T.C.

BIRUNI UNIVERSITY

INSTITUTE OF GRADUATE EDUCATION

DEPARTMENT OF MOLECULAR AND MEDICAL GENETICS

MOLECULAR AND MEDICAL GENETICS GRADUATE PROGRAM

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

Iman ALI JAMA

SUPERVISOR

Asst. Prof. Dr. Elif Sibel ASLAN

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DECLARATION

I declare that I have written and conducted this meta-analysis thesis entitled "Advanced Parental Age Association With The Development Of Autism Spectrum Disorder In Children". I have no unethical behavior at all stages and have obtained all the information contained in this thesis under academic and ethical rules. All the information I have used from secondary literature has been respectively referenced. I also declare that I have not violated any patents and copyrights during the preparation and writing of this thesis.

Iman Ali Jama

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Iman Ali Jama

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ABSTRACT

Background

Autism Spectrum Disorder (ASD) is one of the most frequent neurological conditions in infancy, afflicting about 1 in 36 children, with a male-to-female ratio of 4:5:1. Children with autism spectrum disorder often struggle with communication, social relationships, and adjusting to rapid changes. In addition to confined repetitive modes of behavior, pursuits, or activities. This systematic review and meta-analysis explore the link between advanced parental age risk factors and the development of autism spectrum disorders (ASDs) in youngsters.

Methods

The search cross-referenced multiple databases including Web of Science, PubMed, EMBASE, Medline, Scopus, CINAHL and Cochrane Library to find relevant studies to incorporate in this review and meta-analysis until June 2022. Data was pulled focusing on (i) bibliographic information (ii) research design (iii) sample size, (iv) exposure and outcomes analytic technique and definitions, (v) risk of bias assessments, (vi) effect estimates (adjusted and unadjusted), (vii) confounding variables. Statistical analysis was performed on Review Manager Version 5.4 to compute the effect sizes of the risk in the form of an odds ratio at a 95% confidence interval.

Results

The search yielded twenty-one studies that were included in the meta-analysis. Advanced parental age compared to the reference points was associated with a 59% surge in the development of risk of autism spectrum disorders in children OR (odds ratio) = 1.59 with 95% CI (1.45-1.74). Meta-regression analysis demonstrated that an increase of 10 years in maternal and paternal age was associated with a 35% and 29% higher risk of autism respectively.

Interpretation

Advanced parental age was associated with the development of autism spectrum disorder in children. More mechanistic studies are required to further clarify this positive association.

ÖZET

Otizm Spektrum Bozukluğu (ASD) bebeklik döneminde en sık görülen nörolojik durumlardan biridir ve 36 çocuktan yaklaşık 1'ini etkiler ve erkek / kadın oranı 4: 5: 1'dir. Otizm spektrum bozukluğu olan çocuklar genellikle iletişim, sosyal ilişkiler ve hızlı değişikliklere uyum sağlamakla mücadele ederler. Sınırlı tekrarlayan davranış biçimlerine, arayışlara veya faaliyetlere ek olarak. Bu sistematik inceleme ve meta-analiz, ileri ebeveyn yaş risk faktörleri ile gençlerde otizm spektrum bozukluklarının (ASD'lerin) gelişimi arasındaki bağlantıyı araştırmaktadır.

Metodoloji

Arama, Haziran 2022'ye kadar bu inceleme ve meta-analize dahil edilecek ilgili çalışmaları bulmak için Web of Science, PubMed, EMBASE, Medline, Scopus, CINAHL ve Cochrane Kütüphanesi dahil olmak üzere birden fazla veritabanına çapraz referans verdi. Veriler (i) bibliyografik bilgiler (ii) araştırma tasarımı (iii) örneklem büyüklüğü, (iv) maruz kalma ve sonuçlar analitik teknik ve tanımları, (v) önyargı değerlendirme riski, (vi) etki tahminleri (düzeltilmiş ve düzeltilmemiş), (vii) karıştırıcı değişkenler üzerinde durularak çekilmiştir. Riskin oran oranı biçimindeki etki büyüklüklerini %95 güven aralığında hesaplamak için Review Manager Sürüm 5.4 üzerinde istatistiksel analiz yapıldı.

Sonuçlar

Araştırma, meta-analize dahil edilen on dört çalışma vermiştir. Referans noktalarına göre ileri ebeveyn yaşı, çocuklarda otizm spektrum bozukluğu riskinin gelişiminde% 59'lık bir artış VEYA% 95 CI (1.45-1.74) ile (odds oranı) = 1.59 ile ilişkiliydi. Meta-regresyon analizi, anne ve baba yaşlarında 10 yıllık bir artışın% 35 ve% 29 daha yüksek otizm riski ile ilişkili olduğunu göstermiştir.

Yorumlama

İleri ebeveyn yaşı, çocuklarda otizm spektrum bozukluğunun gelişimi ile ilişkiliydi. Daha mekanistik çalışmalar bu konuyu daha anlaşılır kılmak pozitif Birliği için gereklidir.

1 INTRODUCTION

1.1 Background

Autism spectrum disease (ASD) is a neurocognitive illness that displays itself early stages of life through difficulties with socialization, effective communication, recurring limiting tendencies, and limited interests, culminating in significant complications in key life domains and decreased standard of living (Bishop et al., 2016). In addition to that, autism spectrum disorder in youngsters commonly leads to friends, family relations, and academic success problems (Rotheram-Fuller et al., 2010). Disorders impeding the central nervous system's architecture, cell differentiation, and operation, together known as "neurodevelopmental disorders," afflict a sizable percentage of the general population (10–15 percent) (Boyle, 2011). The neurological anomalies linked with ASD include numerous impacts on brain function (e.g., cognitive control, social cognition, and top-down reasoning) (Maximo et al., 2014), the social brain, and other neural structures (Misra, 2014). ASD also significantly impacts other critical physiological systems, including the endocrine (Rossignol et al., 2011), immune (Meltzer et al., 2016), and gut microbiota systems (Fattorusso et al., 2019). Moreover, observable symptoms of ASD often begin at the age of six months, develop in the second or third year of the infant's life, and are likely to persist a lifetime (Lord et al., 2018).

In some cases, individuals with ASD may not develop any observable symptoms. Still, they may begin to socially disengage and lose previously taught linguistic and cognitive abilities between 1 and 3 years (Jones et al., 2014). In affected children, the disorder manifests itself in a variety of ways (Ogundele & Micheal, 2018). These children share several symptoms, such as difficulty recognizing social cues, verbal communication and language comprehension limits, repetitive habits or interests, and problems managing emotions (Ogundele & Micheal, 2018). However, all the features that comprise an ASD diagnosis are pervading and broad, resulting in ASD groups that are physiologically and neurologically heterogeneous, with a wide range of underlying biological sub-phenotypes (Masi et al., 2017). Additionally, ASD as

a psychiatric condition has been questioned as society perspectives have evolved, tolerance for neurodiversity has increased, and the relevance of environmental variables supporting the disorder has been recognized (Kapp et al., 2013).

The major objective of this meta-analysis is to examine and analyze the available evidence regarding the etiology of autism spectrum illness in youngsters. The study provides an overview of the disorder and analyzes diagnostic nomenclature and related research concerns. It also evaluates epidemiological findings on prenatal risk factors associated with the disorder's development in children. Furthermore, it outlines the literature search methodology. The search primarily focuses on current findings on children diagnosed with autism and the risk factors that may have contributed, with a particular emphasis on studies on advanced parental age.

Moreover, this thesis delves into the definitions, etiology, and diagnosis of autism and other autistic spectrum disorders. The study also reviews and evaluates the relevant studies included in the meta-analysis and a variety of additional risk variables, such as genetic risk factors, as shown by several other studies completed over the years. Finally, the References section may be helpful for other professionals interested in learning more about childhood autism.

1.2 History of Research on Autism Spectrum Disorder (ASD)

Studies discussing autism spectrum disorder in young people and kids have been described in the literature for decades, most famously Leo Kanner (Kanner, 1943) and Hans Asperger's research (Ghaziuddin, 2005). These cases exemplify the discovery and understanding of the ASD in minors and infants. Asperger pinpointed competent children who had severe social difficulties with their peers. While Kanner described profoundly afflicted youngsters who could not relate to themselves and events as most people do (Thompson, 2013). Their perspectives remained influential in the training of physicians for the following three decades. While this research piqued interest in the theoretical frameworks employed, more study was required to comprehend the complexity surrounding autism spectrum conditions, particularly during infancy.

Over the past several decades, the DSM (American Psychiatric Association) has continued to include new information on pediatric ASD. However, more intense studies on autism spectrum disorder did not begin to emerge till the 1980s. The DSM-III defined *infantile autism* as a pervasive developmental disorder (PDD) distinct from schizophrenia (American Psychiatric Association, 1980). Among the symptoms included significant deterioration of communication skills, lack of responsiveness to others, and unusual reactions to broad environmental factors that occur in a child's first thirty months of life. For individuals who fit most but not all of the clinical guidelines for autistic disorder, the amended DSM-III-R edition in 1987 (American Psychiatric Association, 1987) added a new category of pervasive developmental disability not otherwise defined (PDD-NOS). Moreover, the adjustments to the DSM-IV and DSM-IV-TR in 1994 and 2000 (American Psychiatric Association, 1994, 2000) introduced a fresh approach to pervasive developmental diseases. The complex criterion for autism included developmental disorder-not otherwise specified (PDD-NOS), Rett syndrome, disintegrative disorder, autistic disorders, and Asperger syndrome.

Meanwhile, the later DSM-5 version of the autism diagnosis was intended to be more exhaustive and exact. Thus, it produced a bi-dimensional assessment of autism by separating the DSM-IV-III-TR into two domains: social interaction and limited interest/recurrent tendencies (American Psychiatric Association, 2013). Individuals diagnosed with ASD must have symptoms beginning in early infancy, even if they are not identified until later. Individuals with ASD must have indicators in infancy, even if they are not detected until later. This change in criteria allowed quicker detection of ASD in individuals whose manifestations may not show up until social demands surpass their ability to be diagnosed with ASD.

It was a notable shift from DSM-IV criteria, which were designed to aid school-aged kids with autism-linked issues, but were less accurate in infants and toddlers. Furthermore, the DSM-5 standards were vetted in real-world medical contexts as part of its clinical testing. The findings showed no statistically significant shifts in disorder occurrence once those trials were completed and analyzed (King et al., 2014).

In addition, the broadest and most current research, published in the year October 2012 edition of the American Journal of Psychiatry by (Heurta et al., 2012) delivered the most thorough examination of the DSM-5 criteria for ASD premised on trait extraction from pre - processed data (Frazier et al., 2012). The research concluded that DSM-5 criteria accurately defined 91% of newborns with a clinical DSM-IV PDD diagnosis, demonstrating that the vast majority of kids with DSM-IV PDD diagnoses will retain their ASD diagnosis using the new measurements (Frazier et al., 2012).

1.3 Statement of The Problem

Autism spectrum disorder in youngsters is a prevalent condition, affecting around 1% of the global population (Hahler et al., 2015). The disorder is classified as a trait disorder, implying a life-long condition. Additionally, in terms of disability-adjusted life years, the total burden of ASD surpasses that of other mental diseases such as attention deficit hyperactivity disorder. (ADHD) (Baxter et al., 2015).

With one in every 54 children being confirmed with autism spectrum diseases (ASD) can be defined as relatively common (Bishop et al., 2016). For instance, a study analyzing the condition's incidence rate indicated a five- to tenfold rise in the rate of ASD diagnosis over the previous two decades (Myers et al., 2018). However, this surge in prevalence may be partly explained by confounding variables such as better screening methods and increased knowledge of ASD. Additionally, other underlying variables such as exposure to environmental conditions may increase the incidence rate (Bölte et al., 2018).

Nonetheless, it remains unknown and debated whether environmental elements have a crucial role in the genesis of ASD and which characteristics are uniquely linked to the condition. One explanation for this ambiguity is the disease's complexity with all the implicated genetic, immunological, environmental, and oxidative stress (Lombardo et al., 2019).

The genetic predisposition of autism can be detected in twin studies since the correlation between monozygotic twins is relatively high (Schaefer, 2016). Furthermore, when parents or siblings of afflicted children are studied, milder

symptoms and a subset of autistic features may be identified. This finding might be explained by the discovery of several known ASD genes in their genome (Bolton et al., 1994). As a result, an autistic child's parents and siblings would carry part of the afflicted genes. On the other hand, numerous other research studies do not observe the complete range of autistic characteristics (Gredts et al., 2011).

Single base-pair mutations, copy number variation, and chromosomal rearrangements are the most frequently found genetic changes (Eapen, 2011). Many studies have revealed that the most significant genetic risk factors come from common additive variations, with a modest contribution from de novo and rare inherited variations (Leppa et al., 2016). In addition, in individuals with autism spectrum disorder, de novo CNVs are more commonly found than in healthy individuals (Gonzalez et al., 2018). These de-novo CNVs appear in around 10% of sporadic ASD patients. For instance, the SHANK3 gene is one of the CNV-affected genes (Uchino et al., 2013). A study found that a mutation in one of the alleles was linked with the emergence of autism spectrum condition. Unfortunately, since the observed mutation occurred in a small proportion of individuals, it could be possible that it accounted for the development of ASD only under certain situations (Ruzzo et al., 2019). Additionally, inherited CNVs might well be found in unaffected siblings and parents, implying an incomplete penetrance pattern reliant on the degree of tolerance and function of the afflicted gene(s). Still, there has been no research to date that has discovered a 100% concordance rate between monozygotic twins, which indicates that some environmental elements may have a pivotal role in the genesis of autistic children (Schaefer, 2016).

Furthermore, research examining the heritability estimates of dizygotic twins and singleton siblings demonstrated that dizygotic twins had a greater concordance rate than singleton siblings (Hoekstra et al., 2007). Given that singleton siblings and dizygotic twins share the same amount of genetic relatedness, this greater concordance probability must be due to a cause other than genetics. This factor might be prenatal contact with certain environmental toxins. Consequently, if early exposure to such risk factors occurs, both twins

will be impacted, increasing their probability of developing autism. As such, environmental influences may be critical in the development of autism.

These external influences may originate from various sources (toxicants in the atmosphere, medications, dietary additives, and viral infections) and may act at various phases throughout life (Grabrucker & Andreas, 2013). Prenatal antidepressant exposure, for example, has been demonstrated to enhance the prevalence of unique autistic characteristics and to result in the development of autism in 8.9% of instances (Stein et al., 2014). Apart from particular chemicals, various other general prenatal characteristics, including the parents' ages at conception and mental state, have been linked to autism (Bölte et al., 2018).

According to autism spectrum disorders (ASD) research, researchers have yet to conduct a comprehensive examination of environmental prenatal risk factors from various theoretical perspectives. For instance, due to the apparent high inheritance rate reported in many studies, most cited articles and meta-analyses are likely to have addressed on the risk of acquiring ASD (CDC, 2019), which is exacerbated by a genetic predisposition that comprises many genetic factors. However, other theoretical frameworks, including advanced parental age, parental antidepressant usage, pesticide exposure, maternal diabetes and obesity, need further investigation.

1.4 Purpose of the Study

The major goal of this research is to determine whether there is a link between the parents' ages and their children's occurrence of autism spectrum disease. It was accomplished through (I) reviewing published studies from the years 2000 through 2021 in a systematic manner, (II) establishing a correlation between ASD and advanced parental age through a meta-analysis of studies (Tawfik et al., 2019) that satisfied the inclusionary standards for autism spectrum disorder research, (III) disseminating and appraising meta-analysis findings, and (IV) developing successive research and clinical practice guidelines for ASD.

Populations considered for this study are children of all ages and race/ethnicity diagnosed with autism spectrum disorder utilizing the clinical diagnostic tools used to identify the condition. In addition, the study includes all the disorders in the spectrum, such as Asperger syndrome (Barahona et al.,

2016), Autistic Disorder (Brentani et al., 2013), and Pervasive developmental disorder-not otherwise specified (Fombonne et al., 2016).

1.5 Research Question

The principal objective of this meta-analysis is to ascertain if environmental risk factors, notably advanced parental age, have a profound influence on the development of autism spectrum conditions in children. The study investigates observational studies conducted on the risk of advanced parental age.

The fundamental question that guides this study is as follows.

Is there an association between advanced parental age and autism spectrum disorder in children?

2 OVERVIEW OF METHODOLOGY

2.1 Systematic Review and Meta-Analysis

Systematic reviews and meta-analyses are two independent but complementary methods for synthesizing research. These strategies exemplify a scientific approach to discovering, interpreting, and synthesizing quantitative data from prior investigations when used in conjunction (Sackett et al., 2000). Systematic review and meta-analysis are effective methods for synthesizing massive amounts of research and generating new social work and policy insights. Secondly, systematic reviews and meta-analyses are regarded as evidence-based practices (Sackett et al., 2000). EBP is the approach of integrating the relevant data with medical knowledge and consumer needs (Gambril, 2006) In 1992, a Canadian medical group invented "evidence-based medicine" to refer to using the best available evidence to guide patient treatment and outcome (Gambril, 2006). As the concept gained traction among individuals in partnership with other professionals such as human services and psychiatry, it became EBP. The study defines EBP as

1. Being motivated by the researcher's or clinician's ideals of promoting methodologies.

2. Formulating a very well-defined research topic that provides direction for locating quality standards.

3. Analyzing and depleting the information to address the challenges at hand.

4. Conducting a critical appraisal of the evidence discovered to determine its validity and value.

5. Integrating evidence into process or procedure.

6. Assessing the system's effectiveness.

7. Dissemination of the findings.

Systematic comprehensions address a wide range of research topics, and subsequently, meta-analyses can be used to analyze data from many quantitative research projects. Whilst, systematic reviews and meta-analyses are often undertaken

in conjunction, they may also be conducted individually. A systematic comprehension establishes the appropriateness of conducting a meta-analysis. For example, a meta-analysis may utilize solely quantifiable information (e.g., non-experimental and clinical trials) (Glass, 2000). Similarly, a systematic evaluation of the literature may duplicate only qualitative findings. A content analysis, which is an EBP, would be considered acceptable for explaining study results.

A systematic review follows a predefined format, similar to Gibb's (2003) definition of EBP (Petticrew & Robert, 2006). The steps are as follows:

1. Determine the study query.

2. Identify the sorts of cases required to address research query.

3. Perform a thorough review of the information.

4. Identify whether studies are eligible for inclusion or exclusion depending on inclusionary criteria.

5. Evaluate the listed research critically.

6. Synthesize the studies and determine their degree of homogeneity.

7. Disseminate the findings

2.2 Advantages

Meta-analysis can reduce sampling error and bias to incorporate the expanding body of empirical studies on social work. It also has an essential role in developing expertise in human services. Regrettably, many lists of “evidence-based" methods lack meta-analyses. For example, the traditional narrative literature study evaluations, which often identify "successful" or model programs, are prone to bias from various sources and forms. Therefore, a more systematic assessment is required to provide unbiased evidence assessments (Littel et al., 2008).

A meta-analysis can be a valuable contribution to consumers, practitioners, and policymakers who seek to make informed decisions based on accurate evaluations of existing information. Additionally, it benefits PhD students and social work academics, who may employ meta-analysis to contribute critical information to the knowledge base for all helping professions. On the other hand, a meta-analysis is time

demanding and demands training and dedication. Moreover, as with any technique, meta-analysis has the potential to be (and has been) abused, making it critical to acknowledge its limits.

2.3 Limitations of Meta-Analysis

Meta-analysis does have drawbacks. The sections that follow constrain the challenges of collating oranges and apples, the garbage in, garbage out conundrum, the file drawer issue, and publication bias. These limits represent the vast majority of approaches, but meta-analysis in particular (Cooper & Hedges, 2009).

2.3.1 *It is comparing apples to oranges*

The idiom "apples and oranges" (Glass, 2000) is often utilized to illustrate the hardship of blending research that is dissimilar in some respects. For example, a meta-synthesis may be voided if substantial differences between cases are overlooked. According to others, meta-analysis should not be the purpose of a systematic review (Glass, 2000). Pooling may also be ineffective if the results are not solid or consistent across studies. However, meta-analysis seeks to assess all available research and thus contributes to the precision of the meta-synthesis—additionally, criterion for inclusion and exclusion aid in preventing data that are too divergent from being mixed.

2.3.1.1 *Garbage in, garbage out*

Another contentious aspect of meta-analysis is the adage "garbage in, garbage out." (Glass, 2000)This pertains to the research output considered in the meta-analysis. Since meta-analysis attempts to incorporate all available data, the validity of the comprised studies may be subpar. Therefore, in this situation, the credibility of the analysis is questioned. It was recommended that only well-designed studies be included (Littel et al., 2008). There is, however, no agreement on what constitutes high-quality research. Strict coding processes may aid in the determination of whether research should be included or omitted.

2.3.1.2 *File drawer problem*

The file drawer issue applies to fleeing or grey literature that is difficult to locate. Due to unimpressive findings, it is unclassified and may be accumulating dust in a researcher's "filing cabinet" (Cooper & Hedges, 2009). In compliance with (Cooper & Hedges, 2009) unreported data is often of equal quality as current studies, however, it is not released because the results are not statistically significant. Therefore, it is crucial to Incorporate fugitive data in meta-analyses to quantify the impact magnitude of findings and to compensate for and correct for reporting bias.

2.3.1.3 *Publication bias*

When p-values from issued studies are merged, there may be an upward bias in impact estimates (Kulinskaya, 2008). This impact must be minimized to the greatest extent feasible when researching, especially in meta-analyses. By including grey or fugitive literature, publication bias may be reduced. In addition, since the majority of issued studies refute a conjecture 10 of no impact at a significance value of 0.05, undisclosed findings and presentations will be incorporated into the investigation to eliminate sampling error.

2.4 Significance of the Study

Numerous research has been conducted to enhance autism spectrum disorder (ASD) practice. These qualitative and quantitative studies are grounded in cognitive-behavioral and psychodynamic paradigms. Nonetheless, there is a void in the research about the disorder's origin in youngsters. In addition, parental impacts on the causes and dangers of ASD in children have been studied just in the last decade. Hence, no comprehensive reviews or meta-analyses have been published that thoroughly assess the studies on the advanced age of fathers and mothers. Moreover, few literature reviews and meta-analyses are available, and those are confined to genetics and environmental variables in general (Cauda et al., 2017). By doing a thorough review and meta-analysis of all pertinent research on the role of parental age in the occurrence of autism spectrum disorder in children, this study will tend to close the void in existing literature.

Additionally, understanding more about the origin of ASD may aid physicians and other health care professionals develop more effective therapies and may even assist families in better comprehending how autistic brains operate. This would lessen a great deal of the loneliness and social isolation experienced by autistic persons.

3 LITERATURE REVIEW

3.1 Defining Autism Spectrum Disorder

Autism spectrum disorder is a persistent developmental brain disorder that often impairs person's adequacy to create connections, engage effectively with other people, and behave appropriately in their surroundings (Baird et al., 2006). The spectrum encompasses not only autism but also a group of brain development disorders such as Asperger's syndrome (Brentani et al., 2013) and pervasive developmental disorders (Barahona et al., 2016) such as childhood disintegrative disorder and Rett syndrome (Betancur et al., 2011).

Autism spectrum condition has a broad range of features, severity, and manifestations making it difficult to diagnose and treat (Park et al., 2016). In addition, it is a challenging disorder to cope with since it causes severe hindrance in social relationship and connections and influences every aspect of a child's development. Autism frequently co-occurs with mental retardation: 75% of individuals with autism exhibit moderate or severe developmental delays, while the other 25% function at average levels of intellectual capacity (Sigman & Capps, 1997). ASD is a chronic condition that manifests symptoms in the second year of life between 12 and 24 months.

Autism symptoms may involve a child's speech being confined to a few repeating phrases; usually, the youngster has difficulty interacting with others (Park et al., 2016). There may be a complete cessation of verbal communication, a retreat from physical touch with people, and a desire to be alone. Additionally, the child may be unable to engage in or play with objects that need creativity or lack the desire to play. A typical mannerism of autistic children is that when playing with toys, games, or other objects, they often utilize just one familiar toy or only one piece of a toy, game, or puzzle component. Autistic children are prone to suffer sudden fits and emotional outbursts. Another characteristic of autism is an inability to give or receive affection. Also, a change in routine may be quite distressing for these individuals since they may be ritually fixated. Additional possible symptoms include a failure of or inability to perceive fear or threat, restricted responses to verbal stimuli, physical over-or under-

activity, and odd reactions to sensory events such as loud or high-pitched sounds (Park et al., 2016). While all these traits are present in children with autism spectrum condition, no two infants with autism spectrum diseases exhibit the same mix of symptoms.

Furthermore, autism is a blanket term that applies to a scope of complicated developmental brain abnormalities, referred to as pervasive developmental disability (PDD). Other pervasive developmental disorders are Asperger's syndrome (Brentani et al., 2013), PDD-NOS (pervasive developmental disorder—not otherwise specified) (Barahona et al., 2016), and autistic disorders (Baxter et al., 2015). Moreover, parents and professionals frequently use the phrase "autism spectrum conditions" to specify to these conditions (ASD) (Selvakumaran et al., 2020).

3.1.1 *Autistic Disorder*

The DSM-IV-TR (American Psychiatric Association, 1994, 2000) classified Autistic disorder as one of the five pervasive developmental disorders, comprising Asperger's and Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS). Also, Rett's Disorder (Jacque et al., 2018) and Childhood Disintegrative condition (Grupta et al., 2017) were the only two remaining pervasive developmental disability that could be diagnosed (Barahona et al., 2016). In addition, autistic disorders are distinguished from other conditions by their early onset and the set of social and communicative limitations.

Autistic disorder is classified as a separate disorder under the umbrella of autism spectrum disorder based on the most current version of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013). The latest assessment of autism spectrum conditions comprises of disorders previously referred to as "early infantile autism, Kanner's autism, childhood autism, pervasive developmental disorder not otherwise specified, high functioning autism (Fattorusso et al., 2019), atypical autism, childhood disintegrative disorder, and Asperger's disorder (Hyman et al., 2020). Individuals diagnosed with autism spectrum diseases have chronic difficulties in social relationship and connection and are confined to repetitive interests, behaviors, and hobbies.

3.1.2 *Asperger's Syndrome*

Similar to high-functioning autism, Asperger's syndrome (299.80) has been identified as an autism spectrum disorder (ASD) (Asperger, 1991). The inspiration for the term Asperger's syndrome came from an Austrian doctor named Hans Asperger 1944, who examined and characterized youngsters who lacked nonverbal communication skills, exhibited poor empathy for other children, and were physically clumsy (Ghaziuddin, 2005). However, almost half a century after it was first recognized as a medical diagnosis, many unanswered concerns exist about the illness. Additionally, it has been recommended that Asperger's being phased out and replaced with a severity-based diagnosis of autism spectrum condition (Howlin, 2008).

While children with Asperger's syndrome exhibit repetitive motions and behaviors, conduct disorder symptoms, and clumsy mobility, their IQ and linguistic skills are exceptional (Wright et al., 2015). Children with Asperger's syndrome are strikingly different. A child with Asperger's syndrome would have deficiencies mostly in social domains, such as nonverbal cue interpretation and interpersonal interaction while retaining cognitive and linguistic abilities. Additionally, they may display repetitive behaviors comparable to those linked with autism. Due to an awkward gait or stance, youngsters with Asperger's syndrome (Brentani et al., 2013) often seem clumsy or unsteady (Wright et al., 2015).

Visual-spatial dysfunction is another area of concern that may contribute to the child's clumsiness. Similarly, contrary to classic autism, signs of this illness often manifest later in a child's life (in most cases, autism is diagnosable by the age of 3) (Mosconi et al., 2015). In children diagnosed with Asperger's, their insufficiency in socially developed skills is not detected until they are placed in an environment or circumstance where other similar-aged children thrive at functioning, and the Asperger youngster does not. It is relatively common for infants diagnosed with Asperger's syndrome (Brentani et al., 2013) to exhibit a toll of intelligence or savant characteristics, yet these abilities are relatively uncommon in the broader community. Asperger's syndrome is distinguished from other autism spectrum conditions by how language and cognitive development are preserved (Mosconi et al., 2015).

Perhaps the most severe component of Asperger's syndrome is a lack of empathy. Children with Asperger's syndrome have complications with basic socialization, including an inability to form friendships or find common interests or achievements with other children, a withdrawal from social or emotional mutuality, impaired nonverbal behaviors such as eye contact, facial expression, and posture.

3.1.3 *Pervasive Developmental Disorder—Not Otherwise Specified*

The American Psychiatric Association coined "pervasive developmental disorder" in 1980 (Zaretsky, 2005). In contrast to specific developmental disorders (SDD), the diagnostic category pervasive developmental disorder (PDD) describes a set of five disorders marked by delays in the development of numerous critical functions, including socializing and communication (Zaretsky, 2005). Additionally, most parents observe signs of PDD as early as infancy, and the disorder often manifests before the age of three. PDD does not influence the expected lifespan. It is used when identical behaviors and activities are seen, but the requirements for a particular developmental condition are not satisfied.

One of the reasons that the patient does not meet the disorder's criterion is the age at which the symptoms started, unusual symptomatology, subthreshold indications, or a combination of all of these. Additionally, there are symptoms associated with PDD, including communication difficulties such as trouble using and comprehending language; inability to connect with people, peculiar play with toys and other items, and issues adjusting to schedule or environment changes. and repeated physical gestures or actions (e.g., hand flapping, foot-tapping, hair twirling, or more comprehensible patterns) (Thompson, 2013).

Due to the variety of potential symptoms in this PDD-NOS category, it is difficult to provide a more precise definition of what PDD-NOS is, other than it is a type of autism spectrum condition (ASD). For instance, some children diagnosed with PDD-NOS exhibit characteristics of Asperger's but do not meet the diagnostic criteria. Other children have autism that is virtually diagnosable but lacks broad symptoms. To account for this diversity, psychologists contemplate subdividing PDD-NOS into multiple subtypes.

3.2 History of ASD

The phrase "autism" attains from the Greek word "autos," (Szpir et al., 2006) which means "self," and the earliest historical incidence of autism dates back to Hugh Blair of Brogue's court case (Szpir et al., 2006). Blair's younger brother went to court in 1747 to have Hugh's emotional competence to contract marriage determined. As a result, he petitioned successfully for the termination of his marriage in order to receive his brother's wealth. Hugh indicated that his brother was mentally ill, and although there was no conclusive proof that Hugh was autistic, there was convincing evidence that he had autistic-like behaviors.

Nonetheless, A Swiss physician called Eugen Bleuler was the first to use autism in 1911 (Szpir et al., 2006). He categorized it as a mental illness, confounded with emotional issues and schizophrenia until 1943 (Kanner, 1943). A case study in 1943 by a child psychiatrist, Leo Kanner, had a vital role in autism history and is tightly associated with identifying the illness. Between 1935 and 1943, Kanner recognized eight males and three girls in his clinic at Johns Hopkins. He claimed that the disorder's core aspect is autistic children's incapacity to respond to things as others do. Moreover, their unique behavioral parallels drew psychologists' and medics' attention to autism as an "affective contact" disorder.

Additionally, Hans Asperger, a Viennese doctor, diagnosed an autistic Psychotic trait that would ultimately take his name, Asperger Syndrome (Asperger, 1991), concurrently but independently (Ghaziuddin, 2005). He discovered individuals with typical initial language acquisition but had substantial problems in society with their peers. In the 1940s, mental health professionals and psychoanalysts affirmed that autistic patterns of behavior mirrored childhood schizophrenia; this conceptual framework persisted into the 1950s and 1960s, leading to the etiological hypothesis that autism was caused by emotional distress monumentally based on an unusual parent-child psychodynamic approach, such as emotionally distant or emotionally cold parents (Volkmar et al., 2009). However, both Kanner and Asperger were very circumspect in their attempts to separate their disorders from infantile schizophrenia and learning disabilities.

The psychodynamic hypotheses for autism began to erode in the 1970s as scientific data established that autism is a neurological illness (Herbert et al., 2006). For example, neuropsychological and neuroradiological experiments have shown neurological abnormalities in autism and identified a high consonance incidence of autism in fraternal twins and an elevated frequency and prevalence of seizures and epilepsy (Roberto et al., 2009). Be that as it may, in the 1980s, the DSM-III classification of infantile autism as a distinct pervasive developmental disease (PDD) from schizophrenia was established (American Psychiatric Association, 1980). It classified children into three categories: those who lack responsiveness to others, those with significant impairments in communication abilities, and those who have atypical reactions to broad environmental components throughout the first 30 months of a child's life.

In addition, the age-onset requirement was eliminated from the upgraded DSM-III-R issue in 1987 (American Psychiatric Association, 1987). Instead, it launched a separate category of pervasive developmental impairment (PDD-NOS) for youngsters who qualify the vast majority but not all prognosis for autism (American Psychiatric Association, 1987). Finally, in 1994 and 2000, the DSM-IV and DSMIV-TR revisions included an approach to pervasive developmental disorders (American Psychiatric Association, 1994, 2000). They added five subgroups to the complicated criteria for autistic disorder: autistic disorder, Asperger disorder (Brentani et al., 2013), pervasive developmental disorder-not otherwise defined (PDD-NOS) (Barahona et al., 2016), Rett syndrome (Jacque et al., 2018), and disintegrative disorder (Grupta et al., 2017). Nevertheless, the late DSM-5 version of the autism diagnosis is intended to be more exhaustive and exact. Thus, it adopted a hybrid clinical framework for autism, separating the DSM-IV-three TR themes into socialization and limited attention conduct (American Psychiatric Association, 2013). Individuals diagnosed with the illness ASD must have the traits beginning in infancy, even if they are not identified afterwards. This adjustment in standards promotes preceding identification of ASD and enables persons whose ailments may not manifest ultimately until societal expectations surpass their competence to acquire the prognosis.

3.3 Family Impact

Parents whose kid is diagnosed with ASD have challenges, and the family dynamics shift as daily routines must be adjusted. The kid with ASD will need more parental care. Discovering that a child is autistic may cause parents to experience various emotions (Kiami & Goodgold, 2017). Each family approaches their child's vision differently. As with the spectrum, each family's experience is also unique. When parents learned of their child's diagnosis, one research found that " fifty two percent felt relief, while forty three percent felt sadness and loss, and twenty nine percent felt astonished or surprised, and ten percent felt self-blame (Giovagnoli et al., 2015). While parents are often glad that their kid's symptoms have been identified, this does not eliminate the emotional stress of parenting a child with autism.

Parents may face stressful conditions after an initial diagnosis that concerns their child's conduct, such as adjusting to a new living condition and the difficulty of obtaining suitable treatments helpful to the family. In addition, stressors associated with an ASD diagnosis may strain parents' marriages, impose financial strains on the family, and prompt parents to withdraw socially. Parents reported stress due to having to adapt objectives and activities for their kid diagnosed with autism and implementing various arrangements for the child's schooling and bereavement as a product of their child's reduced chances (Giovagnoli et al., 2015). One of the most significant contributors to distress for parents is their child's inability to communicate fundamental needs. This is not very reassuring for both parent and child. The parent will have difficulties articulating their child's demands, while the youngster will have problems expressing themselves. This often results in aggression, primarily non-verbal, among children diagnosed with ASD since parents may be unaware that their child is hungry, ill, exhausted, injured, unhappy, or angry.

Another source of stress for parents is financial concerns. Each new pediatric diagnosis of autism has unique socio-economic repercussions for the family, community, and country. These begin with the child or autistic adult to the immediate family and then rapidly expand to include the health care financing system, health professional interpretations, educational systems, adult employment for disabled adults, the demand for long-term halfway houses, and the income progression of the autistic person and his or her close family members.

One research in the United Kingdom estimated that supporting children with autism was 2.7 billion pounds per year, while the cost for adults was 25 billion pounds per year, based on a mix of autism prevalence data, services offered and lost productivity (Buescher et al., 2014). In addition, children with autism and their families experience a significant decline in their quality of life in various dimensions (e.g., social, economic, educational, psychological). Parents of autistic children were seven times more likely to report that childcare issues had impacted their work than parents of generally developing children. A child ascertained with autism stipulates diversified services to aid with their provision of care, which may be financially draining for the kins. A youngster may need examinations, home programs, and various treatments, all of which are extravagant.

While parenting an autistic kid may be challenging and life-changing, families may not have a terrible experience. Parents may develop resilience due to their child's autism diagnosis and acknowledge the good ways autism has touched their lives. Moreover, a child diagnosed with autism enables the family to see life through the lens of their child's abilities. The autistic child teaches parents and siblings to be more empathic and compassionate toward other children who are seen as different.

3.4 Other Neurodevelopmental Disorders on DSM-5

3.4.1 *Attention-deficit/Hyperactivity Disorder (ADHD)*

Attention deficit and hyperactivity disorder (ADHD) is a neurodevelopmental condition with a high worldwide incidence of 5.29 per cent, associated with elevated and impairing deficits with restless overactivity, sustained attention, and impulse control (Wilens et al., 2010). While lack of hyperactivity, attention, and impulsivity are core symptoms of ADHD, the condition is very diversified and is linked with many abnormalities involving cognitive and behavioral deficiencies (Kessler et al., 2006).

The ICD-10 (Steindel & Steven, 2010) and the DSM 5 (American Psychiatric Association, 2013), are often used to diagnose ADHD in children, adolescents, and adults. Both guides employ the same criteria for diagnosing 18 symptoms and specify the exact two fundamental domains, which correspond to inattentive and hyperactive-impulsive tendencies (Kessler et al., 2006). To attain the clinical definition for inattentive or hyperactive-impulsive subcategories, an individual must exhibit six or

more of the nine traits listed in each category (18 possible traits in all). ADHD is mainly equipped to assess school-aged children when it emerges as classroom disruption and trouble performing school obligations. In addition, it is more common for males than females to experience this disorder.

Mounting data indicates that ADHD and ASD have diagnostic overlap and similarities (Martinussen et al., 2005). For instance, both diseases often co-occur, with 20–50% of children with ADHD achieving the criteria for ASD and 30–80% of children with ASD achieving the criteria for ADHD (Nanda et al., 2010). Moreover, co-occurring ASD and ADHD features increase with age, especially in infants with severe ASD and ADHD traits and a lower IQ.

Three different clinical presentations of ADHD have been characterized, depending on their most salient characteristics (Pena et al., 2020). Predominantly inattentive (ADHD-I): The individual has difficulty organizing or completing a job, forgets aspects of everyday activities, has difficulty focusing, and is quickly sidetracked. Secondly, primarily hyperactive-impulsive (ADHD-H) individuals have difficulty staying still for an extended period. They also speak often and fidget excessively. Finally, in the combination (ADHD-C), the individual exhibits symptoms from the preceding two categories.

Although the origins and imperilments for ADHD are vague, current exploration specifies that congenital traits may be an influence. For example, current twin findings have linked genes to ADHD (Faraone et al., 2018). Along with heredity, scientists are fact-finding other probable rationales and imperilments, such as brain damage, exposure to environmental variables during gestation or at infancy, preterm birth, and alcohol consumption.

3.4.2 *Schizophrenia*

Schizophrenia is a severe brain condition that impairs a person's ability to reason, behave, express emotions, apprehend reality, and interact with others (Freedman, 2003). It may manifest itself psychologically in many formats, including hallucinations, delirium, and an inability to communicate clearly and effectively. The highest risk factor for schizophrenia is family history (Prior et al., 2014). In addition, obstetric complications, maternal infection, perinatal hypoxia, preterm delivery, and low birth weight are risk factors.

Additionally, schizophrenia is defined by positive and negative symptoms that may affect a patient's cognition, judgment, speech, mood, and actions (Cauda et al., 2017). Positive symptoms include hallucinations, voices speaking to or about the patient, and paranoid delusions. The term "positive" refers to the existence of symptoms in this context (rather than absence). Negative symptoms relate to the missing or impairment of normal mental function; they include diminished effect, a diminished feeling of pleasure, will drive, and social retreat (Cauda et al., 2017). The condition often manifests throughout adolescence or early adulthood and frequently becomes chronic and severe. Schizophrenia affects 1% of the population in all ethnicities and is equally prevalent in men and women. However, men commonly get the condition in their late adolescent years or early twenties, while women typically develop it in their late twenties or early thirties (Lionel et al., 2013). Although the disease's origin is mainly unclear, a neurodevelopmental hypothesis proposes that interplay between several genes triggers and guides a chain of neuropathological processes that commences during gestation and continues throughout adulthood.

Furthermore, until 1971, autism was considered a precursor to schizophrenia; it was sometimes referred to as "childhood psychosis" or "schizophrenic condition of childhood" (Zheng et al., 2018). Many studies have shown numerous parallels between autism and schizophrenia. Numerous behavioral deficiencies in social interaction and cognition, impairments in executive function, distortion of emotional processing and sensorimotor gating are similar psychopathological hallmarks of both diseases. Additionally, individuals with schizophrenia and autism have similar neuronal activation deficits during a social cognition test, with both patient groups exhibiting diminished stimulation in the right amygdala, ventrolateral cerebral cortex (Prata et al., 2017), and fusiform gyrus.

3.4.3 *Intellectual disability (ID)*

Intellectual disability (ID) is a collective name for mental retardation (MR) (Andearsan et al., 1982). It refers to impairments in fundamental cognitive skills that influence two areas of functioning: responsive functionality (routine life such as conversations and independent living) and psychological functioning (such as problem-solving, learning, and judgment).

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR) (American Psychiatric Association, 1994, 2000) defines intellectual disability in three ways: severely below-average academic performance, which results in deficits in adaptive behavior, all of which reveal themselves during the formative years of childhood. Intellectual disability is a chronic issue that impacts around 1% and 3% of the general population. During the formative stage, intellectual and adaptive deficiencies begin to manifest (Srivastava et al., 2014). It also has a comparable effect on males and females. Additionally, more than 75% of individuals with intellectual disabilities have a mild intellectual disability, for which an intrinsic precise biologic cause is less likely to be identified.

In contrast, a small percentage of individuals with severe intellectual disabilities have a severe intellectual disability for which an underlying specific biologic cause is highly likely to be identified (Trevisan et al., 2020). Significant causes of severe to profound intellectual impairment include genetic disorders, congenital metabolic problems, and brain deformities. Also, the etiology, severity, cognitive capacities, and adaptive function of individuals with intellectual disabilities vary and must be considered while designing a treatment plan (Preou et al., 2013).

The threshold between autism and intellectual disability is so hazy that clinicians often confuse or diagnose just one of the two when both are present. One explanation for this is that most of the genes associated with autism also cause intellectual disability (Trevisan et al., 2020).

4 ETIOLOGY OF AUTISM SPECTRUM DISORDER

4.1 Prevalence of Autism

Autism is prominent in every nation and region globally, including families of different races, ethnic origins, religious beliefs, and socioeconomic statuses (Rice et al., 2012). Autism occurs in approximately one to two persons out of every thousand children and is three to four times more ubiquitous in males than females (Bishop et al., 2016). Additionally, girls diagnosed seem to have a broader range of more severe symptoms and a lower IQ score.

Autism is a relatively recent disorder compared to other disorders; however, it has likely been misdiagnosed for many years, and research indicates that it is increasing in prevalence (Rice et al., 2012). Moreover, ASD epidemiology presented a shifting dynamic, with the incidence rising from 2-4/10,000 children documented in the 1940s (Wing et al., 2002) to approximately 4-5/10,000 children in the 1960s and 1970s (Gillberg et al., 1999) (Fombonne et al., 2005). Globally, prevalence estimates for ASD are already available, either via monitoring programs that use preexisting education and health databases or through targeted population surveys (Elsabbagh et al., 2012).

According to a 2012 analysis, the median worldwide prevalence of autistic disorders was seventeen in ten thousand (Elsabbagh et al., 2012) (about one in 588 children) and 62/10,000 (Elsabbagh et al., 2012) (approximately 1 in 161 children) for all-pervasive developmental disability. In addition, the Centers for Disease Control and Prevention (Zablotsky et al., 2015) surveillance study found a cumulative estimated frequency of 1 in 68 children aged eight years who lived with their parents or guardians in eleven locations throughout the United (Zablotsky et al., 2015). Furthermore, a more comprehensive CDC report released in 2015 suggested that one in every 45 children in the United States had ASD (CDC, 2010). Based on another study conducted by the United Kingdom's National Autism Society, one in every hundred individuals has an autism spectrum illness (The Autistic Society, 2014).

Similarly, a comprehensive review and meta-analysis of ASD occurrence findings conducted in mainland China, Hong Kong (Sun et al., 2009), Taiwan (Sun et

al., 2013), and Macau found a mean prevalence of 24.4/10,000 children (Elsabbagh et al., 2012). Further assessment of epidemiological research studies since 2000 in the Western Pacific area (covering Japan and China) revealed currency deems ranging from 2.8 in ten thousand to 94 in ten thousand (Cubells et al., 2013), with a median of 11.6 in ten thousand.

Furthermore, the Middle East's incidence of ASD was reported at 1.4/10,000 in Oman (Salhia et al., 2014), 4.3/10,000 in Bahrain (Al Ansari et al., 2013), and 29/10,000 in the United Arab Emirates (Al Gadani et al., 2009). Another epidemiological investigation from Mexico published an overall occurrence of 87/10,000 (Fombonne et al., 2016), while a population survey from India in 2017 revealed a frequency rate of 1 in 667 children (Raina et al., 2017). The NEDSAC in Canada also disclosed that ASD was among the most prevalent developmental disorders, impacting one in every 94 children (Ouellete et al., 2012).

Males have a 4:1 frequency of ASDs over females (Werling et al., 2013). This conclusion has been replicated across several demographic studies and geographic locations, indicating a significant role for sex-specific biological variables in the etiology of ASD. In addition, substantial ethnic differences were detected, with non-Hispanic white children having the most significant occurrence and Hispanic children having the lowest (Becerra et al., 2014). However, this wide geographical and ethnic disparity in the prevalence of ASD is unknown. Nonetheless, it may be clarified by ascertainment heterogeneity due to varying screening techniques, cultural differences, and disparities in access to medical care.

The World Health Organization data documented that ASD sways around one in every 160 individuals universal (Becerra et al., 2014). However, some developing countries such as Africa lack population-based autism surveys; thus, the extent to which they contribute to this burden remains uncertain (Newton et al., 2013). Fortunately, the data collected in these regions are primarily from hospitals and clinics in a few nations within this continent. For example, Nigeria documented a prevalence rate of 2.3 per cent (1 in 43.5) of children observed among 2,320 first-time visitors to a child psychiatric clinic (Langunju et al., 2014). On the other hand, research in Uganda found an unacclimated ubiquity of ASD of 6.8 in one thousand (Kakooza et al., 2014) children aged two and nine years.

Various factors might account for the lower prevalence of autism in developing nations. For instance, a disability diagnosis is likely to be stigmatized in certain cultures (Newton et al., 2013). This stigma significantly discourages parents from obtaining assistance or information about the disease, impeding timely and appropriate treatment. In other circumstances, parents may be eager for their child to attend a public education school rather than being assigned to a special education school. Consequently, even when they know the child's issues, parents may underreport them to evaluators and physicians.

The low frequency of ASD in developing nations might result from underreporting or a lack of competent diagnostic procedures (Mojeed et al., 2010). For instance, in developing countries, screening techniques are not widely accessible (Mojeed et al., 2010). In addition, these screening tools are also published in English, which may be a problem for nations that do not speak English, such as Africa, which has over a thousand distinct languages, resulting in ASD misdiagnosis in children. This notion was confirmed by research on infants born to African immigrants in Sweden, which found that this subset of the population had a higher prevalence rate than the indigenous people (Neggers et al., 2014).

Another theory is that the probability of late diagnosis or misdiagnosis is higher for children in Third World nations than for children in more developed countries (Gillberg et al., 1995). Different results suggest children in developing countries are more likely to receive a late diagnosis of ASD. The diagnosis mainly relies on parental reporting with limited time and opportunity for assessors to examine and engage with the child to reach an agreement. On the other hand, parents will only seek a diagnosis in low-income nations if they identify the seriousness of their child's difficulties and do not disclose lesser forms of the condition (Barnevick et al., 2008). In contrast, parents in Western nations may be eager to identify their child's issues to access further resources. These variables contribute to a lower incidence of ASD in developing countries than in Western countries with better-established health and education systems.

The rising deems of ASD in Western nations (developed countries) is due mainly to clinical definition advancements in both the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association) and the

International Classification of Diseases (ICD) (American Psychiatric Association). Additionally, increased awareness increases accessible resources for children with ASD, and the age of diagnosis decreases, both of which contribute to the increased incidence of ASD. Although a significant portion of the increase in most ASDs may be explained by a more accurate assessment of ASD incidence studies (new cases per year). Furthermore, it demonstrates that, despite some enhancements in resources available, there has been a progressive rise in recent decades, suggesting that part of the increasing prevalence may be the consequence of a significant increase in the ASD rate. For example, research undertaken in developed nations such as the United Kingdom and Israel, where diagnostic and treatment technologies have evolved significantly over the previous decade, indicates an increasing prevalence of ASD (Davidovitch et al., 2012). This, however, might be mostly attributable to environmental influences since genetic, ethnic, and regional characteristics cannot drastically in a short period.

These analyses, which assessed the worldwide prevalence of ASD, revealed a high degree of diversity in prevalence rates, highlighting the need of focusing further attention on possible causes for the majority's reported increases (Reference). First, the methodological discrepancies in case classifications and case-finding techniques are a significant source of heterogeneity in prevalence estimates (Matson et al., 2011). Secondly, the disparate data sources make it hard to choose a specific monitoring technique for determining the frequency of ASD occurrences. For instance, population-based designs contribute significantly to research quality since they include all children living in designated areas that adhere to the selected ASD criteria and are often assessed in "natural" group situations (Frans et al., 2017). However, the source of identification, such as teachers, specialists, or parents, the assessor's lack of blindness, and the sensitivity of the screening methods all represent possible biases that may affect the prevalence estimates acquired via population research. Moreover, the questionnaire or interview to be administered to parents or teachers may influence how the questions presented in the survey-based prevalence are interpreted, adding to a wide variance in prevalence rates.

4.2 Pathogenesis

The broad-spectrum aspect of autism spectrum disorder implies that there may be several etiologies with overlapping impairment profiles rather than a single cause (Schaefer et al., 2013). Whereas the cause of autism spectrum illness is undetermined, current data and research from twin studies and family studies support the hypothesis that physiological and genetic components play a role (Schaefer et al., 2013).

Currently, researchers believe autism spectrum disorder to be one of the most heritable of all mental disorders, with heritability estimates ranging from 37% to more than 90% based on twin concordance rates (Vortsmen et al., 2017). Furthermore, while 15% of cases of autism spectrum disorder are linked with a confirmed genetic mutation, the remainder appears polygenic, with hundreds of genetic loci potentially impacting the disorder and resulting in considerable phenotypic diversity (Tammimies et al., 2016).

Several alternative hypotheses of autism spectrum disorder propose that the condition might be caused by diet, gastrointestinal pathology, chemical imbalance, or heightened immunological dysfunction. However, more research into the underlying pathways is necessary (Rossignol & Frye, 2013) (Taurines et al., 2012). Numerous studies have also addressed the etiological plausibility of early exposure to antibiotics and vaccinations, particularly the measles-mumps-rubella (MMR) immunizations, in which most have concluded that there was no causative link (Madsen et al., 2002).

Another perception is that autism develops due to aberrant brain architecture impairing functionality (Marcel et al., 2012). For instance, some cells might form incorrectly in the brain. If there are issues with the neural pathways or neurotransmitters, it is likely that some components of the "communication network" will not operate properly. A communication network failure might jeopardize the whole design of sensory information, thoughts, emotions, and behaviors working together. According to certain research, children who are extraordinarily high functioning, despite being labelled with autism, do have deficiencies in the amygdala, which controls social and emotional functioning elements (Shih et al., 2010).

The etiopathogenesis of autism spectrum condition is complicated. However, numerous studies have shown that environmental influences may be the primary cause

of the condition by modifying and changing existing genetic variables associated with ASD development (Hyman et al., 2020). Recently, researchers have examined the impact of pesticides, heavy metals, and other toxins on infant neurodevelopment and its relationship to autism spectrum conditions (Bölte et al., 2018). This finding is especially significant for individuals such as farmers who are frequently exposed to pesticides regularly.

Due to the intricacy of autism, a handful of rationales have been proffered to account for its etiology. According to one concept, autism is a very heterogeneous disorder. For instance, certain types of autism may be primarily caused by heredity, while environmental circumstances may cause others (Hallmayer et al., 2011). Another view is that autism develops due to a genetic predisposition and a particular environmental trigger (Gardener et al., 2011).

In conclusion, in both hypotheses, an environmental component is at least in a proportion of the cases suspected to have a role in the condition's onset.

4.3 Genetics and ASD

One significant step forward in grasping autism pathophysiology has been recognizing a sizable genetic component to the etiology of ASD (Hallmayer et al., 2011). There are four critical areas of evidence that support genetic etiology in ASD: twin studies, comparisons of monozygotic and dizygotic twins (MZ/DZ), family studies that assess the rate of autism in first-degree relatives of affected probands to the general population, and rare genetic syndromes with a comorbid autism diagnosis (Volkmar et al.,, 2004)

Analyzing and comprehending the genesis of autism is very beneficial for families because it enables the monitoring of relapse risks, the prediction of other related medical problems, and the development of a prospective therapy technique. Since monozygotic twins share 100% of their genetic material, dizygotic twins share 50%, similar to non-twin siblings (Tick et al, 2015). A higher rate of illness co-occurrence in monozygotic twins than in dizygotic twins establishes genetic causation. Over the years, twin studies on ASD have consistently indicated a heritability of roughly 70–80 per cent (Volkmar et al., 2004).

A study examining the relative recurrence ratio (RRR) and ASD aggregation in families utilizing all pairs of twins that are monozygotic and dizygotic twins, full siblings, half-siblings, and cousins discovered that monozygotic twins have a higher relative recurrence ratio (RRR) than dizygotic twins and cousins have the lowest relative recurrence ratio (RRR) (Warren et al., 2011). Nonetheless, there was an aggregation of the disorder within families. Additionally, the researchers determined that the heritability of ASD and autistic disorder is about 50% and that genetic interrelationship increased with an individual's risk of ASD and autistic impairment. As a result, it became apparent that twins-family autism research is critical in establishing those biological relatives of the cohort with autism are at higher probability of evolving to autism and have a higher incidence of milder autistic-like conditions (Sandin et al., 2014). It also substantially contributed to the notion of a greater autism phenotype, named 'the broader phenotype,' which is defined by features similar to those seen in autistic persons but less severe (Constantino et al.,, 2010). For example, a considerable number of non-autistic siblings exhibit linguistic delay. Moreover, distinct clinical traits (IQ, clinical symptoms) exist amongst monozygotic twins who share 100% of their heritable DNA (Constantino et al.,, 2010).

ASD's genetic architecture is heterogeneous in terms of frequency (common vs rare), method of inheritance (inherited vs de novo variation), mode of variation (single nucleotide, indel, or copy number variation), and mechanism of action (dominant, recessive, or additive) (Liu et al., 2015). The phrase "common variation" (Connolly et al., 2012) refers to genetic variants that differ from the attributed genome and are observed in more than 1% of the population. Multiple studies have demonstrated that common variants with minor effects contribute additively to the development of complex characteristics in ASD (Connolly et al., 2012). The first molecular genetic research on autism focused on candidate genes intending to identify prevalent genetic variations in single-nucleotide polymorphisms (SNPs) (Liu et al., 2014). Nevertheless, a significant drawback is that it needs previously accumulated anatomical, biochemical, or functional information, either limited or not at hand. Additionally, this research has been hampered by insufficient sample sizes and insufficient genotyping, which has resulted in a lack of replicable markers, except for a few viable genes.

The gamma-aminobutyric acid (GABA) (Cochran et al., 2015), serotonin transporter (SLC6A4) (Devlin et al., 2005), a receptor, beta 3 (GABRB3) (Chen et al., 2014) , reelin (RELN) (Lammert et al., 2016), and oxytocin receptor (OXTR) (Sebat et al., 2007)are the most consistently documented genes among the common variants. In addition, GABRB3 is involved in genomic instability, gene expression, recombination, and imprinting and is located on chromosome 15q11-q13. This region in the chromosome has attracted much interest because a deletion in this site is linked to the monogenic etiology of ASD, Prader-Willi syndrome (Dykens et al., 2011), and Angelman's syndrome (Weiss et al., 2008).

Autism research involving individuals with rare genetic variants (1% of the population) provides further information (Geschwind et al., 2008). Rare variations may be passed on (inherited) or de novo, where they arise from the parent germs (sperm or oocytes) or later during fertilization, referred to as post-zygotic somatic variants. Advances in discovering rare genetic variations via the study of genetic disorders have substantially contributed to the knowledge of and ability to identify ASD risks. The syndromic ASD, in particular, has shed light on the disorder's pathogenesis. For example, persons with tuberous sclerosis complex (TSC) (Dykens et al., 2011), Fragile X, Rett (Jeste et al., 2016), or Angelman syndromes (Bonati et al., 2007) are more prone to have ASD phenotypes. Recent discoveries from TSC, a condition caused by a mutation in the TSC1 or TSC2 gene (Neale et al., 2012) that results in overactivation of the mammalian regulator of rapamycin (mTOR) signalling pathway, altering cell proliferation and differentiation, indicated that it was affiliated with an elevated chancy of autism (Geschwind et al., 2008). Recent findings from another study have also shown that repeated seizures may have an additive impact, owing to the rising prevalence of autistic characteristics in newborns with TSC (Jossifov et al., 2012). Furthermore, this disease has been employed as a model to explore the cerebellum's part in the augmentations of ASD.

Prior findings on rare variants have primarily centred on a form of copy number variations (CNVs), which are DNA sites with hundreds to millions of base pair variants due to duplication and deletion (Stefano et al., 2019). There has been significant interest in the disease causing part of de novo CNVs as a cause of ASD in comparison to inborn variations, particularly in the setting of sporadic vs familial ASD patients

(Woodburry-Smith & Scherer , 2018). For instance, a study (Leppa et al., 2016) discovered that familial occurrences of rare inherited CNVs were more frequent than sporadic occurrences. These data show that in sporadic cases of ASD, de novo CNVs are primarily responsible. In contrast, inherited CNVs are the leading cause of familial cases of ASD (Leppa et al., 2016). However, another research (Stamouli et al., 2018) found no statistically significant difference in the frequency of de novo CNVs between sporadic and familial occurrences.

Validated de novo CNVs have been illustrated to be substantially linked with ASD (Timothy et al., 2013). There is, however, no conclusive discovery that de novo CNVs increase the likelihood or severity of the illness more than inborn variants. On the other hand, the mechanisms of CNV inheritance and consequent vulnerability to ASD are problematic: an autistic person with a risk associated CNV may acquire that CNV from a parent who does not display autistic symptoms (Mazina et al., 2015). Additionally, an autistic person may have unaffected siblings who have inherited the same CNV, or one afflicted sibling in a multiplex family may have a risk of conferring CNV while the other affected siblings do not.

Extensive research seeking to connect genotype and phenotype has revealed considerable phenotypic diversity amongst people carrying the same genetic variants, both in disease presence and severity (Perez-grijalba et al., 2019). For instance, autistic individuals with CNVs at the 15q13.3 (Morrow et al., 2010) and 16p11.2 loci have shown autistic symptoms such as facial dysmorphism and the degree of intellectual impairment that might vary amongst patients with the same CNV (Morrow et al., 2010). One model formulated to overcome some of the concerns around how CNVs contribute to ASD suggests that particular CNVs at specific loci enhance an individual's susceptibility to developing an ASD by a "threshold" of disease severity (Baccelli et al., 2020). The most common of these elevated vulnerability CNVs include maternal duplications at 15q11-q13 (Baccelli et al., 2020), deletions at 16p11.2, and deletions at loci encoding cell adhesion proteins such as neuroligins (Baccelli et al., 2020).

Regardless of these results, the mechanism through which a CNV may take a part in the etiology of ASD remains unknown. The rudimental process is gene dosage, in which the deletion or duplication (Hastings et al., 2009) of a gene or genes at a given

CNV region leads to changed or disrupted amounts of a gene product. Additionally, a loss at a particular cite may lead to discovering a recessive gene on the corresponding chromosomal area (Ebert et al., 2013), allowing it to have a harmful impact. Some examples of this mechanism implicated in disease etiology discovered in autistic persons include point mutation in the DIAPH3 gene (Vortsman et al., 2010) located in the paternal chromosome and 10Mb maternally inherited deletion on chromosome 13q (Pagnamenta et al., 2008). Given that the proband's of healthy siblings may also have the DIAPH3 mutation but lack the accompanying deletion, it is tempting to conclude that the maternal deletion revealed a recessive mutation in the paternal DIAPH3 gene, which impacted the proband's development of ASD. Additionally, since many CNVs are large enough to encompass 50 or more genes, determining which genes are involved in ASD pathogenesis within a specific CNV locus is very challenging.

Moreover, numerous researchers have hypothesized that ASD characteristics result from imprinting and sex-related genetic pathways analogous to known chromosomal disorders (Sanders et al., 2012). One of these chromosomal anomalies is on chromosome 15, leading to ASD-specific characteristics inherited exclusively from mothers (Pagnamenta et al., 2008). In addition, numerous sections of chromosomal X, 15 and maternal inheritance data support the existence of a gene expression imprinting mechanism (Szatmari et al., 2011). An imprinting mechanism might account for the lack of evidence for the Mendelian primary gene concept. Many have speculated on a recessive X-related genetical model because of the overlap with fragile X syndrome and the high prevalence of male cases with ASD (Bailey et al., 2008)

On the other hand, family studies contradict this concept, given the finding of certain male-to-male conveyance and the omission of the X chromosome in some correlation studies (Schutz et al., 2002) . Furthermore, associations between the fragile X cite and ASD have not been proven conclusive. Currently, an interesting domain of imprinted X-correlated transmission has been presented to account for both results and be consistent with ASD's male preponderance (Robinson et al., 2013).

The intricacy of ASD genetic architecture has inspired a continuous endeavor to discover concurrent molecular methodology that might codify genetic modifications with matched impacts on neurodevelopment, therefore demonstrating the observed

characteristic similarities. Indeed, multiple studies indicate that, despite the substantial variability of a gene-centric perspective of ASD genetic origins, a greater degree of convergence becomes evident when examined by affected molecular processes and pathways. Specifically, the major emerging pathways are epigenetic regulation of gene expression, alternative splicing, translation regulation, and synaptic activity. The evidence for epigenetic and transcriptional dynamics as a functional area consistently associated with ASD is particularly strong for genes encoding DNA and RNA binding proteins. For example, CHD8 and CHD2 (Bernier et al., 2014), CTNBB1 (together with CHD8, working on the WNT pathway) (Cotney et al., 2015), MECP2, and HDAC4 (Bernier et al., 2014) are examples of significant regulators of chromatin remodelling with a well-established relation to ASD. In addition, transcription factors TBR1 and FOXP1 are critical in neurodevelopment (Hoed et al., 2018). Also, FMRP (Fragile X mental retardation protein) (Bonaccorso et al., 2015) is a textbook example of an RNA-binding protein involved in mRNA dynamics. Finally, in terms of synaptic functioning, impacted genes include essential roles in glutamatergic and GABAergic transmission (El Ansari et al., 2014) and scaffolding proteins such as the SHANK family (Jiang et al., 2013)and neurexin cell adhesion molecules (wright et al., 2011). Even more intriguing, new studies show that this functional convergence may remain true when studying a variety of NDDs and mental diseases. Indeed, alterations in chromatin regulators and transcription factors are among the most frequently occurring genetic causes of NDDs, accounting for almost 150 of them in the Simons Foundation Autism Risk Initiative (SFARI) database (Simons Foundation, n.d.). This is a preliminary step toward elucidating the more significant phenotypic connections across numerous NDDs, highlighting the critical role of discovering similar gene regulation networks in better classifying brain illnesses and developing novel treatment targets.

Wide-ranging whole-exome sequencing (WES) studies displayed that no one gene may impart a substantial risk for autism (Schaaf et al., 2011). Rather than that, the most likely scenario is that many risk variations distributed over hundreds of genes are responsible. Approximately 4,000 genes are responsible for gene regulation, molecular pathways, and functional domains, all of which may have a role in neurodevelopmental disorders (Pinto et al., 2014). Among the genetic variants associated with ASD, the most often documented are mutations in synaptic genes such

as multiple ankyrin repeat domains (SHANK) (Jiang et al., 2013), and neurexin (NRXN) (wright et al., 2011). Notably, the same genes may cause many illnesses, implying an etiological overlap. For example, population-based twin studies are being conducted to test for autism spectrum disorders and associated illnesses (Hallmayer et al., 2011). The findings indicated that autism was not the only heavily hereditary ailment but shared 33% of its genetic variance with attention-deficit/hyperactivity disorder (ADHD) (Ghiradi et al., 2017). In addition, there was a substantial overlap between autism and perceptive, motor activity issues, and developmental abnormalities due to genetic effects (Satterstorm et al., 2020). These data imply that hereditary factors contribute significantly to comorbidity in various neuropsychiatric diseases, including cognitive difficulties.

As part of a recent meta-analysis of eight conditions, including anorexia nervosa (AN) (Gaffney et al., 2021), ADHD (Ghiradi et al., 2017), autism (Baxter et al., 2015), major depression (Magnuson et al., 2011), obsessive-compulsive disorder (OCD) (Meier et al., 2015), schizophrenia (Meyer et al., 2011), and Tourette syndrome (Huisman et al., 2016), more than 100 loci linked with more than one disorder were found to be remarkably involved in neurodevelopment and expressed in the fetus, as well. Autism was shown to have the highest genetic associations with ADHD (rg = 0.44) (Ghiradi et al., 2017), depression (rg = 0.45) (Magnuson et al., 2011), and schizophrenia (rg = 0.22) (Meyer et al., 2011). Unlike any of these other conditions, autism is not responsive to pharmacological therapy, and even those who show progress do not react to the same therapies. Evidently, with many autism risk genes implicated, determining the biochemical basis of ASD is very hard, even more so given the difficulty of reproducing the phenotypic symptoms of autism using animal and cellular models.

While these data suggest that genetic elements are extensively important to ASD etiology, candidate genes and copy-number variations only account for roughly twenty% of symptomatic and non-symptomatic ASD cases (Faraone et al., 2018). This number will undoubtedly increase as whole-genome sequencing becomes more widely used in clinical settings, but it will never elucidate all ASD cases. Common genetic variants portray for at least 50% of ASD vulnerability (Bonaccorso et al., 2015), leaving ample room for environmental contributions due to their limited incidence and

cumulative effects. In addition, (Hallmayer et al., 2011) and colleagues discovered in one study that environment accounted for 55% of the diversity in autism risk among twins in the largest twin research to date. According to the current hypothesis, many causes presumably function in most individuals, including various genes and environmental variables.

Over the last decade, many environmental factors studies linked with ASD have increased exponentially. While the topic is still in its infancy, research is based on physiologically plausible pathways and is focused on important phases of neurodevelopment.

4.4 Environmental Risk Factors

Along with the complexity of the genetic architecture underpinning ASD, several studies have explored the co-presence of multiple environmental influences and genetic components (Zoeller et al., 2012). One primary source of evidence is twin and family studies, which demonstrate the disorder's heredity and the involvement of the environment. Recent research found that heredity is less important than previously believed, implying a greater significance for environmental influences (Hallmayer et al., 2011). While one twin study discovered that a shared environment, such as family socioeconomic status, plays a significant role in ASD etiology, most family and twin studies revealed an individual's non-shared environment, such as birth complications, medications, or maternal infection, is more influential. However, pinpointing particular unique environmental influences is difficult since sampling errors, social chance, random biological disturbance, immunological response, and genetic variances between identical twins (Turkheimer & Waldron, 2000). One of the primary difficulties in interpreting the role of non-shared environmental influences in the genesis of ASD is that these variables are almost certainly cumulative rather than single causative agents (Modabbernia et al., 2017).

Autism is a developmental condition characterized by the interruption or change of particular brain maturational processes necessary for the illness to develop. However, determining exactly when this interruption happens is complicated. Evidently, with autism being regularly diagnosed before the age of two, vulnerable

developmental windows are more likely to emerge during the prenatal and early postnatal stages of development.

4.4.1 *Parental Age*

Older parental age has been implicated in various congenital illnesses and adverse reproductive outcomes such as miscarriage, infant mortality, autoimmune diseases, and other neuropsychiatric diseases (Shelton et al., 2010) (Hultman et al., 2002). Similarly, old parental age has garnered reasonable interest as a significant hazard factor for autism in offspring. Thus, the primary objective of examining the link between parental age and autism is to gain insight into the molecular mechanisms underlying autism.

While research indicates that advanced maternal or paternal age is a hazard factor for autism (Durkin et al., 2008) (Lampi et al., 2013), many studies also reported that the relative hazard of acquiring autism increases with the age of the father rather than maternal age (Lauritsen et al., 2005). Furthermore, the risk of having ASD was 5.75 times greater among children born to fathers over 40 than in children born to fathers under 30. Even after adjusting for confounding variables such as parental place of birth, parental psychiatric history, and prenatal complications, the relationship between paternal age and offspring autism risk persisted.

One potential reason is that males genetically predisposed to have an autistic child reproduce later than usual, maybe because they exhibit traits of the broad autism phenotype that make them less attractive to a partner. Another explanation is that random genetic mutations occur more often due to exposure to various environmental pollutants throughout the lifetime (Schaaf & Zoghbi, 2011). Toxins, for example, have been proven to induce DNA damage, germline mutations, and global hypermethylation of germ cells, all of which have been linked to long-term developmental impacts in the offspring of older parents (Buwe et al., 2005). For instance, it is estimated that throughout life, spermatogonia stem cell divisions result in increased mutation rates and cytogenetic abnormalities in older men's sperm (Yamada et al., 2016). In addition, experiments involving advanced paternal age mice models indicated that the offspring of older sires had a considerably greater chance of de novo copy number variations, with some of these mutations including previously associated genes with autism (Yauk et al., 2008).

Old maternal age is also a hazard factor as there can be some hurdles during gestation or due to maternal immune system activation and the emergence of autoimmune illnesses (Sotgiu et al., 2020). These hazards get severe with old age. Also, immune system stimulation may cause an increase in the discharge of proinflammatory cytokines and chemokines, which can disrupt the fetus's developing brain (Yockey et al., 2018). A meta-analysis conducted to investigate the link between maternal age and autism found considerable evidence for an increase in the risk of autism among mothers 35 years or older compared to moms younger than that age (Sandin et al., 2012). This estimated risk remained unchanged even when adjustments for potential confounders were included, with all the findings governing for paternal age and child gender, justifying for socioeconomic status, birth order, birth year, and perinatal factors such as fetal distress gestational age, birth weight and Apgar score.

Validation of the relationship between the parents' age and autism hazard might have significant consequences for public health, given that both mother and paternal ages have increased over the last several decades. Moreover, it is considered an effective tool in searching for etiological variables since the age-related reproductive systems of men and women vary. Several meta-analyses on this topic suggest a relationship between old maternal age and the hazard of autism (Sandin et al., 2012). In contrast, other research shows a more prominent correlation between old paternal age and autism risk (Lauritsen et al., 2005).

However, most of these studies analyzed the parental age separately and are also not current. Therefore, a systematic review and meta-analysis were conducted of updated evidence for the relationship between maternal and paternal advanced age and the risk of autism in children. Systematically examining and meta-analyzing the extant data on the effects of advanced parental age may inform practice and future research directions.

5 METHODOLOGY

This research complies to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Moher et al., 2009). The PRISMA guidelines describe the fundamental principles for performing comprehensive reviews and meta-analyses, allowing other researchers to replicate a systematic review and meta-analysis if they so want.

5.1 Search Strategy and Inclusion Criteria

The cases were selected based on their relevance to the research subject. All findings were authored in the English language. The literature review and meta-analysis employed two techniques to generate search queries for Web of Science, PubMed, Scopus, and CINAHL to optimize the query results. These methods comprised keywords, Boolean operators, field tags, and truncations. The search algorithm was created in the following manner:

((“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]). Moreover, a “snowball searching” was performed, which comprised of hand-searching the source lists of all relevant findings and review articles archived in the screening process.

5.2 Study Selection

Studies fulfilling the following inclusion criteria were included: study design: cohort study, case-control, cross-sectional, and observational studies. The prognosis of autism spectrum disorders in accordance with the Diagnostic Statistical Manual (DSM), International Classification of Diseases (ICD), Autism Diagnostic Interview-Revised (ADI-R), and The ADOS (Autism Diagnostic Observation Schedule). All populations, sex, ethnicity and children of all ages (0 to adults).

Studies that were excluded from the final analysis were studies that centered on genetic syndromes linked with ASD (e.g. Fragile X, Tuberous Sclerosis, etc.), other neurodevelopmental diseases, and single case or case series methodologies.

5.3 Data Extraction and Quality Assessment

One investigator performed the data extraction from the included relevant studies. Using Microsoft Excel, a consistent data collecting form was created to extract the following information:(i) bibliographic information; (ii) research design; (iii) sample size; (iv) exposure and outcome diagnostic technique and definitions; (v) risk of bias assessment; (vi) effect estimates (adjusted and unadjusted); and (vii) confounding variables. When there were numerous publications from the same population, the article with the most or latest data was incorporated. Whenever there was uncertainty in the inclusion or exclusion of a study, it was resolved by discussions with the supervising professor.

The Review Manager Software (RevMan5.4) (Cochrane, 2020) was used to conduct a meta-analysis of the different sub-group data that was collected from the observation studies; a descriptive analysis of the collected data was also completed.

To evaluate the quality of observational studies, the modified Newcastle-Ottawa scale was utilized (Stang, 2010). The scale is made up of eight components classified into three dimensions: participant selection, comparison of autism spectrum disorder and non-autistic spectrum disorder children, and outcome evaluation. The overall quality grade was a 9-point scale. Articles with ≥6 points were deemed of good quality.

5.4 Statistical Analysis

In most studies analyzed, parental age was categorized into numerous categories. A midpoint parental age category was selected as the referenced group to compute the odds ratio of autism spectrum diseases based on the lower age categories versus the midpoint and the higher age categories versus the midpoint. Other studies mainly evaluated the likelihood of autistic spectrum diseases based on higher age categories against lower age categories or lower age categories versus higher age categories. Thus, it was not feasible to establish a specific age range as the reference

group due to the reference groups highly varying in the studies. As a result, only meta-analyses of risk estimates comparing the lowest parental age to the highest parental age group were possible. The descriptive grouping of advanced parental age and the odds ratio of autism spectrum diseases according to the referenced point in each of the included studies are shown in table 6.1.

Risks linked with advanced maternal and progressive paternal age were pooled independently. In addition, linear regression meta-analyses of parental age and the relationship with autistic spectrum conditions employing previously described methods were performed, allowing for the prediction of OR for both maternal and paternal age. Also, in this analysis, a prediction of the odds ratio per unit 10 years rise or drop of the parents' age for each study was calculated and then pooled together. If the research did not give the median exposure group, a conversion of the parental age categories based on the computed midpoint of age was also done.

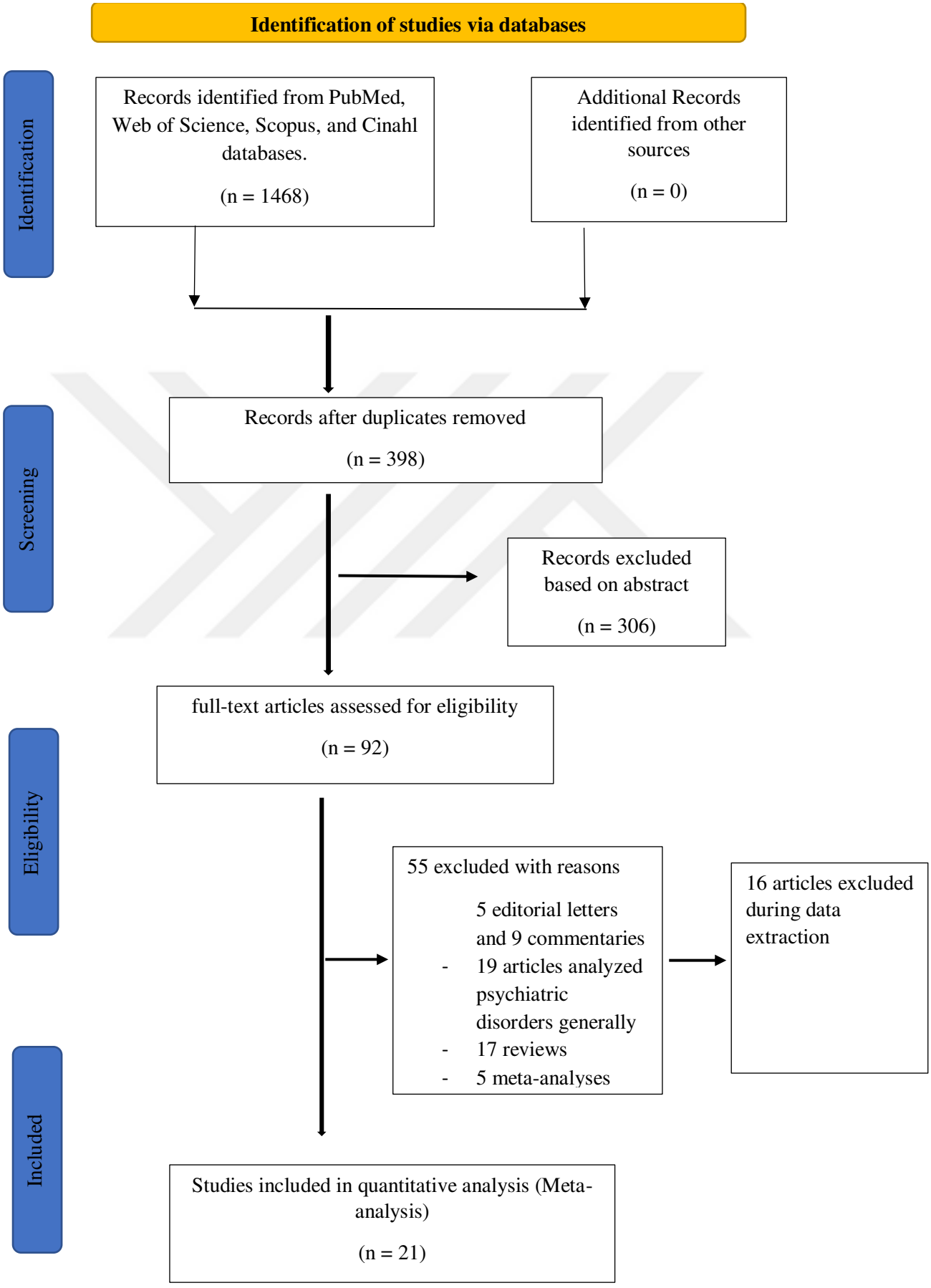
This meta-analysis used the random-effects model to account for the heterogeneity between studies due to the difference in research design and measuring period across the studies. The implementation of I squared (I^2) and Q-statistics to examine the heterogeneity across studies was assimilated in this study. Large I^2 (>50%) or $P < 0.1$ for Q-statistic illustrates possible heterogeneity across trials. A multiple subgroup analysis: Study design (cohort or case-control), geographical region (North America, Europe, or Asia and Oceania), and the diagnostic procedure were performed. Funnel plots were used to look for evidence of publication bias.

6 RESULTS

6.1 Study Selection

The initial query of database servers with the above-given keywords yielded 1,468 results. After removing duplicates, only 398 studies were remaining. The abstracts and titles of 398 papers were appraised for their relevance to the systematic review. After removal, 92 articles remained; after a full-text perusal, just 55 articles remained, and 16 more were eliminated during data extraction. In the end, 21 articles that met the established eligibility criteria were identified. Diagram 6.1 below shows the PRISMA diagram for the selection process.

Figure 6.1: PRISMA Flow Diagram



6.2 Data Extraction and Analysis

The main characteristics of the selected studies are listed in table 6.2. These studies were carried out between the years 2002 and 2022. The sample sizes varied from 292 to 6502555, totaling 22308289 participants. All of these participants were youngsters of ages (0 to adults). Among these studies were nine case-control studies and twelve cohort studies in this research. The features of the included studies are summarized in the table below.

Table 6.1: Characteristics of the Included Studies in the Meta-analysis

Author	Study Design	Country	Sample Size	Diagnostic Method	Effect sizes	Factors Adjusted For	NOS Score	Outcome
Al Mamari et al., 2021	Case-control	Oman	278 ASD 722 sample	DSM-V ADOS ADI-R	2.71[2.00, 3.66]	Child's age, delivery mode, parental age, maternal education, the governorate of residence	7	ASD
Bilder et al., 2009	Case-control	USA	120 ASD 13192 control	DSM-IV-TR	1.75[1.06, 2.90]	Primary cesarean delivery	7	ASD
Buizer-Voskamp et al., 2011	Case-control	The Netherlands	2262 ASD 9048 controls	DSM-IV-TR	1.17[1.00, 1.36]	Age differences between parents, social-economic status, and ethnic background	6	ASD
Burstyn et al., 2010	Cohort	Canada	1136 ASD 217934 controls	ICD-9	1.27[1.13, 1.43]	Maternal weight, height, pre-pregnancy diabetes, bleeding 20 weeks less, gestational diabetes, smoking, parity, socio-economic status of the mother	7	ASD
Croen et al., 2007	Cohort	USA	593 ASD 132251 sample	ICD-9	1.69[1.42, 2.00]	Age of the other parent, parity, sex of the child, maternal and paternal education, race/ethnicity	8	ASD

Author	Study Design	Country	Sample Size	Diagnostic Method	Effect sizes	Factors Adjusted For	NOS Score	Outcome
Durkins et al., 2008	Cohort	USA	1251 ASD 253347 sample	DSM-IV-TR	1.45[1.25, 1.68]	Other parent's age, birth order, maternal education, gender, child's race/ethnicity, multiple births, gestational age and birth weight	8	ASD
Fajardo et al., 2020	Case-control	Mexico	168 ASD 906 controls	DSM-IV	1.43[1.02, 1.98]	Opposite parental age, child's sex and age	6	ASD
Frans et al., 2013	Case-control	Sweden	5936 ASD 30923 control	ICD 9/10	1.35[1.28, 1.43]	Parental history of psychiatric, parental education, county, birth year, sex and age of the other parent	9	ASD
Gao et al., 2020	Cohort	Denmark	27 616 ASD 1449167 sample	ICD 10	1.31[1.28, 1.34]	Analysis of parental age: child's birth year, gender, parity, psychiatric history maternal education and origin and spouse age. Analysis of grandparental age: birth year of the parents, parity, grandmaternal education and origin, spouse age.	9	ASD

Author	Study Design	Country	Sample Size	Diagnostic Method	Effect sizes	Factors Adjusted For	NOS Score	Outcome
Grether et al., 2009	Cohort	USA	20 701 ASD 6502555 sample	DSM-IV	1.55[1.50, 1.61]	Child's sex and birth weight, age of the other parent, maternal race/ethnicity, paternal race/ethnicity, maternal education, paternal education, parity, gestational age, delivery method.	9	ASD
Hultman et al., 2011	Cohort	Sweden	860 ASD 1035487 sample	ICD 9/10	2.29[1.35, 3.89]	Paternal age, paternal education, maternal country of origin, maternal psychiatric hospitalization, paternal psychiatric hospitalization, birthweight, fetal distress, and parity	8	Childhood Autism
Lampi et al., 2013	Case-control	Finland	2264 ASD 9030 control	ICD 9/10	1.21[1.07, 1.37]	Child learning disorders, maternal social class, birth order, child's body weight, maternal and paternal mental history	7	ASD
Lundstrom et al., 2010	Cohort	Sweden UK	230 ASD 24646 sample	DSM-IV	2.73[1.82, 4.09]	Maternal age, zygosity, and socioeconomic status	6	ASD

Author	Study Design	Country	Sample Size	Diagnostic Method	Effect sizes	Factors Adjusted For	NOS Score	Outcome
Lyall et al., 2020	Cohort	USA	378 ASD 478 sample	DSM-IV	2.05[1.56, 2.70]	Other parent's age, parental education, parental race and ethnicity, child's sex	7	ASD
Parner et al., 2012	Cohort	Denmark	9556 ASD 1231720 sample	ICD 8/10	1.74[1.67, 1.81]	None	9	Childhood autism
Reichenberg et al., 2006	Cohort	Israel	110 ASD 132161 sample	ICD 10	1.90[1.27, 2.84]	Year of birth, socioeconomic status, and maternal age	8	ASD
Sandin et al., 2016	Cohort	Denmark Israel Norway Sweden Australia	30902 ASD 5766794 sample	ICD	1.25[1.22, 1.28]	Child's sex and birth year	9	ASD
Shelton et al., 2010	Case-control	USA	12159 ASD 4947935 controls	ICD-code	1.94[1.87, 2.02]	Other parent's age, both parents race/ethnicity, year of birth, parental education, parity and insurance type	9	ASD
Sasanfar et al., 2010	Cohort	Iran	179 ASD 549354 sample	DSM-IV-TR	1.42[1.05, 1.92]	Paternal education, maternal education, birth order, gender, consanguinity, and urbanization	8	ASD

Author	Study Design	Country	Sample Size	Diagnostic Method	Effect sizes	Factors Adjusted For	NOS Score	Outcome
Tsuchiya et al., 2008	Case-control	Japan	84 ASD 292 controls	DSM-IV	2.99[1.47, 6.06]	Age, gender, birth order, socio-economic status, other parent's age	7	ASD
Van Balkom et al., 2012	Case-control	Aruba	95 ASD 347 controls	DSM-IV	2.36[1.41, 3.94]	Paternal and maternal age, low birth weight, preterm birth and parental immigrant status	8	ASD

Note: ASD= Autism Spectrum Disorder, DSM=Diagnostic Statistical Manual, ICD=International Classification of Diseases, NOS=Newcastle-Ottawa Scale, ADI-R= Autism Diagnostic Interview-Revised, ADOS= Autism Diagnostic Observation Schedule.

6.3 Quality Assessment

The chosen studies' quality was evaluated using the Newcastle-Ottawa Scale (NOS). The median Newcastle-Ottawa Scale (NOS) score of the included studies was 8 (the quality of each included study ranged from 6 to 9 stars).

Table 6.2: NOS Quality Assessment of the Included Studies

STUDY	Selection	Comparability	Outcome	Total NOS Score
Al-Mamari et al., 2021	2	2	3	7
Bilder et al., 2009	3	1	3	7
Buizer-Voskamp et al.,2011	2	1	3	6
Burstyn et al., 2010	3	2	2	7
Croen et al., 2007	3	2	3	8
Durkin et al., 2008	3	2	3	8
Fajardo et al., 2020	3	2	1	6
Frans et al., 2013	3	3	3	9
Gao et al., 2020	3	3	3	9
Grether et al., 2009	3	3	3	9
Hultman et al., 2011	4	2	2	8
Lampi et al., 2013	3	2	2	7
Lundstrom et al., 2010	2	2	2	6
Lyall et al., 2020	2	2	3	7
Parner et al., 2012	3	3	3	9
Reichenberg et al., 2006	2	3	3	8
Sandin et al., 2016	3	3	3	9
Sasanfar et al., 2010	3	3	2	8
Shelton et al., 2010	3	3	3	9
Tsuchiya et al., 2008	3	2	2	7
Van Balkom et al., 2012	3	2	3	8

6.4 Statistical Results: Advanced Parental Age and Autism Spectrum Disorder in Children

The 21 included studies indicated a high level of heterogeneity meaning that they were not homogenous. This was evidenced by the results of the I^2 statistic I^2 = 97% (Heterogeneity: Chi^2 = 619.07, df = 20 (P < 0.00001); I^2 = 97%). Advanced parental age compared to the reference points was associated with a 59% increase in development of risk of Autism Spectrum Diseases in children OR (odds ratio) = 1.59

with 95% CI 1.45-1.74. The analysis indicated an overall effect of Z = 9.95 (P < 0.00001). Results of this analysis are represented in the forest plot below.

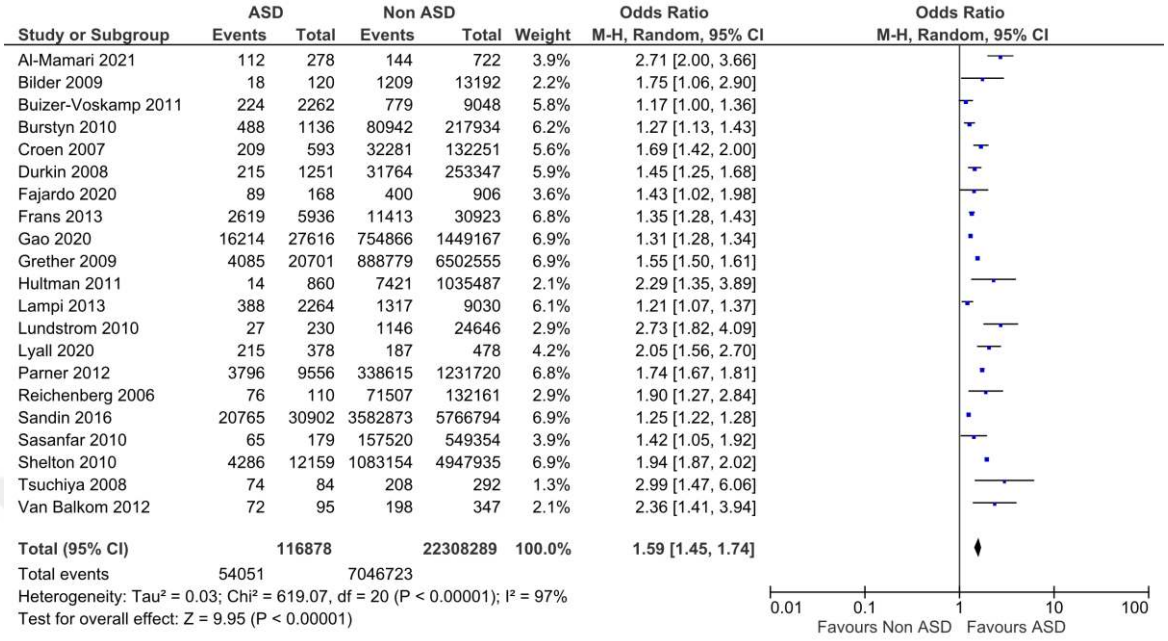


Figure 6.2: A forest Plot of the Studies

Results of individual studies: statistical results from figure expounded.

(Al Mamari et al., 2021)

The researchers applied multivariate logistic regression to investigate the connection between advanced parental age and the onset of autism spectrum disorders (ASD). The odds ratio (OR) of maternal age as a risk factor for ASD substantially rose with increasing age category (age <25 as a reference, OR = 3.39, 6.12, 7.86, and 13.13 for age ranges 25–29, 30–34, 35–39, and ≥40 years, respectively). The ORs of raising paternal age as a risk factor for ASD was also statistically significant (using age <30 as a reference, OR = 2.20, 2.36, and 3.12 for age categories 30–34, 35–39, and 40–44 years, respectively); however, the effect decreased with paternal age 45 years (OR = 1.42; 95% CI: 0.64–3.12).

(Bilder et al., 2009)

The study evaluated the influence of prenatal, perinatal, and neonatal variables on ASD risk using multivariate logistic regression analysis. A substantial connection was found between maternal age and the likelihood of ASDs. Offspring of women ≥ 35 years of age were more susceptible to having an ASD than offspring of mothers 20

to 34 years of age (OR: 1.68 [1.01–2.78]; P=.043). When adjusted for maternal age and gestational age, children with autism were substantially more likely to be firstborn than their birth cohorts (OR: 1.79 [95% CI: 1.20–2.40] P=.005). No correlation was found between the risk of autism and father age, paternal education, smoking, or gestational age.

(Buizer-Voskamp et al., 2011)

The researcher applied a logistic regression which revealed a substantial link between increasing paternal age and ASD risk in the children (OR=1.27, 95% Confidence Interval:1.05, 1.53): Older fathers at >40 years of age have a 3.3-fold increased odds ratio (OR) of having a child with ASD compared to younger fathers. Because Pearson's correlation coefficient for both mother and paternal age indicated that both ages were significantly connected across all diagnostic groups, only the paternal age connection was explored.

(Burstyn et al., 2010)

Researchers examined maternal characteristics and obstetric problems related to autism spectrum conditions in children. The study demonstrated that advanced maternal age (> 35 years vs ≤ 25 years: RR = 1.57, 95% CI = 1.25-1.97) was quantitatively related to an elevated risk of autism spectrum disorder (ASD) in a child, with the majority of the higher risks in women older than 25. (Note: all groups with age greater than the reference category appeared to be at an increased risk).

(Croen et al., 2007)

The researchers discovered that the incidence of autism spectrum diseases rose considerably with each 10-year rise in maternal and paternal age (adjusted relative risk [RR], 1.31; 95% confidence interval [CI], 1.07-1.62). (RR, 1.28; 95 percent CI, 1.09-1.51). Adjusted relative risks for both mother and paternal age were increased for autistic disorder offspring (maternal age: RR, 1.18; 95 percent CI, 0.87-1.60; paternal age: RR, 1.34; 95 percent CI, 1.06-1.69). Girls had considerably greater correlations with parental age than boys, however, gender differences were not statistically significant.

(Durkin et al., 2008)

After modifying for the other parent's age, maternal education, birth order, and other confounders, the researchers determined that maternal and paternal age were inversely correlated with autism (adjusted odds ratio for maternal age ≥35 vs. 25-29 years = 1.39, 95 percent confidence interval: 1.1, 1.6; the adjusted odds ratio for paternal age ≥40 vs. 25-29 years = 1.54, 95% confidence interval: 1.1, 1.8). In addition, firstborn offspring of 2 older parents were three times more probable to develop autism than a third- or later-born offspring of moms aged 20-34 and dads aged 40 (odds ratio = 3.1, 95% confidence interval: 2.0, 4.7).

(Fajardo et al., 2020)

Using a multivariate logistic regression model, the odds ratio (OR) and 95% confidence intervals (CI 95%) of paternal and maternal age were estimated. In the first regression model, maternal age was not substantial as a risk factor for ASD (OR = 1.02, 95% CI [.99, 1.06], p =.07). In contrast, paternal age was linked to a higher likelihood of ASD (OR = 1.04, 95% CI [1.02, 1.07], p .001). Also, in the stratified analysis (five categories of parental age), advanced paternal age elevated the likelihood of ASD, but only if the father was between the ages of 40 and 49 (OR = 2.57, 95% CI [1.47, 4.47], p .001). Additionally, a younger parental age, particularly between 20 and 29 years, lowered the number of ASD. In contrast, advanced maternal age did not raise the incidence of ASD in the stratified analysis. Moreover, when the father was older than the mother by 10 years, the risk for ASD rose (OR = 3.37, 95% CI [1.65, 7.21], p <.001). Also, when the mother was older than the father, a greater risk was seen, although this model achieved only marginal statistical significance.

(Frans et al., 2013)

The investigators implemented Logistic regression, which revealed a substantially sharp increase in the risk of childhood autism across all paternal age groups older than 35 years. After accounting for the mother's age, the paternal age impact was shown for fathers 30 years and older. Additional changes had no discernible impact on the point estimates or confidence intervals. In the fully adjusted model (Model 4), men 50 and older had the most substantial risk (OR = 2.26; 95% CI = 1.63 to 3.03). After correcting for the father's age and the other covariables, they

additionally observed no trend for higher risk of autism in the kids of older mothers, except for an excess of moms aged 40 and older in cases.

(Gao et al., 2020)

The researchers employed logistic regression analysis to measure the relations between parental or grandparental age and ASD in youngsters. They found that advanced paternal or maternal age over 30 years was monotonically linked with elevated ASD risk, with odds ratios (ORs) of 1.56 (95% CI, 1.45-1.68) for maternal age 40 years and older and 1.57 (95% CI, 1.39-1.78) for paternal age 50 years and older, compared with parents aged 25 to 29 years. In the multigenerational cohort, 9364 grandchildren (1.7%) had ASD.

(Grether et al., 2009)

In adjusted models that included the age of the other parent and demographic covariates, a 10-year rise in maternal age was linked with a 38% increase in the odds ratio for autism (odds ratio = 1.38, 95% confidence interval: 1.32, 1.44), and a 10-year rise in paternal age was linked with a 22% increase (odds ratio = 1.22, 95% confidence interval: 1.18, 1.26).

(Hultman et al., 2011)

Multiple studies were carried out, including a 10-year birth cohort, families within the birth cohort with autism-discordant siblings, and a meta-analysis. All of these models discovered that the probability of autism rose monotonically with paternal age. After adjusting for maternal age and known risk factors for autism, kids of males aged ≥ 50 years were 2.2 times (95% confidence interval: 1.26–3.88; P = 0.006) more inclined to develop autism than offspring of men aged ≤ 29 years. Adjusting for maternal age and parity, an in-family study of discordant siblings revealed that affected siblings had older paternal ages (P< 0.0001).

(Lampi et al., 2013)

The researcher employed a conditional logistic regression to independently investigate the relationship between the ASD prognosis and parental age for the three major subtypes, notably childhood autism, Asperger's syndrome, and PDD. In all studies, maternal and paternal ages were linked with ASD subgroups differently.

Advanced paternal age (35–49 years) was connected with childhood autism, whereas advanced maternal age was associated with both Asperger's syndrome and PDD (35 years or more and 40 years or more, respectively).

(Lundstrom et al., 2010)

Using regression models based on generalized estimating equations (GEE), this research assessed the relationship between paternal age and ASD. Odds ratio (OR) and accompanying two-sided 95% confidence intervals of the Wald type (CIs). Fathers older than 50 had three times the elevated risk of having children with ASD. This relation remained after controlling for maternal age, zygosity, gender, and socioeconomic status. In both cohorts, there was evidence of a nonlinear, U-shaped link between paternal age and ASD (Sweden p =.035, UK p =.055, one-tailed).

(Lyall et al., 2020)

The researchers generally did not observe any significant relationships between advanced maternal age with clinical ASD diagnosis, Social Responsiveness Scale, or Vineland Adaptive Behavior Scales scores. In contrast, they discovered an elevated risk of Autism Spectrum Diseases with paternal age of 30 years or older (adjusted odds ratio [AOR] = 2.05, and 95 percent confidence intervals [CI] = 1.56–2.40).

(Parner et al., 2012)

The researchers discovered that both maternal and paternal age are related to an elevated risk of ASD in kids (hazard ratios ranging from 1.21 (1.10-1.34) to 1.65 (1.09-2.48) relying on permutations of parental age groups; 35, 35-39, and 40+ years). For moms younger than 35 years, the risk of ASD rose with the father's age group. For fathers under 35 years of age, the likelihood of ASD rose as maternal age increased.

(Reichenberg et al., 2006)

This research indicated a substantial monotonic relation between rising paternal age and ASD risk. After adjusting for potential confounders and mother age, kids of males 40 years or older were 5.75 times (95 percent confidence range, 2.65-12.46; P<.001) more prone to have Autism Spectrum Diseases than children of men younger than 30 years. They also reported that there was no connection between maternal age and Autism Spectrum Diseases after accounting for paternal age.

(Sandin et al., 2016)

After controlling for covariates and the other parent's age, the authors noted that advancing paternal and maternal ages were each correlated with a higher RR of Autism Spectrum Disorder (mothers 40–49 years vs. 20–29 years, RR=1.15 (95 percent confidence interval (CI): 1.06–1.24); fathers older or 50 years vs. 20–29 years, RR=1.66 (95 percent CI: 1.49–1.85)). Younger maternal age was also related to an elevated risk for ASD (RR=1.18 (95% CI: 1.08–1.29), P<0.001; mothers 20 years vs. 20–29 years, 95% CI: 1.08–1.29).

(Sasanfar et al., 2010)

The researchers used the Cox regression model to conduct conditional logistic regression on the matched data. They discovered that father age, but not mother age was strongly linked to a higher prevalence of autism. An investigation of the collective impact of parental age and education indicated that parents with a greater level of education had a higher chance of producing autistic children, with parental age having a dose-response relationship.

(Shelton et al., 2010)

A multivariate logistic regression model demonstrated that independent of father age, mother age increased the risk of autism uniformly. The adjusted odds ratio (AOR) for mothers 40+ years was 1.51 (95 percent CI: 1.35–1.70), and relative to moms 25, AOR=1.77 (95 percent CI, 1.56–2.00). In contrast, autism risk was related to rising paternal age predominantly among women younger than 30: AOR = 1.59 (95% CI: 1.37–1.85) when comparing dads 40+ vs. 25–29 years old. However, among moms over 30, the AOR for men 40+ vs. 25–29 was 1.13 (95 percent CI: 1.01–1.27), virtually equal to the AOR for fathers 25 years.

(Tsuchiya et al., 2008)

The researchers found an Increase in paternal, but not maternal, age was associated with an elevated risk of high-functioning autistic-spectrum disorder. They also established that a one-level advance in paternal age class corresponded to a 1.8-fold increase in risk, after adjustment for covariates.

(Van Balkom et al., 2012)

The study reported that advanced paternal age was related with a higher risk of autism spectrum disorders (ASDs) in kids. Autism risk rose 2.18 times for children born to dads in their thirties, 2.71 times for men in their forties, and 3.22 times for fathers in their fifties and older. For all other paternal age groups, however, the impacts became insignificant.

7 RESULTS II: META-REGRESSION AND SUBGROUP ANALYSIS

7.1 Meta-Regression Analysis

7.1.1 Paternal Age Modelling

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

Figure 7.1 below displays this increased risk graphically indicating the OR (y-axis) of having an autistic spectrum disorder child at various paternal ages(x-axis). There was a linear relationship between paternal age and the development of autism spectrum conditions in children.

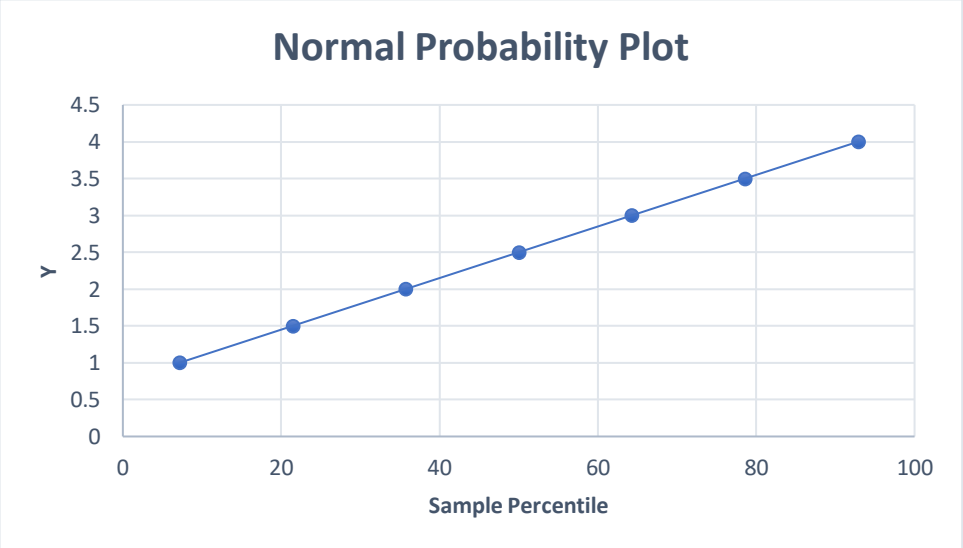


Figure 7.1: Modelling of Paternal Age(x-axis) to Predict Risk Odd Ratio(y-axis) of ASD

7.1.2 Maternal Age Modelling

Additionally, maternal age was modelled as a continuous variable. Adjusting for all other relevant variables, the risk of autistic spectrum disorder 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 7.2 below displays this elevated risk graphically revealing the OR (y-axis) of having an autistic spectrum conditions child at various maternal ages. The relationship between maternal age and autism spectrum conditions was observed to be linear as shown in the figure below.

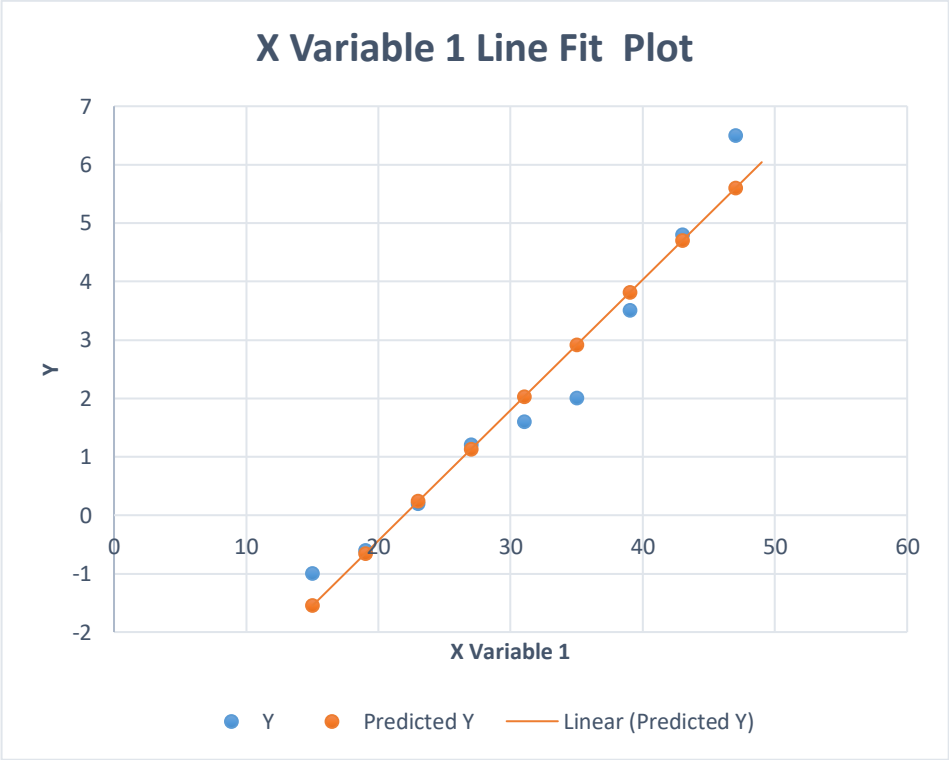


Figure 7.2: Modelling of Maternal Age(x-axis) to Predict Risk Odd Ratio(y-axis) of ASD

7.2 Subgroup Analysis

A subgroup study encompassed study design (cohort or case-control), geographical region (North America, Europe, Asia and Oceania), and diagnostic procedure. The findings of the subgroups are shown below, and a summary of these results can be viewed in table 7.1.

7.2.1 Study Design

This subgroup analysis indicated an odds ratio (1.55[1.41, 1.70] and odds ratio (1.66[1.36, 2.03]) for cohort and case-control studies, respectively. In addition, both studies revealed that they are similar and no heterogeneity between them, with a subgroup difference of chi^2=0.37, df=1 (p=0.54), I^2=0%. The figure below shows the forest plot of the subgroup.

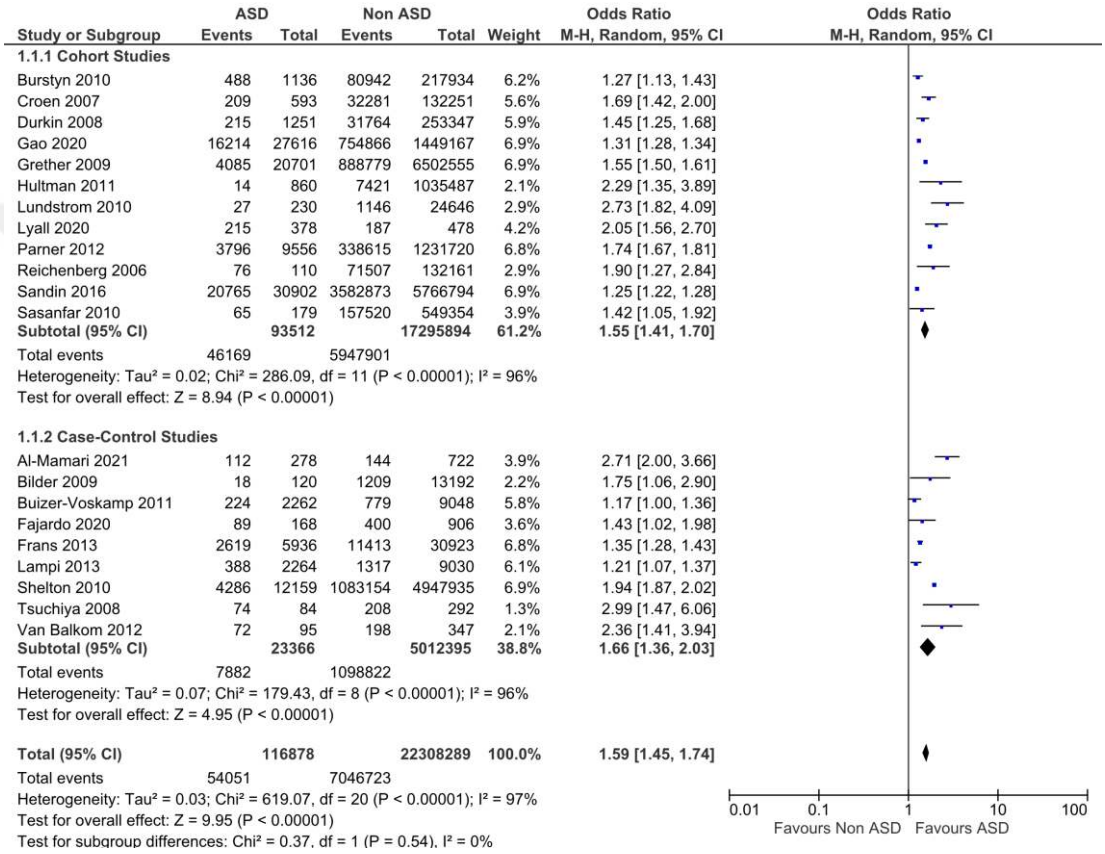


Figure 7.3: A Forest Plot of the Study Design

7.2.2 Paternal Age and Maternal

In this subgroup, the risk of ASD in individuals linked with advanced parental age reported an odds ratio (1.58[1.41, 1.76]) and odds ratio (1.61[1.46, 1.70]) for maternal age and paternal age, respectively. The subgroup differences chi^2=0.05, df=1, (p=0.82), I^2=0%, indicated that there is no significant heterogeneity and both ages have similar affect. Below is a forest plot for the subgroups.

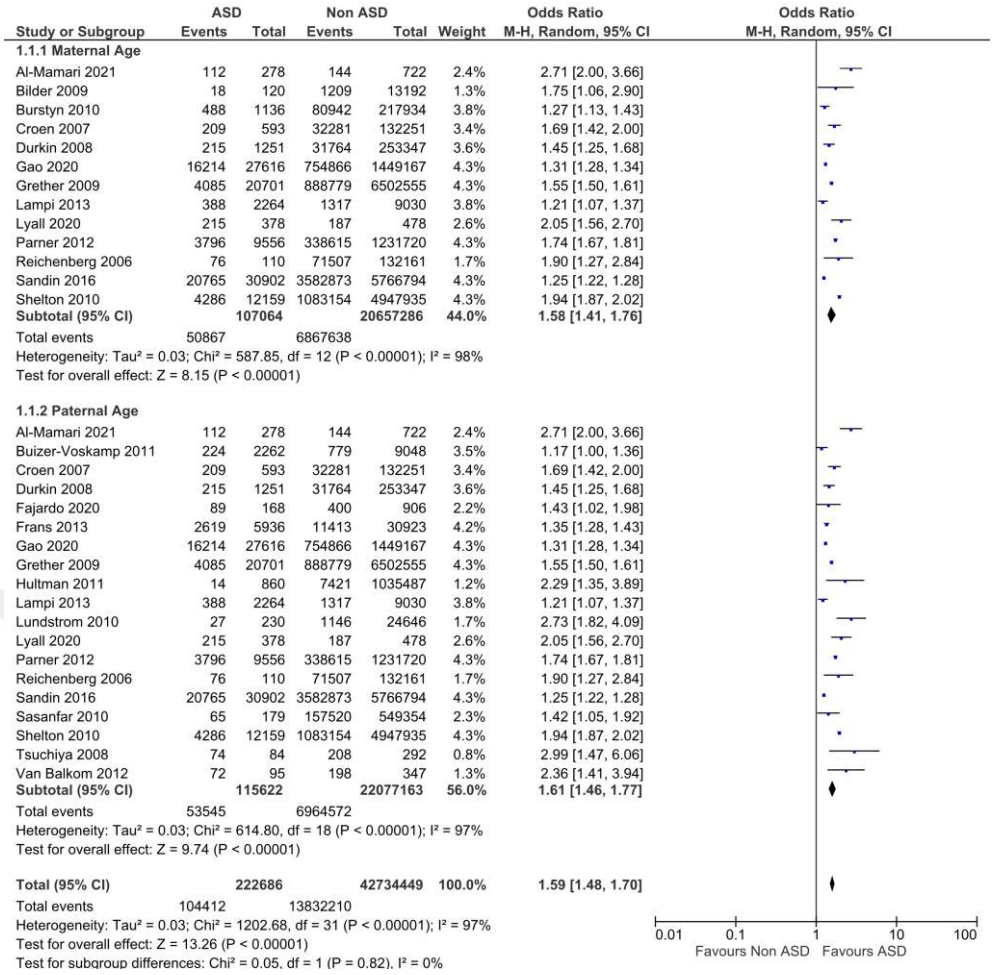


Figure 7.4: A Forest Plot of Maternal and Paternal Ages

7.2.3 Diagnostic Methods

In this subgroup, the diagnostic methods employed in these studies were observed, with an odds ratio (1.72[1.49, 1.99]) and odds ratio (1.50[1.32, 1.70]) for DSM and ICD, respectively. Also, the subgroup differences indicated that they are not similar and considerable heterogeneity, with chi^2=2.11, df=1 (p=0.15), and I^2=52. Below is a forest plot of the subgroups.

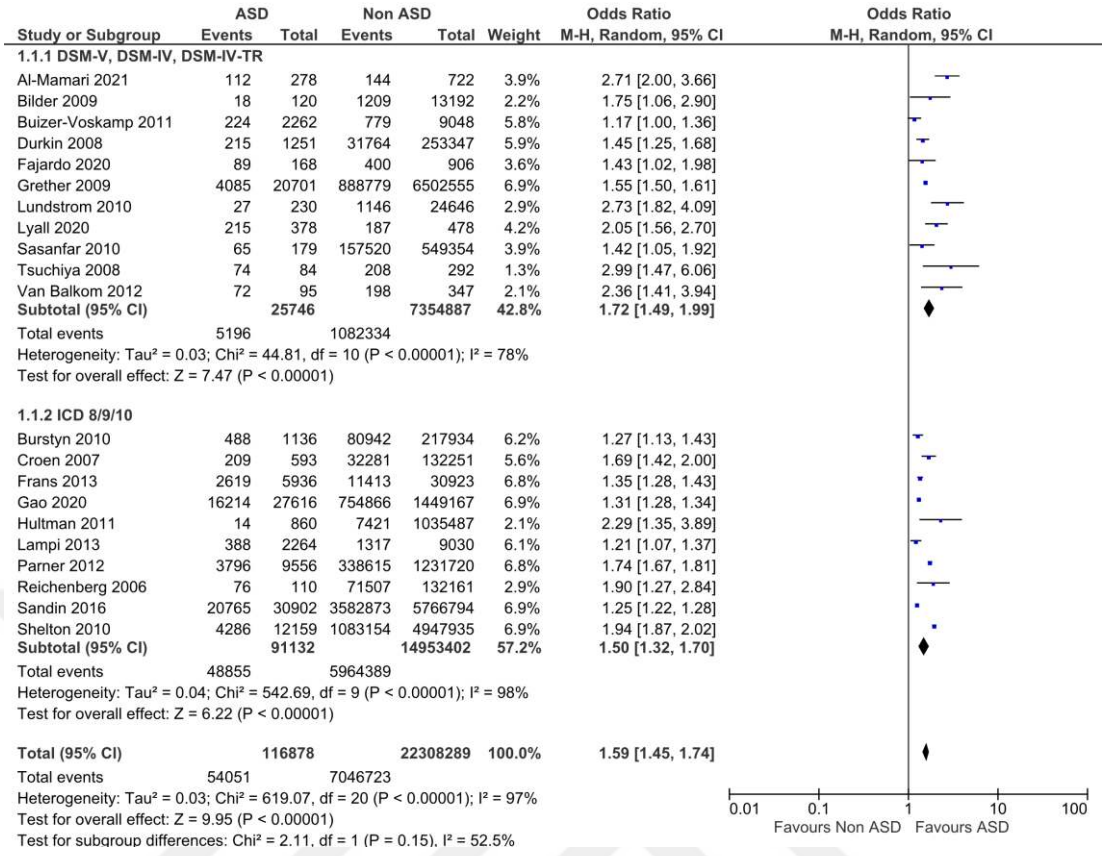


Figure 7.5: A Forest Plot of the Diagnostic Methods

7.2.4 Geographical regions

This subgroup evaluated the development of ASD in youngsters in different geographical regions. An odds ratio (1.41[1.27, 1.57]), odds ratio (1.64[1.44, 1.86]), and odds ratio (2.07[1.45, 2.97]) for Europe, North America, Asia, respectively was observed. Also, subgroup differences revealed a chi^2=28.12, df=3 (P<0.0001), and I^2=89.3%, indicating the presence of substantial heterogeneity. Below is the forest plot of the subgroups.

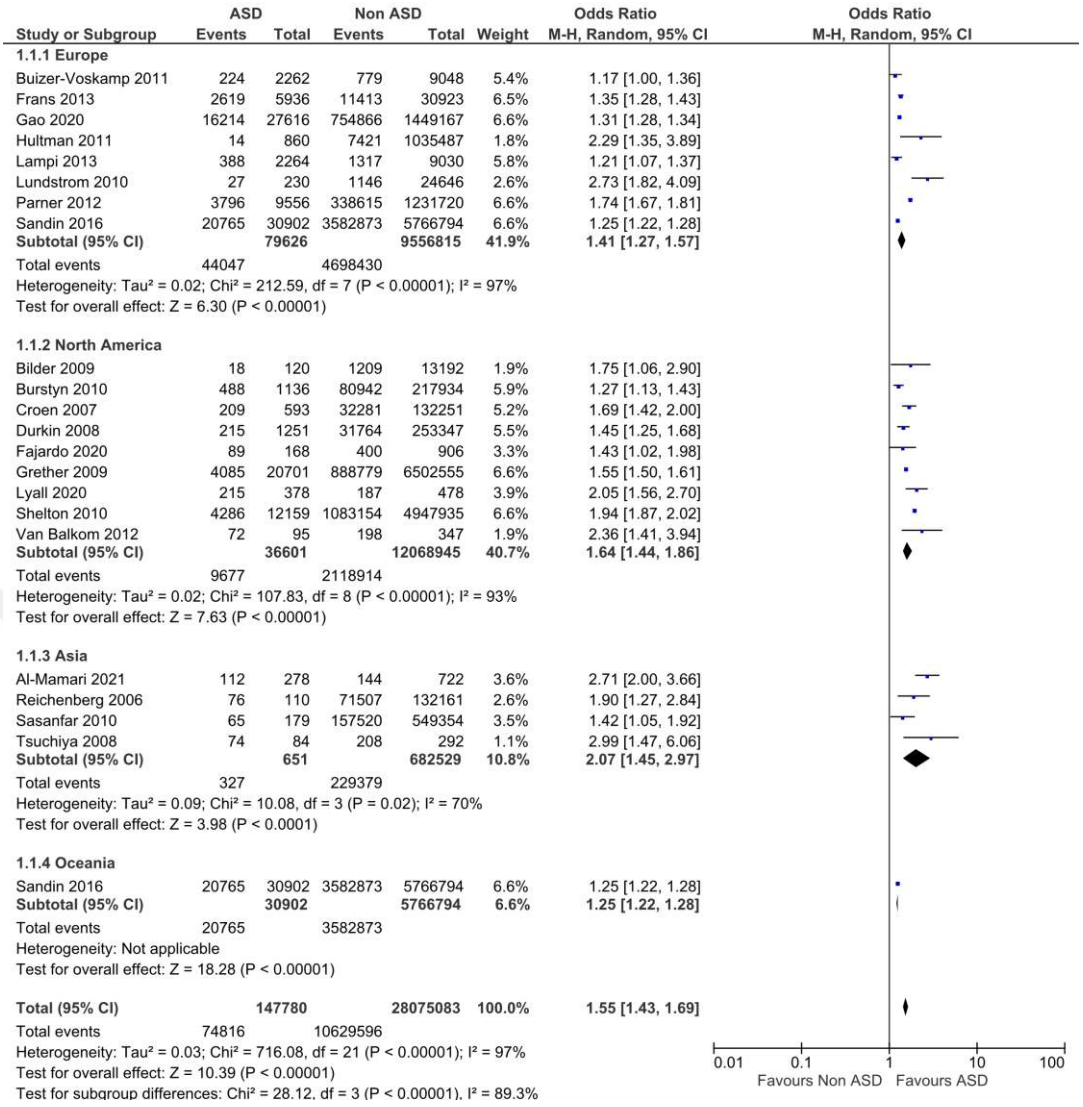


Figure 7.6: A Forest Plot of the Geographic regions

Table 7.1: Subgroup Analysis of the Included Studies

Subgroup analysis	N	Odds ratio (OR, CI)	Subgroup differences
Cohort	12	(155[1.41,1.70]) Heterogeneity:Tau^2=0.02; chi^2=286.09, df=11(p<0.00001);I^2=96%, Z=8.94 (P<0.00001)	Chi^2=0.37, df=1(p=0.54); I^2=0%
Case-control	9	(1.66[1.36,2.03]) Heterogeneity:Tau^2=0.07; chi^2=179.43, df=8(p<0.00001);I^2=96%, Z=4.95 (P<0.00001)	

Subgroup analysis	N	Odds ratio (OR, CI)	Subgroup differences
Paternal age	19	(1.61[1.46,1.77]) Heterogeneity:Tau^2=0.03; chi^2=614.80, df=18(p<0.00001);I^2=97%, Z=9.74 (P<0.00001)	Chi^2 =0.05, df=1 (p=0.82), I^2 =0%
Maternal age	13	(1.58[1.41,1.76]) Heterogeneity:Tau^2=0.03; chi^2=587.85, df=12(p<0.00001);I^2=98%, Z=8.15 (P<0.00001)	
DSM	11	(1.72[1.49,1.99]) Heterogeneity:Tau^2=0.03;chi^2=44.81, df=10(p<0.00001);I^2=78%, Z=7.47 (P<0.00001)	Chi^2 =2.11, df=1 (p=0.15), I^2 = 52.5%
ICD	10	(1.50[1.32,1.70]) Heterogeneity:Tau^2=0.04; chi^2=542.69, df=9(p<0.00001);I^2=98%, Z=6.22 (P<0.00001)	
Europe	8	(1.41[1.27,1.57]) Heterogeneity:Tau^2=0.02; chi^2=212.59, df=7(p<0.00001);I^2=97%, Z=6.30 (P<0.00001)	Chi^2 =28.12, df=3 (p<0.00001); I^2 =89.3%
North America	9	(1.64[1.44,1.86]) Heterogeneity:Tau^2=0.02; chi^2=107.83, df=8(p<0.00001);I^2=93%, Z=7.63 (P<0.00001)	
Asia	4	(2.07[1.45,2.97]) Heterogeneity:Tau^2=0.09;chi^2=10.08, df=3(p=0.02);I^2=70%, Z=3.98 (P<0.00001)	
Oceania	1	(1.25[1.22,1.28]) Heterogeneity not applicable , Z=18.28 (P<0.00001)	

7.3 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 (Fig. 7.3). 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. Five studies were filled with the trim and fill approach, and the concluded pooled result was (OR = 1.48 with 95% CI 1.36 –1.62).

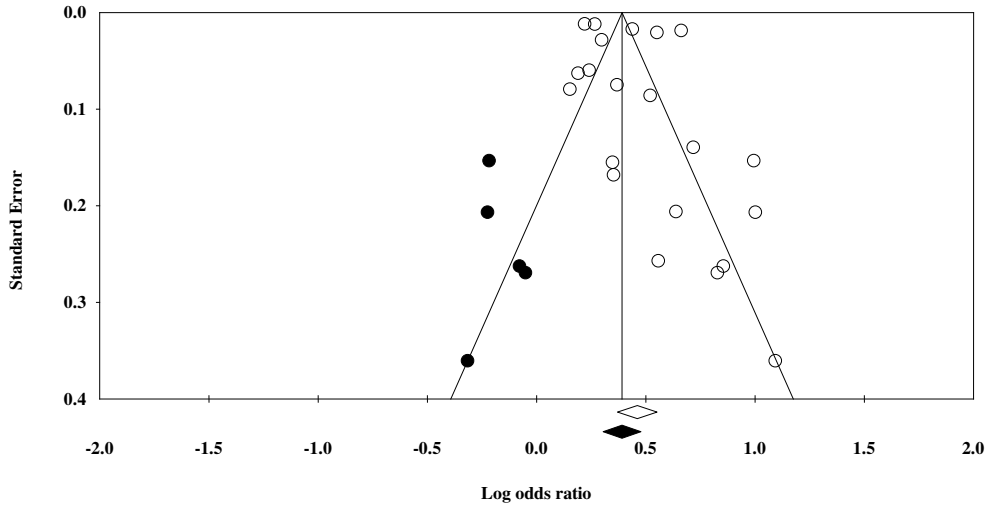


Figure 7.7: A funnel Plot For Assessing Publication Bias

8 DISCUSSION

A total of 21 epidemiological published studies addressing the influence of parental age on autism spectrum conditions in youngsters fulfilled the inclusion criteria. The current meta-analysis solely intended to examine the link between parental older age and autism spectrum conditions in youngsters. The most significant conclusions of this meta-analysis are as follows; (i)lower parental age was linked to a reduced likelihood of autism spectrum conditions in kids, (ii)advanced parental age was affiliated with a greater risk of autism spectrum conditions in youngsters, (iii) a reduction of 10 years in paternal age was linked with a 28% decreased risk of autism spectrum conditions. In contrast, a rise of 10 years in the ages of the mother and father was attributed to a 35% and 29% elevated risk of autism spectrum conditions, respectively.

Moreover, by incorporating estimates from all available published research, it was possible to analyze the validity of advanced parental age as a contributing factor for autism spectrum conditions risk with a more abundant evidence base and more accuracy than in the past. The findings of this meta-analysis are consistent with a prior meta-analysis (Wu et al., 2016) of advanced maternal and paternal age and higher risk of autism, which was based on a large body of data. The present meta-analysis expanded the results of the prior meta-analysis utilizing recently published studies on both paternal and maternal age. In addition, these findings support the theory that having older parents increases the chance of developing mental and psychiatric illnesses (McGrath et al., 2014). Also, these results align with other research indicating that environmental, genetic, and prenatal variables contribute to autism (Hallmayer et al., 2011) (Wu et al., 2015)

The vast majority of the studies have concentrated on the impact of maternal or paternal age on autism. This meta-analysis provided a detailed evaluation of the relationship between maternal and paternal age and the risk of autism spectrum conditions in offspring. The analysis compared the category of the lowest or highest parental age with the referenced age. It is plausible that the risk of ASD in youngsters would have been even more significant if the studies were expanded to compare only the highest parental age category with the lowest age category.

Furthermore, two incorporated studies found a connection between older grandparental age and a higher likelihood of autism spectrum conditions, indicating that the risk of autism spectrum conditions may progress across successive generations (Frans et al., 2013) (Gao et al., 2020). Other studies included in this meta-analysis demonstrated that both rising paternal and maternal ages were related to an elevated risk of ASD; even so, the impact was more significant and persistent among mothers (Al Mamari et al., 2021). This research concurred with two other studies that found a linear link between rising paternal age and the probability that their children may acquire ASD (Reichenberg et al., 2006) (Tsuchiya et al., 2008). Also, several studies considered the parental history of mental health disorder or a broader autism spectrum disorders phenotype (i.e., having a greater count of ASD-related traits within any two of the three main groups of features, notably communication, social inadequacies, stereotyped behavior) (Tsuchiya et al., 2008). (Tsuchiya et al., 2008) also observed that the average paternal age of individuals with ASD did not vary between fathers with and without a broader ASD phenotype.

Individuals with ASD are prone to have a low birth order. Hence, most research considered birth order or parity (Durkin et al., 2008) (Grether et al., 2009) (Sasanfar et al., 2010) (Tsuchiya et al., 2008) (Lyall et al., 2020). Autism spectrum diseases risk tended to be higher for firstborn children, which was inversely proportional to the child's birth order (Durkin et al., 2008) (Grether et al., 2009) (Sasanfar et al., 2010).Some studies that considered an intellectual disability identified a correlation between paternal age and instances of autism spectrum diseases with high functioning (Al Mamari et al., 2021) (Tsuchiya et al., 2008) .

All of these findings demonstrated that advancing maternal and paternal age are linked to a higher risk of autism spectrum condition in offspring. These discoveries are crucial because the identified risk indicators will assist in a deeper comprehension of the causative processes behind autism spectrum disorder in kids, whose exact pathophysiology and likely causation are yet unknown.

9 STRENGTH AND LIMITATIONS

This research has significant merits. Firstly, to the best of our awareness, this is one of the most extensive studies investigating the link between maternal and paternal age and autism spectrum disease outcomes. The pooled analysis has greater power than individual findings to detect disparities. This is obvious in the adjusted analysis that compares the lowest paternal age group to the reference points.

In addition, the 95 percent confidence intervals (CIs) reported by the present meta-analysis were substantially narrower than each research, resulting in more reliable findings. Second, the pooled odds ratios for autism risk were substantially similar across various sensitivity studies. Third, there was no publication bias in the majority of the analyses, except for the small study effect, which is the absence of studies favoring the control that was not published.

Moreover, post hoc subgroup analysis was performed to explain the presence of significant heterogeneity. The geographical regions subgroup showed a substantial difference and a significant P value that may have clarified the heterogeneity.

However, this study has several drawbacks:

I. Observational studies cannot provide definitive proof for the role of older parents in the development of autism spectrum disease outcomes; they can only explain relationships.
II. In the plurality of the included studies, the authors utilized the midpoint of parental age groups as the reference group. It was only plausible to analyze the risk of ASD relative to the youngest or oldest parental age category vs. the referenced age in this meta-analysis. Thus, the risk of autistic spectrum disorders dependent on the lowest vs. highest parental age was not quantifiable based on the current literature. In addition, further investigation is warranted to elucidate the correlation between advanced parental age and autism spectrum diseases in youngsters and to explicate the cause-effect relationship.
III. Heterogeneity was likely present in the vast majority of the analyses.
IV. Although random-effects and subgroup analyses were conducted, it is unlikely that heterogeneity was adequately accounted for.

Consequently, the findings should be regarded with extreme caution. Despite the diversity of the included publications, the observed relationships were pretty consistent. Fifth, it is noteworthy that other variables could also be in place. For example, the logical explanation for late reproductive age at delivery of the first child may potentially influence the risk of autism (Liu et al., 2010), however, it was not feasible to evaluate it as a covariate in this meta-analysis. Lastly, the other parent's age was not controlled in many of the included studies as a critical confounder. Hence the maternal and paternal ages may be correlated and vice versa.

10 CONCLUSION

The current meta-analysis study revealed a sizeable amount of data that advanced parental age is a significant variable in the development of autism spectrum conditions in individuals. However, most of the studies included in this meta-analysis had few participants. Future research should encompass a larger sample size, a more precise evaluation of the diagnosis, clarify the cause-and-effect correlation, and the framework between advanced parental age and an increased risk of autism in kids. In addition, to study the link between older parental age and ASDs, detailed observational data addressing essential confounding variables such as the other parent's age and familial mental history are necessary. This risk's recognition is crucial in both clinical practices and as a public health concern.

Conflict of interest

No conflicts of interest were declared.

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12 CURRICULUM VITAE

13 PLAGIARISM REPORT

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

ORİJİNALLİK RAPORU

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