AUTISM SPECTRUM DISORDER: A LITERATURE REVIEW ON PREVALENCE AND ETIOLOGY MEASURES

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Abstract

Prevalence estimates in the last few decades make autism the fastest-growing neurodevelopmental disability. Autistic symptoms usually lead to significant impairment in social communication, repetitive behavior patterns, and, possibly, fixed and restricted interests. This work aimed to review the recent literature to synthesize and provide a straightforward understanding of the autism etiology, evidencing estimates regarding its prevalence, heritability, and recurrence rates. Taking research with refined methodologies, large populations, multiple geographical areas, and well-known diagnostic procedures, the results show significant variability in prevalence (overall: 1.1-2.1%, females: 0.5-0.9%, males: 1.8-3.6%). Studies that investigated larger sample sizes show overall recurrence rates among siblings of $\approx$ 9-10% (females: $\approx$ 4-5%, males: $\approx$ 14-18%). In comparison, studies that explored relatively small sample sizes presented a higher recurrence with larger variation (overall: $\approx$ 14-27%, females: $\approx$ 9-20%, males: $\approx$ 26-32%). The Broader Autism Phenotype (BAP) recurrence rates also presented higher variation, from 10% to 55% at $\approx$ 36 months of age. Adding autism and BAP estimates, the overall risk for developmental concerns in high-risk siblings ranged from $\approx$ 27% to $\approx$ 77% (overall: $\approx$ 50%, females: $\approx$ 32%, males: $\approx$ 60%). Heritability data also vary, although studies that explored large and diverse samples and applied robust heritability estimation methods pointed to relatively stable estimates, from $\approx$ 80% to $\approx$ 85%.

Keywords: Autism spectrum disorder, autism spectrum disorder prevalence, autism spectrum disorder etiology, autism spectrum disorder recurrence.

1. Introduction

Autism and Autism Spectrum Disorder (ASD) are general terms for a complex neurodevelopmental disorder earlier classified as distinct subtypes (e.g., Autistic Disorder, Childhood Disintegrative Disorder, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), and Asperger Syndrome). Autism is a highly heritable lifelong neurodevelopmental disability currently merged into an umbrella of ASD diagnosis. Symptoms typically emerge during early childhood (between 1 and 3 years of age) and affect domains such as social communication and interaction. Defined by a particular set of behaviors, autism is considered a spectral condition that affects individuals differently and in varying degrees (BAI et al., 2019; ASSOCIATION, 2013). The first autism studies started at the beginning of the 20th-century (SZATMARI, 2000; KANNER et al., 1943). Since then, several changes have been presented regarding ASD classification, prevalence, recurrence rates, and etiology, especially in the last few decades.

Previous autism epidemiological studies suggested an ASD prevalence (the proportion of individuals in the population who have a positive diagnosis) from 0.04% to 0.2%. However, relying on refined research methodologies, some recent epidemiological surveys indicate a much higher ASD prevalence ranging from 1% to 2% in many countries and regions, although estimates over 2% also have been reported (FOMBONNE, 2018), reaching almost 3% as reported in the most recent Autism and Developmental Disabilities Monitoring (ADDM) Network publication (MAENNER et al., 2023). Furthermore, these estimates range widely between genders; ASD is about three to four times more

common among boys than girls (CARVALHO et al., 2020; BAIO et al., 2018; LOOMES; HULL; MANDY, 2017). Despite the heterogeneity between the survey methodologies and results, there is a consensus regarding an increasing trend in ASD prevalence. Estimated increases in the ASD diagnoses, from 6-7% to 15% per year, make ASD the fastest-growing developmental disability in the United States (BONIS, 2016; ÖZERK, 2016).

Proper ASD prevalence estimates are essential for planning public health strategies and actions, such as allocating sufficient funding and providing equitable access to developmental evaluations and interventions (MAENNER et al., 2021; ALVES et al., 2020; CHIAROTTI; VENEROSI, 2020). Furthermore, most methods to estimate the ASD heritability depend on accurate ASD prevalence estimates (TENESA; HALEY, 2013; BONNET, 2016), which also is critical to identify potential sex differences in clinical symptoms, etiology aspects, and risk factors (DELOBEL-AYOUB et al., 2020). Finally, in addition to the significance in the health domain, accurate ASD prevalence estimates likewise provide references and directions for future research and practices (HUIFEN et al., 2021).

Early diagnosis and proper interventions are critical factors in improving autistic behaviors (LANDA, 2018; HAZLETT et al., 2017). However, autism cannot be biologically diagnosed once there are no specific laboratory tests to identify ASD traits (LORD et al., 2018). Therefore, the ASD diagnosis is clinical, performed through direct behavior observation. The importance of early diagnosis motivated several studies regarding groups of people with a greater predisposition to the disorder, named as high-risk for ASD (SHEPHARD et al., 2017). Such studies are characterized by evaluating some characteristics of the individual that could predict a future diagnosis (BUSSU et al., 2018; EMERSON et al., 2017), and by assessing the family members of diagnosed individuals. The most common are studies involving siblings (GANGI et al., 2021; LIN et al., 2021; HANSEN et al., 2019; D'ABATE et al., 2019; PALMER et al., 2017; PISULA; ZIEGART-SADOWSKA, 2015), extensive investigations to explain the ASD etiology (TAYLOR et al., 2020; BÖLTE; GIRDLER; MARSCHIK, 2019; SCHAEFER; MENDELSOHN, 2013), in addition to works focused on diagnose based on medical image (SANTANA et al., 2022; RODRIGUES et al., 2022).

ASD has a multifactorial etiology. Although incompletely understood, genetic and environmental factors and their interactions seem to contribute to ASD etiology (BÖLTE; GIRDLER; MARSCHIK, 2019; LYALL et al., 2017), with most studies showing a largely genetic contribution (up to 97%) (SANDIN et al., 2017). A complex interaction between common and rare genetic variants constitutes the genetic composition of ASD, with common genetic variants accounting for almost all ASD heritability (ROSTI et al., 2014; GAUGLER et al., 2014; HALLMAYER et al., 2011). From 80% to $\approx$ 90% of ASD cases are caused by hereditary factors, with a small environmental contribution (CARVALHO et al., 2020; ALMANDIL et al., 2019; BAI et al., 2019; SANDIN et al., 2017; KRONCKE; WILLARD; HUCKABEE, 2016).

First-degree relatives of individuals with ASD are at increased risk for ASD-related characteristics. The ASD recurrence among relatives of affected family members is high compared to the overall ASD prevalence. Thus, the risk of ASD recurrence in siblings of an ASD individual is an essential measure of the genetic contribution to the

ASD etiology (GRØNBORG; SCHENDEL; PARNER, 2013). Both the level of relatedness and the individuals' gender seem to be determinant factors to the recurrence extent among family members (HANSEN et al., 2019).

As stated, reliable ASD prevalence estimates, as well as proper estimates regarding the ASD etiology, especially related to heritability and recurrence rates, are critical elements to provide references for public health planning, health care practices, and directions for future research. Thus, this work reviewed the recent literature to synthesize and provide a straightforward understanding of the ASD etiology, evidencing reliable estimates regarding ASD prevalence, heritability, and recurrence rates.

The remaining of this paper is structured as follows: Section 2 describes our work methodology, followed by a brief history of the ASD classification evolution in Section 3. Respectively, Sections 4, 5.3, 5.4, and 5.5 review, synthesize, and discuss the estimates regarding ASD prevalence, heritability, and recurrence rates. At last, Section 6 concludes this work.

2. Methodology

The literature was collected and reviewed through a semi-systematic process followed by qualitative content analysis. This literature review was conducted using the search engine Google Scholar including academic journals, magazines, and conference proceedings. The keywords used were: '*prevalence of autism spectrum disorder*', '*recurrence of autism spectrum disorder among siblings*', '*heritability of autism spectrum disorder*', and '*broader autism phenotype in siblings of children with autism spectrum disorder*'.

The term Autism Spectrum Disorder was adopted near 2013, mainly due to the advancement in diagnostic criteria manuals. Therefore, we examined articles published in the last decade (i.e., from 2010 to 2022). Each search returned approximately 20.000 articles on average. Thus, we used Google Scholar's ordering criteria[1] to select the most relevant papers dealing with the subjects studied. This selection of the most relevant articles resulted in approximately 20-30 papers from each subject. We then performed a context analysis on all identified papers. All papers have been assessed by title, abstract, and then by a full-text evaluation. The search was filtered by language (English) and limited to peer-reviewed studies to ensure a level of quality and a sufficient amount of scientific rigor.

Therefore, studies that met the search keywords and published in the past decade were chosen for a quality analysis. All issues covered (prevalence, heritability, and recurrence) depend on the definition of the ASD diagnosis. Thus, an inclusion criterion was the definition of ASD cases based on modern diagnostic and screening tools and certified health professionals. Another inclusion criterion was that each paper had its data clearly exposed and sufficient given the review requirements. The remainder of the quality analysis depended on each issue covered. In prevalence studies, we concentrated on recent surveys with relatively large sample sizes, preferably diversified in terms of the subjects' age and geographical area, as can be seen in Section 4. Regarding heritability, we concentrated on proven tools used to estimate the etiology of complex and quantitative binary

[1]Google Scholar ranks contents weighing the full text of the document, where it was published, who it was written by, and how often and how recently it has been cited.

traits, such as autism, as can be seen in Section 5.3. Because most recurrence works do not hold large sample sizes, we limit the sample size to at least 20 subjects for broader autism phenotype recurrence studies and at least 250 subjects for ASD recurrence studies.

As we did not intend to perform a comprehensive search, from this point we no longer used any systematic searching tool. Instead, the strategy adopted to search for other relevant works was the snowballing technique, a systematically searching for primary studies based on references to and from other studies (WOHLIN et al., 2012). The aim was to broaden the scope of this work and include the maximum number of relevant related works, even some before 2010.

As we analyzed the selected articles, we looked for references that could be included in this review according to the quality criteria. However, as it resulted in several duplicated articles, we do not reapply the snowballing technique. Also, the new articles found went through the same analysis process presented before. The following sections present the selected articles and the essential theories to the review understanding.

3. ASD Classification

The category of autism diagnosis was not immediately recognized as a distinct category. The Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association (APA) has already classified autism as:

- A psychiatric condition, an autistic sign in children with psychosis marked by a detachment from reality (DSM-I) (ASSOCIATION, 1952);
- Infantile schizophrenia, understood as a behavior of schizophrenia in childhood (DSM-II) (ASSOCIATION, 1968);
- A syndrome within the Global Developmental Disorders established with its separate diagnosis and described as a Pervasive Developmental Disorder (PDD), distinct from schizophrenia (DSM-III) (ASSOCIATION, 1980); and
- Invasive Developmental Disorders, characterized by a triad: impaired communication, impaired social interaction, and stereotyped and repetitive behavior, and further divided into sub-conditions such as Classic Autism, Rett Syndrome, Asperger's Syndrome, Childhood Disintegrative Disorder, and Global Development Disorder with no other specification (DSM-IV) (ASSOCIATION, 1994).

The DSM fifth edition (DSM-V) (ASSOCIATION, 2013) named the disorder as Autism Spectrum Disorder. ASD was defined as a neurodevelopmental disorder categorized by the dyad:

- **Communication and social interaction**: showing deficits in socioemotional reciprocity, non-verbal communicative behaviors, and in the development, maintenance, and understanding of relationships; and
- **Repetitive and stereotyped behaviors with fixed and restricted interests**: showing deficits in motor movements, stereotyped or repetitive speech or use of objects, fixed and highly restricted interests that are abnormal in intensity or focus, strong adherence to routines and ritualized patterns of verbal or non-verbal behavior, hyper/hypo reactivity to sensory stimuli or unusual interest in the environment sensory aspects.

Alternatively, clinicians in many countries use the International Statistical Classification of Diseases and Related Health Problems (ICD), a global standard for health data, clinical documentation, and statistical aggregation. Released in the 1990s, ICD already classified autism as:

- Infantile Autism, listed under the Schizophrenia group (ICD-8) (OUSLEY; CERMAK, 2014; LEEKAM et al., 2002);
- Infantile Autism, Disintegrative Psychosis, Other, and Unspecified, listed under the Psychoses with Origin Specific to Childhood group (ICD-9) (OUSLEY; CERMAK, 2014; LEEKAM et al., 2002);
- Childhood Autism, Atypical Autism, Rett Syndrome, Other Childhood Disintegrative Disorder, Overactive Disorder with Mental Retardation and Stereotyped Movements, Asperger Syndrome, Other PDDs, and PDD Unspecified, listed under the PDD group (ICD-10) (ORGANIZATION et al., 1992);

The ICD eleventh edition (ICD-11) (ORGANIZATION et al., 2018) also named the disorder as Autism Spectrum Disorder, placing ASD inside the Neurodevelopmental Disorders group. ICD-11 characterizes ASD as persistent deficits to initiate and sustain reciprocal social interaction and social communication and by a range of restricted, repetitive, and inflexible behavior patterns, interests, or activities atypical or excessive given the individual's age and socio-cultural context. The disorder's onset occurs during the developmental period, typically in early childhood, but symptoms may not become fully manifest until later when social demands exceed limited capacities.

ICD-11 classifies the disorder as:

- ASD without disorder of intellectual development and with mild or no impairment of functional language;
- ASD without disorder of intellectual development and with impaired functional language;
- ASD with disorder of intellectual development and with mild or no impairment of functional language;
- ASD with disorder of intellectual development and with impaired functional language; and
- ASD with disorder of intellectual development and with absence of functional language.

The DSM and ICD manuals, especially the latest versions, are currently the guides most used by specialized health professionals to provide ASD diagnosis.

4. ASD Prevalence

Prevalence, or prevalence rate, is the proportion of individuals in a population who have a particular disease or attribute at a specified point in time or over a specified period. Prevalence differs from incidence because it includes all cases, new and preexisting, in the population at the specified time, whereas incidence is limited to new cases only (DICKER et al., 2006).

The first autism epidemiological surveys indicated a prevalence from 0.4 to 2 cases for every 1000 people (0.04%-0.2%). Current works show a higher ASD prevalence than previously estimated, although there is no standardization of autism survey methodology.

In 2010 it was estimated 52 million ASD cases worldwide (BAXTER et al., 2015), while in 2016 it was estimated 62.2 million ASD cases (VOS et al., 2017). Despite the heterogeneity between ASD survey methodologies, there is a trend toward an increasing ASD prevalence. Table 1 shows reputable ASD prevalence surveys published in the last decade. These contemporary researches rely on refined methodologies, including large populations, from multiple geographical locations, stratified samples with detailed screening activities, and well-known diagnostic procedures.

Table 1. ASD prevalence.

General (M:F) %	Sex Ratio (M:F)	Site(s)	ASD Criteria	Sample Size	Age (years)	Follow Up Interval	Reference
2.27 (3.7:0.9)	4.2:1	US▷	ICD-9/10	220281⋆	8	2010-2018	(MAENNER et al., 2021)
2.21 (3.6:0.9)	4.5:1	US	⊕	◁	18-84	⊘	(DIETZ et al., 2020)
1.15 (1.8:0.4)	4.1:1	Greece	DSM-V ICD-10	182879	3-10	2008-2019	(THOMAIDIS et al., 2020)
1.01 (1.6:0.4)	3.8:1	Multi⋈	ICD-10	434215	7-9	2006-2015	(DELOBEL-AYOUB et al., 2020)
1.74 (2.7:0.8)	3.4:1	US	•	88530	3-17	1997-2017	(ZABLOTSKY et al., 2019)
1.20 (NA:NA)	NA	Multi⊙	DSM-IV ICD-9/10	2551918	4-17	1998-2015	(HANSEN et al., 2019)
1.10 (1.6:0.5)	3.2:1	Multi⋄	DSM† ICD†	2001631	0-16	1998-2018	(BAI et al., 2019)
1.14 (1.8:0.4)	4.3:1	Qatar	DSM-V	133781	6-11	2015-2018	(ALSHABAN et al., 2019)
1.92 (2.7:1.1)	2.5:1	Sweden⊖	DSM-IV ICD-10	567436	0-17	1984-2011	(XIE et al., 2019)
2.50 (3.9:1.0)	3.5:1	US	∨	43021	3-17	1999-2016	(KOGAN et al., 2018)
1.50 (2.4:0.6)	4.0:1	Canada	DSM-IV/V ICD-9/10	≀	5-17	2003-2015	(OFNER et al., 2018)
2.47 (3.6:1.2)	2.9:1	US	±	30502	3-17	1999-2016	(XU et al., 2018)
1.25 (2.0:0.5)	3.9:1	US○	ICD-9	3166542	4-18	1998-2016	(PALMER et al., 2017)
2.08 (3.3:0.8)	4.2:1	US⊣	DSM-IV-TR	12329	7-9	2001-2010	(HEWITT et al., 2016)
0.80 (1.2:0.3)	4.2:1	Global△	DSM ICD	50378584	NA-27	1980-2009	(BAXTER et al., 2015)
1.18 (NA:NA)	NA	Denmark	ICD-8/10	1546667	06-30	1980-2010	(GRØNBORG; SCHENDEL; PARNER, 2013)
1.15 (1.6:0.7)	2.5:1	Sweden⊖	DSM-IV ICD-10	444154	0-17	1990-2007	(IDRING et al., 2012)
1.20 (2.2:0.5)	4.4:1	NL×	⊗	62505	4-16	NA	(ROELFSEMA et al., 2012)
2.64∧ (3.7:1.5)	2.5:1	South Korea	DSM-IV	55266	7-12	2006-2009	(KIM et al., 2011)
1.57 (NA:NA)	NA	UK‡	ICD-10	11700	5-9	NA	(BARON-COHEN et al., 2009)

(M:F)Male:Female; ▷Arizona, Arkansas, California, Georgia, Maryland, Minnesota, Missouri, New Jersey, Tennessee, Utah, and Wisconsin; ⋆Monitors ASD among children aged 8 years in participating communities; ⋈Denmark, Finland, France, and Iceland; ⊕Reported by parents on the National Survey of Children's Health (NSCH); ◁Estimated the 2017 national and state ASD prevalence by simulation; ⊘2016-2018 state ASD prevalence of male and female children ages 3-17 (born 1999-2015), an estimate of the state populations in 2017, and state mortality rates from 1999 to 2017; •National Health Interview Survey; ⊙California (US), Denmark, Finland, Israel, Sweden and Western Australia; ⋄Denmark, Finland, Sweden, Israel, and Western Australia; †DSM-III-R/IV/IV-TR/V or ICD-8/9/10 according to the period, and in-person diagnosis by psychiatrists or pediatric neurologists with expertise in neurodevelopmental disabilities in Israel before age three; ⊖Stockholm County; ∨Parent reported ASD children at the NSCH who ever received an ASD diagnosis by a care provider; ≀40% of all children and youth aged 5–17 years across Canada (based on 2011 Canadian census); ±Parent report of a physician diagnosis at the NSCH; ○A de-identified database from Aetna; ⊣City of Minneapolis; △Tables S3 and S4 in the (BAXTER et al., 2015) supplementary material; Of ASD cases; ×Netherlands (Eindhoven, Haarlem, and Utrecht); ⊗Diagnoses made by a clinical professional (e.g. psychologists or psychiatrists); ∧After accounting for some sources of uncertainty not taken into account in the original paper, (PANTELIS; KENNEDY, 2016) claimed that a more appropriate confidence interval would be approximately twice as large as reported initially (1.91%, 3.37%); ‡Cambridge City, East Cambridgeshire, South Cambridgeshire, and Fenland districts; NACould not be determined with sufficient precision.

Most studies concentrated on children and adolescents (0-18 years). (DIETZ et al., 2020) simulated ASD prevalence in adults using ASD prevalence data from children and adolescents (3-17 years). (GRØNBORG; SCHENDEL; PARNER, 2013) also worked with adults, although $\approx 75\%$ of their diagnosed ASD cases were adolescents (under 18 years old). The systematic review of (BAXTER et al., 2015) included samples up to 27 years old, despite not finding population-representative data for adults. Indeed, the ASD diagnosis usually occurs up to 17 years of age (OFNER et al., 2018).

Most studies have had follow-up intervals ending in the previous 5-6 years, with a few works with follow-up intervals ending in the latest ten or more years. These recent follow-up intervals guided the adoption of modern, widely used, and well-known ASD diagnostic tools.

These recent researches investigated samples of multiple sizes (small to large), geographically dispersed across states, countries, and even continents. Such a set of characteristics contributes to the reliability of their results, mainly if analyzed collectively. According to these studies' results, the overall ASD prevalence has a mean of $\approx 1.6\%$ (females: $\approx 0.7\%$, males: $\approx 2.6\%$).

Table 2 shows some centrality measures of the ASD prevalence data presented in Table 1. Despite the mean and the median of ASD prevalence data being close for these studies, the standard deviations are relatively high.

Table 2. Central tendencies of ASD prevalence from Table 1.

Measure	General (%)	Male (%)	Female (%)	Sex Ratio (M:F)
Mean	1.6	2.6	0.7	3.7
Standard Deviation	0.6	0.9	0.3	0.7
Median	1.4	2.4	0.7	4.0

Figure 1 shows the dispersion and skewness of the ASD prevalence data. The data dispersion shows variability in ASD prevalence of 1.1-2.1% (females: 0.5-0.9%, males: 1.8-3.6%). Once the data present an asymmetric distribution, especially regarding males and the overall prevalence, the median is the most appropriate central tendency measure since the extreme values influence the mean. Thus, the central position of the data indicates an overall ASD prevalence of 1.4% (females: 0.7%, males: 2.4%).

ASD seems to occur globally irrespective of culture, geography, or degree of industrialization. Some prevalence data from developed countries[2] appear to be more comprehensive and reliable than those from developing countries. In developed countries, the greater availability of screening and diagnostic services usually increases the number of ASD diagnoses. However, even with ASD awareness and more well-defined epidemiological studies, ASD prevalence estimates still vary across and within geographical areas and countries, years of research, and source of data used. Such variation conducts to large variability in the prevalence estimates worldwide (CHIAROTTI; VENEROSI, 2020). For example, the ASD prevalence varied widely across geographic areas in one of the most recent surveys (MAENNER et al., 2023), from 2.3% in Maryland to 4.5%

[2]Developed vs. developing countries according to the United Nations Country classifications 2020.

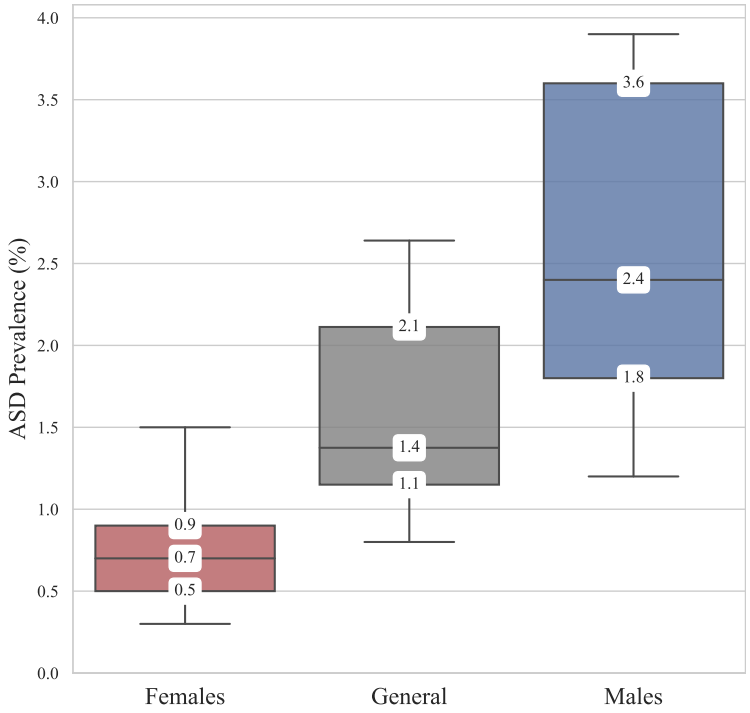

Figure 1. Dispersion and skewness of the ASD prevalence data from Table 1.

in California (overall prevalence of 2.77%). Nevertheless, the global ASD prevalences are rising, even when considering data from both developed and developing countries (ONAOLAPO; ONAOLAPO, 2017; ROTHOLZ et al., 2017; JANVIER et al., 2016).

However, much remains necessary to figure out the ASD prevalence trend, especially in developing countries. While recent ASD prevalence among developed countries tends to percentage values that approach 2%, epidemiological researches in developing countries point to percentage values quite below (e.g., 0.11% in Ecuador, 0.15% in India, 0.27% in Brazil, 0.53% in Caribbean Islands, 0.68% in Uganda, 0.8% in Nigeria, 0.87% in Mexico (ONAOLAPO; ONAOLAPO, 2017)), 0.06% in Iran (SAMADI; MAHMOOD-IZADEH; MCCONKEY, 2012), 0.5% in Israel (1-12 years-old, 2010) (ÖZERK, 2016), and 0.3% in Taiwan (CHIEN et al., 2011).

Even some recent epidemiological researches in developed countries point to ASD prevalences under 1% (e.g., 0.63% in Australia (6-12 years-old, 2005), 0.71% in Denmark (5-6 years-old, 2006), 0.6-0.8% in Norway (0-11 years-old, 2010-2011), 0.9% in United Kingdom (5-16 years-old, 2004) (ÖZERK, 2016)), and 0.8% in Sweden (NYGREN et al., 2012). A recent study estimated a lower ASD prevalence in Norway children ($1-16$ years old), approximately 0.32% (females: 0.13%, males: 0.49%) (ÖZERK; CARDINAL, 2020).

Another recent population-based study across four European countries showed significant variability in the estimates of ASD prevalences for children between 7-9 years old: 0.56% in France (females: 0.21%, males: 0.89%), 0.48% in South-East France and 0.73% in South-West France; 0.76% in Finland (females: 0.32%, males: 1.18%); 1.24% in Denmark (females: 0.51%, males: 1.92%); and 2.68% in Iceland (females: 1.02%, males: 4.24%) (DELOBEL-AYOUB et al., 2020).

A review of the ASD prevalence in Arab Gulf countries (Bahrain, Kuwait, Qatar, Saudi Arabia, Sultanate of Oman, and United Arab Emirates)[3] reported an overall ASD prevalence ranging from 0.014% in Oman to 0.29% in the United Arab Emirates (SALHIA et al., 2014). A recent meta-analysis in nine Asia countries (East Asia: China, Korea, India; West Asia: Lebanon, Bangladesh, Iran, Israeli; and South Asia: Nepal, Sri Lanka) examined 12 primary studies, with 2.195.497 subjects, and estimated an overall pooled ASD prevalence of 0.36% (females: 0.18%, males: 0.45%). The ASD prevalence estimates by region were 0.31% in South Asia, 0.35% in West Asia, and 0.51% in East Asia (QIU et al., 2020).

A comprehensive meta-analysis of ASD prevalence in the general population in China covered 44 studies, comprising 2.337.321 subjects (1.6-8 years old), and presented a pooled ASD prevalence of 0.39% (females: 0.16%, males: 0.73%) (WANG et al., 2018). Another meta-analysis in mainland China, Hong Kong, and Taiwan, with 25 studies, estimated the pooled ASD prevalence in these areas at 0.27% (SUN et al., 2013). Conflicting with these previous studies, a recent meta-analysis in mainland China covered 30 studies and estimated a pooled ASD prevalence of 0.74% among Chinese children and adolescents (0-11 years old) (HUIFEN et al., 2021). Another recent survey in the Chinese city of Jilin showed an ASD prevalence of 1.06%, considerably higher than previous Chinese estimates and approaching Western estimates (SUN et al., 2019). This lower ASD prevalence in China is mainly because most studies: only included the special school population, overlooking the mainstream school population; have not used contemporary screening and diagnostic methods; and have only focused on autistic people with intellectual disabilities, omitting other ASD subtypes (SUN et al., 2019). In addition, significant differences in diagnostic criteria between China and foreign countries also contribute to this difference in ASD prevalence (HUIFEN et al., 2021).

Despite the limitation of the non-verified ASD diagnoses, a recent parent-reported study with 12-13 years old Australian Children estimated an ASD prevalence from 2.9% to 4.4%, resulting in one of the highest reported ASD prevalence in the world to date (MAY; BRIGNELL; WILLIAMS, 2020).

The short ASD prevalences in some countries/regions may explain the low ASD prevalences values from global estimates (BAXTER et al., 2015; ELSABBAGH et al., 2012). Methodological differences in case definition (CHIAROTTI; VENEROSI, 2020), diagnostic criteria (KING; BEARMAN, 2009; MATTILA et al., 2007), sample size (ELSABBAGH et al., 2012), surveyed areas due to educational or health care systems (MATSON; KOZLOWSKI, 2011), the strategy for targeting risk individuals or groups (case-finding procedures) (CHIAROTTI; VENEROSI, 2020; WAZANA; BRESNAHAN; KLINE, 2007), socio-economic factors (DURKIN; WOLFE, 2020; DURKIN et al., 2017), ASD awareness (HERTZ-PICCIOTTO; DELWICHE, 2009) and even cultural influence (TAYLOR; JICK; MACLAUGHLIN, 2013), jointly, also affect the ASD prevalence estimates.

The evolution of the manuals, the ASD diagnosis categories and subcategories, and the differences between multiple versions of ICD and DSM over the past decades also have had an evident impact on the ASD prevalence estimates and rates (ÖZERK, 2016).

[3] Studies identified for Oman, Saudi Arabia, and the United Arab Emirates only.

Among others, some characteristics attributed to the rise of the ASD prevalence are the ability to diagnose, with a possible reflection of the success in identifying children who were previously not diagnosed (HANSEN; SCHENDEL; PARNER, 2015; NEVISON, 2014), and changes in awareness, earlier diagnosis, and redefinition of diagnostic criteria (ZABLOTSKY et al., 2015).

5. ASD Etiology

Etiology refers to the study and determination of the causes of the diseases. Models of etiology try to explain the processes that initiate a particular disorder. The necessary conditions for developing the diseases are known as etiological factors. However, etiological factors are only the causes that directly start the disease process, and necessarily such causes have to precede the onset of the disease in terms of time. Several different conditions (biological, immunological, environmental, etc.) may contribute to defining a particular disease etiology (GELLMAN; TURNER et al., 2013).

Many complex mental and physical disorders (e.g., autism, depression, obesity) have partially unknown etiology. The ASD etiology is multifactorial: neurobiological, genetic, and environmental. Although incompletely understood, genetic and environmental factors and their interactions contribute to ASD etiology (BÖLTE; GIRDLER; MARSCHIK, 2019; LYALL et al., 2017). Twin and family studies have shown a predominant genetic contribution to ASD etiology. A complex interaction between common and rare genetic variants constitutes the genetic composition of ASD, with common genetic variants accounting for almost all ASD heritability (ROSTI et al., 2014; GAUGLER et al., 2014; HALLMAYER et al., 2011).

5.1. Environmental Risk Factors

Environmental factors can be due to an aggregation of factors. Climatic, nutritional, and the interaction of individuals with their environment are usually the most critical factors. Several environmental agents have been pointed as possible ASD risk factors. We can highlight advanced parental age, the significant age difference between parents, preterm birth, pre, peri, and post-natal factors, cesarian delivery, short interpregnancy interval, exposure to air pollution, and still some events during pregnancy, such as the use of valproic acid, maternal infections, and exposure to environmental toxins (HODGES; FEALKO; SOARES, 2020; BAI et al., 2019; BÖLTE; GIRDLER; MARSCHIK, 2019; LYALL et al., 2017; SEALEY et al., 2016).

Some studies suggested that shared environmental factors have at least equal or even more significant influence than genetic factors in ASD risk. The ASD liability variation in a clinical sample pointed primarily to shared environmental factors (58%) than genetic effects (38%) (HALLMAYER et al., 2011). (FRAZIER et al., 2014) suggest an even higher estimate of shared environmental risk factors (64-78%). However, (FRAZIER et al., 2014) did not systematically collect probands from the general population; thus, affected people had no equal chance to be selected.

Despite those previous associations with ASD risk, shared environmental factors have accounted for a tiny percent of increases in ASD diagnosis. Maternal and paternal age contributed to $\approx 2.7\%$ of the 143% ASD prevalence increase among 0-3 years-old children from 1994 to 2001 (QUINLAN et al., 2015). Cesarean delivery, multiple births,

changes in preterm delivery, assisted reproductive technology, and small for gestational age fetuses contributed to less than 1% of the almost 60% ASD prevalence increase among eight-year-old children born in 1994 contrasted to those born in 1998 (SCHIEVE et al., 2011).

Furthermore, a contrasting study using a sample cohort of $\approx$ 2 million people revealed that the individual ASD risk increased with genetic relatedness, with no shared environment effects (SANDIN et al., 2014). A meta-analysis comprising twin studies showed that ASD heritability is due to genetic effects (TICK et al., 2016). Previous studies that pointed to significant shared environmental factors are probably statistical artifacts due to the assumptions regarding ASD prevalence and dizygotic concordant pairs' oversampling. Thus, shared environmental effects seem unable to explain the majority of the ASD variance (TICK et al., 2016). Similarly, a novel study pointed out that shared environmental factors are unlikely to explain the rise in ASD prevalence once the ASD etiology consistently reveals a more significant genetic role (TAYLOR et al., 2020).

5.2. Genetic Risk Factors

A key role in genetics is understanding the relative contribution of genetic and environmental factors to phenotypic variance. The phenotypic (visible characteristic or effect on health) variance of a trait due to genetic differences in a specific population at a given time is known as heritability, also known as the proportion of the phenotypic variation that is not explained by the environment or random chance. The heritability of human traits is usually estimated based on the inference of genetic factors shared among relatives (BASELMANS et al., 2020; LEWIS, 2018; BISWAS; SINGH; REDDY, 2017).

The hereditary units transmitted from parents to offspring are known as genes. Consisting of the long molecules of deoxyribonucleic acid (DNA), human genes instruct our cells to produce specific proteins that regulate the characteristics that comprise our individuality. Genetics defines a trait as single-gene (Mendelian or monogenic) or polygenic. Single-gene traits are rare and caused by DNA changes in one particular gene. Polygenic traits are more common and express actions of one or more genes, usually including the contribution of environmental factors. The environment can influence single-gene and polygenic traits, which indicates that both can be multifactorial. The more factors (inherited or environmental) contribute to a disease, the more difficult it is to estimate the incidence risk (LEWIS, 2018).

Research groups differ significantly on their assessments for the number of genes associated with ASD, ranging from a few to hundreds (SCHAAF et al., 2020). Twins and family studies support the genetic contribution to ASD etiology by exposing high ASD heritability estimates and ASD recurrence rates among siblings (MAENNER et al., 2020; PALMER et al., 2017).

The ASD heritability relies on a complex combination of genes, mutations, and chromosomal abnormalities. The ASD genetic architecture ranges from a rare single gene mutation to polygenic risks. The main components of ASD genetic risk include: 1) *de novo* mutations, which occur spontaneously in offspring; 2) rare inherited single-gene disorders, occurred relatively recently in humans; and 3) polygenic variation, genetic changes in one or many genes widespread in humans. Many of the ASD risk genes operate as regulators of neurodevelopment or neural activity (IAKOUCHEVA; MUOTRI;

SEBAT, 2019; BOURGERON, 2015).

5.2.1. Rare Inherited Variants and *De Novo* Mutations

Human genomics has identified a range of DNA sequence variations, including insertions and deletions of nucleotides and translocations of various chromosome segments. These mutations have been named Copy Number Variants (CNVs). CNVs are a DNA segment present at a variable copy number compared to a reference genome (ZARREI et al., 2015). CNVs are associated with certain human diseases' etiology (GIRIRAJAN; CAMPBELL; EICHLER, 2011; STANKIEWICZ; LUPSKI, 2010), although they are also present in healthy individuals (CONRAD et al., 2010). Genetic analyses like genome sequencing may expose which single-gene disease a person has, carry, or may develop. Tests with infected children and their parents can indicate if the disease cause is a mutation inherited from carrier parents or due to a dominant *de novo* mutation (LEWIS, 2018).

A gene mutation is a permanent alteration in its DNA sequence. A mutation can affect a single DNA base pair or a large chromosome segment, including multiple genes. Gene mutation can be either hereditary (inherited from a parent) or somatic (occurs during the person's life). A *de novo* mutation is a genetic modification present for the first time in a person due to a variant in a germ cell (egg or sperm) of one parent, or also can arise in the fertilized egg itself during early embryogenesis. *De novo* mutations may explain genetic disorders in a person with no family history of the disorder. Therefore, genetic factors unique to an affected individual (*de novo*), even when these factors are associated with a disease, do not contribute to this disease heritability (BASELMANS et al., 2020).

Part of the genetic risk for ASD consists of rare CNVs inherited from parents. Most variants occur as recurrent *de novo* mutations transmitted from a parent, with mild or no symptoms, due to variable levels of cognitive impairments. Thus, part of the ASD genetic architecture consists of rare CNVs inherited from parents who do not meet ASD diagnosis (IAKOUCHEVA; MUOTRI; SEBAT, 2019). *De novo* CNVs rates are up to ten times higher among ASD individuals (RUBEIS et al., 2014; SANDERS et al., 2011; XU et al., 2008), suggesting a substantial role of *de novo* CNVs in ASD. Advanced parental age could be associated with the increased risk of *de novo* spontaneous mutations (usually paternal) (ATSEM et al., 2016; KONG et al., 2012). Approximately 70% of *de novo* mutations originate from the father, and the rate of new mutations increases with the father's age (1-2 mutations per year of age) (MICHAELSON et al., 2012; KONG et al., 2012).

Recent studies aiming to identify ASD susceptibility of *de novo* genes have implicated 102 genes in ASD risk, with 53 genes having a greater frequency in ASD (SATTERSTROM et al., 2018; SANDERS et al., 2015). Despite some estimates that *de novo* mutations contribute to $\approx 30\%$ of ASD cases (IOSSIFOV et al., 2014), rare variants seem to explain at most 17% of ASD heritability (GAUGLER et al., 2014), with rare *de novo* and inherited CNVs limited to 10% of children with nonsyndromic autism (TORRE-UBIETA et al., 2016).

Although *de novo* mutations are considered genetic factors, they do not contribute to the ASD heritability once they are present only in the infected descendant (exclud-

ing rare germinal mosaicisms present in parental germline and transmitted to offspring). Thus, *de novo* could be considered environmental causes of ASD acting on the DNA. From 500 to 1000 genes could account for these monogenic forms of ASD, reinforcing the high level of genetic heterogeneity (HUGUET; BOURGERON, 2016).

5.2.2. Common Polygenic Risk

As polygenic disorders result from the joint contribution or interaction of several independent genes and occur more frequently in humans, their genetic variance is essentially due to the additive effects of recessive alleles of different genes. Few dominant alleles can significantly affect the phenotype for some traits, but they do not contribute to heritability considerably because they are rare (LEWIS, 2018; LVOVS; FAVOROVA; FAVOROV, 2012).

A person carries nearly three million genetic variants compared with a reference genome. Most of these variants ($\approx 95\%$) are called common variants (FU et al., 2013). The most prevalent genetic variant in humans is called Single Nucleotide Polymorphisms (SNPs). Each SNP expresses a variation in a single nucleotide (a DNA building block). Polygenic Risk Score (PRS) is a genetic measure that summarizes all common SNPs' contributions to a trait (DUDBRIDGE, 2013).

There are pieces of evidence for the additive contribution of multiple rare and common genetic variants to ASD risk. Thus, common polygenic variation can also influence the diagnosis of individuals who carry a rare variant of significant effect. Compared with typically developing controls, ASD individuals with *de novo* mutations have significantly increased PRSs for ASD (WEINER et al., 2017). All three categories of ASD risk genes are similar once a gene regulatory network broadly distributes their effects. For example, a genetic effect from a single gene mutation can influence other ASD genes' functions and spread extensively (IAKOUCHEVA; MUOTRI; SEBAT, 2019). (IAKOUCHEVA; MUOTRI; SEBAT, 2019) suggest that the genetics of ASD is typically compatible with an Omnigenic model (BOYLE; LI; PRITCHARD, 2017), in which the genetic basis of a complex trait is highly polygenic, being challenging to distinguish core genes with direct effects from several marginal genes with indirect effects.

5.3. ASD Heritability Estimates

High levels of heritability characterize the ASD etiology, with a genetic factor estimated up to 98%, with a small environmental contribution. Although genetics is already a widely accepted risk factor for ASD, there is no consensus on the percentage of autism caused by genetic factors. Researches point to percentages ranging from 38% to 98% (BAI et al., 2019; ALMANDIL et al., 2019; SANDIN et al., 2017; TICK et al., 2016; KRONCKE; WILLARD; HUCKABEE, 2016; HALLMAYER et al., 2011; BAILEY et al., 1995; FOLSTEIN; RUTTER, 1977). In part, these discrepancies can be explained by the variation of the research methods. Thus, the ASD heritability estimates are sensitive to the research methods, once these methods require several and often untestable assumptions (SANDIN et al., 2017).

Table 3 presents reputable researches regarding ASD etiological origins. Most studies decompose the ASD liability variance into four components: (A) additive genetic

effects, which means inherited additive effects from different alleles; (D) nonadditive genetic (dominance) factors, usually due to the interaction effects between alleles at the same locus; (C) shared environmental effects, which means nongenetic influences contributing to similarity within relatives; and (E) nonshared environmental effects, which make relatives dissimilar. This liability model is usually known as the ACDE model (NEALE; CARDON, 2013). Since most studies in Table 3 have emphasized additive genetics, total heritability correlates with the additive component, except for works by (SANDIN et al., 2017), (GAUGLER et al., 2014), and (SANDIN et al., 2014).

Table 3. ASD Etiology Measures.

	Heritability (%)		Environmental (%)		2*Sample Size	3*Statistical Model	3*Reference
1-3 5-6 **Total**	**Additive (A)**	**Nonadditive (D)**	**Shared (C)**	**Nonshared (E)**	**(Total)**		
81	81-83	NE	≈ 0.3	≈ 18	(2001631) 1392096⊙ 1748450⊘	GLMM	(BAI et al., 2019)
85	73-87	NE	≈ 0.2	≈ 15	(776212) 98570⊙ 11780± 14865∓ 650997⊘	GLMM	(YIP et al., 2018)
83	79-87	≈ 10	≈ 4	≈ 17	(2049973) 37570⊕ 2642064⊙ 445531± 432281∓	LTM	(SANDIN et al., 2017)
≈ 81⋆	64-93	NE	6-35	1-3	(21-7982) ⊕	LTM	(TICK et al., 2016)
≈ 61	47-75	NE	NE	≈ 40	(75) ⊕	CTM	(DENG et al., 2015)
≈ 60	52	7	•	•	(3046) ⊕ ⊙ ± ∓ ⊘	GCTA	(GAUGLER et al., 2014)
50	33-50	≈ 16	≈ 5	≈ 48	(2049973) 37570⊕ 2642064⊙ 445531± 432281∓ 5799875⊘	LTM	(SANDIN et al., 2014)
21-35	21-35	NE	64-78	NE	(1136) ⊕	DF LTM	(FRAZIER et al., 2014)
38	14-67	NE	≈ 58	NE	(384) ⊕	CTM	(HALLMAYER et al., 2011)
≈ 80	73-87	NE	0-15	13-27	(90) ⊕	SEM	(TANIAI et al., 2008)
57	43-68	NE	NE	≈ 43	(464) 370⊕ 94⊙	SEM	(HOEKSTRA et al., 2007)

[NE]Not estimated; ⊙Full siblings; ⊘Cousins; ±Paternal half-siblings; ∓Maternal half-siblings; ⊕Twins; ⋆An approximate median/average of the additive genetic effects from the six different meta-analyses configurations; •41% for environmental (shared + nonshared); [GCTA]A software for Genome-wide Complex Trait Analysis based on Linear Mixed Models (YANG et al., 2011); [DF]DeFries-Fulker Regression (DEFRIES; FULKER, 1985); [SEM]Structural Equation Modeling.

Some studies also decompose the ASD liability variance into maternal effects (M). Maternal effects indicate the effect of mothers on the environment of their offspring (i.e., noninherited genetic influences originating from mother beyond what is inherited) (NEALE; CARDON, 2013). However, such studies reveal the modest contribution, if any exists, of maternal effects to the ASD liability (BAI et al., 2019; YIP et al., 2018).

Because of a time-to-event approach concerning the ASD diagnosis, the work

of (SANDIN et al., 2014) underestimates the sibling pairs concordant for ASD (possibly missing about half of the concordant pairs). This underestimate may have reduced their heritability estimates. Years later, (SANDIN et al., 2017) demonstrated this hypothesis regarding underestimated heritability by performing a reanalysis of the same population. However, they used an alternative methodology to define sibling pairs as concordant or discordant for ASD. Their new heritability estimate increased $\approx 66\%$ (from 50% (SANDIN et al., 2014) to 83% (SANDIN et al., 2017)).

Liability collectively defines both the genetic and environmental factors that contribute to the development of multifactorial diseases. A person will be affected by a condition when it accumulates a specific liability. The diagnosis of several human disorders results in a set of binary (e.g., affected or unaffected) or ordered (e.g., mild, moderate, or severe) values. There are four primary methods to estimating the etiology of complex and quantitative binary traits: Liability Threshold Model (LTM), Classical Twin Model (CTM), Falconer Model (FM), and (Generalized) Linear Mixed Model (GLMM) (BONNET, 2016; TENESA; HALEY, 2013).

Based on the correlation of the disease status among pairs of relatives of a specific type extracted from a random sample of the population (known as tetrachoric correlation) (PEARSON; LEE, 1900), LTMs assume that the disease's liability is (or can be transformed in) a normal distribution with a threshold above which all subjects manifest the disease and below which no individuals manifest the disease. The disease prevalence is the metric that usually defines the threshold estimates, and the model variables are all genes and environmental conditions protecting or increasing the risk of disease (NEALE, 2005). This normal distribution of the liability is supported by the complex etiology of most human diseases (VERHULST; NEALE, 2021) and by Genome-wide Association Studies (GWAS) results, suggesting that the more complex a disease, the more polygenic it is (BOYLE; LI; PRITCHARD, 2017). As much as this model description of the disease liability appears simplistic, LTMs design has proven valuable, and no empirical data have shown a reason to discard it (BASELMANS et al., 2020). Besides autism, LTMs using family members also have been used to describe the etiology of other traits such as skin cancer (LINDSTRÖM et al., 2007), preeclampsia (NOH et al., 2006), and schizophrenia.

CTMs analyze the similarity among monozygotic and dizygotic twins (BOOMSMA; BUSJAHN; PELTONEN, 2002). CTMs strength comes from the similarity in genetic sharing of monozygotic twins (100% of genetic sharing) and dizygotic twins (50% of additive genetic sharing and 25% of dominant genetic sharing). Such genetic sharing allows partitioning the phenotype variance into an ACDE model, assuming that these combined sources result in the phenotypic variance. In CTMs, dominant effects tend to reduce the dizygotic correlation relative to the monozygotic correlation, while the shared environment increases the dizygotic correlation close to the monozygotic correlation. Thus, dominant and shared effects are negatively confounded, and CTM studies usually estimate shared or dominant effects (LITTLE, 2014). Indeed, this bias due to the common environment and dominant effects is often a concern in full siblings studies (TENESA; HALEY, 2013).

The GLMMs (HOPPER, 1993) are the most flexible approach to estimate etiology variance in families (TENESA; HALEY, 2013). GLMMs allow handling complex family trees of diverse size and structure, which are a limitation of the previous methods once the

data are structured into defined families of the same size. Broadly used in several areas (e.g., agriculture, biology, and genetics), LMMs also have been used for heritability estimates of binary human diseases (BONNET et al., 2015), as well as to measure genotypes in GWAS with large samples using a large number of SNPs to identify genetic variants that explain phenotypic variances (BASELMANS et al., 2020; YANG et al., 2011).

LMMs also support splitting the phenotypic variance into separate components: a genetic variance, usually separated into additive, dominance, and epistatic; an environmental, traditionally divided into common, maternal influence, and the stochastic; and possibly a gene-environment interaction component. LMMs perform heritability estimates by the portion of total variation attributed to additive genetic components and the amount of total variation attributed to other variance components similarly estimated (BASELMANS et al., 2020; PAWITAN et al., 2004). GLMMs have shown exemplary performance in experimental groups despite being computationally hard to fit. The statistical and computing advancements, allied with the ability to exploit complex family trees, make GLMMs the preferred approach in practice (TENESA; HALEY, 2013).

Disorders with low prevalence rates (affecting one in a hundred) require huge samples to estimate heritability and recurrence rates among relatives (BASELMANS et al., 2020; HILKER et al., 2018). Small sample sizes can lead to heterogeneous heritability estimates (TENESA; HALEY, 2013). Many twin and family studies regarding ASD heritability usually run with samples of small size, which is generally recognized as a limitation (TICK et al., 2016; DENG et al., 2015; GAUGLER et al., 2014; FRAZIER et al., 2014; HALLMAYER et al., 2011; TANIAI et al., 2008; HOEKSTRA et al., 2007). Sample ascertainment bias and different measurement tools also are potential causes for the heterogeneity in ASD heritability (COLVERT et al., 2015).

However, recent studies (Table 3) that explored large and more diverse samples (twins, full- and half-siblings, and cousins) and applied more flexible and robust heritability estimation methods (GLMMs, LTMs, and SEMs), point to ASD heritability estimates ranging from $\approx 80\%$ to $\approx 85\%$ (CARVALHO et al., 2020; BAI et al., 2019; YIP et al., 2018; SANDIN et al., 2017; TICK et al., 2016). It is important to note that ASD heritability may vary across populations, environments, sub-groups of people with different characteristics (e.g., age) and may change over time, even in these more elaborated studies (VISSCHER; HILL; WRAY, 2008).

5.4. Recurrence Rate Among Siblings

The risk of ASD recurrence in siblings of an ASD child is an essential measure of the genetic contribution to the ASD etiology (GRØNBORG; SCHENDEL; PARNER, 2013). The ASD recurrence among relatives of affected family members is high compared to the overall ASD prevalence. Both the level of relatedness and the individuals' gender seem to be determinant factors to the recurrence extent among family members (HANSEN et al., 2019).

The estimated ASD recurrence rates in siblings of an ASD proband (usually named high-risk siblings) who do not manifest other diseases or syndromes range from $\approx 9\%$ to $\approx 25\%$, varying according to the individual's gender (Table 4). The ASD risk in younger siblings range from $\approx 32\%$ to $\approx 50\%$ if there are two or more ASD children in the family (WOOD et al., 2015; SCHAEFER; MENDELSOHN, 2013; OZONOFF et

al., 2011; SIMONOFF, 1998). This high ASD recurrence risk in affected families also reflects the heritable nature of ASD (GIRAULT et al., 2020).

Table 4. ASD Recurrence Among Siblings.

3-9 Sample Size	ASD Criteria	ASD ARR (ASD RRR) Male ↓ Female	Female ↓ Female	Male ↓ Male	Female ↓ Male	Both ↓ Female	Both ↓ Male	Both ↓ Both	Reference
20.882⊕	ICD-9	4.2	7.6	12.9	16.8	4.9	13.7	9.3	(PALMER et al., 2017)
13.997⊕	DSM-IV ICD-9/10	3.8⋆ (7.5)	5.1⋆ (10.2)	13.0⋆ (6.6)	19.3⋆ (9.8)	4.1⋆ (8.2)	17.5⋆ (8.9)	10.1• (8.4)	(HANSEN et al., 2019)
13.533⊖	DSM-III-R DSM-IV	5.1	6.7	14.1	17.0	5.3	14.5	10.1	(RISCH et al., 2014)
592⊙	DSM-IV-R	6.1	6.1	15.4	19.3	6.2	16.1	11.3	(XIE; PELTIER; GETAHUN, 2016)
319⊕	DSM-IV-R	18.5	25.0	33.8	26.5	19.6	32.4	26.6	(ZWAIGENBAUM et al., 2012)
385⊕	DSM-IV-R	-	-	-	-	12.8	30.1	23.1	(GIRAULT et al., 2020)
1.241⊕	ADOS DSM-IV	-	-	-	-	10.3	26.7	19.5	(MESSINGER et al., 2015)
664⊕	ADIR ADOS SCQ	-	-	-	-	9.1	26.2	18.7	(OZONOFF et al., 2011)
19.710⊕	DSM-III-R DSM-IV	-	-	-	-	-	-	10.1	(HOFFMANN et al., 2014)
13.164⊕	ICD-8/10	-	-	-	-	-	-	6.1	(GRØNBORG; SCHENDEL; PARNER, 2013)
1.235⊖	ADIR ADOS	-	-	-	-	-	-	14.2	(CONSTANTINO et al., 2010)
299⊖	DSM-IV ICD-10	-	-	-	-	-	-	24.7	(WOOD et al., 2015)

[ARR] Absolute Recurrence Risk; [RRR] Relative Recurrence Risk; ⊖ Families having one or more child with ASD; ⊕ Infants with an older sibling with ASD; ⊙ Infants with ASD with at least one older sibling; ¯ Not available; • Estimated based on the overall ASD prevalence of (HANSEN et al., 2019) (1.2%); ⋆ Estimated based on the ASD prevalence by sex of (PALMER et al., 2017) (male: 2.0%; female: 0.5%);

The ASD Relative Recurrence Risk (RRR) quantifies the ASD risk increase among individuals who have one or more family members with ASD compared to the overall ASD risk (prevalence) among individuals who do not have any family member with ASD (HANSEN et al., 2019). The ASD Absolute Recurrence Risk (ARR) rate quantifies the ASD probability among individuals with one or more family members with ASD (PALMER et al., 2017).

Table 4 presents reputable researches that investigated the ASD recurrence among siblings. The data are ordered by the level of information detail (sex-specific) and sample size. Those works that investigated large sample size, (PALMER et al., 2017) ($\approx$ 21 thousand siblings), (HOFFMANN et al., 2014) ($\approx$ 20 thousand siblings), (HANSEN et al., 2019) ($\approx$ 14 thousand siblings), (RISCH et al., 2014) ($\approx$ 13.5 thousand siblings), showed similar recurrence rates estimates (overall: $\approx$ 9-10%, females: $\approx$ 4-5%, males: $\approx$ 14-18%). Except for the work conducted by (GRØNBORG; SCHENDEL; PARNER, 2013), which investigated a large sample size ($\approx$ 13 thousand siblings), although exposed an overall ASD recurrence lower than works mentioned above ($\approx$ 6%, ranging from 4.5% to 10.5% over time).

The remainder of the studies explored relatively small sample sizes (from $\approx$ 300 to $\approx$ 1300 siblings) and presented significantly high recurrence rates than those with larger sample sizes (overall: $\approx$ 14-27%, females: $\approx$ 9-20%, males: $\approx$ 26-32%). Except for the work conducted by (XIE; PELTIER; GETAHUN, 2016), the recurrence rate tends to increase as the samples become too small (GIRAULT et al., 2020; WOOD et al., 2015; ZWAIGENBAUM et al., 2012).

5.5. The Broader Autism Phenotype

The genetic risk to family members of ASD people extends not only to a possible ASD diagnosis but also to less or milder expressions of the social and communication impairments seen in the disorder. Such lesser expressions are usually below the threshold for an ASD clinical diagnosis (SZATMARI et al., 2000). First-degree relatives of ASD people are at increased risk for ASD-related characteristics. Such sub-clinical features, behaviors, and traits, conceptually similar to ASD core symptoms but insufficient to meet diagnostic criteria, have been referred to as the Broader Autism Phenotype (BAP) (GANGI et al., 2021). Since the BAP is strongly associated with ASD, it may be considered a marker of genes contributing to the risk of ASD (LOSH et al., 2009; DAWSON et al., 2002).

The BAP has been associated with difficulties in social relationships and poor mental health outcomes, such as language difficulties or delays, emotion recognition, social functioning deficits, less social interests, restricted or repetitive patterns of behaviors with higher rigidity and intense interests, difficulties in initiating and maintaining friendships in emerging adulthood, lower efficiency in planning, less expressiveness in nonverbal communication, attention shifting, and poorer conversational skills and verbal fluency (JAMIL; GRAGG; DEPAPE, 2017; PISULA; ZIEGART-SADOWSKA, 2015).

More common among the family members of ASD individuals than in the general population, the BAP studies also investigate the genetic mechanisms involved in ASD etiology (RUBENSTEIN; CHAWLA, 2018). Most of the BAP measurement studies, although they vary, have in common a focus on sub-clinical versions of ASD symptoms (less functionally impairments) and reported several cognitive deficits in siblings of ASD children (GANGI et al., 2021). Whereas the BAP and ASD symptoms share a commonality, these symptoms' structures may differ. Therefore, opposed to the severity degree, the number of symptoms confirmed may better differentiate BAP traits (RANKIN; TOMENY, 2019).

Studies suggest different developmental pathways to ASD in children with an older sibling with ASD (high-risk siblings). Assess how ASD develops from birth is crucial to understanding the ASD developmental mechanisms and provides more precise objectives for genetic research (CHAWARSKA et al., 2014). Furthermore, as a complement of studies regarding ASD children, investigations of the BAP in children can specifically inform intermediate developmental trajectories that are often the most difficult to distinguish from typical development (KELLERMAN et al., 2019). In addition, a detailed understanding of ASD developmental pathways can help identify the need for early intervention and improve the range of available intervention options (JONES et al., 2014).

The BAP measurements are difficult due to the variety of functioning levels and countless risk factors combinations. Thus, there are no current standardized criteria for the BAP (KELLERMAN et al., 2019; PISULA; ZIEGART-SADOWSKA, 2015). The main difficulty in studies involving siblings of ASD individuals is to distinguish clearly the ASD symptoms from BAP traits. Mainly because the risk of ASD rather than the BAP characteristics is the primary concern (PISULA; ZIEGART-SADOWSKA, 2015). Usually defined using different domains, measurement tools, and report techniques, the BAP estimates vary significantly across studies (RUBENSTEIN; CHAWLA, 2018). At three

years of age, high-risk siblings present higher ASD symptomatology or lower developmental functioning levels than children without a family history of ASD, despite not receiving an ASD diagnosis (CHARMAN et al., 2017; MILLER et al., 2015; MESSINGER et al., 2013). However, atypical development in domains such as cognition, language, motor coordination, and especially social communication may emerge before three years (OZONOFF et al., 2014).

Table 5 presents reputable researches on BAP in siblings of ASD individuals in the last decade. As social impairment diagnoses tend to be more stable after 30 months of age (TURNER; STONE, 2007), our central focus was to place estimates of BAP effects in younger siblings of ASD individuals, and the ASD recurrence in some cases, around three years.

Thus, we excluded studies with a wide age range because it may compromise the measure of developmental levels across multiple domains or the capability in specific functions. In addition, a wide age range makes it difficult to determine subgroups functioning levels by age, mainly due to small sample sizes, which limits statistical analysis. Studies on siblings at preschool age or older were also avoided, mainly because of the lack of longitudinal studies. Besides, subjects at such age may already overcome some of the difficulties previously identified, losing the diagnosis condition (PISULA; ZIEGART-SADOWSKA, 2015). ASD and BAP measuring around three years of age are especially meaningful. Such researches on infant siblings of ASD probands can provide valuable information on early ASD characteristics, start the investigation of BAP features, and further clarify the ASD genetic mechanisms (JONES et al., 2014).

Younger siblings of ASD children who do not receive an ASD diagnosis themselves present a high risk for developing BAP than siblings with no history of ASD in the family. The BAP estimates among these high-risk siblings range from 10% (HUTMAN et al., 2012) to 55% (MACARI et al., 2012) at $\approx$ 36 months of age. Adding the ASD estimates to the BAP estimates, the overall risk for developmental concerns in high-risk siblings ranges from $\approx$ 27% to $\approx$ 77%, an average of $\approx$ 50%, with the average for males nearly to 60% and the average for females nearly to 32% when excluding uncommon cases in which ASD plus BAP estimates in females surpassed the estimates in males (GLIGA et al., 2014).

Added together, ASD and BAP estimates point to a male:female sex ratio of $\approx$ 1.9:1, which is lower than expected if compared to the ASD prevalence sex ratio, but similar to that reported by (D'ABATE et al., 2019), which suggests a decrease in sex ratio as diagnostic criteria become more rigorous and detailed.

Results showed more elevated severity of ASD traits in younger siblings of ASD individuals than individuals with no family history of ASD. In addition, the ASD severity is even likely higher in multiplex ASD families (those with two or more ASD children). ASD and BAP traits such as less expressiveness in nonverbal communication, less social interest, poorer conversational skills, higher rigidity, and intense interests are more pronounced in siblings from multiplex ASD families than in siblings from simplex ASD families (those families with only one ASD child) (GERDTS et al., 2013; SCHWICHTENBERG et al., 2010).

Some studies assessed ASD symptomatology only in non-affected siblings of

Table 5. ASD and BAP Recurrence Among Siblings.

Sample Size•	Tools⊕	Age⊙	ASD O(M:F) (%)	BAP⊖ O(M:F) (%)	ASD+BAP O(M:F) (%)	Reference
859	ADI-R, ADOS DSM-IV, DSM-V ICD-10, MSEL VABS	36	19	29(33:25)	48	(CHARMAN et al., 2017)
719	ADOS, MSEL	36	22(29:12)	25(28:20)	47(57:32)	(CHAWARSKA et al., 2014)
447	ADOS, MSEL	36	14	21	35	(MESSINGER et al., 2013)
294	ADOS, DSM-IV-TR MSEL	36	17(26:06)	28(31:25)	46(57:31)	(OZONOFF et al., 2014)
288	ADOS, DSM-IV MSEL, VABS	36	36	19	55	(D'ABATE et al., 2019)
204	ADOS, MSEL VABS	36	25(36:11)	15(19:09)	41(55:20)	(LANDA et al., 2012)
188	ADOS, DSM-IV LUI, MSEL	36		31		(MILLER et al., 2015)
135	ADOS, DSM-IV MSEL	36	13(24:03)	27(34:19)	40(57:22)	(SCHWICHTENBERG et al., 2010)
81	ADOS, DSM-IV MSEL	36	17(24:10)	10(12:8)	27(37:18)	(HUTMAN et al., 2012)
58	ADOS, DSM-IV MSEL, SCQ	18-36	29(42:12)	21(18:24)	50(61:36)	(CHRISTENSEN et al., 2010)
53	ADI-R, ADOS-G ICD-10, MSEL SCQ	38	32(53:19)	23(14:28)	55(67:47)	(HUDRY et al., 2014)
53	ADI, ADOS-G DSM-IV	24	23(25:17)	55(63:34)	77(88:52)	(MACARI et al., 2012)
47	ADI-R, ADOS-G ICD-10, MSEL	36	36(22:55)	26(33:15)	62(56:70)	(GLIGA et al., 2014)
45	ADOS, MSEL VABS	24-36	≈ 13	≈ 49	≈ 62	(KELLERMAN et al., 2019)
43	ADI-R, ADOS ICD-10, MSEL	12-36	28(47:15)	26(18:31)	53(65:46)	(WAN et al., 2013)
43	ADI-R, ADOS DSM-IV-TR MSEL, STAT	34	15	20	35	(YODER et al., 2009)
42	ADOS, DSM-IV	30-42	14(21:06)	21(31:09)	36(52:16)	(NICHOLS et al., 2014)
38	ADI-R, ADOS DSM-IV-TR	18-36	21(30:06)	32	53	(CORNEW et al., 2012)
35	ADI-R, ADOS-G ICD-10, MSEL	36	34	26	60	(BEDFORD et al., 2012)
24	ADOS-T, MSEL	24	29	25	54	(PAUL et al., 2011)
20	ADI-R, ADOS DSM-IV, MSEL	33	40	20	60	(DAMIANO et al., 2013)

•Infants at high risk for ASD (have at least one older sibling with an diagnosis of ASD); ⊕ASD/BAP diagnostic and measurement tools; ⊙Age of infants in months when the measurement was performed; ⊖At least one BAP trait or ASD-related behavioral characteristic; O(M:F)Overall(Male:Female).

ASD children. Even in non-affected siblings, their results suggest a higher incidence of deficits in at least one ASD typical domain. However, it is noteworthy that these results are not entirely consistent in terms of the affected domains nor the depth of the deficits (PISULA; ZIEGART-SADOWSKA, 2015).

Other neurodevelopmental abnormalities also are more common among unaffected siblings of ASD children. For example, compared to control groups (no history of ASD in the family), unaffected siblings of ASD children are more likely to develop developmental delays, such as developmental coordination disorder, developmental speech

or language disorder, attention-deficit hyperactivity disorder, anxiety disorders, unipolar depression, intellectual disability, and disruptive behavior disorders (LIN et al., 2021).

Similar BAP results for social and communication domains in parents showed that different genetic transfer mechanisms might operate in simplex ASD families compared to multiplex ones. These results suggest that *de novo* mutations and non-inherited CNVs may be significant risk factors for simplex ASD families, presenting a lesser degree in multiplex ASD families (BERNIER et al., 2012; SEBAT et al., 2007). However, similar studies did not confirm these findings, suggesting a low variability of ASD phenotype in multiplex ASD families (PINTO et al., 2010; SPIKER et al., 1994). In addition, a systematic review quantified the percentage of parents of ASD children who had BAP themselves, presenting a rate of BAP in parents up to to 80%, being more prevalent in fathers than mothers (RUBENSTEIN; CHAWLA, 2018).

Several studies suggest various impairments in infant siblings of ASD children. Qualitative analyses suggest that the overall performance of unaffected high-risk children could be considered at an intermediate level, performing slightly worse than the low-risk children and better than ASD children. Emerging by 24 months, the cognitive differences support the increasing demand for early monitoring of high-risk children to identify risk and promote optimal development (KELLERMAN et al., 2019). Although BAP is not a clinical diagnosis, it does confer risks and challenges, supporting the importance of continuous monitoring in high-risk siblings, even in the absence of a complete ASD diagnosis (GANGI et al., 2021). Some differences in these high-risk siblings are probably due to a later ASD diagnosis. Although, such infant siblings are also at a high risk of developing BAP traits. Details about previous works that studied the early phenotype of ASD and the BAP traits can be seen in Pisula e Ziegart-Sadowska (2015), Jones et al. (2014) and Yirmiya e Ozonoff (2007).

6. Final Thoughts

This work presented an overview of ASD, especially concerning its classification, prevalence, and etiology. We further explored these three domains because they are essential to understanding what autism is, how it is described, the penetration of autism in our society, and the disorder's leading causes.

We started showing the changes in ASD definition over time given by the two primary and most used diagnostic manuals (DSM and ICD). Earlier defined by several distinct nomenclatures, phenotypic descriptions, and diagnostic manuals, autism is currently recognized as a broad spectrum named Autism Spectrum Disorder. Although ASD screening and diagnosis remain complex in practice, it has a more straightforward set of definitions for its phenotypic manifestations and better diagnostic criteria.

Prevalence studies are essential to understand some characteristics of the disease, such as its causes, the demography of affected individuals (e.g., sex and age), social, racial, and geographical aspects. Prevalence rates are also essential to estimate other disease dimensions, such as heredity patterns. Surveys regarding ASD prevalence showed that autism does not seem related to race, ethnicity, or geographic location, with an average prevalence of $\approx 1.4\%$ (females: $\approx 0.7\%$, males: $\approx 2.4\%$), with a male:female ratio of 3-4:1.

Due to the strong genetic nature of ASD, heritability and recurrence rate studies

were sufficiently explored once these two types of studies tried to describe such nature of ASD. Although presenting relatively different results concerning ASD heritability, studies that investigated relatively large sample sizes and employed powerful statistical methods estimate an ASD heritability from $\approx 80\%$ to $\approx 85\%$. ASD recurrence researchers that explored relatively larger populations presented overall recurrence rates from $\approx 10\%$ to $\approx 25\%$, again showing differences between sex (from $\approx 5\%$ to $\approx 20\%$ for females; from $\approx 14\%$ to $\approx 35\%$ for males). BAP recurrence research presented overall recurrence rates from $\approx 20\%$ to $\approx 30\%$, including peaks up to 50%. The BAP estimates show slight differences between sex, with an average of $\approx 32\%$ for males and an average of $\approx 18\%$ for females (male:female ratio of 1.9:1) when excluding uncommon cases in which the BAP estimates in females surpassed the BAP estimates in males.

We accessed recent studies that adopted modern diagnostic tools, had recent follow-up intervals, investigated multiple-sized samples, and employed state-of-the-art research methodologies. Studies that applied robust estimation methods show low variability regarding ASD heritability estimates, despite some works showed results that varied across populations, environments, sub-groups of people, and time. In contrast, the ASD prevalence estimates show significant variability worldwide and even across local areas. In addition, high variability also occurs concerning ASD and BAP recurrence rates.

This variability indicates possible limitations regarding some of these works, their methods, diagnostic criteria, etc., which suggests that much remains necessary to determine the prevalence and recurrence trends of ASD worldwide, especially in developing countries.

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