 (95 % CI 1.58, 1.89)], and small-for-gestational age [β = 1.15 (95 % CI 0.92, 1.37)]. However, it was not associated with a 5-minute low APGAR score [β = 0.14 (95 % CI -0.36, 0.45)]. After adjusting for a range of covariates and adverse birth outcomes, including preterm birth, low birth weight, small-for-gestational age, and low Apgar score, the link between maternal antenatal cannabis use disorder and offspring anxiety disorders remained. However, the effect estimates showed a slight attenuation [β = 0.66 (95 % CI 0.41, 0.91)].

Table S1 summarises the regression coefficients for the NDI, NIE and MTE of maternal antenatal CUD on offspring anxiety disorders. The impact of maternal antenatal CUD on offspring anxiety disorders was mediated by low birth weight [RR = 1.01 (95 % CI 1.001, 1.012)] and small-for-gestational age [RR = 1.01 (95 % CI 1.002, 1.02)]. The proportion of the total effect mediated by low birth weight and small-for-gestational age was only 2.1 % and 2.07 %, respectively, indicating that this mediation effect was small, about 53 times smaller than the direct effect. However, it's important to note that we did not find statistically significant mediation roles for other adverse birth outcomes, including premature birth [RR = 1.004 (95 % CI 0.998, 1.01)] and 5-minute low APGAR scores [RR = 1.001 (95 % CI 0.997, 1.002)], on the observed associations between maternal antenatal CUD and risk of anxiety disorders in children.

4. Discussion

4.1. Summary of key findings

Public health concerns about cannabis use during pregnancy and the postnatal period are growing, given its potential to alter brain development, impairing and increasing the risk of long-term mental health issues in offspring and adolescents. Interestingly, although maternal cannabis use is associated with developmental and mental health risks in children (Ayonrinde et al., 2021; Gu et al., 2024; Natale et al., 2020), some women report continued cannabis use during pregnancy or breastfeeding to manage stress, anxiety, nausea, or other mental health concerns, often perceiving it as low risk (Barbosa-Leiker et al., 2020; Ko, 2020; Vanstone et al., 2021).

This study aimed to investigate the association between maternal CUD during pregnancy and the postpartum period and the subsequent risk of anxiety disorders in offspring using a large sample population-based cohort study. We found that both in-utero and postnatal exposures to CUD significantly increase the risk of developing any AD and PTSD in exposed offspring compared to non-exposed counterparts after adjusting for key confounding factors, including admissions due to substances other than CUD, socioeconomic status, and maternal psychiatric admissions. Specifically, offspring prenatally exposed to CUD had a 1.8-times higher risk of any anxiety disorder, a 2.5-times higher risk of PTSD, a 2.2-times higher risk of GAD, and a 1.9-times higher risk of separation or social (childhood-onset) anxiety disorders compared to non-exposed offspring. Additionally, postnatal exposure to CUD was associated with a 2-fold increased risk of any anxiety disorder and a 3-fold increased risk of PTSD in exposed offspring compared to non-exposed counterparts. After excluding maternal tobacco use disorder from the main analysis, we observed slightly increased risks of any anxiety disorder and PTSD in offspring associated with both gestational and postnatal exposures to CUD, suggesting that maternal CUD is an independent predictor of anxiety disorders in offspring. Furthermore, we observed that only a small proportion (2 %) of the observed associations between maternal antenatal cannabis use disorder and childhood anxiety disorders were mediated by adverse birth outcomes, suggesting a strong link between antenatal CUD and the risk of anxiety disorders in offspring.

Building on these findings, the propensity score matching (PSM) approach provided further insight into the potential causal relationship between maternal CUD and risk of anxiety disorders in offspring. Our findings indicate that, after adjusting for a wide range of potential confounding factors, offspring of mothers with antenatal, postnatal, or overall perinatal cannabis use disorder exhibited more than a 41 % and 76 % increased risk of developing any anxiety disorders and PTSD.

Our study addresses critical gaps in the existing literature by examining both antenatal and postnatal cannabis exposures in relation to childhood anxiety, while balancing baseline characteristics of confounders by matching and accounting for the potential mediating effects of adverse birth outcomes.

4.2. Comparison with existing epidemiological studies

Our findings are consistent with previous epidemiological studies that suggested exposure to maternal cannabis use was associated with a range of anxiety symptoms, including any anxiety, generalized, panic, or separation anxiety in offspring (Fine et al., 2019; Leech et al., 2006; Moore et al., 2023; Rompala et al., 2021). For example, a 2021 study by Paul and colleagues reported that offspring prenatally exposed to maternal cannabis use were 2.5 times at increased risk of anxiety symptoms compared to non-exposed offspring (Paul et al., 2021). However, our findings differ from a few studies that reported no association between maternal cannabis use and the risk of childhood anxiety symptoms and/or disorder (El Marroun et al., 2019; Mensah et al., 2024; Murnan et al., 2021; Nomura et al., 2023; O'Connell and Fried, 1991). For instance, a 2023 study by Nomura and colleagues found that in-utero exposure to maternal cannabis use was not associated with any anxiety disorder, including separation anxiety (SAD), PTSD, or GAD, compared to non-exposed children (Nomura et al., 2023). One possible explanation for these discrepancies is that those studies may have limited statistical power to detect associations between cannabis exposure and childhood anxiety due to relatively small sample sizes (Godleski et al., 2018; Larkby et al., 2011), which may also restrict the inclusion of potential confounders in their analyses, thereby obscuring true associations. Notably, none of the prior studies adjusted for critical confounders such as socioeconomic status and maternal psychopathology, which play a significant role in the relationship between maternal cannabis use and neurobehavioral problems in children and adolescents. Additionally, most prior studies primarily relied on maternal self-reported data to measure cannabis use and parent-reported screening tools to measure anxiety symptoms in children, which are susceptible to several limitations, such as under-reporting and recall bias (Brener et al., 2003; J. Brown et al., 1992), which in turn, influences the observed associations. Our study thoroughly investigated exposures to maternal CUD during antenatal, perinatal, and postnatal and its links to anxiety disorder in offspring. We utilised extensive linked data and objectively measured both maternal cannabis use and clinical diagnoses of anxiety disorder in offspring, providing a more rigorous assessment of these associations. Notably, our findings enhance the evidence supporting these associations and highlight the substantial contribution of this research in addressing existing knowledge gaps in the current literature on this topic. Thus, it is important to note that previous studies may have lacked sufficient power to detect an association between maternal CUD and the risk of anxiety disorders in offspring, potentially attributed to relatively small sample sizes, differences in exposure and outcome ascertainment, or variations in the selection and control of potential confounders.

4.3. Potential mechanisms

Emerging evidence suggests that Δ9-tetrahydrocannabinol (THC), the most potent psychoactive ingredient of cannabis, can easily cross the placenta and is present in breast milk, exposing the fetus and breastfeeding newborn to its effects (Ayonrinde et al., 2021; Cermak and Stanford, 2023; El Marroun et al., 2010; Little and VanBeveren, 1996). Epidemiological data from animal and human studies have identified potential neurobiological pathways through which in-utero and postpartum cannabis exposure may impact neurodevelopmental and neurobehavioral outcomes in exposed children (El Marroun et al., 2010; Houston et al., 2014; Jutras-Aswad et al., 2009; Narouze, 2021; Navarrete et al., 2020; O'Donnell and Meaney, 2016; Thomason et al., 2021). These pathways involve disruptions in brain development, changes in neurotransmitter systems such as GABA and glutamate, and neural connectivity, which can lead to altered neural circuitry associated with anxiety regulation and stress response mechanisms (Ayonrinde et al., 2021; De Genna et al., 2022; Jutras-Aswad et al., 2009; Morris et al., 2011; Pinky et al., 2019; Szutorisz and Hurd, 2018). In-utero exposure to THC has been shown to alter dopamine receptors (D1 and D2), which significantly influence neurobehavioral outcomes and may result in anxiety disorder later in life (Jutras-Aswad et al., 2009; Morris et al., 2011; Szutorisz and Hurd, 2018; Wu et al., 2011). Additionally, existing epidemiological evidence suggests that prenatal cannabis exposure may plausibly alter neurodevelopmental trajectories in offspring through epigenetic mechanisms. For instance, changes in DNA methylation, particularly in stress-response genes such as *FKBP5*, have been observed (Smith et al., 2020). These include potentially heritable alterations in genes and molecular pathways critical for brain development and associated with neurodevelopmental disorders and other psychiatric diseases, including anxiety.

Moreover, an animal study by Natale et al. demonstrated that maternal exposure to Δ9-THC significantly impaired fetal growth, suggesting a potential mechanism for the growth restrictions observed in the offspring of rats exposed to cannabis during pregnancy (Natale et al., 2020). Thus, it is plausible that exposure to cannabis during pregnancy, perinatal, and postnatal periods could influence the fundamental brain developmental processes, thereby increasing the risk of anxiety disorder in exposed offspring. In addition to biological pathways, psychosocial factors and mother-offspring bonding may also contribute to the association between maternal cannabis use and childhood anxiety disorders (Sideli et al., 2020; Sood et al., 2021). Substance use during pregnancy can interfere with emotional connection and caregiving, potentially leading to insecure attachment and poor emotional regulation in children. Maternal cannabis use is also frequently associated with socioeconomic disadvantage and mental health challenges, which may further increase the risk of adverse mental health outcomes in offspring. While these pathways were not directly assessed in our study, they remain important considerations for future research and intervention strategies.

Another potential mechanism linking maternal cannabis use to anxiety disorder in children may involve elevated environmental risks, as well as familial or polygenic risk scores (PRSs) (Gerra et al., 2019; Gu et al., 2024), which could contribute to the increased risk of anxiety disorder in offspring and adolescents. However, while these explanations are plausible, our study did not provide evidence supporting the involvement of these plausible mechanisms.

Another putative mechanism underlying the association between maternal cannabis use and anxiety disorders in children is the indirect effect mediated through adverse birth outcomes. Prior evidence indicates that antenatal exposure to maternal cannabis use disorder (CUD) is associated with an elevated risk of adverse neonatal outcomes, including preterm birth, low birth weight, small-for-gestational-age (SGA), and low Apgar scores (Hayatbakhsh et al., 2012; Huizink, 2014). These early-life health complications may, in turn, have long-term consequences on mental health and emotional development, including increased susceptibility to anxiety disorders. In our causal mediation analysis, we found that low birth weight and SGA accounted for only a small proportion of the observed association between maternal CUD and offspring anxiety risk, suggesting that other pathways may also contribute to this relationship.

4.4. Strengths and limitations of the study

The current study has several significant strengths. Firstly, it benefits from a large sample size derived from both population-based and clinical data, enhancing the generalizability of the findings. By employing objectively measured maternal CUD as the exposure and anxiety disorder in offspring as the outcome, the study strengthens the reliability of its results. Secondly, this study is unique as the first to explore the risk of anxiety disorders in offspring of mothers with CUD across both gestational and postnatal periods using high-quality linked data. Thirdly, we conducted sensitivity analyses by maternal tobacco use, a key confounder associated with both childhood anxiety and maternal CUD. This approach addresses the complex interplay between tobacco and

cannabis use and their impacts on anxiety problems in offspring, which prior research has highlighted as critical (De Genna et al., 2021; Rompala et al., 2021; Ståhlberg et al., 2020). Finally, the large sample size from linked data allowed us to account for a broader range of key confounders in the main analysis, likely enhancing the validity of the observed associations. We also conducted mediation analysis to estimate the natural direct and indirect effects of maternal CUD on childhood anxiety disorders, strengthening causal inference in observational studies. Finally, we conducted a propensity score matching analysis to balance baseline characteristics of exposed and non-exposed groups across potential confounders, thereby suggesting the independent effect of maternal CUD on childhood anxiety disorders in offspring.

This study acknowledges several limitations. It is important to note that despite using linked health registries, the data may not be complete enough to capture all diagnoses of anxiety disorder in offspring. Reliance on registry data introduces the risk of coding errors or misclassification, which may influence the observed findings. The study included only hospitalized mothers, which may have excluded those with less severe CUD who did not require hospitalization, resulting in underreporting of maternal CUD. Additionally, the follow-up duration for anxiety disorder diagnoses in offspring varied depending on data availability within the linked health registries, potentially limiting our ability to capture diagnoses that occur later in adolescence. Our cohort included children born between 2003 and 2005, with follow-up extending to 2018, yielding a maximum observation period of approximately 15 years. This restricted timeframe may have led to underascertainment of anxiety disorders, particularly for cases that emerge during later adolescence or early adulthood, or those with milder symptoms not requiring clinical attention. Additionally, our dataset lacked information on certain perinatal risk factors, including maternal pre-pregnancy BMI and specific obstetric complications such as anaemia, which limited our ability to assess their role as potential effect modifiers.

Another important limitation is the absence of neuroimaging and biospecimen data, such as THC metabolite levels in maternal blood or urine or infant cortisol levels, to biochemically confirm cannabis exposure. Furthermore, although our study focused on clinically diagnosed cannabis use disorder during the perinatal period, reflecting more severe and impairing patterns of use, we lacked data on the frequency, duration, and quantity of cannabis consumed. As such, we were unable to assess potential dose-response relationships between maternal cannabis use and anxiety disorders in offspring.

Moreover, we also acknowledge that our data did not include paternal mental health or substance use disorders, which may contribute to unmeasured familial risk for offspring psychiatric conditions. Existing literature suggests that paternal behaviours and psychiatric traits can influence both maternal cannabis use during the perinatal period and child developmental outcomes, including neurobehavioral outcomes and emotional problems in offspring (Bolhuis et al., 2018; Epstein et al., 2018; Kosty et al., 2015; McLaughlin et al., 2012; Sujan et al., 2022; Xerxa et al., 2021). Additionally, our dataset did not capture familial psychiatric history or genetic predisposition to anxiety disorders, such as polygenic risk scores. Therefore, the potential for residual confounding remains, and findings should be interpreted with caution.

5. Conclusion

Our study revealed that offspring exposed to maternal CUD during pregnancy and postnatal periods have a consistently higher risk of developing anxiety disorder (AD) compared to those who were not exposed. Notably, our findings suggest that the mediating role of adverse birth outcomes in the association between maternal CUD exposure and anxiety disorder risks in offspring is minimal, indicating the observed associations are robust. Additionally, our sensitivity analyses accounting for maternal tobacco use did not alter these associations, indicating that maternal CUD is an independent predictor of anxiety disorder in offspring. This study highlights the importance of early screening for CUD in women who are planning to conceive, are pregnant, or are lactating, as a crucial step in reducing the risk of anxiety disorder in their offspring.

CRediT authorship contribution statement

Abay Woday Tadesse: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Getinet Ayano:** Writing – review & editing, Supervision, Software. **Berihun Assefa Dachew:** Writing – review & editing, Supervision. **Kim Betts:** Writing – review & editing, Supervision. **Rosa Alati:** Writing – review & editing, Supervision.

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Declaration of competing interest

The authors declare no conflicts of interest related to this study. All funding sources are acknowledged, and there are no financial relationships that could influence the research outcomes.

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Annex I. List of tables

Table 1
Maternal demographic, obstetric, mental health, and neonatal factors by diagnosis of anxiety disorder in offspring ($N = 222{,}706$).

List of predictors	Categories (if any)	Overall N (%)	Anxiety disorder in offspring (any AD)		
			Yes N (%)	No N (%)	P-value
Maternal age (in years)	<20	8600 (3.9)	341 (7.5)	8259 (3.8)	<0.001
	20–24	31,559 (14.2)	834 (18.4)	30,725 (14.1)	
	25–29	61,391 (27.6)	1169 (25.7)	60,222 (27.6)	
	30–34	76,013 (34.1)	1310 (28.8)	74,703 (34.2)	
	35+	45,143 (20.3)	889 (19.6)	44,254 (20.3)	

(*continued on next page*)

Table 1 (*continued*)

List of predictors	Categories (if any)	Overall N (%)	Anxiety disorder in offspring (any AD)		
			Yes N (%)	No N (%)	P-value
Socioeconomic Index for areas (SEIFA in quantile)	1st (most disadvantaged)	58,954 (26.5)	1369 (30.1)	57,585 (26.4)	<0.001
	2nd	48,676 (21.9)	997 (21.9)	47,679 (21.9)	
	3rd	54,379 (24.4)	1048 (23.1)	53,331 (24.4)	
	4th (least disadvantaged)	60,697 (27.3)	1129 (24.9)	59,568 (27.3)	
Completed maternal education level (N = 222,629)	Degree & above	42,228 (19.0)	914 (20.1)	41,314 (18.9)	<0.01
	Certificate	32,925 (14.8)	605 (13.3)	32,320 (14.8)	
	Diploma	56,879 (25.5)	1229 (27.1)	55,650 (25.5)	
	Non-school qualifications	61,442 (27.6)	1028 (22.6)	60,414 (27.7)	
	Unknown/not stated	29,155 (13.1)	765 (16.8)	28,390 (13.0)	
Maternal occupation (N = 222,451)	Managerial	34,966 (15.7)	596 (13.1)	34,370 (15.8)	<0.01
	Professional worker	64,254 (28.9)	1202 (26.5)	63,052 (28.9)	
	Nonpaid worker	53,268 (23.9)	1237 (27.2)	52,031 (23.9)	
	Tradeswoman	44,606 (20.0)	776 (17.1)	43,830 (20.1)	
	Unknown/not stated	25,535 (11.5)	730 (16.1)	24,805 (11.4)	
Child sex	Female	107,806 (48.4)	2562 (56.4)	105,244 (48.2)	<0.001
	Male	114,900 (51.6)	1981 (43.6)	112,919 (51.8)	
Low birth weight at birth (<2500 g)	Yes	11,718 (5.3)	305 (6.7)	11,413 (5.2)	<0.001
	No	210,988 (94.7)	4238 (93.3)	206,750 (94.8)	
Small-for-gestational age (<10th percentile)	Yes	3998 (1.8)	127 (2.8)	3871 (1.8)	<0.001
	No	218,708 (98.2)	4416 (97.2)	214,292 (98.2)	
Prematurity at birth (<37 weeks)	Yes	13,554 (6.1)	327 (7.2)	13,227 (6.1)	<0.01
	No	209,152 (93.9)	4216 (92.8)	204,936 (93.9)	
5-minute APGAR score (<7)	Yes	2524 (1.1)	88 (1.9)	2436 (1.1)	<0.001
	No	220,182 (98.9)	4455 (98.1)	215,727 (98.9)	
APGAR score at 1st minute of birth (<7)	Yes	21,340 (9.6)	487 (10.7)	20,853 (9.6)	<0.01
	No	201,366 (90.4)	4056 (89.3)	197,310 (90.4)	
Admitted to NICU	Yes	5423 (2.4)	135 (3.0)	5288 (2.4)	0.016
	No	217,283 (97.6)	4408 (97.0)	212,875 (97.6)	
Birth plurality	Single	216,158 (97.1)	4413 (97.1)	211,745 (97.1)	0.785
	Twins or more	6548 (2.9)	130 (2.9)	6418 (2.9)	
Parity	Nil	92,153 (41.4)	2002 (44.1)	90,151 (41.3)	<0.001
	Primi-para	76,095 (34.2)	1445 (31.8)	74,650 (34.2)	
	Multi-para	54,458 (24.5)	1096 (24.1)	53,362 (24.5)	
Smoking in pregnancy	Yes	32,115 (14.4)	1214 (26.7)	30,901 (14.2)	<0.001
	No	190,591(85.6)	3329 (73.3)	187,262 (85.8)	
Pre-existing diabetes mellitus	Yes	1228 (0.6)	29 (0.6)	1199 (0.5)	0.485
	No	221,478 (99.4)	4514 (99.4)	216,964 (99.5)	
Gestational diabetes mellitus (GDM)	Yes	10,151 (4.6)	193 (4.2)	9958 (4.6)	0.329
	No	212,555 (95.4)	4350 (95.8)	208,205 (95.4)	
Pre-existing hypertension	Yes	2284 (1.0)	52 (1.1)	2232 (1.0)	0.465
	No	220,422 (99.0)	4491 (98.9)	215,931 (99.0)	
Pregnancy-induced hypertension (PIH)	Yes	11,791 (5.3)	287 (6.3)	11,504 (5.3)	<0.001
	No	210,915 (94.7)	4256 (93.7)	206,659 (94.7)	
Maternal substance use- and mental health disorders					
CUD diagnosis during pregnancy	Yes	1319 (0.6)	71 (1.6)	1248 (0.6)	<0.001
	No	221,387 (99.4)	4472 (98.4)	216,915 (99.4)	
CUD diagnosis during postnatal periods	Yes	281(0.1)	18 (0.4)	263 (0.1)	<0.001
	No	222,425 (99.9)	4525 (99.6)	217,900 (99.9)	
Perinatal CUD diagnosis	Yes	1500 (0.7)	79 (1.7)	1421 (0.7)	<0.001
	No	221,206 (99.3)	4464 (98.3)	216,742 (99.3)	
Admissions due to substances other than cannabis during pregnancy	Yes	1637 (0.7)	99 (2.2)	1538 (0.7)	<0.001
	No	221,069 (99.3)	4444 (97.8)	216,625 (99.3)	
Admissions due to substances other than cannabis in postnatal periods	Yes	580 (0.3)	32 (0.7)	548 (0.3)	<0.001
	No	222,126 (99.7)	4511 (99.3)	217,615 (99.7)	
Psychiatric admissions in pregnancy	Yes	4269 (1.9)	243 (5.3)	4026 (1.8)	<0.001
	No	218,437 (98.1)	4300 (94.7)	214,137 (98.2)	
Psychiatric admissions in postnatal periods	Yes	3183 (1.4)	174 (3.8)	3009 (1.4)	<0.001
	No	219,523 (98.6)	4369 (96.2)	215,154 (98.6)	
Perinatal psychiatric admissions	Yes	6219 (2.8)	327 (7.2)	5892 (2.7)	<0.001
	No	216,487 (97.2)	4216 (92.8)	212,271 (97.3)	

Keynotes: SEIFA- Socio-economic indexes for areas, CUD- cannabis use disorder. Any anxiety disorder in children includes generalized anxiety, phobic anxiety, obsessive-compulsive disorder, posttraumatic stress disorder, other anxiety (unspecified), or early childhood-onset anxiety disorder (i.e., separation and social). Maternal admissions due to substance use other than cannabis use include- tobacco use-, stimulant use-, alcohol use-, opioid use-, or polysubstance use disorders. Psychiatric maternal hospitalisations, including schizophrenia, depression, anxiety, or bipolar disorders.

Table 2
Associations between maternal CUD during pregnancy and risk of anxiety disorder in offspring (N = 222,706).

Anxiety disorder in offspring	Offspring exposed to CUD during pregnancy			
	Model 1 RR (95 % CI)	Model 2 RR (95 % CI)	Model 3 RR (95 % CI)	Sensitivity analysis RR (95 % CI) (N = 222,473)
Any Anxiety disorder	2.66 (2.10, 3.32)***	1.87 (1.46, 2.35)***	1.79 (1.40, 2.26)***	1.86 (1.45, 2.34)***
PTSD	4.45 (3.27, 5.90)***	2.65 (1.91, 3.57)***	2.46 (1.78, 3.33)***	2.54 (1.83, 3.44)***
GAD	2.51 (1.15, 4.7)**	2.25 (1.06, 4.74)*	2.18 (1.03, 4.60)*	2.29 (1.09, 4.84)*
Childhood-onset emotional anxiety disorder+	2.49 (1.40, 4.04)***	2.08 (1.14, 3.48)**	1.91 (1.05, 3.21)*	2.03 (1.11, 3.39)*
PAD	0.97 (0.3, 2.25)	0.74 (0.22, 1.82)	0.75 (0.22, 1.86)	*NA*
Other anxiety disorders*	1.70 (1.01, 2.67)*	1.52 (0.88, 2.43)	1.40 (0.81, 2.23)	1.47 (0.85, 2.34)

Model 1 was an unadjusted estimation. Model 2 adjusted socioeconomic status indicators, maternal age, maternal substance use disorders (i.e., tobacco use, alcohol use, and other illicit drug use-related disorders), maternal psychiatric admission diagnoses (i.e., depression, schizophrenia, bipolar disorder, and anxiety disorders), and maternal medical and obstetric conditions (pre-existing diabetes, gestational diabetes, pre-existing hypertension, pregnancy-induced hypertension, and parity). Model 3 adjusted for covariates in Model 2 and child-related factors, including child sex, birth plurality, birth order, and admission to NICU.
Keynotes: RR- relative risks, CI- confidence intervals, CUD- cannabis use disorder, PTSD- posttraumatic stress disorder, GAD- generalized anxiety disorder. Other (unspecified) anxiety disorders* include obsessive-compulsive disorders and unspecified anxiety disorders. NA- not applicable due to an inadequate number of events (PAD) in offspring and limited maternal CUD for this specific analysis (Model 4). Childhood-onset anxiety disorder+ - this includes separation and social anxiety disorder diagnosed in early childhood. *P < 0.05, **P < 0.01, and ***P < 0.001. Sensitivity analyses were conducted by excluding comorbid maternal CUD and tobacco use disorders from the main analysis.

Table 3
Association between maternal CUD in postnatal and risk of anxiety disorder in offspring (N = 222,706).

Anxiety disorder in offspring	Exposure to CUD diagnosis during postnatal period			
	Model 1 RR (95 % CI)	Model 2 RR (95 % CI)	Model 3[a] RR (95 % CI)	Sensitivity analysis RR (95 % CI) *N* = 222,652
Any anxiety disorder	3.15 (2.01, 4.93)***	2.14 (1.49, 2.39)***	2.02 (1.22, 3.14)**	2.07 (1.25, 3.20)**
PTSD	6.09 (3.38, 9.90)***	3.12 (1.63, 5.44)***	2.97 (1.56, 5.17)***	3.28 (1.76, 5.62)***

Model 1 was an unadjusted estimate. Model 2 adjusted socioeconomic status indicators, parity, maternal age, maternal antenatal and postnatal substance use disorders (i.e., tobacco use, alcohol use, and other illicit drug use-related disorders), psychiatric admission diagnoses (i.e., depression, schizophrenia, bipolar disorder, and anxiety disorders), and maternal medical conditions such as pre-existing and gestational diabetes and hypertension. Model 3 adjusted for covariates in Model 2 and child-related factors, including child sex, birth plurality, and birth order.
Keynotes: RR- relative risks, CI- confidence intervals, CUD- cannabis use disorder, and PTSD- posttraumatic stress disorder. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. Sensitivity analyses were performed by excluding comorbid maternal CUD and tobacco use disorders from the main analysis.
[a] The final model was further adjusted to adverse birth outcomes, including premature birth, small-for-gestational-age, low birth weight, admission to NICU, and 5-minute low APGAR scores.

Table 4
Association between maternal CUD and risk of anxiety disorder in offspring using PSM approach.

Anxiety disorder in offspring	Model 1 RR (95 % CI)	Model 2 RR (95 % CI)
Antenatal exposure to CUD		
Any anxiety disorder (matched data)	1.58 (1.20, 2.08)***	1.56 (1.18, 2.06)** 1.45 (1.09, 1.94)
PTSD (matched)	1.95 (1.36, 2.80)***	1.73 (1.18, 2.54)***
GAD (matched)	1.66 (0.63, 4.34)	1.35 (0.0.60, 3.06)
Childhood-onset emotional anxiety disorder+ (matched)	1.25 (0.67, 2.35)	1.37 (0.68, 2.76)
Postnatal exposure to CUD[a]		
Any anxiety disorder (matched)	1.48 (1.18, 2.43)	1.46 (1.07, 2.46)*
PTSD (matched)	2.97 (1.16, 3.88)	2.10 (1.10, 4.04)*
Overall exposure to CUD (perinatal)[a]		
Any anxiety disorder (matched data)	1.41 (1.09, 1.82)**	1.39 (1.07, 1.81)**
PTSD (matched)	1.76 (1.24, 2.50)**	1.72 (1.19, 2.47)**
GAD (matched)	1.32 (0.56, 3.09)	1.49 (0.63, 3.54)
Childhood-onset emotional anxiety disorder+ (matched)	0.91 (0.51, 1.65)	0.83 (0.45, 1.52)

Model 1 was an unadjusted model. Model 2 adjusted socioeconomic status indicators, parity, maternal age, maternal substance use disorders (i.e., tobacco use, alcohol use, and other illicit drug use-related disorders), psychiatric admission diagnoses (i.e., depression, schizophrenia, bipolar disorder, and anxiety disorders), and maternal medical conditions such as pre-existing and gestational diabetes and hypertension. Model 3 adjusted for covariates in Model 2 and child-related factors, including child sex, birth plurality, and birth order.
Keynotes: RR- relative risks, CI- confidence intervals, CUD- cannabis use disorder, and PTSD- posttraumatic stress disorder. *P < 0.05, **P < 0.01, and ***P < 0.001.

[a] The final model was further adjusted to adverse birth outcomes, including premature birth, small-for-gestational-age, low birth weight, admission to NICU, and 5-minute low APGAR scores.

Annex II. List of figures

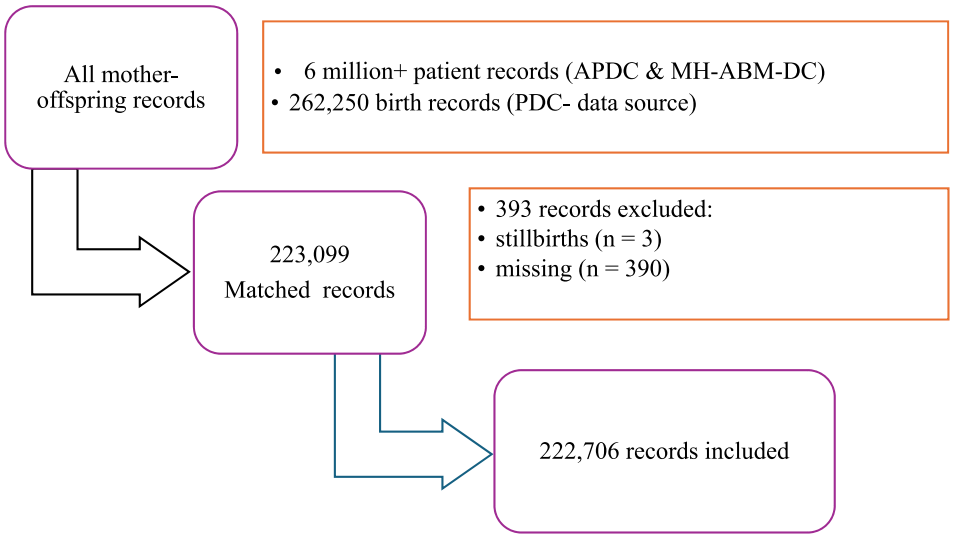

Fig. 1. The birth cohort profile from January 2003 to December 2005 in NSW state and observations were included in our final analysis. Keynotes: OCD- Obsessive-compulsive disorders, GAD- Generalized anxiety disorder, PAD- Phobic anxiety disorder, CAD- early Childhood-onset anxiety disorders, PTSD- posttraumatic stress disorder.

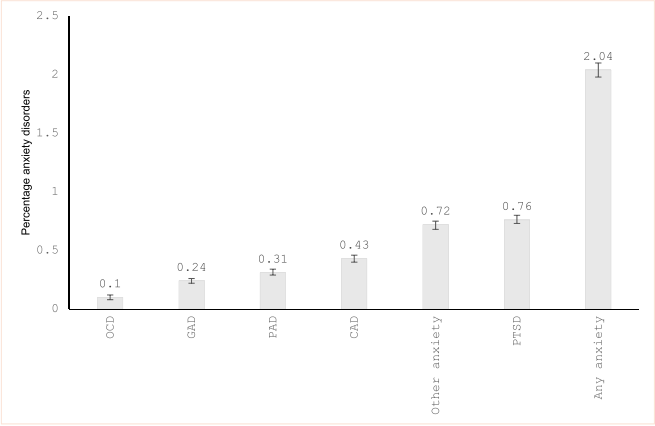

Fig. 2. Types of anxiety disorders in school-age children (N = 222,706). Key notes: CUD: Cannabis Use Disorder, APGAR: Appearance Pulse Grimace Activity Respiration, SGA: Small-for-gestational-age, LBW: low birth weight, PTB: Preterm birth, CI: Confidence interval. The values on (i) and (ii) represented the effect estimates without and with mediators, respectively. All path estimates referred by standardized beta coefficients (β) were adjusted for socioeconomic status(SES indicators), parity, maternal age, tobacco use, alcohol use disorders, other illicit drug use-related diagnoses, maternal psychiatric hospitalizations (depression, schizophrenia, bipolar and anxiety disorders), maternal diabetes and hypertension, child sex, birth plurality, and admission to NICU. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

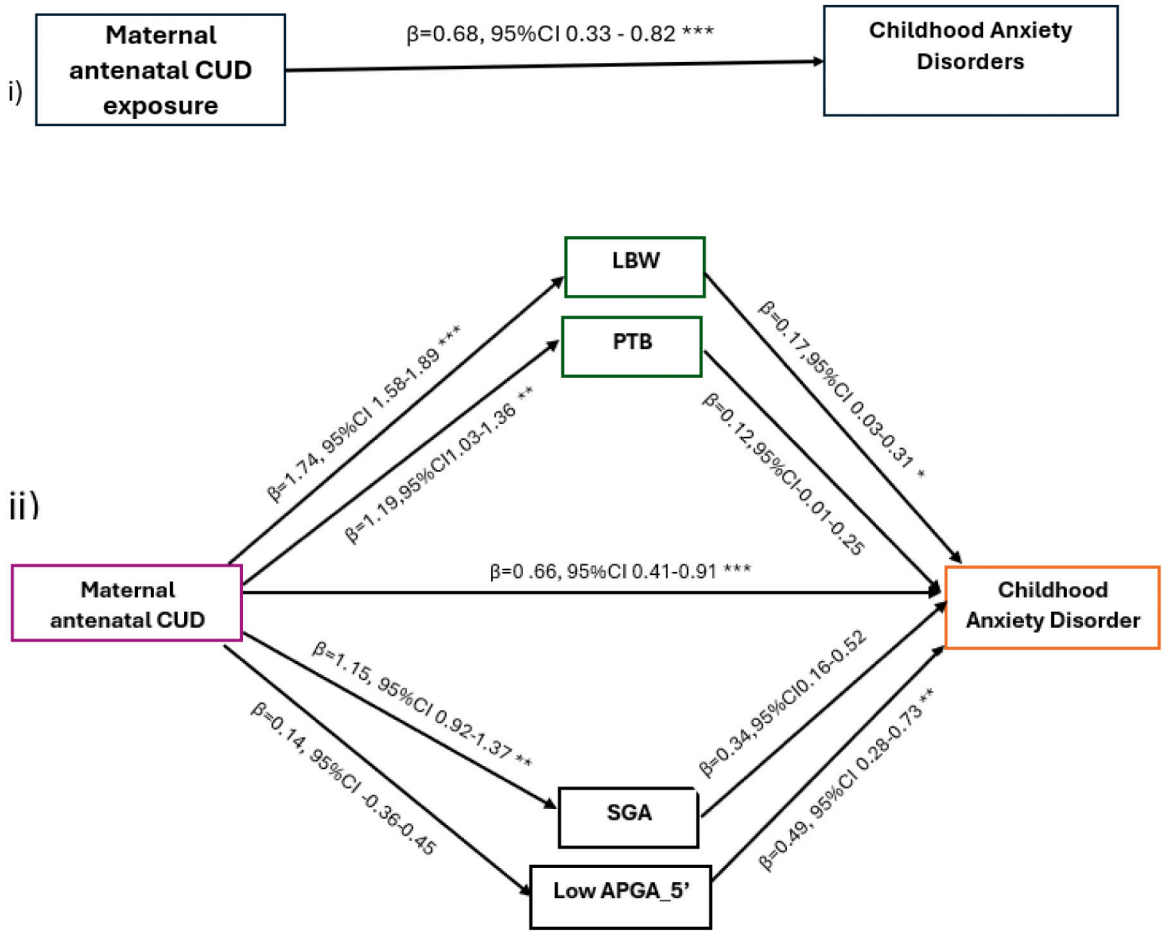

Fig. 3. The mediation role of adverse birth outcomes (premature birth, LBW, SGA, and low APGAR scores) on the associations between maternal antenatal CUD exposure and anxiety disorder risks in children.

Annex III. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.119743.

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