MATERNAL DEPRESSION AND RISK OF AUTISM IN OFFSPRING

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MATERNAL PRE- AND PERINATAL DEPRESSION AND THE RISK OF AUTISM SPECTRUM DISORDERS IN OFFSPRING: SYSTEMATIC REVIEW AND META-ANALYSIS

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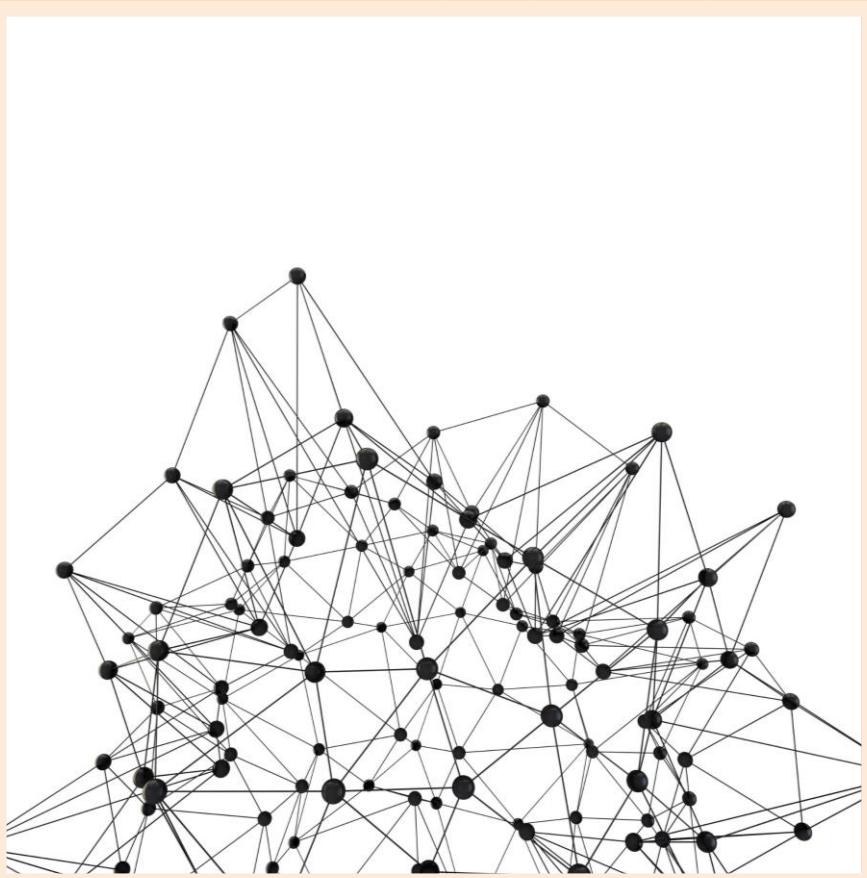
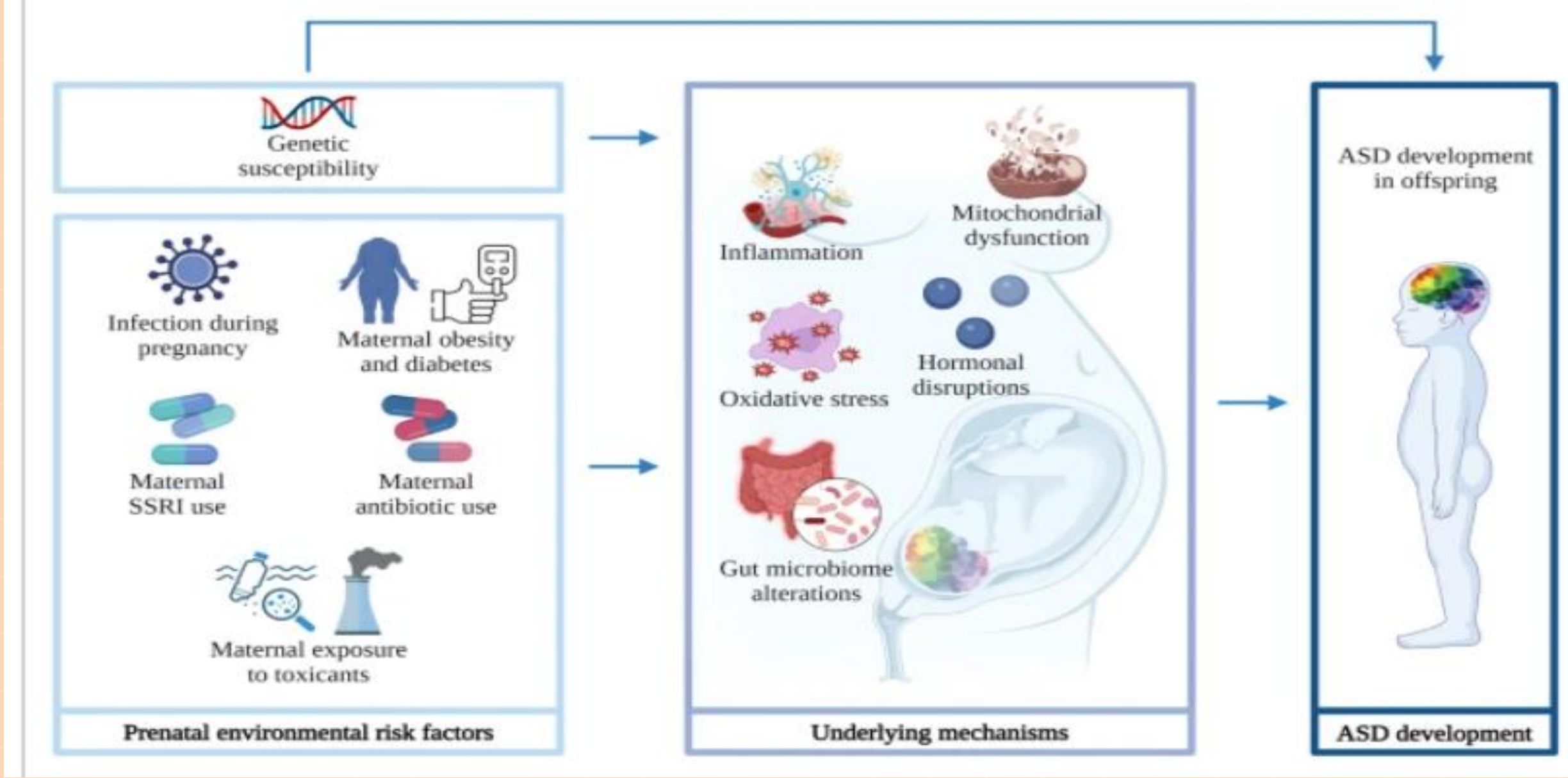
Introduction and Background

Overview of Autism Spectrum Disorders (ASD)

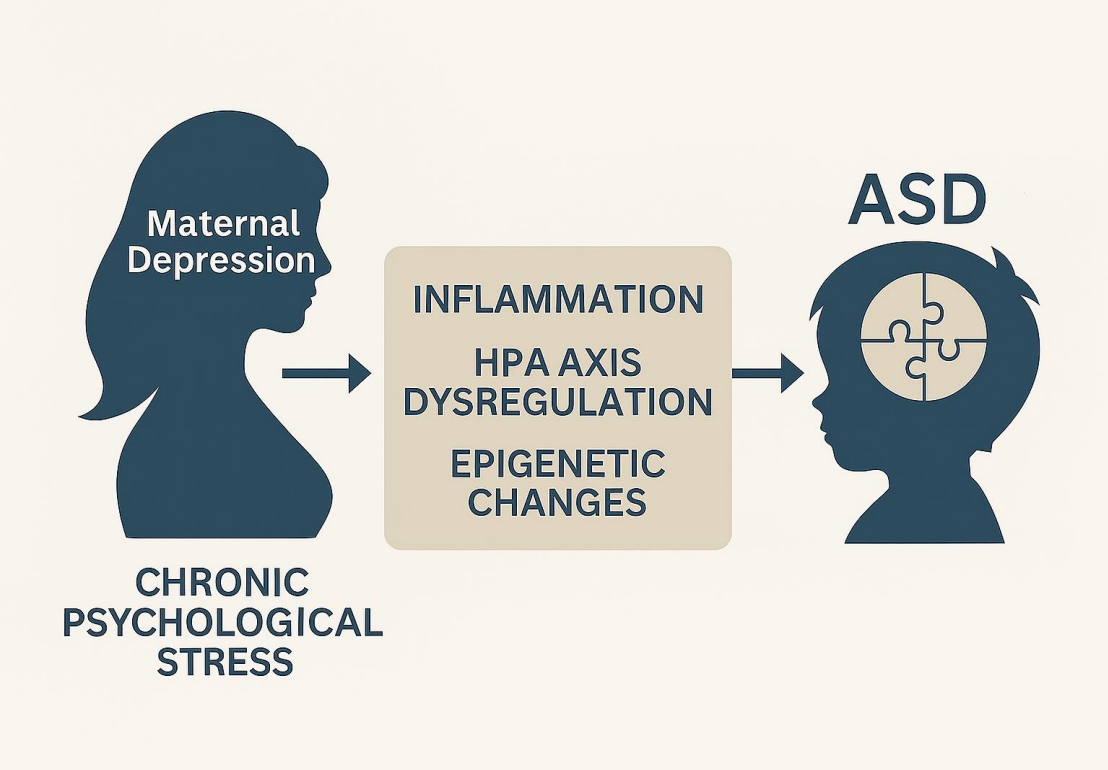


- ASD is marked by enduring impairments in reciprocal social communication and social interaction, and restrictive and repetitive behaviors and interests (RRBI) affecting daily life.
- The spectrum includes idiopathic forms, including autism, Asperger syndrome and Pervasive Developmental Disorder - Not Otherwise Specified, and Childhood Disintegrative Disorder and certain genetic disorders like Rett syndrome, which can exhibit autistic traits.
- Global prevalence of 0.82% among children of 6 to 12 years age
- Higher occurrence in males than females.
- Lifelong neurodevelopmental condition with individual and economic burden.
- Multifactorial origin of genetic, environmental, physical and psychological factors.



Love, C., Sominsky, L., O'Hely, M. *et al.* Prenatal environmental risk factors for autism spectrum disorder and their potential mechanisms. *BMC Med* **22**, 393 (2024).

Role of maternal mental health



- Maternal depression is relatively common - in around 21% of women during pregnancy and 14% after childbirth.
- Evidence concerning risk of ASD in mothers experiencing depression is crucial for timely interventions for at risk children.
- Lack of consistency in the findings of existing studies- some showed link and some didn't. Lack of updated evidence.

Study Objectives and Methodology

Objectives of the Study

To examine and consolidate the existing evidence on the association between maternal pre- and perinatal depression and the risk of ASD in children and adolescents.

To help formulate initiatives targeting maternal health and risk of neurodevelopmental disorders like ASD.

Methodology Overview

Study design

Systematic review and meta-analysis reported in accordance with PRISMA guidelines.

Literature search

PubMed, Medline, EMBASE, Scopus, CINAHL and PsycINFO from period of inception to 21 February 2024.

Eligibility criteria

All observational studies

Exposure variable- maternal depression (before and during pregnancy or after childbirth) - independent variable. (ICD, DSM, EPDS, CES-D)

Outcome- ASD in children and adolescent – dependent variable. (ICD, DSM)

English

Excluded- animal studies, case reports, case series, correspondence, abstracts and reviews.

Quality and Data Analysis

Two independent reviews- data extraction then quality and elimination of biases using Newcastle-Ottawa Scale into low, medium and high-quality studies.

Meta-analysis using random-effects models and summary effect estimates with odds ratio.

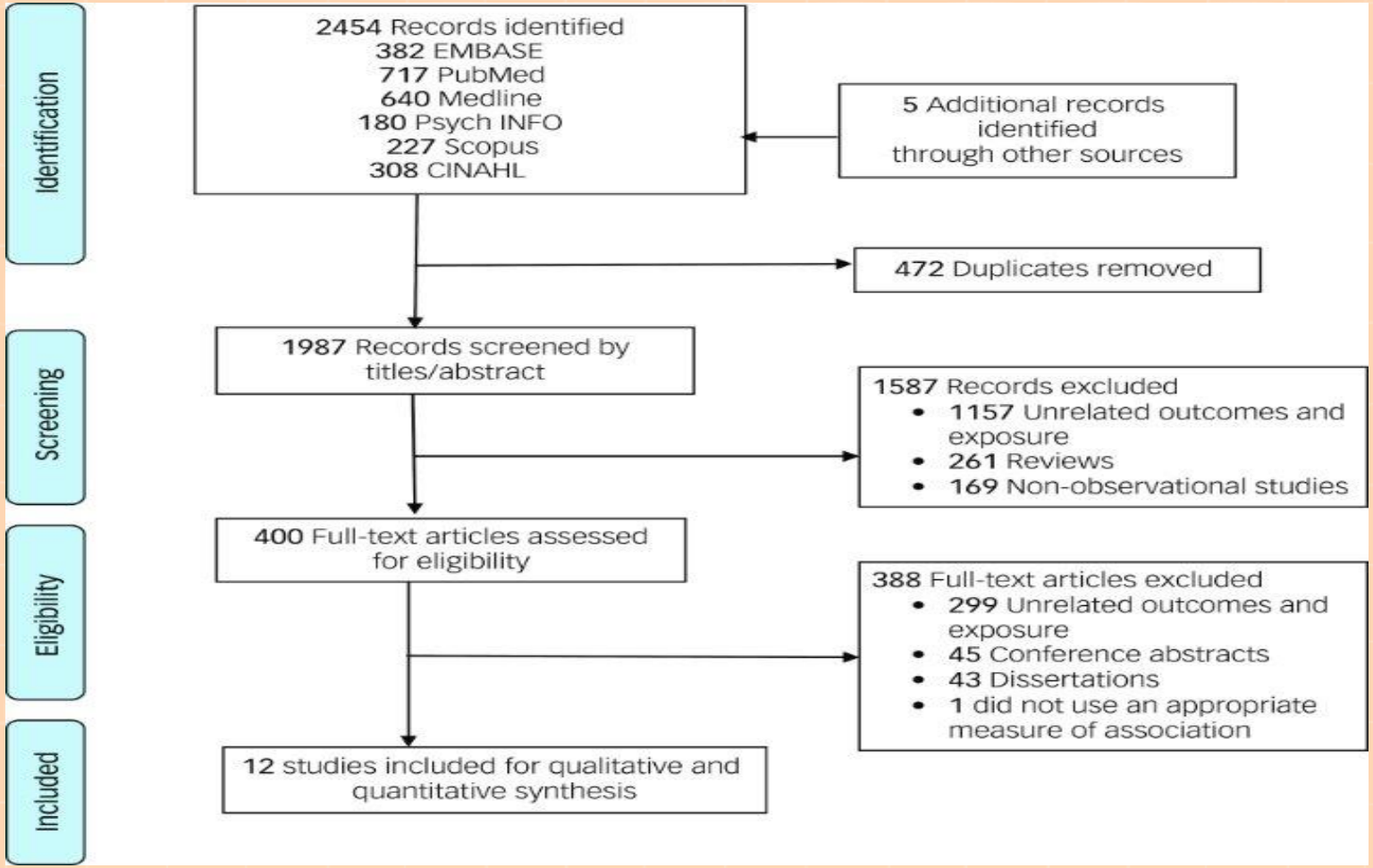
For statistical heterogenicity- Cochran's Q and I^2

Subgroup and sensitivity analyses were performed to evaluate the reliability of study findings.

For publication bias- funnel plots and Egger's regression test.

Key Findings and Interpretation

Search results



Characteristics of included studies

12 studies comprising of 1, 655, 966 mother offspring pairs.

Between 2011 and 2023

Across seven different countries- 5 in USA, 2 in Turkey and 2 in Denmark.

8 case control and 2 cohort studies.

9 studies reported antenatal depression, 3 studies postnatal depression and 5 pre-pregnancy depression

9 studies adjusted for at least one confounding factor in their effect estimates. 8 considered socioeconomic factors, 6 for maternal substance use, 5 studies for antidepressant use, 4 for other psychiatric disorders, 2 for paternal depression.

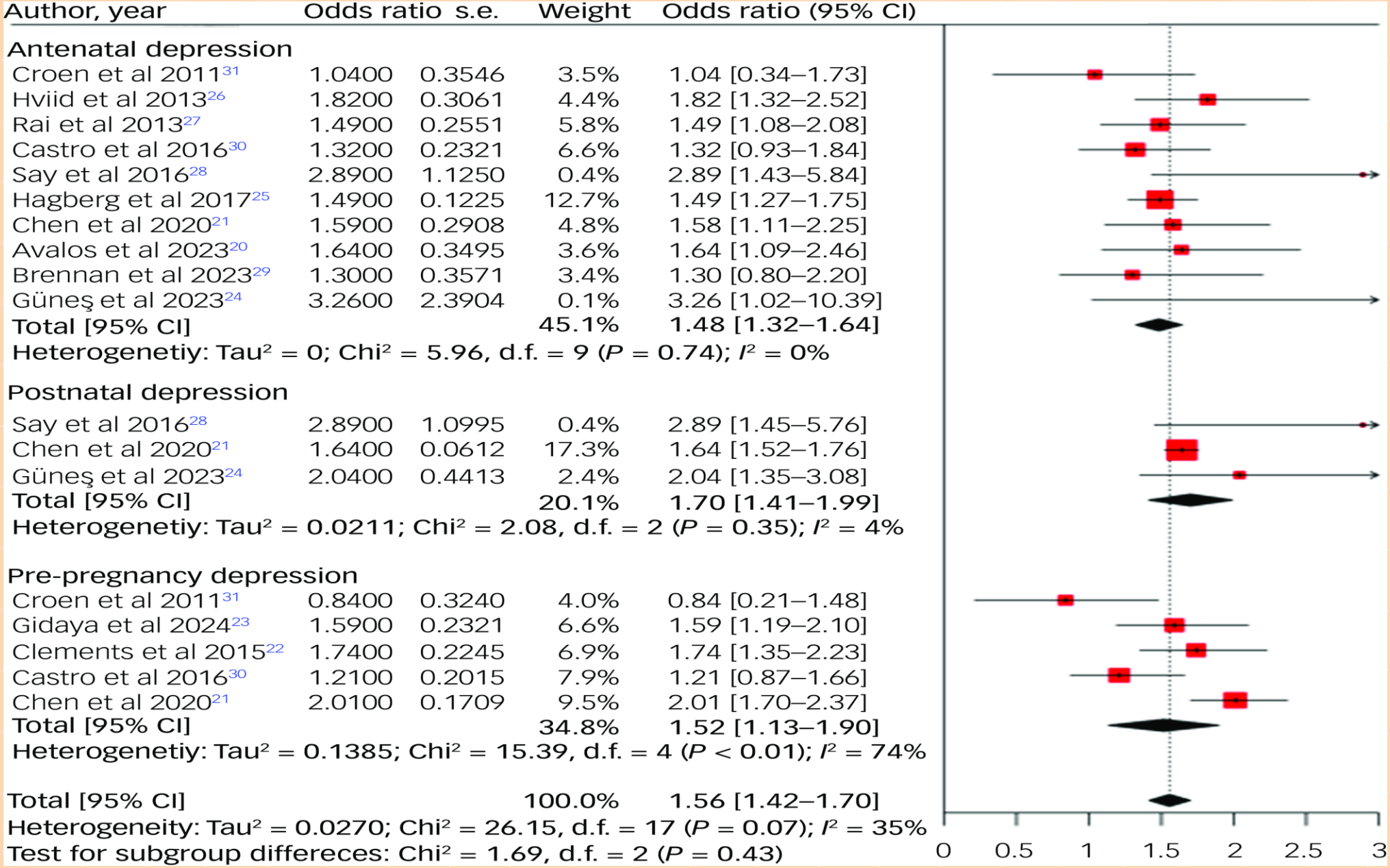
Based on NOS quality assessment, 8 studies were of high quality and 4 of medium quality.

Author, year	County of study	Study design	Sample size	Time of exposure	Measure of exposure	Offspring age at measurement	Measures of outcomes	Measures of effect
Avalos et al 2023[20]	USA	Cohort study	3994 (635 exposure and 3359 non-exposed)	Antenatal depression	ICD-9	12 years	SRS	Odds ratio 1.64, 95% CI 1.09–2.46
Brennan et al 2023[29]	USA	Cohort study	2377	Antenatal depression	Not reported	1.5–12 years	ADOS	Odds ratio 1.30, 95% CI 0.80–2.20
Castro et al 2016[30]	USA	Matched case–control	4650 (1455 cases and 3405 controls)	Pre-pregnancy depression	ICD-9	2–19 years	ICD-9	Odds ratio 1.21, 95% CI 0.87–1.66
				Antenatal depression		2–19 years		Odds ratio 1.32, 95% CI 0.93–1.84
Chen et al 2020[21]	Taiwan	Cohort study	708 515 (53 489 exposed and 655 026 non-exposed)	Pre-pregnancy depression	ICD-9	0–11 years	ICD-9	Hazard ratio 2.01, 95% CI 1.70–2.37
				Antenatal depression		0–11 years		Hazard ratio 1.58, 95% CI 1.11–2.25
				Postnatal depression		0–11 years		Hazard ratio 1.64, 95% CI 1.52–1.76
Clements et al 2015[22]	USA	Matched case-control	5399 (1377 cases and 4022 controls)	Pre-pregnancy depression	ICD-9	2–19 years	ICD-9	Odds ratio 1.74, 95% CI 1.35–2.23
Croen et al 2011[31]	USA	Unmatched case–control	1805 (298 cases and 1507 controls)	Pre-pregnancy depression	ICD-9	3.6–3.8 years	ICD-9	Odds ratio 0.84, 95% CI 0.21–1.48
				Antenatal depression				Odds ratio 1.04, 95% CI 0.34–1.73
Gidaya et al 2014[23]	Denmark	Matched case–control	57 365 (5215 cases and 52 150 controls)	Pre-pregnancy depression	Not reported	Not reported	ICD-9	Odds ratio 1.59, 95% CI 1.19–2.10
Güneş et al 2023[24]	Turkey	Matched case–control	452 (211 cases and 241 controls)	Antenatal depression	Not reported	2–6 years	DSM-V	Odds ratio 3.26, 95% CI 1.02–10.39
				Postnatal depression				Odds ratio 2.04, 95% CI 1.35–3.08
Hagberg et al 2017[25]	UK	Matched case–control	196 648 (2154 cases and 194 494 controls)	Antenatal depression	Not reported	0–8 years	Read diagnostic code	Relative risk 1.49, 95% CI 1.27–1.75
Hviid et al 2013[26]	Denmark	Cohort study	626 875 (3482 exposure and 623 393 non-exposed)	Antenatal depression	No tools are used	4–7.5 years	ICD-10	Relative risk 1.82, 95% CI 1.32–2.52
Rai et al 2013[27]	Sweden	Matched case–control	47 706 (4429 cases and 43 277 controls)	Antenatal depression	ICD-10	0–17 years	ICD-10	Odds ratio 1.49, 95% CI 1.08–2.08
Say et al 2016[28]	Turkey	Matched case–control	180 (100 cases and 80 controls)	Antenatal depression	Self-report	3–18 years	DSM-IV	Odds ratio 2.89, 95% CI 1.43–5.84
				Postnatal depression		3–18 years		Odds ratio 2.89, 95% CI 1.45–5.76

Maternal depression and risk of ASD

Studies with significant relationship	9
Studies with no association	3

Depression	Odds Ratio	95% CI	Increased risk of ASD
Pre-pregnancy	1.52	1.13-1.90	52%
Antenatal	1.48	1.32-1.64	48%
Postnatal	1.7	1.41-1.99	70%


Author, year
Odds ratio
s.e.
Weight
Odds ratio (95% CI)
Antenatal depression
Croen et al 2011[31] 1.0400 0.3546 3.5% 1.04 [0.34–1.73]
Hviid et al 2013[26] 1.8200 0.3061 4.4% 1.82 [1.32–2.52]
Rai et al 2013[27] 1.4900 0.2551 5.8% 1.49 [1.08–2.08]
Castro et al 2016[30] 1.3200 0.2321 6.6% 1.32 [0.93–1.84]
Say et al 2016[28] 2.8900 1.1250 0.4% 2.89 [1.43–5.84]
Hagberg et al 2017[25] 1.4900 0.1225 12.7% 1.49 [1.27–1.75]
Chen et al 2020[21] 1.5900 0.2908 4.8% 1.58 [1.11–2.25]
Avalos et al 2023[20] 1.6400 0.3495 3.6% 1.64 [1.09–2.46]
Brennan et al 2023[29] 1.3000 0.3571 3.4% 1.30 [0.80–2.20]
Güneş et al 2023[24] 3.2600 2.3904 0.1% 3.26 [1.02–10.39]
Total [95% CI] 45.1% 1.48 [1.32–1.64]
Heterogenetiy: Tau² = 0; Chi² = 5.96, d.f. = 9 (P = 0.74); I² = 0%
Postnatal depression
Say et al 2016[28] 2.8900 1.0995 0.4% 2.89 [1.45–5.76]
Chen et al 2020[21] 1.6400 0.0612 17.3% 1.64 [1.52–1.76]
Güneş et al 2023[24] 2.0400 0.4413 2.4% 2.04 [1.35–3.08]
Total [95% CI] 20.1% 1.70 [1.41–1.99]
Heterogenetiy: Tau² = 0.0211; Chi² = 2.08, d.f. = 2 (P = 0.35); I² = 4%
Pre-pregnancy depression
Croen et al 2011[31] 0.8400 0.3240 4.0% 0.84 [0.21–1.48]
Gidaya et al 2024[23] 1.5900 0.2321 6.6% 1.59 [1.19–2.10]
Clements et al 2015[22] 1.7400 0.2245 6.9% 1.74 [1.35–2.23]
Castro et al 2016[30] 1.2100 0.2015 7.9% 1.21 [0.87–1.66]
Chen et al 2020[21] 2.0100 0.1709 9.5% 2.01 [1.70–2.37]
Total [95% CI] 34.8% 1.52 [1.13–1.90]
Heterogenetiy: Tau² = 0.1385; Chi² = 15.39, d.f. = 4 (P < 0.01); I² = 74%
Total [95% CI] 100.0% 1.56 [1.42–1.70]
Heterogeneity: Tau² = 0.0270; Chi² = 26.15, d.f. = 17 (P = 0.07); I² = 35%
Test for subgroup differeces: Chi² = 1.69, d.f. = 2 (P = 0.43)
0
0.5
1
1.5
2
2.5
3

Subgroup analysis

Subgroups	Number of studies	Pooled odds ratio (95% CI)	Heterogeneity across the studies (I^2)	Heterogeneity between the groups (*P*-value)
Exposure measures				
Screening	5	1.57 (1.39–1.76)	0.0%	0.64
Diagnostic	7	1.60 (1.50, 1.69)	54.9%	
Study design				
Cohort	4	1.67 (1.56–1.78)	9.9%	0.03
Case–control	8	1.45 (1.31–1.59)	24.1%	
Year of publication				
2011–2016	7	1.44 (1.23–1.64)	33.1%	0.10
2017–2023	5	1.66 (1.49–1.83)	16.8%	
Quality of study				
Medium	4	1.57 (1.36–1.77)	0.0%	0.72
High	8	1.59 (1.50–1.69)	47.9%	
Adjusted for any confounding factors				
Yes	9	1.52 (1.36–1.68)	49.0%	0.20
No	3	1.77 (1.39–2.16)	0.0%	
Adjusted for socioeconomic factors				
Yes	8	1.61 (1.52–1.71)	49.2%	0.95
No	4	1.53 (1.34–1.71)	0.0%	
Adjusted for other maternal psychiatric disorders				
Yes	4	1.62 (1.52–1.71)	43.6%	0.57
No	8	1.49 (1.31–1.68)	0.0%	
Adjusted for maternal substance use				
Yes	6	1.49 (1.32–1.66)	0.0%	0.52
No	6	1.58 (1.35–1.81)	50.5%	
Adjusted for antidepressant use				
Yes	5	1.40 (1.22–1.58)	19.3%	0.04
No	7	1.65 (1.55–1.75)	24.7%	
Adjusted for paternal depressive disorders				
Yes	2	1.67 (1.56–1.78)	37.4%	0.07
No	10	1.47 (1.33–1.61)	19.7%	

Summary of findings

- Offspring exposed to maternal pre-conception, antenatal and postnatal depressions exhibited a **48–70%** increased risk of ASD independent of other factors.
- Possible mechanisms proposed-
  - Shared genetic predisposition between depression and ASD increasing co-occurrence in families
  - Maternal depression leading to epigenetic changes of DNA methylation of fetus.
  - Maternal depression can affect the maternal-child interaction- bonding, finding it challenging to respond to needs of children at risk of ASD, suboptimal breastfeeding, elevated maternal cortisol and other inflammatory makers through breast milk.
- From study findings, differences between the types of maternal depression was not statistically significant, effect estimate slightly higher for postnatal depression.
- Antidepressant use and depression together and independently contributing to the risk.
- Socioeconomic factors and substance use and depression together and independently contributing to the risk of ASD.
- Possible other factors like paternal depression.

Strengths

Comprehensive overview of the existing research.

Accounted for heterogenecity.

High methodical quality of the studies.

Limitations

Variations of assessment in individual studies

Possible publication bias

Potential confounders like parental neurodevelopmental disorders, maternal physical comorbidities, prenatal health conditions and obstetric complications, were not accounted for in the majority of studies.

Generalisability worldwide

Next steps to consider-

Role of maternal depression as an independent factor leading to increased risk of ASD in offsprings.

Need for more targeted research to understand how strong this association is.

Importance of identification of antenatal and postnatal depression and treatment.

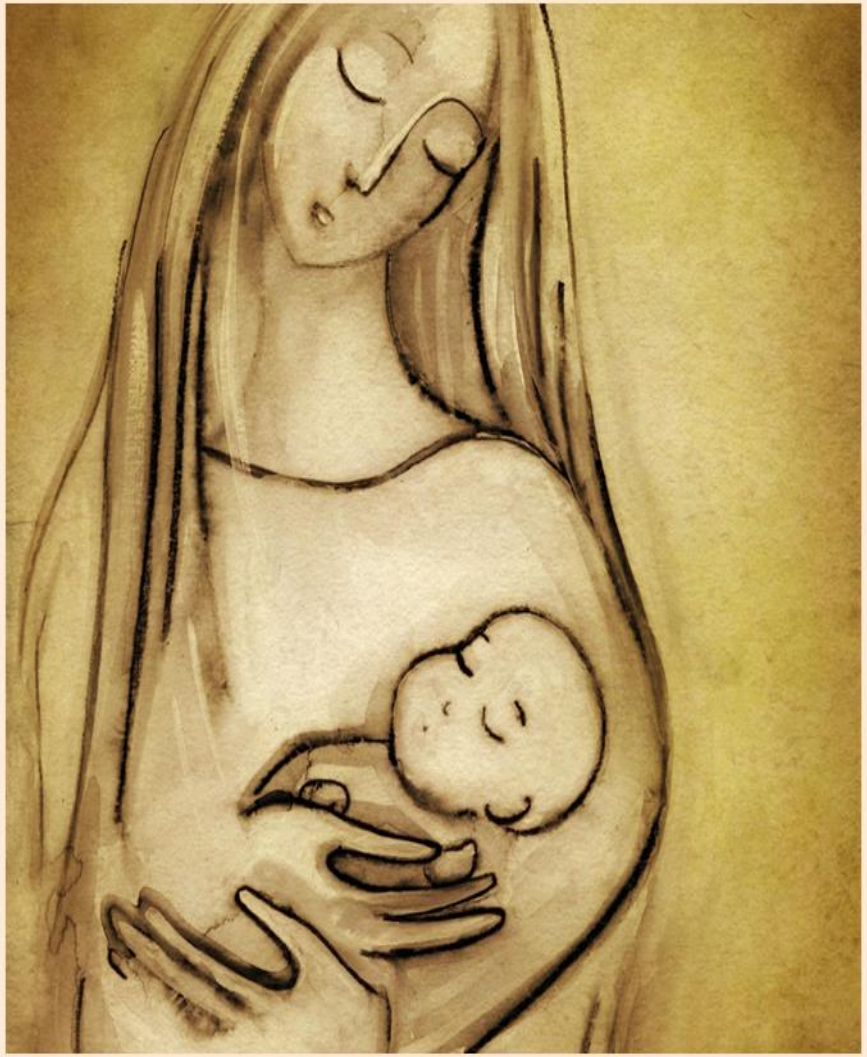
Pre-pregnancy counselling and identification and treatment of depression in women planning for pregnancy.

Offsprings of women with depression likely need specific interventions for early identification and prevention.

Need for these strategies at primary and secondary level of care.

“When we neglect mothers we neglect society”

– Andrea Fitmom Page



MOTHERHOOD IS VALUED.
MOTHERS ARE NOT.
IT IS TIME TO PRIORITIZE
MATERNAL MENTAL HEALTH.

we cannot do it all.
-a mom who needs more support

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Thank you