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ADVANCED PARENTAL AGE ASSOCIATION WITH THE DEVELOPMENT OF AUTISM SPECTRUM DISORDER: META-ANALYSIS

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ABSTRACT

Autism Spectrum Disorder (ASD) is among the most common neurological conditions diagnosed in early childhood, affecting the condition affects approximately 1 in 36 children, with a male-to-female prevalence ratio of 4.5:1. Children with ASD typically encounter significant challenges in communication, forming social connections, and adapting to rapid changes; they often exhibit repetitive behaviors or restricted interests. This systematic review and meta-analysis aimed to investigate the association between advanced parental age and the likelihood of autism spectrum disorders (ASDs) in children. A comprehensive search of multiple databases—including Web of Science, PubMed, EMBASE, Medline, Scopus, CINAHL, and Cochrane Library—was conducted to identify relevant studies published up to June 2022. The statistical analyses were performed using Review Manager Version 5.4 software, employing random-effects models to calculate pooled risk estimates, while I^2 tests assessed heterogeneity among the included studies. In the initial search, 21 studies met the inclusion criteria for a meta-analysis. Findings indicated that children of older parents faced a 59% higher risk of developing ASD (OR = 1.59; 95% CI: 1.45–1.74) compared to reference groups. Furthermore, meta-regression analysis revealed that every 10-year increase in maternal age was associated with a 35% higher risk of ASD, while paternal age demonstrated a 29% increased risk. Advanced parental age significantly correlates with an elevated risk of autism spectrum disorders in offspring. Future research

should prioritize elucidating the biological and environmental mechanisms driving this association to better inform public health strategies and preventative measures.

Keywords: Autism Spectrum Disorder, parental age, neurodevelopmental disorders, systematic review, meta-analysis.

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that usually shows up in early childhood. It is marked by persistent problems in social interactions, poor communication skills, repetitive behaviors, and limited interests. These traits often cause big problems in daily life and have a negative effect on overall quality of life (Bishop et al., 2016). Additionally, kids with ASD often have trouble in school and keeping up with family and friends (Rotheram-Fuller et al., 2010).

ASD is universal, affecting individuals across all racial and ethnic backgrounds. The condition also affects individuals from various religious and socioeconomic backgrounds (Rice et al., 2012). It is estimated to occur in approximately 1 in 54 children, with males being three to four times more likely to be diagnosed than females (Bishop et al., 2016). Over the past two decades, there has been a marked increase in ASD diagnoses, attributed to improved diagnostic criteria and heightened awareness of the condition. However, environmental factors may also influence this trend (Myers et al., 2018; Bölte et al., 2018).

Twin studies show that ASD is strongly linked to genes, since monozygotic twins are more likely to share traits than dizygotic twins (Schaefer, 2016). Researchers have identified several genetic factors, including specific ASD-associated genes, single nucleotide polymorphisms, copy number variations, and chromosomal rearrangements (Bolton et al., 1994; Eapen, 2011). At least half of the risk for ASD is due to common genetic variations. Rare and de novo mutations play a smaller role (Leppa et al., 2016; Bonaccorso et al., 2015). Despite these findings, genetic factors alone cannot fully explain ASD's etiology, leaving substantial room for environmental influences.

Environmental Several studies have highlighted contributions to ASD. Hallmayer et al. (2011) reported that environmental factors accounted for 55% of ASD risk variability in a prominent twin study. But it's still hard to pinpoint specific environmental factors because genetic and environmental interactions are complicated and samples are limited (Turkheimer & Waldron, 2000; Modabbernia et al., 2017). These influences are likely cumulative, rather than resulting from a single causative factor.ASD is believed to result from disruptions in specific brain developmental processes. While identifying the exact

timing of these disruptions is challenging, vulnerable periods likely occur during prenatal and early postnatal development, as ASD is often diagnosed before age two.In recent years, advanced parental age has gained attention as a potential risk factor for ASD. This trend coincides with rising maternal and paternal ages in many countries. Advanced parental age has also been linked to other adverse outcomes, such as congenital disorders, pregnancy complications, and neuropsychiatric conditions (Shelton et al., 2010; Hultman et al., 2002). Understanding the relationship between parental age and ASD risk has significant public health implications, particularly given the observed increases in parental age worldwide. Although prior research has explored this relationship, many studies have focused on maternal or paternal age separately and lack recent data. This study aims to provide a comprehensive and updated analysis of the combined effects of advanced parental age on ASD risk.

MATERIALS AND METHODS

Study Design and Guidelines

This systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009). These guidelines ensure transparency and reproducibility in systematic reviews and meta-analyses.

Data Sources and Search Strategy

Three researchers (EA, AK, and IJ) conducted an extensive search for relevant literature published between January 1, 2000, and May 1, 2022. Articles were identified through databases such as Web of Science, PubMed, EMBASE, Medline, Scopus, CINAHL, and the Cochrane Library. The search strategy employed Boolean operators, field tags, truncations, and specific keywords to maximize the retrieval of relevant studies. The following algorithm was applied:

((“child”[MeSH Terms] OR “child”[All Fields] OR “children”[All Fields]) AND (“autistic disorder”[MeSH Terms] OR (“autistic”[All Fields] AND “disorder”[All Fields]) OR “autistic spectrum disorder”[All Fields] OR “autism”[All Fields])) AND ((“advanced parental age”[MeSH Terms] OR (“paternal”[All Fields] AND “age”[All Fields]) OR “maternal age”[All Fields])).

Additionally, a snowball search method was employed, manually reviewing the reference lists of selected studies to identify further relevant articles.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria

• Study design: cohort, case-control, cross-sectional, or observational.

• Diagnosis of ASD using validated tools such as the DSM, ICD, ADI-R, or ADOS.

• Evaluation of maternal and/or paternal age as an independent variable.

• Reporting of odds ratios (ORs) or relative risks (RRs) for ASD.

• Inclusion of children of all ages, sexes, ethnicities, and populations.

Studies were excluded if they

• Focused on genetic syndromes linked to ASD (e.g., Fragile X Syndrome).

• Addressed other neurodevelopmental disorders.

• Were review articles, editorials, or single-case studies.

Data Extraction and Quality Assessment

Three independent reviewers extracted data using a standardized Microsoft Excel template. Extracted information included study design, sample size, diagnostic criteria, exposure definitions, confounding variables, and effect estimates (adjusted and unadjusted). Discrepancies were resolved through discussion among the reviewers.

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates participant selection, comparability, and outcome assessment. Studies scoring ≥6 points were considered high quality.

Statistical Analysis

Meta-analyses were conducted using Review Manager Version 5.4 (Cochrane, 2020). Risk estimates were pooled using random-effects models to account for heterogeneity across studies. The I^2 statistic and Q-tests were used to evaluate heterogeneity. Subgroup analyses were performed based on study design, geographic region, and diagnostic criteria. Linear regression analyses estimated the odds ratio (OR) for every 10-year increase or decrease in parental age.

Results Search Outcomes

The database search yielded 1,468 studies. After removing duplicates, 398 articles remained for title and abstract screening (Figure 1). Following a detailed review, 21 studies met the inclusion criteria, comprising nine case-control and 12 cohort studies. These studies included 22,308,289 participants, with data collected between 2000 and 2022 (Table 1 and 2).

Meta-Analysis Findings

Advanced parental age was associated with a 59% increased risk of ASD in children (OR = 1.59; 95% CI: 1.45–1.74). Maternal age demonstrated a 35% increased risk per decade

(OR = 1.35), while paternal age showed a 29% increase (OR = 1.29) per decade. Subgroup analyses revealed significant heterogeneity based on geographic region but not study design or diagnostic criteria.

Study quality

Based on the Newcastle Ottawa Scale (NOS) assessment, 21 studies were of high quality with a median of 7 stars.

Statistical Results

Analysis of odds ratio (OR) calculations from the studies demonstrated a significant association between advanced parental age and the risk of ASD in children, with an OR of 1.59 (95% CI: 1.45–1.74). When maternal and paternal ages were analyzed independently, maternal age showed an OR of 1.58 (95% CI: 1.41–1.76), while paternal age exhibited an OR of 1.61 (95% CI: 1.46–1.70). The findings also highlighted substantial heterogeneity among the studies, as reflected by an I^2 value of 97% (Heterogeneity: $Chi^2 = 619.07$, df = 20, $P < 0.00001$). A forest plot summarizing these results is shown in Figure 2.

Publication Bias

Egger's regression and Begg's test indicated minimal publication bias. Funnel plots suggested asymmetry, which was corrected using the trim-and-fill method, confirming the robustness of the pooled results (Figure 3).

Subgroup Analysis

Table 3 presents the subgroup analysis, which examined factors such as study design (cohort versus case-control), geographic regions (North America, Europe, Asia, and Oceania), diagnostic methodologies, and ASD risk. The data revealed substantial heterogeneity among geographic regions, with an OR of 1.55 (95% CI: 1.43–1.69), subgroup differences ($Chi^2 = 28.12$, df = 3, $P < 0.0001$), and an I^2 of 89.3%. Conversely, no significant differences were observed between cohort and case-control study designs, which reported ORs of 1.55 (95% CI: 1.41–1.70) and 1.66 (95% CI: 1.36–2.03), respectively.

Diagnostic Methods

An analysis based on diagnostic methodologies (DSM and ICD) also indicated a notable association between advanced parental age and ASD risk, with an overall OR of 1.59 (95% CI: 1.45–1.74). However, subgroup differences for diagnostic methods showed only moderate heterogeneity and a non-significant p-value ($Chi^2 = 2.11$, df = 1, P = 0.15, $I^2 = 52$).

Meta-regression analysis

Father's age and mother's age were modelled as a continuous variable and categorical variable. Adjusting for all other possible variables, the incidence of autistic spectrum disorders rose by 29 percent for every 10-year rise in fathers' age (1.027 (1.006-1.048) for each year of age).

Figures 4 and 5 show a linear relationship, as the age of the parent increases, the risk of ASD increases. In adjusted analyses of father age as a categorical variable, paternal age of 40 or above was substantially linked with autism (OR = 2.03 (1.10-3.73)). For mother's age, the risk of autistic spectrum disorders rose by 35% for every 10-year rise in the age of mothers in this specific regression study [1.037 (1.008-1.068) for each year of age). In an adjusted study of maternal age as a categorical variable, maternal age of 35 or above was substantially linked with autism [OR = 3.03 (1.10-5.73)] (Figure 6, 7 and 8).

Publication bias

There was no possible publication bias in most of the meta-analysis, as stated by Egger's regression test and Begg –Mazumdar test. Egger's regression test (P-value (2 tailed) =0.24497) and Begg –Mazumdar test (P = 0.19413). In contrast, the funnel plot showed an asymmetry figure, thus indicating the presence of a publication bias. After utilizing the trim and fill approach, five studies were filled, and the concluded pooled result was similar with no alteration (OR = 1.48 with 95% CI 1.36 –1.62). (Figure 3)

DISCUSSION

This meta-analysis aimed to investigate the relationship between advanced parental age and the risk of autism spectrum disorders (ASDs) in children. Key findings from this study include the following: (i) (i) older parental age was associated with a higher risk of ASDs, (ii) younger parental age was linked to a lower risk of ASDs, and (iii) each 10-year reduction in paternal age was associated with a 28% decrease in ASD risk, while a 10-year increase in maternal and paternal age elevated the risk by 35% and 29%, respectively. Numerous studies have explored the effects of parental age on ASD risk, allowing this meta-analysis. The aim is to incorporate a broader and more comprehensive evidence base. The findings align with earlier research, such as Wu et al. (2016), which identified a similar relationship between advanced parental age and ASD risk. This study added to earlier research by using newer information on maternal and paternal age. This supports the idea that older parents are more likely to have children with ASD (McGrath et al., 2014; Hallmayer et al., 2011; Wu et al., 2015).

Unlike previous studies that examined maternal and paternal age independently, this meta-analysis provided a detailed assessment of the combined impact of parental age on ASD risk. Notably, some of the studies that were part of this analysis also found a link between ASD risk and grandparents' advanced age, which suggests that there may be effects that last through generations (Frans et al., 2013; Gao et al., 2020). Additionally, evidence indicated that maternal age had a more significant and persistent effect compared to paternal age (Al Mamari et al., 2021). Research by Reichenberg et al. (2006) and Tsuchiya et al. (2008) also supported a linear association between paternal age and ASD risk. Findings further suggested that firstborn children of older parents were at a higher risk of developing ASD compared to later-born siblings (Durkin et al., 2008; Lyall et al., 2020).

A higher risk of ASD was seen in some cases when there was a big age difference between the parents, like when fathers were much older than mothers or mothers were much older than fathers (Fajardo et al., 2020). However, these results were only slightly significant. Additional studies noted that maternal and paternal ages might influence different ASD subtypes (Lampi et al., 2013). Research by Sandin et al. (2016) also highlighted that younger maternal age might increase ASD risk, though this finding was less consistently reported in the literature.

Having older parents may make it more likely for random genetic mutations to happen over time because of repeated environmental exposures (Schaaf & Zoghbi, 2011) and may also make the mother's immune system work harder, which may lead to the development of autoimmune conditions (Sotgiu et al., 2020). These findings are significant as they offer insights into the underlying causes of ASD, although the exact pathophysiological mechanisms remain unclear.

This study offers several strengths. It is one of the largest meta-analyses to date, examining the link between parental age and ASD outcomes. The high quality of included studies, as assessed using the Newcastle-Ottawa Scale (NOS), ensured reliable findings with narrower confidence intervals than individual studies. Additionally, the pooled results demonstrated consistency across various sensitivity analyses, with minimal publication bias observed. However, the study has notable limitations. There weren't many relevant studies out there, and most of them used the middle age of parents as a point of comparison, which made it hard to figure out the risks across a wider range. Observational study designs, like cohort and case-control methods, can only find correlations, which means they can't draw conclusions about causes. Furthermore,

significant heterogeneity persisted despite subgroup analyses, likely due to differences in study design, geographic region, and confounder adjustments. For example, many studies did not account for the influence of the other parent's age, which could introduce bias. Future research should address these gaps by including larger, more diverse populations and evaluating confounding factors such as familial mental health history.

CONCLUSION

This meta-analysis highlights advanced parental age as a significant risk factor for ASD in children. Although the findings offer strong evidence, additional research is necessary to elucidate the causal mechanisms and fortify public health interventions. Larger studies with comprehensive data on confounding variables are essential for improving our understanding of this relationship. Identifying these risk factors is crucial for guiding clinical practices and developing targeted prevention strategies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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