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Prenatal cannabis use and the risk of attention deficit hyperactivity disorder and autism spectrum disorder in offspring: A systematic review and meta-analysis

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ABSTRACT

Background: It is plausible that exposure to cannabis in-utero could be associated with an increased risk of neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) symptoms and autism spectrum disorder (ASD) during childhood and adolescence; however, mixed results have been reported. This study investigated whether there is an association between prenatal cannabis use and ADHD symptoms and ASD in offspring using a systematic review and meta-analysis methodology.

Methods: A systematic literature search was conducted in PubMed/Medline, Scopus, EMBASE, Web of Science, Psych-Info, and Google Scholar to identify relevant studies. The study protocol has been preregistered in the Prospective Register of Systematic Reviews (PROSPERO) (CRD42022345001), and the Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the methodological quality of included studies. An inverse variance weighted random effect meta-analysis was conducted to pool the overall effect estimates from the included studies.

Results: Fourteen primary studies, consisting of ten on ADHD and four on ASD, with a total of 203,783 participants, were included in this study. Our meta-analysis underscores an increased risk of ADHD symptoms and/or disorder [$\beta = 0.39$: 95 % CI (0.20–0.58), $I^2 = 66.85$ %, $P = 0.001$)] and ASD [RR = 1.30: 95 % CI (1.03–1.64), $I^2 = 45.5$ %, $P = 0.14$] associated with in-utero cannabis exposure in offspring compared to their non-exposed counterparts. Additionally, our stratified analysis highlighted an elevated risk of ADHD symptoms [$\beta = 0.54$: 95 % CI (0.26–0.82)] and a marginally significant increase in the risk of diagnostic ADHD among exposed offspring compared to non-exposed counterparts [RR = 1.13, 95 % CI (1.01, 1.26)].

Conclusion: This study indicated that maternal prenatal cannabis exposure is associated with a higher risk of ADHD symptoms and ASD in offspring.

1. Introduction

Emerging epidemiological evidence suggests that cannabis use among pregnant women is increasing substantially (Hasin et al., 2015; Mark et al., 2016; Peacock et al., 2018). The global prevalence of cannabis use during pregnancy has ranged between 1.4 % and 29.3 % (Beatty et al., 2012; Corsi et al., 2019; Ebrahim and Gfroerer, 2003; El Marroun et al., 2008; Hayatbakhsh et al., 2012; Mark et al., 2016; Velez et al., 2019; Volkow et al., 2019). The prevalence rates of cannabis use during pregnancy vary significantly between countries: the lowest prevalence rate was reported in Canada (Corsi et al., 2019) while the highest was reported in the USA (Mark et al., 2016; Volkow et al., 2019). Though maternal self-reports may underestimate the prevalence (Young-Wolff et al., 2020), it is believed to be high in many developed countries (Degenhardt et al., 2013; Peacock et al., 2018). This might be attributed to the decriminalization (Abuse, 2012; Bhatia et al., 2022) and recreational cannabis use (Reece and Hulse, 2019) in these countries. Therefore, it seems that the prevalence of cannabis use during pregnancy is escalating steadily (Volkow et al., 2019; Young-Wolff et al., 2017). It is also crucial to note that the legalization or banning of cannabis use in different countries, coupled with changes in pregnant women's perception of its safety, which may contribute to a significant

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impact on neurodevelopmental disorders in exposed offspring (Lupattelli and Trinh, 2022; Musardo and Bellone, 2018).

According to the fifth Diagnostic and Statistical Manual of Mental Disorder (DSM-5), attention deficit and/or hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined by impaired levels of inattention and/or hyperactivity-impulsivity (APA, 2013). Furthermore, ADHD could be presented in any of its three main forms: inattentive (ADHD-I), hyperactive-impulsive (ADHD-HI), and combined (ADHD-C) (Ayano et al., 2020). Any of the three types has been used in the medical diagnosis of attention deficit hyperactivity disorder (Ayano et al., 2020; Hesslinger et al., 2001; Lahey and Carlson, 1991). Similarly, Autism spectrum disorder is characterized by persistent deficits in social communication and social interaction across multiple contexts, including deficits in social reciprocity, nonverbal communicative behaviors used for social interaction, and skills in developing, maintaining, and understanding relationships (APA, 2013). ADHD and ASD have been commonly diagnosed in school-age children, but they can also occur in any age group (Ayano et al., 2020; Li et al., 2022; Salari et al., 2023).

Existing evidence has indicated potential implications of prenatal cannabis exposure in animals has been associated with deficits in memory, attention, and executive functions. Additionally, studies have suggested potential long-term consequences, such as increased susceptibility to psychiatric disorders or cognitive impairments later in life (Antonelli et al., 2004; de Salas-Quiroga et al., 2015; Mohammed, 2018).

It is plausible that exposure to cannabis in utero could be associated with an increased risk of neurodevelopmental disorders [attention deficit hyperactivity disorder (ADHD) symptoms and/or disorder and autism spectrum disorder (ASD)] during childhood and adolescence in humans; however, the results of the existing studies are highly inconsistent. While some studies have found prenatal cannabis exposure (PCE) associated with a greater risk of ADHD (Cioffredi et al., 2022; Day et al., 1991; El Marroun et al., 2011; Goldschmidt et al., 2000; Leech et al., 1999; Paul et al., 2021) as well as ASD (Corsi et al., 2020) in exposed offspring, others have reported null associations (DiGuiseppi et al., 2022; Garrison-Desany et al., 2022; Murnan et al., 2021). For example, a 2011 study by El Marroun and colleagues found that offspring exposed to cannabis in utero were 2.75 times more likely to develop ADHD when compared with unexposed offspring (El Marroun et al., 2011). More recently, a cohort study by Paul et al. found a 3.82 increased risk of ADHD in offspring exposed to maternal cannabis (Paul et al., 2021). Similarly, a 2020 study by Corsi and colleagues found that offspring exposed to cannabis in utero were 1.51 time more likely to have ASD when compared with unexposed counterparts (Corsi et al., 2020).

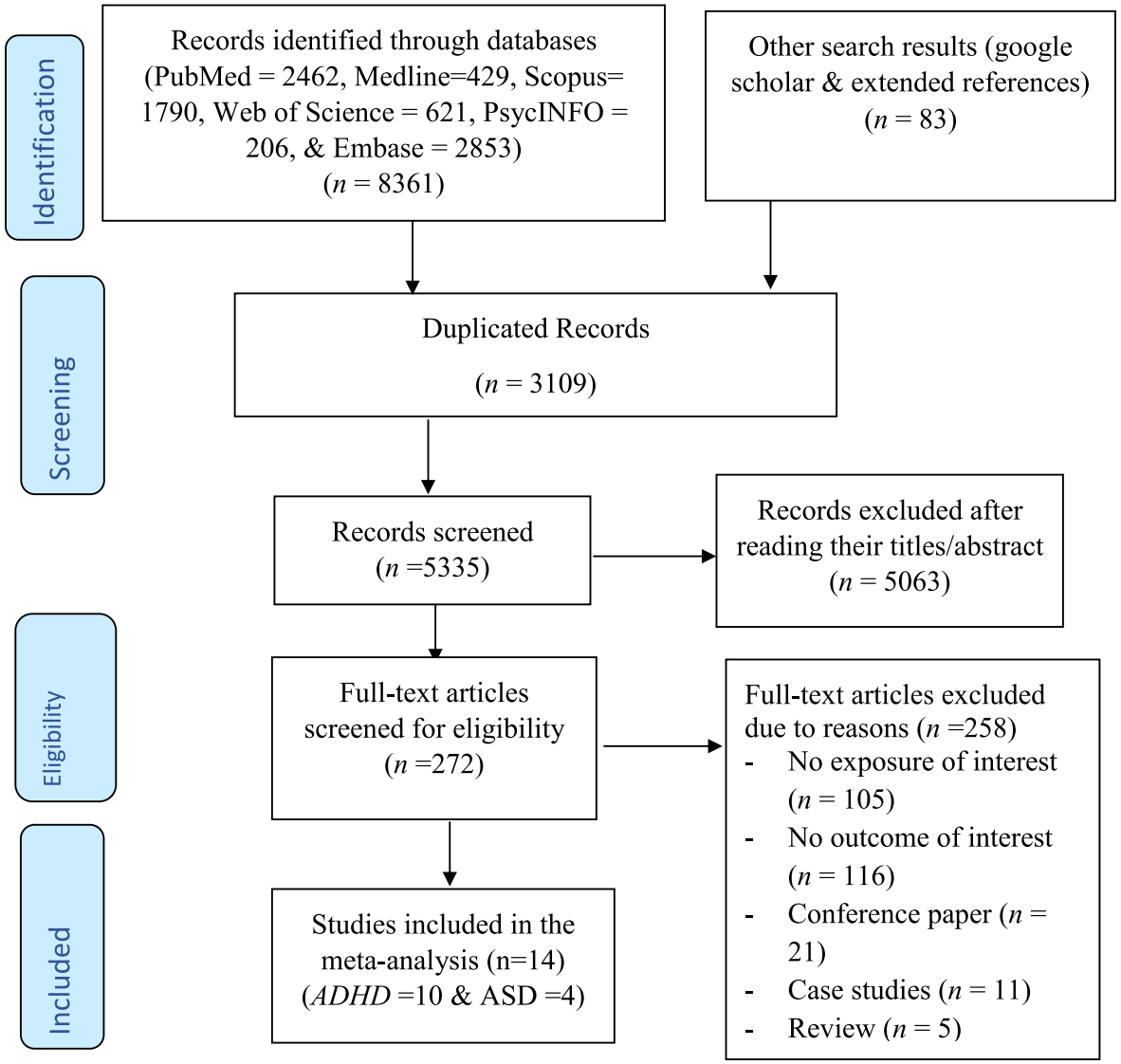

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart to screen the studies to be included in the review.

Although the above studies have found a significant link between prenatal cannabis use and increased ADHD and ASD risk in offspring; these results are not consistent throughout the literature. There are other studies that identified no significant associations between prenatal cannabis exposer and increased risk of ADHD (Daniel J Corsi et al., 2020; Murnan et al., 2021; Vanina et al., 2022) as well as ASD (DiGuiseppi et al., 2022). Therefore, the primary aim of this systematic review and meta-analysis is to pool the existing literature's findings to address whether there is a risk association between prenatal cannabis use and neurodevelopmental disorders in offspring (i.e., ADHD symptoms and ASD). To the best of our knowledge, this is the first meta-analytic systematic review to consolidate the evidence on the subject.

2. Methods

2.1. Research design and protocol registration

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Review and Meta-analyses (Fig. 1) (Page et al., 2021). The study protocol has been preregistered in the Prospective Register of Systematic Reviews (PROSPERO) (Registration number: *CRD42022345001)*.

2.2. Eligibility criteria

All observational studies (i.e., case-control, cohort, case-cohort, nested case-control or cross-sectional designs) reporting the association between prenatal cannabis use and neurodevelopmental disorders, specifically ADHD or ASD, in offspring were included in this study without publication year restrictions. In this study, we included studies that measured one of the three ADHD forms (i.e., inattentive: ADHD-I, hyperactive-impulsive: ADHD-HI, or combined form: ADHD-C) using both increased symptoms of ADHD, as measured by screening tools, and the presence of the disorder itself (ADHD), as measured by diagnostic tools. However, we excluded studies solely examined individual symptoms such as attention, hyperactivity, or impulsivity. Furthermore, studies published in a language other than English, animal studies, non-peer reviewed articles, editorials, case reports, commentaries, and conference proceedings were excluded.

2.3. Data sources and search strategies

A systematic literature search was conducted in PubMed/Medline, Scopus, EMBASE, Web of Science, and PsycINFO), and Google Scholar. We also used extended referencing of included articles. We included articles published until May 12, 2023.

We used Medical Subject Heading (MeSH) terms and free text search terms combined using different Boolean operators. Search terms include ["cannabis" [Mesh] OR "cannabinoids" [Mesh] OR "marijuana smoking" [Mesh] OR "marijuana abuse" [Mesh] OR cannabinoid OR cannabinol OR tetrahydrocannabinol OR THC OR cannabidiol OR "cannabis sativa" OR "cannabis use" OR "cannabis use disorder" "cannabis abuse" OR "cannabis dependent" OR "cannabis exposure" OR "substance use" OR "substance abuse" OR "substance dependent" OR "substance-related disorders" OR marijuana OR "marijuana use" OR "marijuana abuse" OR "marijuana dependent") AND (prenatal OR "during pregnancy" OR antepartum OR antenatal OR pregnancy OR "peri pregnancy" OR perinatal OR preconception OR maternal) AND (offspring OR adolescents OR youths OR young OR child OR infant OR childhood OR "young adults") AND ("Attention Deficit Disorder with Hyperactivity" [Mesh] OR "Autism Spectrum Disorder" [Mesh] OR "Child Development Disorders, Pervasive" [Mesh] OR "Neurodevelopmental Disorders" [Mesh] OR "Attention Deficit and Disruptive Behavior Disorders" [Mesh] OR "attention deficit" OR "attention deficit hyperactivity disorder" "Attention Deficit Disorder with Hyperactivity" OR inattention OR impulsivity OR ADHD OR "neurodevelopment" OR "brain development" OR autism OR "autism spectrum disorder" OR ASD OR "externalizing behaviors" OR "externalizing behaviours") (Table S1). Moreover, we applied snowballing to screen the references of identified articles for potentially relevant studies. Studies identified by our database searching strategies have been retrieved and managed using Endnote 20 reference manager.

2.4. Data extraction

The standardized data extraction form was employed for extraction of the eligible articles in accordance with the PRISMA guidelines (Shamseer et al., 2015). The extraction form includes first author name, year of publication, country in which the study was conducted, study design, sample size, exposure and outcome ascertainment in offspring, studies adjusted for potential confounders, age of offspring when the outcome measured, and point estimate with 95 % Confidence Intervals (CI). Any sources of prenatal cannabis use either self-report or clinical report was included in the review.

2.5. Study quality assessment

Newcastle Ottawa Quality Assessment Scale (NOS) for case-control and cohort was employed to assess the methodological quality of each study and to determine the extent to which a study addressed the possibility of bias in its design, conduct, and analysis (Wells et al., 2011). To minimize possible reviewer bias, two independent reviewers conducted the methodological quality assessment (A.W.T and G.A). We applied the three standard grading categories of NOS: high quality (scored 7–9), moderate quality (scored 4–6), and low quality (scored 0–3) (McPheeters et al., 2012). These scores were derived from 1) selection of the study groups (four items); 2) comparability between the groups (one item with two scores); and 3) ascertainment of outcome and exposure variables (three items). Except for comparability between the groups, a maximum of one point could be given to all broad perspectives. Conflicting scores between the two reviewers were resolved by discussion. According to NOS rating scores, if a study has the NOS score of six or greater, it can be considered as an article with low risk of bias.

2.6. Data synthesis and analysis

The extracted data were entered into a Microsoft Excel Database and then imported into STATA version 17 with meta-analysis packages. We used tables and figures to summarize the results. A summary effect estimate was calculated as a weighted average of the effects estimated in the individual studies (Deeks et al., 2019), which was calculated using the formula: weighted average equals sum of (estimate multiplied by weight) divided by sum of weight. The effect of prenatal cannabis use on ADHD symptoms and/or disorder and ASD in offspring was estimated using beta-coefficients or relative risk (RR) and the corresponding 95 % confidence intervals (CI). We presented the RR or beta-coefficients for each outcome along with its 95 % CI using forest plots. The effect sizes in the included studies were reported using different effect measures: relative risk, odds ratio, and beta coefficient. For ADHD symptoms with continuous outcome reported using regression beta-coefficients, we used beta as effect estimates (Altman and Bland, 2011; Hansen et al., 2022; Wilson, 2016) to facilitate the direct interpretation and to ensure consistency with established practices in conducting meta-analyses. Furthermore, we also considered the risk ratios as approximations of odds ratios based on the assumption commonly employed in epidemiology, specifically when the outcome of interest is rare and the incidence of an outcome of interest in the study population is lower than <10 % (Alavi et al., 2020; Kim, 2017; Viera, 2008; Zhang and Yu, 1998).

We assessed heterogeneity using Cochran's Q statistic test [26] and I^2 statistic test (J. P. Higgins and Thompson, 2002). The I^2 value of 25 %, 50 %, and 75 % represents low, moderate, and high heterogeneity, respectively (J. P. Higgins and Thompson, 2002). As the included studies

are heterogeneous, ($I^2 > 75$ %), we used random effect model to derive the pooled estimate (DerSimonian and Laird, 1986). We did subgroup analyses by confounders/covariates adjustment (i.e., if a study adjusted at least one potential confounder), outcome ascertainment tool (screening/diagnostic), and dose-response (heavy/light-to-moderate) to identify the source of heterogeneity between included studies. We also did leave-one-out sensitivity analyses to see the independent effect of each study on the pooled estimates (Hansen et al., 2022).

We examined the existence of publication bias by using the visual inspection of funnel plots (Liu, 2011), and Egger's test (Egger et al., 1997). Finally, we did the Duval and Tweedie's trim-and-fill method (Duval and Tweedie, 2000) to adjust the effect of the existing publication bias.

3. Results

3.1. Selection process of the included studies

All the retrieved articles were exported into endnote version 20 for duplication removal and screening. Of the 8444 articles retrieved initially, 3109 were removed due to duplication and 5063 were excluded after checking the titles and abstracts. The remaining 272 full-text articles were assessed for eligibility and 258 articles were excluded as they did not meet the inclusion criteria. Finally, 14 studies met the inclusion criteria to undergo the final systematic review and meta-analysis on prenatal cannabis exposure and the risk of neurodevelopmental disorders (ADHD = 10 and ASD = 4) in offspring (Fig. 1).

3.2. Description of the included studies

This study included ten studies to estimate the effect of prenatal cannabis use on ADHD symptoms in offspring and the included studies were published between 1999 (Leech et al., 1999) and 2022 (Cioffredi et al., 2022; Garrison-Desany et al., 2022) and all of these studies were cohort studies. While seven of the included studies were conducted in the United States (Cioffredi et al., 2022; Garrison-Desany et al., 2022; Goldschmidt et al., 2000; Leech et al., 1999; Murnan et al., 2021; Paul et al., 2021), the rest were conducted in Canada (Daniel J Corsi et al., 2020; Vanina et al., 2022) and the Netherlands (El Marroun et al., 2011). In this meta-analysis, a total of 203,783 participants were involved.

This meta-analysis also included four studies conducted to assess the relationship between prenatal cannabis use and risk of ASD in prenatally exposed offspring. Of these four studies: two conducted in the US (DiGuiseppi et al., 2022; Nutor et al., 2023), one in Australia (Pham et al., 2022), and the other in Canada (Corsi et al., 2020) and these studies involved a total sample of 173,035 participants (Table 1).

3.3. Quality assessment of studies included in meta-analysis

Of the studies included in the quantitative analysis to estimate the effect of prenatal cannabis use on ADHD symptoms in offspring ($n = 10$); eight scored high quality (7–9) and the rest two scored moderate quality (4–6) scores based on NOS quality rating scales. Therefore, all studies included in this meta-analysis had scored moderate and above; hence, had a low risk of bias. Moreover, the same quality assessment tool was applied for studies ($n = 4$) examining the association between prenatal cannabis use and the risk of ASD in offspring (two studies scored high quality and the rest two scored moderate NOS scores) (Table S*2*).

3.4. Prenatal cannabis uses and risk of ADHD and ASD

Our meta-analysis underscores an increased risk of ADHD symptoms and/or disorder [β = 0.39: 95 % CI (0.20–0.58), I2 = 66.85 %, P = 0.001)] and ASD [RR = 1.30: 95 % CI (1.03–1.64), I2 = 45.5 %, p = 0.14] associated with in-utero cannabis exposure in offspring compared to their non-exposed counterparts (Figs. 2 and 3). Additionally, our stratified analysis highlighted an elevated risk of ADHD symptoms [β = 0.54: 95 % CI (0.26–0.82), $I^2 = 71.08$ %, P = 0.001] and a marginally significant increase in the risk of diagnostic ADHD among exposed offspring compared to non-exposed counterparts [RR = 1.13, 95 % CI (1.01, 1.26), $I^2 = 0.00$ %, p = 0.73] (*Suppl. Figs. 1 and 2*).

3.5. Subgroup and sensitivity analysis

We observed moderate heterogeneity ($I^2 = 66.8$ %, Q = 27.15, P = 0.001) between included studies for ADHD symptoms and/or diagnosis, which needs handling with different statistical techniques. First, we did subgroup analysis to handle the reported heterogeneity between included studies. While some of the studies included in our meta-analysis fully or partially adjusted for different confounders, others did not. Of the ten included studies, eight adjusted for maternal prenatal tobacco use (Cioffredi et al., 2022; Corsi et al., 2020; El Marroun et al., 2011; Garrison-Desany et al., 2022; Goldschmidt et al., 2000; Leech et al., 1999; Paul et al., 2021), six for maternal mental health (Cioffredi

Table 1
Summary of studies included in this systematic review and meta-analysis.

First author, year	Study setting	Study design	Outcome ascertained by:	Prenatal Exposure Trimester	Age of offspring (in years)	Sample size (total)	sample size (PCE)	Reported effect sizes
Cioffredi et al. (2022)	US	Cohort	CBCL	Any trimesters	9 to 10	11,489	224	RR = 1.47
Corsi et al. (2020)	Canada	Cohort	ICD	First trimester	5	173,035	2,364	HR = 1.11
El Marroun et al. (2011)	Netherlands	Cohort	CBCL	First trimester	1.5	4077	88	OR = 2.75
Garrison-Desany et al. (2022)	US	Cohort	ICD	Any trimesters	12	3138	123	B = 0.28
Goldschmidt et al. (2000)	US	Cohort	CBCL	Second/third trimester	10	635	121	B = 0.70
Hunter et al. (2022)		Cohort	CBCL	First trimester	5	162	12	B = 0.47
Leech et al. (1999)	US	Cohort	CPT	Second/third trimester	6	608	31	B = 0.15
Murnan et al. (2021)	US	Cohort	CBCL	Any trimesters	3.5	63	15	OR = 1.41
Paul et al. (2021)	US	Cohort	CBCL	Any trimesters	9 to 11	8168	242	B = 1.34
Vanina et al. (2022)	Canada	Cohort	ICD	Any trimesters	4 to 8	2408	86	HR = 1.22
Autism Spectrum disorder (ASD)								
Corsi et al. (2020)	Canada	Cohort	ICD	First trimester	5	173,035	2,364	HR = 1.51
DiGuiseppi et al. (2022)	US	Case-control	DSM	Any trimesters	3.5	4284	98	OR = 1.21
Nutor et al. (2023)	US	Cohort	DSM	First trimester	2	172	60	B = 0.13
Pham et al. (2022)	Australia	Cohort	DSM	Any trimesters	4	1074	19	OR = 3.95

Key Notes: *US: United States, (1) screening tools* **[***CBCL: Child Behaviour Checklist, CPT: continuous performance test], (2) diagnostic tools [ICD: International Classification of Diseases and DSM: diagnostic and statistical manual of mental health disorders], (3) effect measures [OR: odds ratio, HR: hazard ratio, RR: relative risk, and b: beta coefficients].*

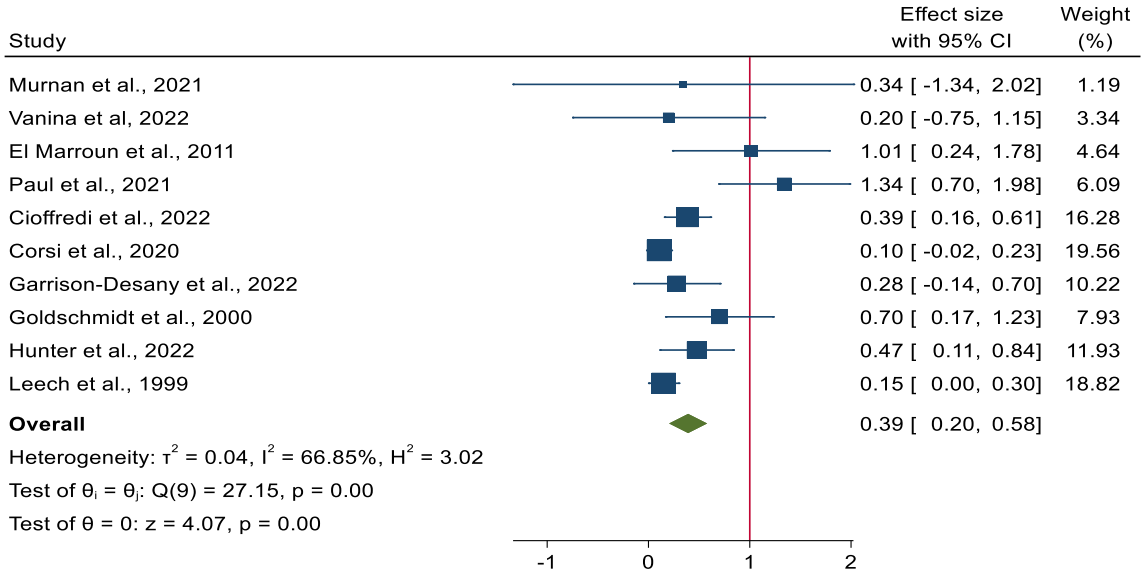

Fig. 2. Random effect model with DerSimonian-Laird estimates the pooled risk of maternal prenatal cannabis use on ADHD symptoms &/or disorders in offspring (n = 10 studies).

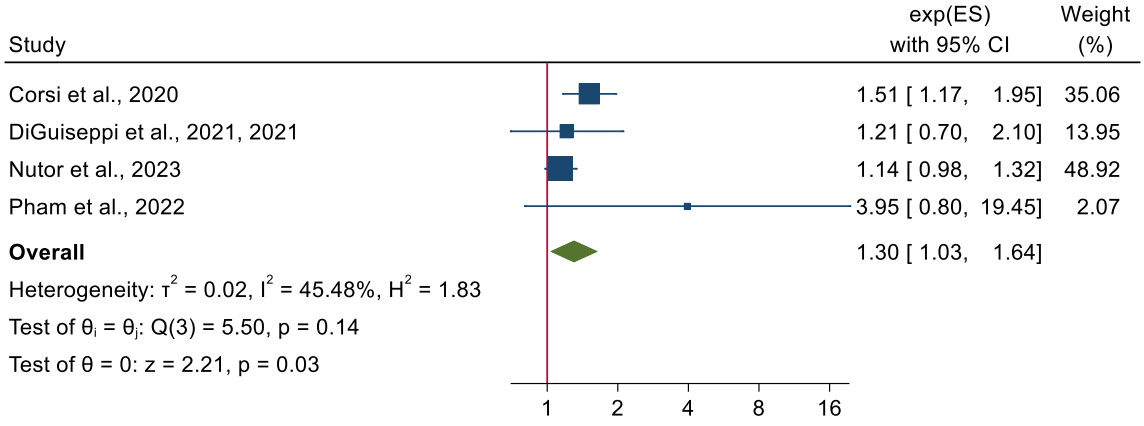

Fig. 3. An inverse variance random effect model with DerSimonian-Laird estimates the pooled risk of maternal prenatal cannabis use on ASD in offspring (n = 4 studies).

et al., 2022; El Marroun et al., 2011; Garrison-Desany et al., 2022; Goldschmidt et al., 2000; Paul et al., 2021; Vanina et al., 2022), and seven studies for maternal prenatal alcohol use (Cioffredi et al., 2022; Daniel J Corsi et al., 2020; Garrison-Desany et al., 2022; Goldschmidt et al., 2000; Leech et al., 1999; Paul et al., 2021; Vanina et al., 2022) (Table S3 & S4).

In this subgroup analysis, studies adjusted for maternal tobacco smoking had similar estimate to the pooled estimate of the effect of prenatal cannabis use on ADHD symptoms in offspring [β = 0.39: 95 % CI (0.18–0.60)] compared to studies did not adjust for tobacco smoking [β = 0.47: 95 % CI (0.12–0.82). Similarly, studies adjusted for maternal alcohol intake reported closure estimate to the overall pooled estimate of the effect of prenatal cannabis use on ADHD symptoms in offspring [β = 0.34: 95 % CI (0.14–0.54) compared to studies did not adjust for alcohol consumption [β = 0.56: 95 % CI (0.24–0.88)]. Furthermore, our subgroup analysis revealed an increased risk of ADHD symptoms in first, second/third, and any trimesters of pregnancy exposure. However, the effect was statistically significant only for any trimester [β = 0.51: 95 % CI (0.14–0.88) while not reaching significance for the first and second or third trimesters.

Finally, our subgroup analysis also indicated an increased risk of ADHD symptoms when screening tools were employed [(β = 0.54 (0.26–0.82)]. Similarly, when diagnostic tools were utilized, our analysis indicated an elevated risk of ADHD [RR = 1.13 (1.01–1.26)] (Table 2 and Suppl. Figs. 4–10).

Furthermore, we also carried out sensitivity analysis for ASD by removing one study (Pham et al., 2022), which seems an outlier on the forest plot, but we found similar estimates [RR = 1.26 (1.03–1.54)] compared to the overall estimate [RR = 1.30 (1.03–1.64)] (Suppl. Fig. 3). Importantly, we can conclude that neither of the outcome of interests affected by outlier studies included in the final analysis.

Table 2
Subgroup analysis for covariates/confounders adjusted in the included studies to estimate the risk of ADHD symptoms in offspring prenatally exposed to cannabis.

Subgroup analysis by:	Category	Number of studies reported	Effect estimates, beta (β) with 95 % CI
Studies reported adjusted (RR)	Yes	8	0.385 (0.182–0.593)
	No	2	0.470 (0.113–0.824)
Outcome ascertainment	Screening	7	0.542 (0.262–0.824)
	Diagnostic	3	0.112 (0.010–0.231)
Prenatal Exposure period	First trimester	3	0.405 (0.01–0.833)
	All trimester	5	0.513 (0.140–0.884)
	2nd &/or 3rd trimester	2	0.365 (−0.163–0.884)
Studies adjusted for maternal mental health problems	Yes	6	0.604 (0.293–2.50)
	No	4	0.157 (0.039–0.270)
Studies adjusted for maternal prenatal tobacco smoking	Yes	8	0.385 (0.182–0.593)
	No	2	0.47 (0.113–0.824)
Studies adjusted for maternal alcohol intake	Yes	7	0.344 (0.140–0.542)
	No	3	0.565 (0.239–0.884)

3.6. Leave-one-out meta-analysis

We conducted a leave-one-out sensitivity analysis by excluding each study at a time to see the effect of a single study on the overall estimate. We found that the pooled estimates for ADHD symptoms in offspring varied between 0.35 [β = 0.35: 95 % CI (0.17–0.55)])] and 0.48 [β = 0.48: 95 % CI (0.25–0.70)). This suggests our overall estimates were not substantially affected by individual studies included for ADHD. We also carried out a leave-one-out sensitivity analysis among studies included for ASD and we found estimated risk ratio varied between 1.20 [RR = 1.20 (1.01–1.51)] and 1.48 [RR = 1.48 (1.18–1.87)], which indicated the estimate was not substantially influenced by the individual studies [RR = 1.30 (1.03–1.64)] (Table 3).

Table 3
Leave-one-out sensitivity analysis for the association between prenatal cannabis exposure and risk of ADHD & ASD in offspring after removal of each study one at a time.

Study omitted	For ADHD studies [Effect estimates, beta- β]	95 %CI
Murnan et al. (2021)	0.40	0.20–0.59
Paul et al. (2021)	0.29	0.14–0.44
Vanina et al. (2022)	0.40	0.21–0.60
Corsi et al. (2020)	0.48	0.25–0.70
Cioffredi et al. (2022)	0.40	0.19–0.62
El Marroun et al. (2011)	0.35	0.17–0.54
Garrison-Desany et al. (2022)	0.41	0.21–0.62
Goldschmidt et al. (2000)	0.36	0.17–0.55
Leech et al. (1999)	0.48	0.23–0.72
Hunter et al. (2022)	0.38	0.18–0.59
Leave-one-out for ASD studies (effect estimate, RR)		
Corsi et al. (2020)	1.20	1.01–1.51
DiGuiseppi et al. (2022)	1.34	0.99–1.82
Nutor et al. (2023)	1.48	1.18–1.87
Pham et al. (2022)	1.26	1.03–1.54

Key. The analysis was done using random effect with DerSimonian-Laird model of meta-analysis.

3.7. Publication bias and trim-fill analysis

We did visual inspection of the funnel plot for symmetrical distribution of included studies and egger's test to check the presence of publication bias. Visual inspection of the funnel plot showed asymmetric funnel plot (Fig. 4) and Egger's test also demonstrated evidence of publication bias (p = 0.004). We did trim and fill analysis to handle the effect of studies unpublished for different reasons and five studies were imputed (Fig. 5).

4. Discussion

In this systematic review and meta-analysis, we found that offspring exposed to prenatal cannabis use had an increased risk of ADHD symptoms and ASD compared with unexposed offspring. Adjustment for maternal mental health problems, maternal alcohol use, and tobacco smoking did not substantially alter the observed associations. The findings suggest the importance of implementing prevention and early interventions among offspring exposed to prenatal cannabis use.

The mechanism of how prenatal cannabis use may cause neurodevelopmental disorders such as ADHD symptoms and ASD in human offspring is not well understood. Animal studies indicate some direct impacts of prenatal cannabis use on offspring neurodevelopment. Prenatal cannabis use in rats associates with change in the dopaminergic activity of the corpus striatum which associates with neurodevelopmental alterations, involving the prefrontal cortex that associates with cognitive impairment and emotional dysregulation (Navarrete et al., 2020; Trezza et al., 2012). Animal based studies also showed that prenatal exposure in rodents to be associated with an increased rate of ultrasonic vocalisations when separated from the mother. This triggers an increase in levels of anxiety that are related to the presence of CB1 receptors in the cortex, the hippocampus, the lateral septum, the nucleus accumbens and the amygdala, which regulate the release of 5-HT, dopamine, CCK and CRF peptides (Gray et al., 2005; Trezza et al., 2012). These are all anxiogenic peptides that contributed to cognitive and neurodevelopmental impairments in exposed offspring.

Prior human studies have also suggested direct and indirect mechanisms for how prenatal cannabis use may affect the neurodevelopmental conditions in offspring. This includes observations that Delta-9-tetrahydrocannabinol (THC), the psychoactive ingredient of cannabis, can cross the placenta and the foetal blood-brain barrier, causing interruptions in the endogenous cannabinoid signalling involved in embryonic neurodevelopment of the foetus (Brents, 2016; Richardson et al., 2002). This can be considered as one of the direct mechanisms linking intra-uterine exposure of THC on the growing foetus. Furthermore, neurodevelopmental data in humans suggested that prenatal exposure to THC may lead to subtle, persistent alterations in behavioural, cognition and psychological well-being (Grant et al., 2018; Huizink and Mulder, 2006; Navarrete et al., 2020). Existing studies have indicated that the impact of prenatal cannabis exposure in the first trimester of gestations, where the epigenetic changes has occurred, increased the risk of ADHD symptoms like impulsivity, inattention, and hyperactivity problems (Cioffredi et al., 2022; Goldschmidt et al., 2000; Leech et al., 1999; O'Connell and Fried, 1991; Paul et al., 2021) in offspring. On the other hand, the existing evidence has suggested the role of genetic mechanisms as the deep-rooted aetiology for neurodevelopmental disorders, specifically ADHD and ASD (Schachar, 2014). For example, a review study by Akutagava-Martins et al. (2013) reported that genes play a key role in ADHD aetiology, with an estimated heritability of approximately 76 % (Akutagava-Martins et al., 2013). Similarly, Bölte et al. (2014) generated strong evidence for the associations between familial genetics and ADHD and ASD in twin offspring (Bölte et al., 2014).

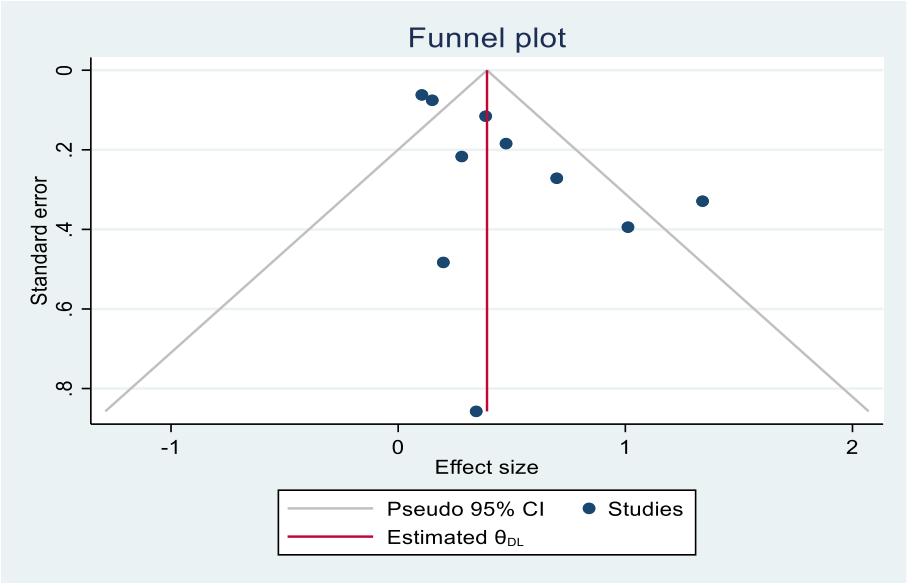

Fig. 4. Funnel plot to assess distribution of included studies for ADHD symptoms (n = 10 studies).

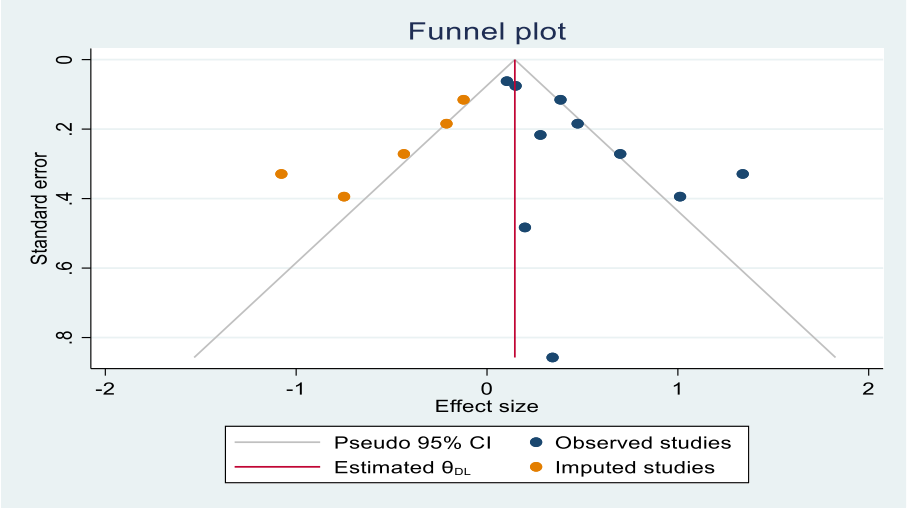

Fig. 5. Trim and fill funnel plot to fill excluded studies due to publication bias for ADHD symptoms (n = 5 studies imputed).

Our finding is consistent with the findings of an epidemiological review study by Navarrete et al. (2020) that was including the articles from the three known cohort studies: Gen R study, the Maternal Health Practices and Child Development Study (MHPCD), and the Ottawa Prenatal Prospective Study (OPPS) (Navarrete et al., 2020). This review study revealed that perinatal cannabis exposure was associated with cognitive deficits (attention, learning, and memory), disturbances in emotional response leading to aggressiveness, high impulsivity, or affective disorders, and higher risk to develop a substance use disorder.

In the subgroup analysis, studies adjusted for maternal tobacco smoking had lower estimate compared to studies did not adjust for tobacco smoking, but similar estimate to the pooled overall estimate of the effect of prenatal cannabis use on ADHD symptoms in offspring. Similarly, studies adjusted for maternal alcohol intake reported similar estimate to the overall pooled estimate of the effect of prenatal cannabis use on ADHD symptoms in offspring compared to studies did not adjust for alcohol drinking during pregnancy. Importantly, studies suggested that pregnant women who use cannabis are more likely to use other substances such as alcohol, tobacco, and other illicit drugs (Luke et al., 2019; Mark et al., 2016; van Gelder et al., 2010), which may confound the effect prenatal cannabis use on neurodevelopmental disorders in offspring. On the other hand, this subgroup analysis found that the estimate of prenatal cannabis use and risk of ADHD was higher in studies that used screening outcome ascertainment compared to studies that used diagnostic ascertainment. In Epidemiological aspects, screening tools are highly sensitive compared with diagnostic tools, which may bias the estimate of measured effect sizes. It is also important to note that there was significant imbalance between studies used diagnostic tool and studies used screening tools to ascertain ADHD in offspring (i.e., three & seven studies, respectively).

Our subgroup analysis also revealed an increased risk of ADHD symptoms in first, second/third, and any trimesters of pregnancy exposure. However, the effect was statistically significant only for any trimester, while not reaching significance for the second/third and first trimesters. The existing evidence on the trimester-based effects of cannabis use during pregnancy has suggested that cannabis use in any trimester of pregnancy may have a more pronounced impact (Thompson et al., 2019).

4.1. The strengths and limitations of the study

This systematic review and meta-analysis have several strengths. Firstly, it is the first meta-analytic systematic review to consolidate the evidence on the subject. Secondly, the methodological quality of included studies was assessed using a standard and well-accepted methodological quality assessment tool (NOS). None of the studies included in this review were poor quality studies. Thirdly, we carried out subgroup analyses to explore the source of heterogeneity and leave-one-out-sensitivity analysis to identify highly influential studies on the pooled estimate.

The current review also has some limitations. We have synthesized data from observational studies with varying samples and methodologies. Therefore, we observed considerable heterogeneity between the included studies in the association between prenatal cannabis exposure and neurodevelopmental disorders: ADHD and ASD. According to Cochrane Library handbooks for systematic reviews, meta-analysis is the statistical combination of results from two or more separate studies (Deeks et al., 2019; Julian PT Higgins and Green, 2008), but it is equally important to acknowledge the impact of a small number of studies on the interpretation of our findings, particularly in few subgroup analyses and the main analysis for ASD. This could potentially result in wider confidence intervals, which affects the precision of the findings. We also noted that the level of adjustment for confounders was inconsistent in the studies included in the review, indicating that the results could be biased by residual confounding. Hence, caution should be considered when interpreting and generalizing the findings of this study.

5. Conclusion

We found offspring exposed to prenatal cannabis use had an increasing risk of ADHD symptoms and/or disorders and ASD compared to non-exposed. Studies with large sample size are required, particularly for the risk of ASD. In addition, studies on the mechanisms underlying the association between prenatal cannabis use and increasing risk of ADHD and ASD are needed.

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CRediT authorship contribution statement

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

Declaration of competing interest

All authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.01.045.

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