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Meta Analysis
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# Meta Analysis: Effects of Polycystic Ovarian Syndrome and Maternal Diabetes on the Risk of Autism in Children

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## ABSTRACT

**Background:** Autism is a condition of developmental abnormalities in social, communication and behavior aspects. Polycystic ovary syndrome and maternal diabetes during pregnancy contribute more than 50% to the risk of ASD offspring. This study aims to analyze and estimate the influence of polycystic ovarian syndrome and maternal diabetes on autism in children.
**Subjects and Method:** The meta-analysis was carried out according to the PRISMA flow chart and the PICO model. Q: Child, I: Mother with PCOS and maternal diabetes, C: T Mother without PCOS and maternal diabetes, O: Autism. Search for articles in this study through databases that include Google Scholar, Pubmed, ScienceDirect and Sage Journal. With keywords including: Polycystic Ovarian Syndrome" AND "Maternal Diabetes" OR "Gestational Diabetes Mellitus" AND "Autism" OR "Autism Spectrum Disorder" AND "Cohort". A full paper article with an observational cohort study, the research subject was a child, the size of the relationship used was the adjusted odds ratio, the research outcome was autism. Analysis was performed with Revman 5.3.
**Results:** There were 13 articles with cohort designs originating from America, Denmark, England, Sweden, Israel, China with a total of 4,641,483 research samples. A meta-analysis of 13 cohort studies concluded that children of pregnant women with PCOS had a 1.36 times greater risk of developing autism than those without PCOS, and the effect was statistically significant (aOR= 1.36; 95% CI= 1.24 to 1.49; p<0.001). In addition, pregnant women with maternal diabetes have a 1.24 times higher risk of having a child with autism than those without maternal diabetes, and this effect is statistically significant (aOR= 1.24; 95% CI= 1.08 to 1.43; p=0.002).
**Conclusion:** Pregnant women who have PCOS and maternal diabetes increase the risk of autism in children.

**Keywords:** polycystic ovarian syndrome, maternal diabetes, autism.

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## BACKGROUND

Autism Spectrum Disorder (ASD) is a collection of developmental disorder conditions characterized by difficulties in social interaction, verbal and nonverbal communication problems, accompanied by shallow and

obsessive repetition of behavior and interests (Dewi et al., 2018). Autism is often marked by repetitive movements and focusing on one thing without paying attention to the surroundings. Children with autistic disorders have limitations in their development, such as social difficulties, language and speech delays, and behavioral problems. This neurological disorder can be seen from the abnormal EEG and MRI results (Sultana et al., 2017).

The World Health Organization (WHO) estimates that the international prevalence of ASD is 0.76%. However, this prevalence only accounts for around 16% of the global child population (Baxter et al., 2015). The Centers for Disease Control and Prevention (CDC) estimates that around 1.68% of United States (US) children aged 8 years old (or 1 in 59 children) are diagnosed with ASD (Baio et al., 2018). In Indonesia, the prevalence of children with ASD in 2012 was 1.68 per 1,000, which means that more than 112,000 ASD sufferers in Indonesia are > 5 years old. This number continues to increase from year to year (Hernawan et al., 2018). The Indonesian Central Bureau of Statistics in 2020 explained that there were around 270.2 million with a growth ratio of around 3.2 million children with autism (Central Bureau of Statistics, 2020).

The cause of autism still can not be clarified yet. However, there are several agents that are suspected to be the cause, including genetic, neuroanatomical, environmental, immune and pathological conditions, which interact and contribute in different ways and degrees to the onset and development of autism disorder (Tsopanidou and Drigas, 2022).

Modabbernia et al. (2017) mentioned several risk factors for autism are mothers experiencing obesity, diabetes, and cesarean section (C/S). Lu et al. (2022) added that environmental risk factors for maternal diabetes, polycystic ovary syndrome (PCOS), maternal depression, and prenatal exposure to organophosphate have a percentage that increases the risk of ASD by more than 50%, where maternal diabetes was 62% and PCOS by 59%.

Mothers with PCOS are considered to contribute autistic traits to their children. High prenatal testosterone levels are associated with an autistic phenotype in children of mothers with PCOS (Homburg et al., 2017). This level causes developmental changes in the brain, which involve permanent structural, epigenetic, and/ or molecular changes, such as effects on neuronal apoptosis, gene and protein expression, glial changes, and synaptic plasticity (Katsigianni et al., 2019).

In addition, about 7% of pregnant women are characterized by inadequate insulin production or indications and are diagnosed with GDM. In GDM, blood glucose levels increase to inappropriate levels (Aviel-Shekler et al., 2020). Exposure to GDM and higher maternal glucose levels were associated with more autistic traits. Intrauterine exposure to a GDM hyperglycemic environment may predispose to autistic traits even among developing children (Alves et al., 2022).

A total of 17 studies showed that mothers with GDM have a significantly increased risk of their children having ASD. The results of the study indicated an increased risk of ASD if the mother had GDM (OR = 1.59, 95% CI= 1.05 to 2.4). Although the timing of the diagnosis of GDM is uncertain, there is many evidence that a diagnosis of GDM before 30 weeks of gestation can have an impact on the outcome (Mohsen and Lauszus, 2022).

The risk of a child with ASD will be exacerbated if the mother has both PCOS and diabetes. Research conducted in the United States (US), showed a higher risk of developmental delays and neurodevelopmental disorders among children born to mothers with

PCOS, due to the potential for exposure to a hyperandrogen environment and insulin resistance in utero (Bell et al., 2018; Greger et al., 2020).

This study aims to analyze previous primary studies and assess the effect of polycystic ovarian syndrome and maternal diabetes on autism in children.

## SUBJECTS AND METHOD

### 1. Study Design

The meta-analysis was carried out with the PRISMA flowchart using Google Scholar, PubMed, ScienceDirect and Sage Journal databases. The keywords used in this study are "Polycystic Ovarian Syndrome" AND "Maternal Diabetes" OR "Gestational Diabetes Mellitus" AND "Autism" OR "Autism Spectrum Disorder" AND "Cohort".

### 2. Steps of Meta-Analysis

Meta analysis was carried out in 5 steps as follows:

1) Formulate research questions in PICO format (Population, Intervention, Comparison, Outcome).
2) Search for primary study articles from various electronic and non-electronic databases such as PubMed, ScienceDirect, Google Scholar, Scopus, and so on.
3) Perform screening to determine inclusion and exclusion criteria and carry out critical assessments
4) Extracting primary study data and synthesizing effect estimates using the RevMan 5.3 application.
5) Interpret the results and draw conclusions.

### 3. Inclusion Criteria

Full paper article with an observational cohort study, research subjects were children, the size of the relationship used was adjusted odds ratio, the research outcome was autism.

### 4. Exclusion Criteria

Statistical results are reported in the form of bivariate analysis, articles published in languages other than English.

### 5. Definition of Operational Variable

Articles in this study are adapted to PICO. In this study, the population was children, with PCOS intervention and maternal diabetes and autism as outcomes.

**Polycystic ovarian syndrome** is a hormonal imbalance accompanied by reproductive, metabolic, and psychological sequelae.

**Maternal diabetes** is hyperglycemia during pregnancy.

**Autism** is a neurodevelopmental disorder characterized by symptoms of social isolation, restricted and repetitive patterns of behavior, interests or activities that appear during the early period of child development.

### 6. Instrument of the Study

Quality assessment in this study used a critical assessment checklist from the Cohort Study Checklist published by CASP.

### 7. Data Analysis

The articles in this study were collected according to the PRISMA flowchart and analyzed using the Review Manager 5.3 application. The analysis was carried out by calculating the effect size and heterogeneity consistency value ($I^2$) of the selected research results.

## RESULT

The process of searching for articles is done through several journal databases which include PubMed, Google Scholar, Pubmed, Science Direct, and Sage Journal. The process of reviewing related articles can be seen in the PRISMA flow diagram in Figure 1.

The primary research articles originate from 3 countries, namely Europe, America and Asia. The European continent consists of England, Sweden and Denmark. The Americas consist of the Americas and the Asian continent consists of the countries of Taiwan, Israel, China (Table 2)

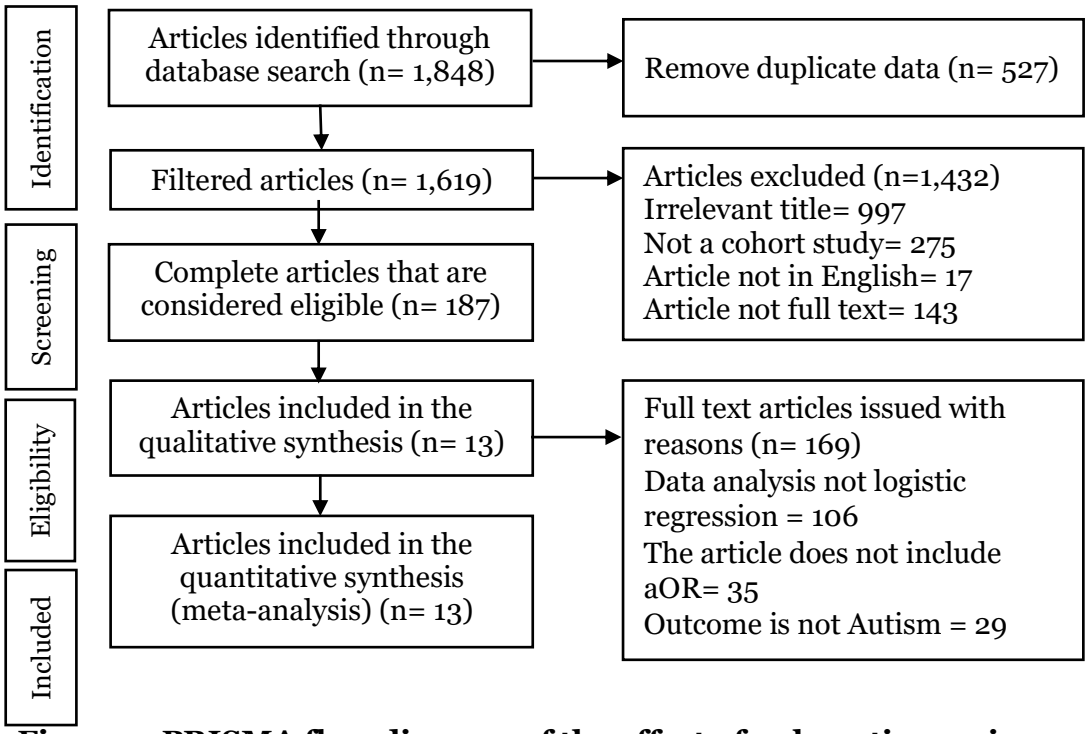


**Figure 1. PRISMA flow diagram of the effect of polycystic ovarian syndrome and maternal diabetes on autism in children**

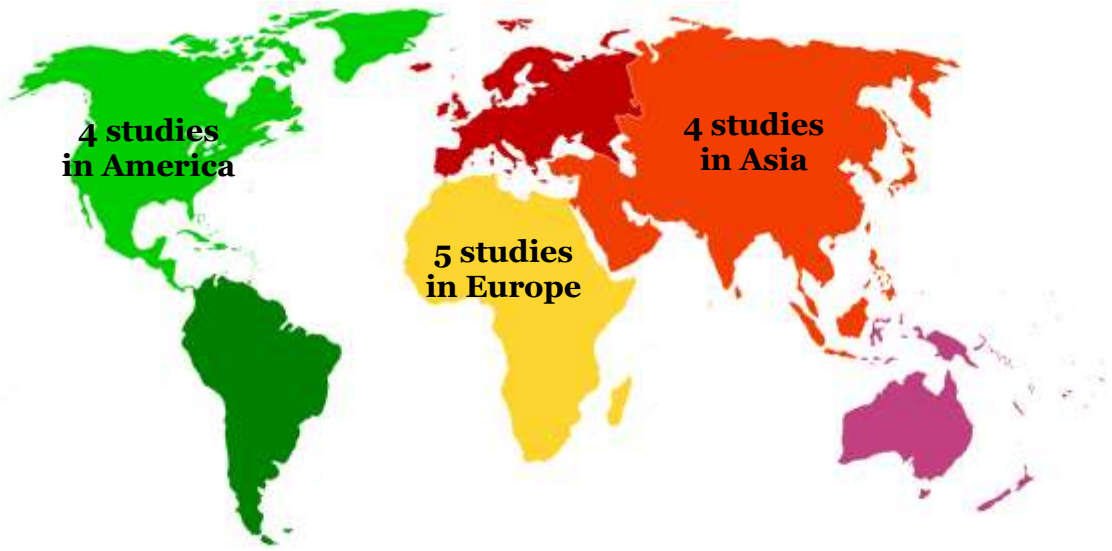


**Figure 2. Map of research areas on the effect of polycystic ovarian syndrome and maternal diabetes on autism in children**

**Table 1. Results of Cohort Study Quality Assessment of the Effect of Polycystic Ovarin Syndrome and Maternal Diabetes on Autism in Children**

| Author (Year) | Question Criteria | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Berni et al. (2018) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |

| Author (Year) | Question Criteria | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Cherskov et al. (2021) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Hisle-Gorman et al. (2018) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Kosidou et al. (2016) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Palm et al. (2022) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Rotem et al. (2021) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Schieve et al. (2018) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Carter et al. (2022) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Chang et al. (2023) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Chen et al. (2022) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Cordero et al. (2019) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Nahum Sacks et al. (2016) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |
| Zhu et al. (2021) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 24 |

All primary articles were assessed for research quality using Critical Appraisal Questions for Cohort (CASP), which are shown in Table 1. Assessment of the quality of cohort studies at CASP by answering 12 questions, including:

1. Does the cohort study clearly address the clinical problem?
2. Are the cohorts (study subjects in both exposed and unexposed groups) selected in the right way?
3. Are polycystic ovarian syndrome and maternal diabetes accurately measured to minimize bias?
4. Is the outcome (autism) accurately measured to minimize bias?
5. Does the researcher identify all important confounding factors? Does the researcher consider the confounding factors in the design and/ or analysis?
6. Do the research subjects fully complete the research time? Are the research subjects followed up for a sufficiently long time?
7. Are the results of this study reported in the OR?
8. What is the precision of the results?
9. Are the results reliable?
10. Are the results applicable to the local population?
11. Are the results of this study compatible with the available evidence?
12. What are the implications of this research for practice?

**Description of the answer score:**

0= No

1= Uncertain

2= Yes

Table 2 describes a summary of the primary research on the effect of polycystic ovarian syndrome on autism in children. A meta-analysis of 7 articles was carried out with various research locations, from Denmark, Israel, UK, US and Sweden. Similarities were found in the study, namely the cohort study design, the research subjects were children of mothers who had certain conditions during pregnancy, the intervention was pregnant women with PCOS conditions and the comparison did not experience PCOS during pregnancy. In this study there were also differences in the number of samples, the smallest was 1,538, and the highest was 437,222.

Table 3 showed that the estimated effect of each primary study that were included in this meta-analysis research was different. The primary research data that has been extracted was then carried out in a quantitative meta-analysis synthesis using

RevMan 5.3. The results of a meta-analysis of the effect of polycystic ovarian syndrome on autism in children are presented in Figure 3.

**Table 2. Summary of cohort primary study articles in the meta-analysis with each PICO (N=774,817)**

| Author (year) | Country | Sample | P | I | C | O |
|---|---|---|---|---|---|---|
| Berni et al. (2018) | UK | 16,986 | Children (2 years old) | PCOS | Not PCOS | Autism |
| Cherskov et al. (2021) | UK | 49,719 | Children (3 months) | PCOS | Not PCOS | Autism |
| Hisle-Gorman et al. (2018) | US | 35,04 | Children (2 years old) | PCOS | Not PCOS | Autism |
| Kosidou et al. (2016) | Sweden | 232,538 | Children (4 years old) | PCOS | Not PCOS | Autism |
| Palm et al. (2022) | Denmark | 1,777 | Children (3 years old) | PCOS | Not PCOS | Autism |
| Rotem et al. (2021) | Israel | 437,222 | Children (< 8 years old) | PCOS | Not PCOS | Autism |
| Schieve et al. (2018) | US | 1,538 | Children (2-5 years old) | PCOS | Not PCOS | Autism |

**Table 3. Adjusted Odds Ratio (aOR) effect of polycystic ovary syndrome on autism in children**

| Author (year) | aOR | 95% CI | |
|---|---|---|---|
| | | Lower Limit | Upper Limit |
| Berni et al. (2018) | 1.75 | 1.27 | 2.46 |
| Cherskov et al. (2021) | 1.42 | 1.09 | 1.84 |
| Hisle-Gorman et al. (2018) | 1.07 | 0.86 | 1.33 |
| Kosidou et al. (2016) | 1.26 | 0.98 | 1.61 |
| Palm et al. (2022) | 1.50 | 0.89 | 2.53 |
| Rotem et al. (2021) | 1.40 | 1.22 | 1.61 |
| Schieve et al. (2018) | 2.7 | 1.2 | 6.1 |

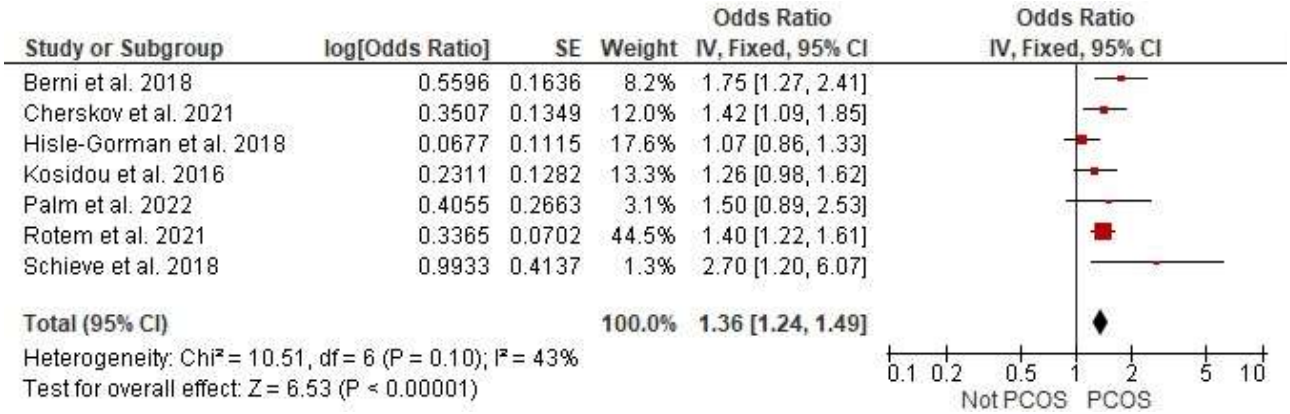


**Figure 3. Forest plot of the effect of polycystic ovary syndrome on autism in children**

Forest plot in Figure 3 shows that there was an effect of polycystic ovarian syndrome on the risk of autism in children. Children of mothers who had PCOS during pregnancy had a 1.36 times higher risk of developing autism compared to those without PCOS,

and the effect was statistically significant (aOR= 1.36; 95% CI= 1.24 to 1.49; p<0.001). The forest plot also shows heterogeneous effect estimates ($I^2$ = 42%; p=0.11). Thus, the calculation of the average effect estimate used the fixed effect model approach.

The funnel plot in Figure 4 shows an asymmetric effect distribution to the right and left of the estimated mean vertical line. The effect estimates were more distributed to the right of the vertical line than to the left, indicating publication bias. Because the distribution of effect estimates is mostly located to the right of the same vertical line as the location of the average effect estimate (diamond shape) which was also located to the right of the vertical line in the forest plot description, the publication bias tends to overestimate the true effect.

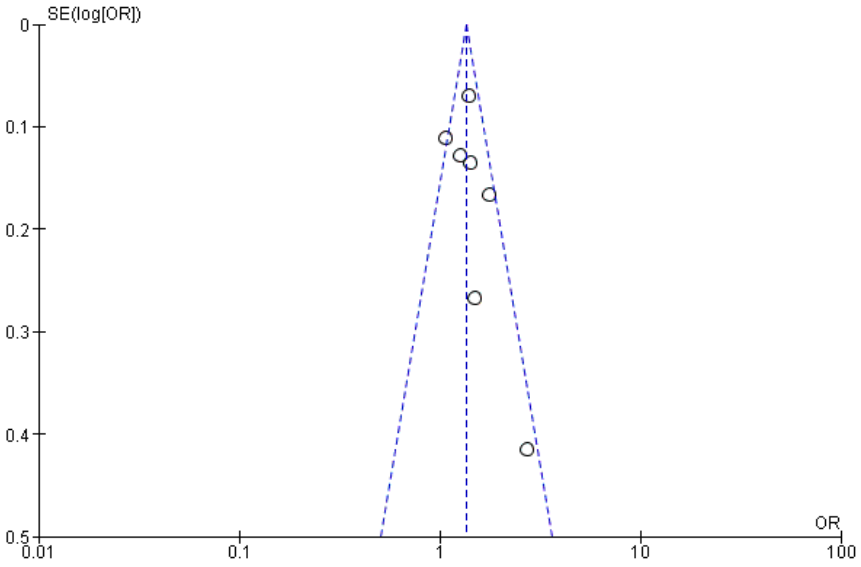


**Figure 4. Funnel plot of the effect of polycystic ovarian syndrome on autism in children**

**Table 4. Summary of cohort primary study articles in the meta-analysis with each PICO (N=3,866,666)**

| Author (year) | Country | Sample | P | I | C | O |
|---|---|---|---|---|---|---|
| Carter et al. (2022) | US | 308,536 | Children (5 years old) | Maternal diabetes | Not maternal diabetes | Autism |
| Chang et al. (2023) | Taiwan | 916,315 | Children (1-4 years old) | Maternal diabetes | Not maternal diabetes | Autism |
| Chen et al. (2022) | Sweden | 2,369,680 | Children (>1 years old) | Maternal diabetes | Not maternal diabetes | Autism |
| Cordero et al. (2019) | US | 2,564 | Children (30-68 months) | Maternal diabetes | Not maternal diabetes | Autism |
| Hisle-Gorman et al. (2018) | US | 35,040 | Children (2-18 years old) | Maternal diabetes | Not maternal diabetes | Autism |
| Nahum Sacks et al. (2016) | Israel | 231,271 | Children (> 1 years old) | Maternal diabetes | Not maternal diabetes | Autism |
| Zhu et al. | China | 3,260 | Children | Maternal | Not maternal | Autism |

| Author (year) | Country | Sample | P | I | C | O |
|---|---|---|---|---|---|---|
| (2021) | | | (18-36 months) | diabetes | diabetes | |

Table 4 described an overview of primary research on the influence of maternal diabetes on the risk of autism in children. A meta-analysis of 7 articles was carried out with various research locations, from the US, Sweden, China and Israel. Similarities were found in the study, namely the cohort study design, the research subjects were children of mothers who had certain conditions during pregnancy, the intervention was pregnant women with maternal diabetes and the comparison did not experience maternal diabetes during pregnancy. In this study there were also differences in the number of samples, the smallest was 2,198, and the highest was 2,369,680.

**Table 5. Adjusted Odds Ratio (aOR) the effect of maternal diabetes on autism in children**

| Author (year) | aOR | 95%CI | |
|---|---|---|---|
| | | Lower Limit | Upper Limit |
| Carter et al. (2022) | 1.50 | 1.28 | 1.76 |
| Chang et al. (2023) | 1.17 | 1.10 | 1.25 |
| Chen et al. (2022) | 1.35 | 1.06 | 1.72 |
| Cordero et al. (2019) | 0.95 | 0.71 | 1.27 |
| Hisle-Gorman et al. (2018) | 1.02 | 0.94 | 1.10 |
| Nahum Sacks et al. (2016) | 4.44 | 1.55 | 12.69 |
| Zhu et al. (2021) | 1.49 | 1.11 | 2.00 |

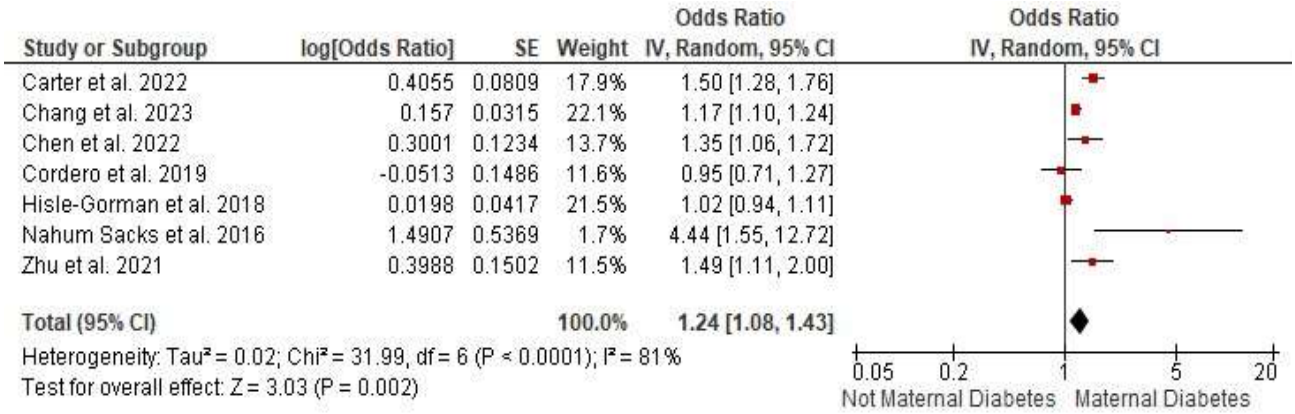


**Figure 5. Forest plot of the maternal influence of diabetes on autism in children**

Forest plot Figure 5 showed that there was an effect of maternal diabetes on the risk of autism in children. Children of mothers who experienced maternal diabetes during pregnancy had a risk of developing autism by 1.24 times higher compared to those without maternal diabetes, and the effect was statistically significant (aOR= 1.24; 95% CI= 1.08 to 1.43; p=0.002). The forest plots also showed heterogeneous effect estimates (I2 = 81%; p<0.001). Thus, the calculation of the average effect estimate used the random effect model approach.

Table 5 showed that the estimated effect of each primary study that were included in this meta-analysis study was different. The primary research data that has been extracted was then carried out in a quantitative meta-analysis synthesis using RevMan 5.3

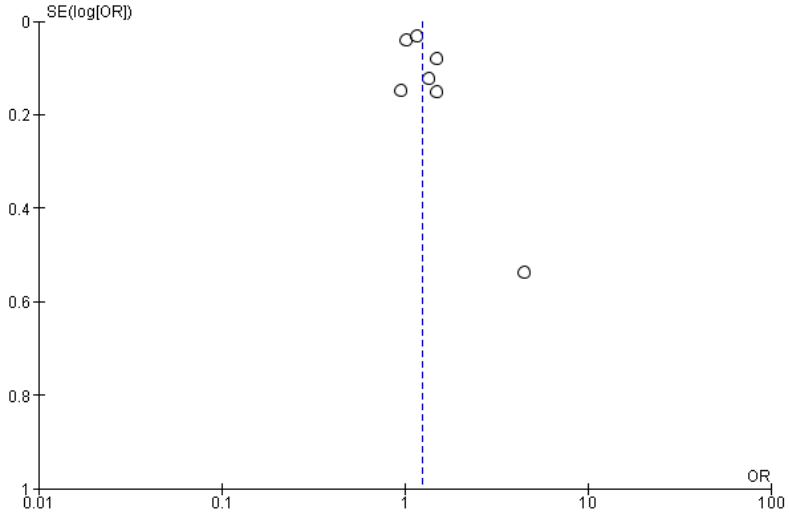


**Figure 6. Forest plot of the effect of maternal diabetes on autism in children**

The funnel plot in Figure 6 showed an asymmetric effect distribution to the right and left of the estimated mean vertical line. The effect estimates were more distributed to the right of the vertical line than to the left, indicating publication bias. Because the distribution of effect estimates is mostly located to the right of the same vertical line as the location of the average effect estimate (diamond shape) which was also located to the right of the vertical line in the forest plot description, the publication bias tend to overestimate the actual effects.

## DISCUSSION

### 1. Effect of Polycystic Ovarin Syndrome on Autism in Children

Primary research on meta-analysis of polycystic ovarian syndrome on autism in children totaled 7 primary articles originating from Denmark, Israel, UK, US and Sweden. This meta-analytic study included 774,817 children from 7 primary research cohort studies. This study was identified from 2015 to 2023 with each article having an aOR statistical outcome.

Based on the results of the analysis of 7 primary studies that were carried out systematic reviews and meta-analyses showed that heterogeneity was quite low between studies ($I^2$= 42%; p= 0.110), which means that the results of the effect estimates between these studies were high and came from different populations so that the combined effect estimates of all studies used the fixed effect model approach. This heterogeneity is based on variations or differences between study populations. In addition, the funnel plot showed that there was a publication bias.

This meta-analysis used studies that have controlled for confounding factors because they use an adjusted odds ratio (aOR) effect size in selected primary studies. This study concluded that the effect of polycystic

ovary syndrome on autism in children was 1.36 times compared to mothers who had normal pregnancies, and these results were statistically significant (aOR= 1.36; 95% CI= 1.24 to 1.49; p=0.110). This meta-analysis study provide evidence that mothers who experience PCOS during their pregnancy were at high risk of having a child with autism.

The results of this study indicate that mothers who experience PCOS during pregnancy increase the risk of their child being born with autism. In line with research conducted by Rotem et al. (2021) which stated that children of mothers with PCOS have a higher chance of ASD compared to children of mothers without PCOS (aOR = 1.42, 95% CI = 1.24 to 1.64). Chersko et al. (2021) in his study added that there is a possibility of significantly increasing the risk of children with autism, even after adjusting for the mother's psychiatric condition, obstetric complications, and the mother's metabolic condition. (aOR= 1.35; CI 95%= 1.06 to 1.60; CI 95%= 1.28 to 2.00).

In addition, the possibility of increasing the risk of children with autism can occur due to differences in gender. Palm et al. (2022) stated that for boys, the relationship between maternal PCOS and ASD traits was significant (aOR = 2.5; p= 0.009), whereas the relationship was not significant for girls. In accordance with a systematic review and meta-analysis previously reported that maternal PCOS was associated with a 66% higher incidence of childhood ASD (Katsigianni et al., 2019).

Palm et al. (2022) stated that PCOS is associated with a higher risk of early birth <37 weeks, this indicates a higher risk of placental dysfunction. In line with higher maternal testosterone levels and mothers having PCOS it is closely related to placental dysfunction (Sun et al., 2020). Placental function alters fetal testosterone exposure because placental aromatase activity protects the fetus from androgen exposure. Prenatal exposure to testosterone resulted in placental insufficiency and intrauterine growth restriction of the infant. In addition, placental tissue in women with PCOS exhibits increased steroidogenesis and a higher capacity for androgen production which may further increase androgen exposure in the fetus (Kelley et al., 2019).

**2. The Effect of Maternal Diabetes on Autism in Children**

A meta-analysis of research on the influence of maternal diabetes on autism in children resulted 7 primary articles originating from the US, Sweden, China and Israel. This meta-analytic study included 3,866,666 children from 7 primary research cohort studies. This study was identified from 2015 to 2023 with each article having an outcome statistical aOR. Based on the results of the analysis of 7 primary studies that were carried out systematic review and meta-analysis, it showed high heterogeneity between studies ($I^2$ = 81%; p <0.001), which means that the calculation of the effect estimates of all studies used the random effect model approach. This heterogeneity is based on variations or differences between study populations.

This meta-analysis uses studies that have controlled for confounding factors because they use an adjusted odds ratio (aOR) effect size. The results of this study indicate that the effect of mothers who experience maternal diabetes in pregnancy on autism in children is 1.24 times higher compared to mothers who do not experience maternal diabetes during their pregnancy (aOR= 1.24; CI 95%= 1.08 to 1.43; p=0.002)

The results of this study are in line with Zhu et al. (2021) who stated that the prevalence rate of autistic traits increased from 13.86% to 48.6% when observed among children born to mothers with GDM

(aOR= 1.49, 95% CI= 1.11 to 2.00). Carter et al. (2022) added that pregnant women with diabetes have a 1.50 chance of experiencing ASD accompanied by GID (aOR= 1.50; 95% CI= 1.28 to 1.76).

A meta-analysis of women aged <20 to 40 years old showed that the risk of GDM was linearly related to maternal age (p <0.001). For every one-year increase in maternal age from 18 years, the risk of GDM for the overall, Asian, and European population increased by 7.90%, 12.74%, and 6.52%. Subgroup analysis showed that from the age of 25 years old, Asian women had a significantly higher risk of developing GDM than European women (p<0.001) (Li et al., 2020). Pregnant women with GDM have a high risk of complications for their fetus. The reason is that mothers who experience insulin resistance make the placenta work for the fetus to be not optimal. So that the placenta will not be able to protect the baby because of fat deposits from insulin resistance (Etminan-Baksh et al., 2020).

## AUTHORS CONTRIBUTION

Laksmy Dewi Sukmakarti as the main researcher who selected topics, searched for and collected research data. Bhisma Murti and Rita Benya Adriani analyzed the data and reviewed research documents.

## FUNDING AND SPONSORSHIP

This study is self-funded.

## CONFLICT OF INTEREST

There is no conflict of interest in this study.

## ACKNOWLEDGEMENT

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