

Association with Maternal Age and Autism Spectrum Disorder in Pediatrics: A Systematic Review

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Abstract

Objectives: To comprehensively evaluate the existing literature on the relationship between maternal age and the development of ASD, focusing on potential biological, genetic, and social factors contributing to this association.

Methods: Electronic databases including PubMed, Science Direct, Cochrane Library, and Scopus were thoroughly searched. Qualifying papers were assessed and data was extracted by two impartial reviewers.

Results: Our data consists of eight studies with 2765 children, 1968 (71.2%) of whom were males. The results from various studies exploring the association between maternal age and ASD demonstrate mixed findings. In some studies, no significant association was found between maternal age and the incidence of ASD. However, several other studies reported a significant correlation between advanced maternal age and ASD.

Conclusion: This systematic study concludes by highlighting the strong correlation between older mothers and a higher risk of autism spectrum disorder in their offspring. The overwhelming body of data suggests that mothers 35 years of age or older may be at risk, even if certain studies did not find any discernible correlation. Subsequent investigations ought to concentrate on identifying the biological pathways and examining the impact of additional elements that could potentially contribute to this correlation.

Keywords: Autism spectrum disorder; Advanced age; Maternal age; Risk factors; Systematic review.

Introduction

ASD is a neurodevelopmental disease that affects how a person perceives and interacts with other people, making communication and social interaction difficult [1]. ASD is classified as a neurodevelopmental disease by the Centers for Disease Control and Prevention (CDC) [2]. It is believed to be brought on by differences in the brain. Individuals with ASD frequently have repetitive or restricted interests and activities, as well as difficulty communicating and interacting with others. Additionally, there can be variations in the approaches used by people with ASD to movement, learning, and attention [2].

ASD is more prevalent in men and prematurely born children, and there is a strong genetic association between it and the fragile X disease [3]. Between the ages of 18 and 24 months, early childhood is when ASD is frequently diagnosed, and with time, this prevalence has increased. Globally, the percentage of new and old cases with ASD increased from 0.62% to 1.0% between 2012 and 2021 [4].

Genetic factors are the main focus of most credible neurodevelopmental hypotheses of autism [5]. Nonetheless, there is proof that environmental exposures, prenatal or perinatal events, and/or nonheritable factors may also play a major etiological role [6]. There are two primary reasons to investigate the connection between autism and older mothers. First, a correlation between autism and mother's age may offer insights into the molecular mechanisms underlying the condition. Increased frequencies of chromosomal abnormalities have been linked to older maternal ages [7]. Additionally, older moms are more likely to experience problems during childbirth, maybe as a result of uterine muscle weakness and a declining blood supply with age [8, 9].

A complicated neurodevelopmental disorder known as ASD is characterized by confined, repetitive activities and difficulties in social communication. There are many contributing factors to the genesis of ASD, including environmental and genetic factors. Maternal age has become known as a potential risk factor for ASD among environmental factors; research indicates that children born to older moms have a higher prevalence of ASD. Although the exact biological reasons causing this relationship are unknown, they could include problems connected to pregnancy, epigenetic modifications, and genetic abnormalities. Comprehending the correlation between maternal age and ASD is essential for prompt identification and risk assessment in pediatrics, particularly in demographics where postponed parenthood is becoming prevalent. In order to fully assess the body of research on the connection between mother age and the onset of ASD, this systematic review concentrates on the possible biological, genetic, and social variables that may play a role in this link.

Methods

For the purpose of conducting this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] were followed. Among other bibliographic databases, we used PubMed, Web of Science, SCOPUS, Cochrane Library, and Science Direct in our comprehensive electronic search. English-language research on the association between maternal age and ASD was the focus of our search approach. The following keywords were used; “Maternal age,” “paternal age,” “Autism spectrum disorder,” and “behavioral disorders.” To guarantee a comprehensive search, we employed pertinent terms associated with both maternal age and ASD. Two unbiased reviewers selected papers that satisfied the inclusion criteria, removed data, and utilized reliable assessment tools to rate the methodological quality of the included research in order to maintain their objectivity.

Eligibility Criteria

Inclusion criteria:

- Studies that investigate the association between maternal age and ASD.
- Studies that included the pediatric ASD population.
- Studies included children only (<18 years).
- Only studies written in English.
- Randomized controlled trials (RCTs), observational studies, cohort studies (retrospective and prospective), case-control studies, or cross-sectional studies.

Exclusion criteria:

- Studies that do not focus on the association between maternal age and ASD.
- Studies written in languages other than English.

- Case studies, opinions, comments, letters, reviews that do not include original research, and abstracts from conferences.

Data Extraction

Using pre-established inclusion and exclusion criteria, titles and abstracts discovered through the search were vetted for accuracy and consistency in screening, as well as relevance to the study question. Rayyan (QCRI) [11] and other reference management tools were used to encourage efficient screening and reduce bias. Both reviewers proceeded to a full-text inspection of research that they both felt was relevant. All disagreements about inclusion were resolved through discussion and consensus. Using a standardized data extraction form, important data from the included studies was retrieved, including titles, authors, publication year, research setting, participant demographics (age and gender distribution), ASD diagnostic tool, mean maternal age, and primary outcomes. Furthermore, the included studies' risk of bias was evaluated by the use of a known tool for methodological quality assessment.

Data Synthesis Strategy

To give a qualitative summary of the research findings and components, summary tables were created using data from pertinent studies. Following the completion of data collection for the systematic review, the appropriate use of the data from the included studies was decided.

Risk of Bias Assessment

The Joanna Briggs Institute (JBI) [12] critical evaluation criteria for studies reporting prevalence data were used to evaluate the study's quality. This is a nine-question tool where a positive response is worth one point, while a negative, unclear, or irrelevant response is worth zero points. Less than 4, 5 to 7, and 8 or more will be classified as poor quality, moderate quality, and excellent quality, respectively. Researchers evaluated the study's quality independently, and disagreements were settled through conversation.

Results

Search results

An extensive search turned up 714 study publications after 411 duplicates were eliminated. 244 papers were rejected after 303 studies' titles and abstracts were examined. There were four missing reports out of the 59 that needed to be collected. Out of the 55 papers that were screened for full-text review, 31 had improper study findings, 12 had erroneous population types, 2 had abstracts, and 3 had editor's letters. According to the qualifying criteria, eight research publications were included in this systematic review. An overview of the methodology used to choose the study is shown in **Figure 1**.

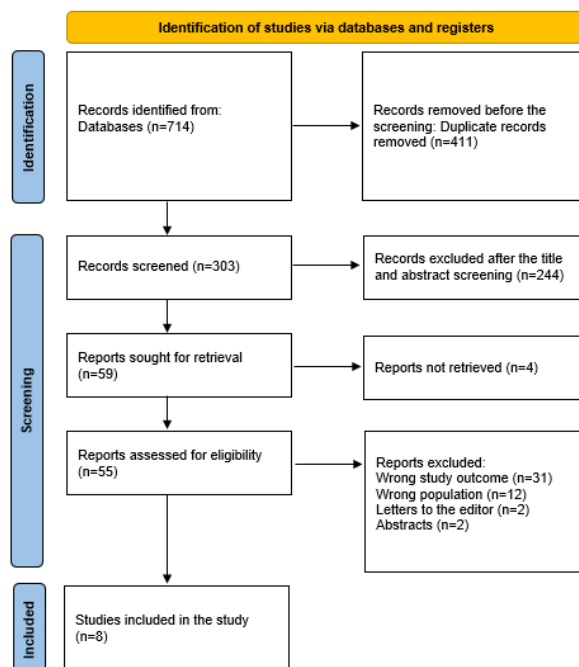


Figure 1: A PRISMA diagram summarizes the decision-making process used in the study.

Sociodemographic parameters of the researched subjects

Table 1 illustrates the demographic data from the research articles. Our data consists of eight studies with 2765 children, 1968 (71.2%) of whom were males. Five studies were case-controls [15, 16, 17, 18, 20], two were cross-sectionals [13, 19], and one was a retrospective cohort [14]. Three studies were conducted in the USA [16, 17, 8], one in Bangladesh [13], one in Canada [14], one in Finland [15], one in Saudi Arabia [19], and one in Iran [20].

Clinical outcomes

The clinical parameters are displayed in **Table (2)**. The results from various studies exploring the association between maternal age and ASD demonstrate mixed findings. In some studies, no significant association was found between maternal age and the incidence of ASD [13, 19]. For instance, in one study, maternal age was not significantly associated with ASD incidence, with a p-value of 0.678 [13], indicating that maternal age may not be a contributing factor in certain populations.

However, several other studies reported a significant correlation between advanced maternal age and ASD. One study found that ASD was significantly correlated with maternal age at delivery of 35 years or older, with an odds ratio (OR) of 2.22 and a 95% CI of 1.08 to 4.57. Another study also reported a significant correlation between higher maternal age at delivery (mean age 30.2 ± 5.4) and ASD, with a p-value of less than 0.001 [14, 17, 18, 20].

Additional findings indicated that the risk of ASD rose sharply with increasing maternal age, particularly when using maternal age under 25 as a reference. In this study, the OR for ASD increased for maternal age categories of 25–29, 30–34, 35–39, and 40 years or older, with OR values ranging from 3.39 to 13.13 [16]. This suggests a clear trend toward higher ASD risk with advancing maternal age.

Table 1: Sociodemographic variables of the interested populations.

Study ID	Study design	Country	Participants	Mean age	Males (%)
Faruk et al., 2023 [13]	Cross-sectional	Bangladesh	404	2 to 18	221 (54.7%)
Busque et al., 2022 [14]	Retrospective cohort	Canada	47	NM	36 (77%)
Cheslack-Postava et al., 2021 [15]	Case-control	Finland	962	NM	760 (79%)
Al-Mamari et al., 2021 [16]	Case-control	USA	278	0 to >7	213 (76.6%)
Saroukhani et al., 2020 [17]	Case-control	USA	343	61 ± 19.6 (months)	282 (82.2%)
Lyall et al., 2020 [18]	Case-control	USA	397	NM	249 (62.7%)
Khalil et al., 2020 [19]	Cross-sectional	Saudi Arabia	134	NM	101 (75.4%)
Jenabi et al., 2020 [20]	Case-control	Iran	200	NM	106 (53%)

Table (2): Clinical and epidemiological outcomes.

Study ID	ASD diagnostic tool	Mean maternal age	Main outcomes	JBI
Faruk et al., 2023 [13]	CARSc	NM	Maternal age was not significantly associated with the incidence of ASD (P=0.678)	Moderate
Busque et al., 2022 [14]	ADOS, ADOS-2	34 ± 8	ASD was significantly correlated with maternal age ≥35 years at delivery (aOR 2.22, 95% CI 1.08 to 4.57).	Moderate
Cheslack-Postava et al., 2021 [15]	FIPS-A	30.2 ± 5.4	ASD was significantly correlated with higher maternal age at delivery (<0.001)	Moderate
Al-Mamari et al., 2021 [16]	ADI-R & ADOS-R	NM	Utilizing age <25 as a reference, the OR of maternal age as a risk for ASD rose sharply with increasing age category (OR = 3.39 and 13.13 for those aged 25–29, 30-34, 35–39, and ≥40 years, correspondingly).	High
Saroukhani et al., 2020 [17]	ADOS-2	NM	ASD was significantly correlated with maternal age ≥35 years at delivery (P=0.012).	Moderate
Lyall et al., 2020 [18]	NM	34.2 ± 4.4	ASD was significantly correlated with maternal age ≥35 years at delivery	Moderate
Khalil et al., 2020 [19]	QEESI	27.6 ± 6.1	Maternal age was not significantly associated with the incidence of ASD (P=0.621)	Moderate
Jenabi et al., 2020 [20]	ADI-R	NM	ASD was significantly correlated with maternal age ≥35 years at delivery (P=0.049).	Low

*NM=Not-mentioned

*CARSc=Assessment of childhood autism rating score, ADOS, ADOS-2=The Autism Diagnostic Observation Schedule, FIPS-A=Finnish Prenatal Study of Autism, ADI™-R =Autism Diagnostic Interview-Revised, ADOS™-2=the Autism Diagnostic Observation Schedule, Second Edition, QEESI=The Quick Environmental Exposure and Sensitivity Inventory, and ADI-R=autism diagnostic interviewrevised

Discussion

The results from various studies in this review exploring the association between maternal age and ASD demonstrate mixed findings. In some studies, no significant association was found between maternal age and the incidence of ASD [13, 19]. For instance, in one study, maternal age was not significantly associated with ASD incidence, with a p-value of 0.678 [13], indicating that maternal age may not be a contributing factor in certain populations. However, several other studies reported a significant correlation between advanced maternal age and ASD. One study found that ASD was significantly correlated with maternal age at delivery of 35 years or older, with an odds ratio (OR) of 2.22 and a 95% CI of 1.08 to 4.57. Another study also reported a significant correlation between higher maternal age at delivery (mean age 30.2 ± 5.4) and ASD, with a p-value of less than 0.001 [14, 17, 18, 20].

Sandin *et al.* reported that their meta-analysis corroborates the notion that an increasing mother's age increases her child's chance of autism. With an increasing mother's age, the RR rose monotonically [21]. Higher mother age was independently correlated with autism, and this link held true even after controlling for the effects of paternal age and other potential confounders [22]. A well-established component of the risk for chromosomal abnormalities such as Down syndrome and neurodevelopmental disorders like ASD, ADHD, and schizophrenia is the result of older parents [23]. A growing body of research indicates that mother exposure to a variety of environmental contaminants as she ages results in DNA damage, hypermethylation, and germline mutations that may be the cause of ASD in the offspring [24]. ASD is highly predisposed genetically, mostly as a result of X chromosomal mutations that may be inherited from one generation to the next [25].

These results emphasize the need of taking mother age into account as a potential risk factor for ASD during prenatal consultations from a therapeutic standpoint. Healthcare professionals should talk to older expecting mothers—especially those 35 years of age and older—about the possible elevated risk of neurodevelopmental problems in their offspring. In order to enable prompt intervention and management, early screening and careful observation of neurodevelopmental markers in children born to older moms may aid in the early discovery of ASD. In addition, it is imperative for healthcare institutions to establish protocols tailored to the distinct requirements of this demographic, encompassing improved prenatal care and genetic counseling.

Limitations

Another limitation is the potential for unaccounted confounding variables, such as paternal age, genetic predisposition, socioeconomic status, and environmental exposures, which were not uniformly controlled for across studies. These factors could influence both maternal age and the risk of ASD, potentially confounding the observed associations. Moreover, not all studies included information on important modifiers like maternal health status or access to prenatal care, which might further influence the relationship between maternal age and ASD.

Another drawback is the possibility of unrecognized confounding factors, which were not consistently controlled for in different research, such as paternal age, genetic predisposition, socioeconomic status, and environmental exposures. These variables may affect the risk of ASD as well as maternal age, which could skew the results. Furthermore, not all studies reported on significant moderators that could further affect the association between mother age and ASD, such as maternal health status or access to prenatal treatment.

Conclusion

This systematic study concludes by highlighting the strong correlation between older mothers and a higher risk of autism spectrum disorder in their offspring. The overwhelming body of data

suggests that mothers 35 years of age or older may be at risk, even if certain studies did not find any discernible correlation. Subsequent investigations ought to concentrate on identifying the biological pathways and examining the impact of additional elements that could potentially contribute to this correlation. Clinically speaking, early screening techniques and risk assessments for ASD that take the mother's age into account will benefit at-risk children's results. The multifaceted relationship between ASD and maternal age can help healthcare systems better serve pregnant moms and encourage early detection and intervention techniques.

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