Influence of Sex Differences in Comorbidities of Autism Spectrum Disorder

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study does not involve any kind of animal trial or human trial.

Abstract

Comorbidity is classified as the co-occurrence of two or more conditions in the same individual at the same time. Individuals with autism spectrum disorder (ASD) are more likely than others to have one or more comorbid conditions. A significant incidence of comorbid psychiatric, biological and neurodevelopmental problems can be observed among autistic individuals compared to neurotypicals. This research evaluates the evidence on gender variations in the clinical presentation of ASD and the comorbidities that are linked with the disorder (ASD). Overall, it was observed that females have a higher prevalence of epilepsy, intellectual impairment, and anorexia nervosa than their male counterparts. Psychopathological comorbidities, on the other hand, yielded conflicting results when it came to identifying gender differences. According to these data, there are significant differences in comorbidity patterns between genders, which may aid in the development of effective sex-specific diagnostic and treatment approaches for autism spectrum disorder and comorbid conditions.

Keywords: Autism Spectrum Disorder, Comorbidity, Gender, DSM-5, adolescents

Dedication

Dedicated to my family

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List of Acronyms

ASD	Autism Spectrum Disorder
AD	Asperger's disorder
ID	Intellectual disability
RRBI	Recurring and Restricted interests
ADHD	Attention-Deficit/Hyperactivity Disorder
EBs	Eating behaviors
EDs	Eating disorders
PB	Behavioral Problems
CNV	Copy number variants
WES	Whole-exome sequencing
ILAE	International League Against Epilepsy
IEDs	Interictal epileptiform discharges
AN	Anorexia Nervosa
DSM - 5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
MDD	Major Depressive Disorder
OCD	Obsessive Compulsive Disorder

Chapter 1

Introduction

Autism spectrum disorder (ASD) is a term that refers to a set of neurodevelopmental disorders that consists Autistic disorder, Asperger's disorder (AD) and Pervasive developmental disorder. ASD is characterized by variable presentation of early emerging social impairments such as: defective communication reciprocity, stereotypical or repetitive sensory–motor behaviours, recurring and restricted interests (RRBI) etc. (American Psychiatric Association, 1994). It is an uncommon disorder which is narrowly defined because of its heterogeneity. But recent theoretical developments have revealed that these conceptions regarding autism spectrum disorder (ASD) are factually incorrect as approximately 7 in 1,000 children and adolescents in the general population are affected by it (Mack, 2011). Because of it's high heterogeneity, severity of autism related characteristics differ from patient to patient such as variable cognitive and communication ability, language skills etc which can cause difficulty in diagnosis (Kim et al., 2011).

Occurrence of a secondary chronic disorder alongside the primary disease where both of them exhibit unique core symptoms is known as comorbidity. In the past few years, comorbidity in case of ASD has received a considerable amount of attention in the literature. According to Mannion and Leader (2013), comorbidities that are generally seen in Autism spectrum disorder are: epilepsy, Intellectual disability (ID), eating disorder such as anorexia nervosa, sleep disorder and comorbid psychological disorders such as: ADHD, depression, mood disorder and bipolar disorder. In research from Simonoff et al. (2008), it is very clear that comorbidities with ASD is a

very common occurrence as in his studies, more than 70% of the children and adolescents had at least one and 41% had more than one comorbid disorder.

Comorbid Disorders	ASD Population (0-18 years)	Non-ASD popu. (0-18 years)	ASD Population >18 years	Non-ASD popu. >18 years
ID	39%	2.6%	-	-
ADHD	42.99%	1.478%	16.51%	1.2%
Epilepsy	41.12%	3.2%	24.31%	3%
Bowel Disorders	24.30%	9.56%	19.45%	8.44%
Sleep Disorders	5.09%	0.16%	-	0.28%
Eating Disorders	27%	7.8%	-	3.4%
CNS/ cranial anomalies	17.76%	2.42%	5.05%	1.02%
Anxiety	44%	28%	11%	6.5%
Schizophrenia	4.77%	0.07%	18.18%	0.6%
Depression	30%	13%	20%	5.7%
Bipolar Disorder	15%	2.8%	27%	4%

Table 1: Common comorbidities of ASD *(Tuchman & Rapin, 2002; Supekar et al., 2017)*

The prevalence of intellectual disability (ID) in those with ASD ranges from 60-75% where it was observed that severity of particular features of ASD, for example - communication reciprocity, speech issues, self-injury is affected by the severity of ID (Matson & Nebel-Schwalm, 2007). ID

can also increase the chances of other comorbidities in the patient. For example, sleep disturbances might be present in approximately 80% of ASD patients who also struggle with ID, based on established studies. According to the results of the study conducted by Ghaziuddin et al. (2008), 80% of individuals with autism have a concomitant psychological condition.

In a very recent analysis, Rau et al. (2020) asserted that Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most frequent mental comorbidities, with rates of co-occurrence ranging from 30-76 % in children. Similarly to attention deficit hyperactivity disorder (ADHD), higher frequencies of anxiety disorders (11–84 %) have been documented in children with autism spectrum disorder (ASD) as compared to the general population, which is 6.5–24%. Tuchman et al. (1991) found epilepsy to be another major comorbidity seen in ASD patients. According to him, more than one third of adolescents with ASD suffer from epilepsy which is developed in childhood. In his other studies (Tuchman & Rapin, 2002), he observed that some 30.5% - 38% prevalence of epilepsy can be seen in autism whereas for the general population the percentage is only 2%-3%. As stated by West et al. (2014) in their literature review, a significant percentage (at least 37%) is also seen to suffer from comorbid eating disorders such as anorexia nervosa.

In order to better understand the distribution of sex to gender ratios across the autism spectrum, numerous investigations have been conducted. A number of scholars have recognized that there is a significant sex imbalance in the rate of diagnosis, and that ASD tends to impact boys at a greater rate than females in terms of prevalence (Brugha et al., 2011). Research reveals that the male to female ratio in the case of ASD detection is approximately 4:1, but this ratio is not consistently distributed across the whole spectrum (Mattila et al., 2011). Recent research conducted by Mattila

et al. (2011) in accordance with the DSM-IV-TR demonstrates that the lower functioning end of the autistic spectrum, including those with comorbid ID, has a gender ratio of roughly 1.8:1. Furthermore, a growing number of research from a diverse perspectives and methodologies have looked into the relationship between sex/gender differences and autism. This raises the question of whether there is any relationship between the comorbidities of autism and sex/gender differences.

A large number of existing studies in the broader literature have examined the prevalence of ASD in male compared to females and studies have almost exclusively focused on the etiology of this difference. However our understanding regarding the autism comorbidity prevalence in one particular gender remains largely unclear. Several authors including Lai et al. (2015) indicated that female ASD patients tend to be diagnosed with more severe autistic symptoms compared to males and biological characteristics difference was one of the significant reasons for this. Even then the research in comorbidity ratio among gender remains limited as many studies failed to identify the gender difference in such disorders.

Among some existing literature, Banach et al. (2008) point out some prominent findings. According to their review, intellectual disability, which is a common comorbidity, shows more preference for females. As females who are diagnosed with ASD tend to be more at risk in case of low cognitive function, this increases the possibility of ID (Fombonne, 2009). Presence of ID as comorbidity can enhance the probability of other comorbid disorders. For example: increased internalizing behavioral problems and aggressive behavior, sleep disorder can be observed in

female patients due to their comorbid ID (Kyrkou, 2005; Rzepecka, McKenzie, McClure & Murphy, 2011).

Another comorbid disorder that is seen frequently in autistic females is epilepsy. Amiet et al. (2008) suggest that prevalence of epilepsy as comorbidity may be related to the sex of the patient. Additionally, Amiet et al. (2008) notes that ASD with comorbid ID can also emphasize the extensiveness of epilepsy which was derived from the meta-analysis of 23 studies. The relationship between gender difference and occurrence of comorbid eating disorder such as - Anorexia nervosa is still insufficiently explored. But there are various ongoing hypotheses which conclude high instances of comorbidity of these disorders among females (Odent, 2010). Only a few investigations have addressed at the gender gap in terms of psychiatric comorbidity with ASD. Because of which, findings from previous studies provide inconsistent results and cannot be considered as conclusive. For example: many investigations have reported no link between sex/gender distinctions and psychiatric comorbidities including depression and anxiety (Park et al., 2012; Solomon et al., 2011; Lai et al., 2011). However, Lai et al. (2019) contradicted their prior findings, claiming that autistic males have higher rates of psychiatric comorbidity than females. Salazar et al. (2015) backs up his assertion by revealing female sex to be a protective barrier for psychiatric comorbidities such attention deficit hyperactivity disorder (ADHD) in autistic children.

1.2 Aim

The key focus of this study was to highlight the sex variances that can be detected in autism comorbidity.

1.3 Objectives

The objectives of the study were-

(i) to determine the prevalence of current comorbidities and behaviors, as well as to look into the prevalence of intellectual impairment, epilepsy, and anorexia nervosa in females.

(ii) to evaluate the significant etiological explanations for these comorbidities in terms of their impact on different sex.

(iii) to avoid misinterpretation and misunderstanding of these conditions.

Chapter 2

Methodology

Various search engines were employed to find academic papers and books for this research. PubMed, science direct, google scholar, nature, Elsevier, Mendeley, research gate, NCBI resources, Scopus, and other databases were used as sources of literature. Several surveys were studied in order to acquire the necessary information on the subject. The dates of publication of the studies ranged from 2000 to 2021. In addition, important data and terminology were obtained from different books.

The keywords that we have used to search for relevant articles were: Autism Spectrum disorder, autism, Comorbidity, gender, sex, Intellectual disability, Epilepsy, Anorexia nervosa, ADHD, depression, OCD, meta-analysis etc.

Chapter 3

Findings and Discussion

This search yielded a total of 99 papers, case reports, and clinical opinions, all of which describe or help to inform our understanding of gender variations in ASD comorbidities. In the analyses, we have made the following comparisons:

- Prevalence rate of certain comorbidities in both genders
- Any specific neurobiological characteristic difference seen in men and women in case this comorbid conditions.
- Molecular mechanism difference

3.1 An overview of the comorbid psychiatric and medical disorders in ASD

At the beginning, different psychological and medical disabilities diagnosed alongside ASD were assumed to be additional symptoms of autism. However, an increasing number of studies have concluded that, other than the core diagnostic features of autism which are- defective communication reciprocity, stereotypical or repetitive sensory–motor behaviours, recurring and restricted interests(RRBI), etc, associate dysfunctions seen in the patient typically indicate comorbid conditions. Not every patient encounters the same comorbidities and it can be categorized into different subtypes (Doshi-Velez et al., 2014). The different subgroups are- (i) Pathophysiological comorbidity- epilepsy, sleep disorder, Neurotransmitter disorders, Musculoskeletal disorders, Metabolic disorders, GI disorders, Diabetes (ii) Psychiatric comorbidities - anxiety, depression, bipolar disorder, self-aggressiveness, hetero–aggressiveness,

self-harm, obsessive-compulsive disorder, and attention deficit hyperactivity disorder (Romero et al., 2016). (iii) Developmental comorbidities (iv) Nutritional and eating disorders.

These comorbid diseases do not have cumulative effects when combined with ASD, but they do have the potential to exacerbate the severity of core autistic traits, which can have a negative impact on patients' day-to-day lives. According to Diane et al. (2016), the most important factors contributing to the emergence of comorbidities in conjunction with ASD include:

- Aging is a non-changeable risk factor for comorbidity, which can result in a variety of health problems.
- Gender is another non-changeable factor that may help identify specific comorbidities (e.g., anorexia nervosa)
- Obesity or poor nutrition, insulin resistance, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and stroke may occur in people with ASD due to the absence of activity, a poor diet, the use of certain drugs (e.g., neuroleptics), food selectivity, and hereditary factors.

The reported prevalence of such comorbidities vary significantly due to differences in data sources, study periods, types of ASD investigated, and sample sizes, all of which might lead to inaccurate information about these comorbidities. The ability to recognize and precisely identify patterns of comorbidity in the autism spectrum population is important since these co-occurring disorders have an effect on the overall prognosis and degree of long-term adaptability of individuals on the spectrum. For the purposes of this review, we will especially discuss three comorbidities that are allegedly more common in females (ID, epilepsy, and anorexia nervosa), as well as some psychological comorbidities.

3.1.1. Intellectual Disability

- **What is Intellectual Disability?**

Intellectual disability is a developmental disorder that is characterized by notable reduction in intellectual performance and limitations in adaptive behavior that consequently affects social interaction and functional abilities (Schalock et al., 2009).

Intellectual disability (ID) and autism spectrum disorders (ASD) are neurodevelopmental impairments that affect children's cognitive and adaptive behavior from birth. Almost 60-70% of ASD cases occur in conjunction with ID which severely affects social interaction and cognitive skills of the patients. Even though ID is considered as a comorbid condition of ASD where etiology and symptomatology of one should be unrelated to the other, several circumstances show that both of them can be related in terms of their pathogenesis. This explains the high rate of co-occurrence of these two disorders to certain extent (Waterhouse, 2013). As cited by Vivanti et al. (2013), the impact of severe social-communication deficiencies on the experience-dependent mechanisms underlying neurocognitive development could be one of the reasons to lead to ID in ASD. In comparison to people with ID or ASD alone, people with both have a higher risk of psychiatric disorders (PD), behavioral problems (PB), stereotypies, speech difficulties, and social impairment.

- **Causal Genes and Molecular Mechanisms of ID:**

As suggested by Vivanti et al. (2013), the severity of ASD induced social-communication impairments moderates the environment needed for "normal" brain development. So, as the intensity of ASD socio-behavioral problems rises, the chance of poor cognitive developmental

outcomes rises as well and can be a risk factor for low IQ. When a child is born with severe ASD symptoms, these might inhibit their brain from receiving major environmental inputs in the early developmental stage. This ultimately affects their cognitive development and intellectual performance. The presence of both disorders has been linked to an increased likelihood of hospitalization and psychopharmacological treatment.

Other than the induced effect of ASD, there are also different genetic causes of why ID occurs with ASD as a common comorbidity. The causal genes for both intellectual disability and autism spectrum disorder can be quite similar and also varied. According to Srivastava and Schwartz's (2014) literature review, previous studies have emphasized on duplication or deletion of Copy number variants (CNV) and single gene mutation as one of the leading origin for both conditions. However, Liu et al. (2013)'s study on whole-exome sequencing (WES) of 1,039 subjects revealed that risk variants for both ASD and ID can be found in multiple genes and no single gene mutation was responsible for it. Furthermore, evidence of same mutation of different genes such as NRXN1, CNTNAP2, NLGN4, SHANK2, SHANK1, etc. has been found to be linked to causation of both ASD and ID (Berkel et al., 2010, Sato et al., 2012, Liu et al., 2013). Liu et al. (2013) also talked about alteration of other genes incorporated in various cellular and molecular processes which are speculated to be involved in the expression of intellectual disability and perhaps ASD.

Biological Function	Genes
Presynaptic vesicle cycling and transport	*αGDI, CASK, AP-1, AP-2, AP-3, AP-4, AP4BP1, AP4E1, AP4S1, AP4M1, IL1RAPL1, OPHN1, RAB39B, STXBP1, SYN1, SYN11, SYP*
Cytoskelton dynamics	*ARHGEF6, ARHGEF9, FGD1, IQSEC2, LIMK1, OPHN1, OCRL1, MEGAP, PAK3*
Cell-adhesion and trans-synaptic signaling	*CASK, CDH9, CDH10, CDH15, CNTN4, CNTNAP2, KIRREL3, NLGN3, NLGN4X, NRXN1, PTCHD1, PCDH9, PCDH10, PCDH19, SHANK2, SHANK3*
Translational regulation, protein degradation and turnover	*CUL4B, FBXO40, FMRP, HUWE1, MID1, MEF2, PARK2, PCDH10, RFWD2, UBR1, UBE2A, UBE3A, UBE3B, UPF3B, UPF3A, SMG6, EIF4A3, RNPS1*

Table 2: List of ID and ASD associated genes *(Srivastava & Schwartz, 2014)*

The above mentioned genes are responsible for regulating several cellular and neuronal functions Such as: controlling synaptic vesicle transport, maintaining cell membrane receptors, synaptic protein level, transcriptional regulation etc which in turn monitors cognition and behavior function. So, researchers suspecting dysfunction of these genes as a causative agent of ASD and comorbid ID are not very far-fetched.

3.1.2 Epilepsy

- **What is Epilepsy?**

As defined by ILAE (International League Against Epilepsy), "Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition".

This neurological disorder is known as one of the leading comorbid conditions of ASD as almost 38% of patients who are diagnosed with autism show comorbid epilepsy symptoms. Compared to general population (only 1-2%), individuals with ASD tend to have a higher prevalence of epilepsy (25-40%) and more often than not, the onset appears at infancy or adolescence (Tye et al., 2019). Several studies have shown that all focal and generalized seizures can be associated with ASD but

the prevalence rate tends to vary. For example, two groups of Swedish and American researchers indicated that autistic patients with epilepsy most commonly suffered from generalized tonic-clonic, absence, and myoclonic seizures (Steffenburg et al., 1996; Tuchman et al., 1991). But later on, this result was refuted by Matsuo et al. (2011) as they emphasized that complex partial seizures are most prevailing in ASD. Another severe form of epilepsy which is Epileptic Encephalopathy can also be commonly seen as a comorbidity in ASD. Compared to other forms of seizures, this disorder is much more damaging to the victim as it can give rise to critical behavior and cognition impairment. In Epileptic Encephalopathy, recurring ictal epileptiform activity and interictal epileptiform discharges (IEDs) can be seen which are mostly intractable (Berg et al., 2010). The intensity of comorbid epilepsy not only depends on the type of seizure the patient faces but also if they have any traces of ID or not. As stated by Amiet et al. (2008), emergence of epilepsy is closely associated with severity of ASD and cognitive disability traits in the victim.

A number of authors have recognized that people with comorbid epilepsy show extensive compulsive and repetitive behaviors, self-injurious tendencies, low social adaptiveness, and overall reduced quality of life (Bolton et al., 2011; R. Tuchman et al., 2010; Tye et al., 2019). Higher chances of abnormal neurological dysfunctions and cerebral lesions are also present in individuals with ASD + epilepsy (R. Frye., 2016).

- **Causal Genes and Molecular Mechanisms of Epilepsy:**

In general, origin of epilepsy is very versatile. For example: it can be due to genetic mutations, focal neurologic deficits, diffuse brain injuries, metabolic defects or other idiopathic causes (Tye et al., 2019). Till date, distinguishing any association between causal mechanisms of both epilepsy

and ASD has proven to be a complex endeavor. The earliest assumption about shared genetic or neurodevelopmental cause of both of these disorders was by Gustafsson (2004) where he stated that error in gama-aminobutyric acid (GABA)ergic fibers due to autism may increase the occurrence rate of epilepsy. Later, promising findings from several researchers demonstrated that different genetic disorders which are associated with epilepsy, such as- TSC (Tuberous Sclerosis Complex), Dravet syndrome, Angelman syndrome etc can also enable autism in individuals (Trillingsgaard & Østergaard, 2004 ; Wolff et al., 2006). In more recent studies, it was revealed that epilepsy as a comorbidity depends heavily on cognitive impairment and IQ and there is a close relationship between neurobiological mechanisms of all three conditions (Woolfenden et al., 2012; Berg & Plioplys, 2012).

In some cases, presence of epilepsy since birth can also result in development of ASD in infants. For example, a neonate born with epileptic encephalopathy is sure to show autistic traits in later years. As hypothesized by Gilby and O'Brien (2013), shared etiology and pathways such as - common genomic variants, malformation of synapse and its plasticity, excitatory imbalance etc can be causal to these comorbidities. In different studies, numerous genes were discovered where mutation of these genes is associated with ASD, epileptic encephalopathy, and in some cases ID. A table is provided below which summarizes the evidence of involvement of these novel variants in prompting these disorders.

Gene	**Functions of gene**	**Phenotypes observed in patients**
ARX	• encodes transcription factor • important for CNS development	• Autism or autistic behavior • Severe ID • Seizures
CDKL5	• encodes protein kinase • helps in regulating the gene functions needed for brain development	• Autism • Severe ID • Epileptic encephalopathy
FOXG1	• encodes transcription factor • important for CNS development	• Epileptic encephalopathy • severe social-communication deficiencies

GRIN1	• encodes subunit of N-methyl-D-aspartate receptor • important for synaptic plasticity	• ASD or ASD like features • ID • Epilepsy or epileptic encephalopathy
GRIN2A, GRIN2B	• encodes subunit of N-methyl-D-aspartate receptor • important for synaptic plasticity	• Autistic features • Epileptic Aphasia
KCNQ2, KCNQ3	• encodes subunit of voltage-gated K^+ channel • determines neuronal excitability	• Autistic features • Mild ID • Various seizure types
MEF2C	• encodes transcription enhancer • important for myogenesis	• Stereotypies related to autism • Myoclonic, atonic seizures
NRXN1	• encodes cell-surface receptor • helps neuroligins to bind at synapses which ultimately facilitates neurotransmission	• Severe ID, epilepsy and ASD
SCN1A	• encodes alpha subunit 1 of a voltage-gated Na^+ channel	• ASD • Mild to severe ID • Various seizure types
PCDH19	• mediates cell-adhesion, mainly in the brain	• ASD • Focal epilepsy • Mild to severe ID • Mainly effects females
TCF4	• encodes a transcription factor	• profound ID and epilepsy • ASD features
And many more.		

Table 3: Involvement of novel variants in epilepsy *(Srivastava & Sahin, 2017)*

3.1.3 Eating disorders and Anorexia Nervosa

- **Eating disorders related to ASD**

According to the American Psychiatric Association, “Eating disorders are behavioral conditions characterized by severe and persistent disturbance in eating behaviors and associated distressing thoughts and emotions.” Types of eating disorders include anorexia nervosa, bulimia nervosa, binge eating disorder, avoidant restrictive food intake disorder, other specified feeding and eating disorder, pica, and rumination disorder.

According to Spek et al. (2019), eating problems or abnormal eating behaviors (EBs) are frequently perceived in individuals with ASD, which in turn leads to the occurrence of eating disorders. In their research, Sharp et al. (2013) discovered that feeding-related difficulties occurred five times more frequently in children with ASD when compared to a typically developing control group. Following this investigation, Mar-Bauset et al. (2014) concluded that around half of all children with ASD are classified as selective eaters, which refers to food refusal, a restricted number of accepted foods, and a higher frequency of consumption of a certain food etc. Individuals with ASD may also experience rituals around meals as well as food refusal, rapid eating, chewing difficulties, struggles in adapting to eating behaviors in the presence of other people, vomiting, and the consumption of non-food substances (Odar Stough et al., 2015). (Leader et al., 2020). Furthermore, numerous studies have shown that children with ASD are more likely than typical children to exhibit food neophobia (the fear of trying new foods) (Spek et al., 2019). Recent data confirm that having elevated abnormal dietary patterns and symptoms in ASD has a detrimental impact on the likelihood of developing an eating disorder in the future.

Anorexia nervosa (AN) is one of the most prevalent eating disorders reported in people with ASD. Anorexia nervosa is a psychiatric disorder defined by an excessive fear of weight gain that results in severe weight reduction, compulsive behavior to decrease energy intake, and secondary complications linked with malnutrition (Kerr-Gaffney et al., 2021). When it comes to cognitive and socio-emotional functioning, it appears that AN shares some similarities with ASD. For example, in both illnesses, difficulties in set-shifting, weak central coherence and enhanced attention to detail are observed (Lang et al., 2014; Westwood et al., 2016). In light of these striking

commonalities, this comorbidity can frequently result in a poorer prognosis, as the majority of the time, the qualities of comorbid AN are classified as severe ASD symptoms.

The existence of anorexia in an ASD patient is a severe concern since it might impair the development of the somatic and psychological domains in children (Dudova et al., 2015). If it goes undiscovered, it can result in poor treatment outcomes as well as the development of higher degrees of autistic characteristics. Furthermore, a thorough grasp of the relationship between these two illnesses is essential for both diagnosis and treatment. As per Adamson et al. (2020), patients with co-occurring anorexia nervosa and autism respond differently to treatments for both eating disorders and ASD. Their findings imply that people with autism may respond to therapy for anorexia in a different way, and adjustments to the traditional anorexia nervosa treatment pathway can be quite beneficial to them.

- **Causal Genes and Molecular Mechanisms of anorexia nervosa**

There have been a slew of researches conducted to look at the possibility of a link between ED and ASD, due to the elevated occurrence of ASD-like symptoms among ED patients and the presence of disordered eating behaviors among ASD patients. In people with ASD, the fundamental causes of eating problems haven't been identified yet, but sensory hypo- and hyper reactivity as well as restricted interests, behavioral rigidity, and motor impairments appear to have a significant influence (Mar-Bauset et al., 2013). Previously, we discussed how food difficulties and problematic eating behaviors experienced by persons with ASD can be a precursor to anorexia, and Mandy and Tchanturia's observations confirm this assertion (2015). Patients affected by AN have clinical characteristics that are identical to those with ASD, and some of these characteristics may be possible risk factors for developing AN as a comorbidity (Treasure et al., 2015). It is

possible that the parallels in behavioral expression and neuropsychological overlap between the two illnesses are driven by genetic variations that are similar in both ASD and AN (Zhou et al., 2018).

One physiological element which has been established to be accountable for AN development in ASD is involvement of the dopaminergic system. According to Anderson et al. (2008), mutations in dopamine transporters and dopamine receptors gene for example DAT1 and DRD4 are highly associated to ASD. These mutations can lead to dysfunction in the dopamine-mediated reward system. On the other hand, it is known that dopamine is one the essential neuromediator engaged in feeding behavior since mesolimbic dopamine mechanism play a significant role in food reward, anticipation of food and social recognition pathways (Gervasini et al., 2013; Narayanan et al., 2010; Narayanan et al., 2010). Selective variants of DRD4 (DRD4 7R/R) which are related to Autism, might contribute to reduced expression of dopaminergic receptors, which can often be significantly linked to the higher risk of AN (Gervasini et al., 2013;Gervasini et al., 2013).

According to a new analysis on gray matter volumetric characteristics in female autistic patients with AN, stronger autistic traits are associated with changes in neural circuits involved in social cognition and disordered eating (Björnsdotter et al., 2018). The complete neurological mechanism of the connection between AN and ASD, however, is still unknown.

3.1.4. Psychiatric Comorbidities

- **What are psychiatric Comorbidities?**

Comorbid psychological symptoms are fairly prevalent among autistic people, although the presence of comorbid mental diseases are verified when the symptoms can be diagnosed by DSM-IV. In the study of Amr et al. (2012), it was discovered that probabilities for existence of atleast one psychological comorbid condition varied from 63.3 % to 96.4 % in autistic individuals. Mukaddes et al. (2010) revealed similar outcome in their study where they evaluated clinic based reports of children with high functioning autism and Asperger's disorder to suggest that more than 75% of the participants experienced a concurrent psychiatric disorder, in particular ADHD. These comorbid psychopathologies in Autistic people are frequently overlooked because core ASD characteristics often mask psychotic comorbid symptoms, and vice versa. Additionally, there are significant commonalities as to how the symptoms of all these conditions develop (Mazzone et al., 2012; Salazar et al., 2015; Salazar et al., 2015). There are few parameters that can potentially impact the comorbidity frequencies in autistic patients. Like as: gender, age, IQ etc (Van Steensel et al., 2012).

- **Phenomenology and presentation of comorbid psychopathologies**

Literature on phenomenology of comorbid psychopathologies based on new DSM criteria (DSM-5) is still scarce. But researchers are beginning to develop even though there are mixed findings about the symptomatologies. This can be due to the use of different methodologies and small sample size. Here, we discussed a few of these findings regarding the presentation of these comorbidities in autistic individuals.

(i) ADHD: Attention deficit hyperactivity disorder (ADHD) is the most prevalent psychiatric co-morbidity. According to a recent study, the frequency of ASD

and ADHD co-occurring in children is around 37–85% (Leitner, 2014). ADHD is defined by a pervasive pattern of inattention, hyperactivity, and impulsivity that manifests itself in a variety of circumstances and results in varying degrees of functional impairment (Klassen et al., 2004). Prior to the publishing of the DSM-5, ADHD co-morbidity in ASD was assumed to be associated with more severe autism symptoms. Now, an increasing number of researches have confirmed the overlap between ASD and ADHD, with the majority of them supporting the notion of shared neurological pathophysiology in both illnesses (Salazar et al., 2015). Despite the fact that ASD and ADHD have some similar cognitive and behavioral characteristics, there are few to no symptoms that overlap in case of the diagnostic criteria for both diseases (Ghanizadeh, 2010).

There's also evidence that having comorbid ADHD adds to the likelihood of having severe ASD. Jang et al. (2013), for example, found that children with both ASD and ADHD had greater rates of additional comorbid characteristics (such as behavioral issues) than children either with ASD or ADHD alone. Other research has indicated that kids with both ASD and ADHD have a harder time identifying facial expressions than kids who only have one of the disorders (Tye et al., 2013). ADHD comorbidity has also been shown to have a negligible impact on socializing and adaptive abilities in people with autism. Sikora et al. (2012) found that children with ASD and clinically significant ADHD symptoms had greater difficulties in adaptive functioning and impulsivity regulation than children with simply ASD.

(ii) **Anxiety Disorders:** There are great deal of evidences that children and adolescents with autism spectrum condition are much more likely to encounter anxiety and anxiety

disorders. However, it's unclear which of the DSM-IV anxiety disorders this demographic is most likely to experience. Depending on a variety of ASD features, individuals may be vulnerable to particular types of anxiety. According to van Steensel et al. (2012), the frequency of anxiety disorder in individuals with ASD ranged from 31.5 to 50.0 %. They discovered that specific phobia was the most frequent anxiety type, accounting for approximately 30% of the population, trailed by obsessive-compulsive disorder (18%), social anxiety disorder (17%), agoraphobia (15%), generalized anxiety disorder (15%), and separation anxiety disorder (9%). Anxiety as comorbidity manifests a wide range of symptoms, including both traditional and unusual symptomatology which can be misinterpreted as having little to do with anxiety.

Autistic individuals who are minimally verbal and have co-occurring mental retardation, for example, may be unable to communicate their internal emotions and instead show anxiety through ambiguous behaviors (e.g. avoidance, disruptive behavior, stress), which is uncommon for anxiety symptoms. Fears of change, concerns about specialized hobbies, and uncommon phobias, among other things, are common anxiety manifestations in ASD patients but not in neurotypicals (Magiati et al., 2017). Because anxiety symptoms can be modified in appearance or hidden by co-occurrence with ASD, anxiety phenomenology also appears to be linked to the intensity of ASD symptoms (Postorino et al., 2017). Anxiety, on the other hand, could be a causative agent of some characteristics of Autism, according to certain cross-sectional research. For example, it can influence stereotyped and rigid behaviors, as well as

social functioning issues, which are common in people with ASD (Rodgers et al., 2012).

(iii) **Depression:** Depressive symptoms and suicidal thoughts are more common among children with ASD than in the overall population, however the prevalence varies from study to study. Depressive symptoms are present in 1.4 percent to 72 percent of children with ASD (Simonoff et al., 2008;Mayes et al., 2011), and up to 42% of people had suicide ideation (Mukaddes & Fateh, 2010). Sadness, diminished interest in most tasks, neuropsychological symptoms, and suicidal impulses are common in people with ASD, according to the DSM-5. They may also show more unusual depressive symptoms, such as changes in special interests or other repetitive behaviors, reduced adaptive behavior skills and self-care, increased aggression or self-injury, regressive behavior, and so on (Pezzimenti et al., 2019). ASD and depression share common characteristics in numerous crucial areas, which can reduce depression diagnosis precision in ASD samples.

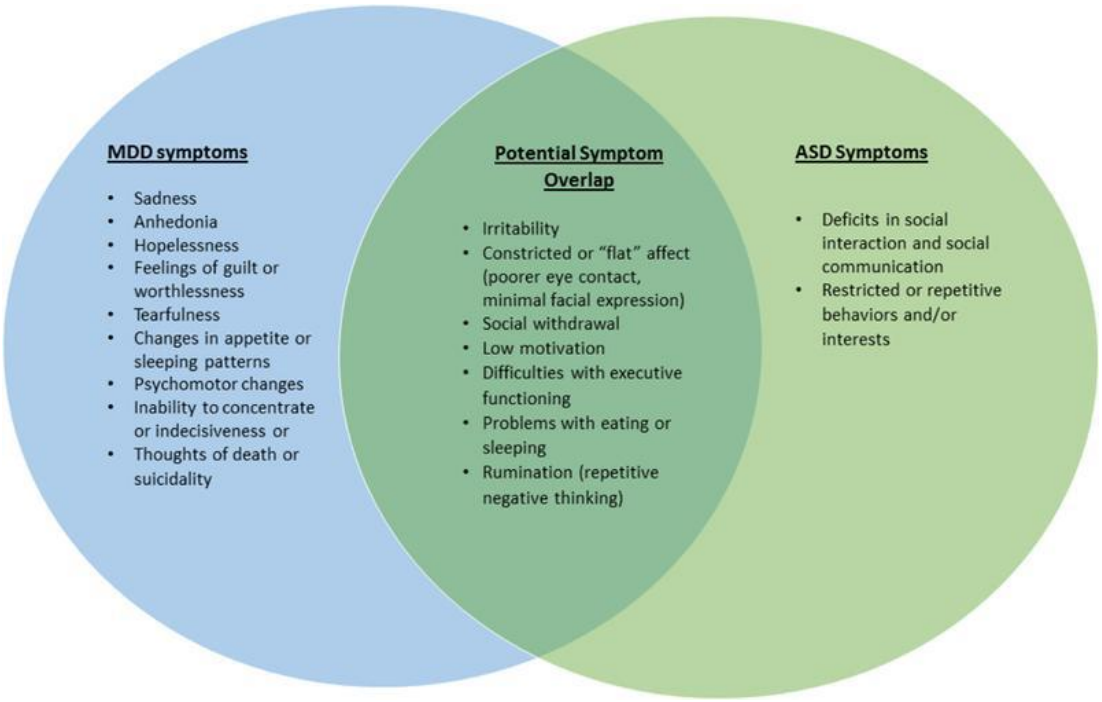

Fig 1: Major Depressive Disorder and Autism Spectrum Disorder Symptom overlap *(Pezzimenti et al., 2019).*

Potential findings from Vasa et al. (2013) have established that anxiety is closely linked to symptoms of depression in individuals with ASD. As a consequence, adolescents with ASD and high anxiety levels frequently experience comorbid depressive symptoms (Wijnhoven et al., 2019). A shared genetic variant has also been discovered in ASD, major depressive disorder, and other mental health issues. Serotonin and dopamine receptor gene variations, for example, have been related to children with ASD having more severe depressive symptoms. This is why co-occurrence of these disorders are pretty common in autistic individuals (Pezzimenti et al., 2019).

3.2. Influence of sex in comorbidity prevalence

3.2.1. Is comorbid ID prevalent in female ASD patients?

An important question associated with comorbid intellectual disability is whether its presence is connected with the patient's sex or not. Even though there are still ongoing debates about this issue, there is consensus among researchers however, that females are more severely affected by ID compared to males and often exhibit lower cognitive ability and intense ASD symptoms (Fombonne, 2009). This is ultimately proven by Cohen et al. (2010) in their study where 2,272 cases were evaluated to identify the distribution of ID spectrum in females and males.

Level of intellectual disability [*N* (%)]	Males	Females
AUTISM		
None	11 (5.3)	0 (0.0)
Mild	57 (27.7)	6 (10.0)
Moderate	20 (9.7)	12 (20.0)
Severe	51 (24.8)	12 (20.0)
Profound	67 (32.5)	30 (50.0)
Not AUTISM		
None	23 (2.0)	12 (1.4)
Mild	352 (30.6)	217 (25.4)
Moderate	178 (15.5)	126 (14.8)
Severe	220 (19.1)	155 (18.2)
Profound	379 (32.9)	344 (40.3)

Table 4: ID characteristics of the groups with and without an AUTISM label by sex

In accordance with the table 4, there is a clear difference in the distribution and range of intellectual disability in the autism group of the study. Even though relatively more male patients had mild to moderate ID, the presence of extreme intellectual disorder is much higher in female autistic patients compared to male autistic patients (50% in females and 32% in males). In the same study by using the IBR-MOAS Aggression Scale, Cohen et al. (2010) also stated that autistic females

with comorbid ID show higher self-injurious (PASLF) and aggressive behaviors and less intellectual performance compared to male participants.

- **Mechanism of action and reason:**

Increased number of rare de novo copy number variant (CNV):

Based on both Gilman et al. (2011) and Levy et al. (2011)'s investigation, gene samples of female ID with ASD patients often show an increased number of rare de novo CNV (copy number variant) in contrast to gene samples collected from males. This finding can indicate that female genes are more prone to mutation in case of both autism and cognitive disability.

X-inactivation:

Another reason for the frequency of severe ASD + ID in females can be X-inactivation mechanism. Different analysis found evidence for involvement of X chromosome in the occurrence of autism. Mutation of gene present in X choromosome can be a leading reason for the causation of ASD. While females have double the amount of X chromosome compared to males, expression of abnormal genes can be easily suppressed by inactivation of the mutant X chromosome (skewing). As discussed by Avner and Heard (2001), in female mammals and humans, one of the two X-chromosomes can randomly be inactivated to equalize the number of active X-genes between males and females, this process is called X-inactivation. As men have single X chromosome present in their cells, inactivation process can't happen to stop gene mutations. Even though preferential X-inactivation may protect females from X-linked mutations and decrease the percentage of autistic females, other autosomal mutations responsible for ASD can still cause damage without any protection (Kirkovski et al., 2013). This is where cognitive disability comes in.

In the research from Fieremans et al. (2015), it was revealed that brain-expressed KDM5C genes can escape X-inactivation and show damaging effects as it can easily mutate after the inactivation occurs. This mutation produces de novo loss-of-function variants of the KDM5C gene which is a contributing factor to severe ID in autistic females. Moreover, few more studies disclosed that another gene named IQSEC2 shows similar characteristics to X-inactivation (Shoubridge et al., 2019). As inactivation of X chromosome doesn't occur in males, mutation of KDM5C and IQSEC2 genes for them is rare as well. This can be a reason why severe comorbid ID can be more frequently seen in females.

3.2.2. Is epilepsy in autism connected with sex?

Meta analysis conducted by Amiet et al. (2008) revealed that prevalence rate of comorbid epilepsy in females was atleast 34.5% whereas in male it was only 18%. To support this argument, in their analysis Supekar et al. (2017) proved that statistically significant sex difference is present in comorbid epilepsy occurrence. The study was conducted by comparing large dataset of 1.8 million individuals where 1,842,575 were non-ASD subjects and 4,790 were ASD subjects. They observed that epilepsy was significantly more common in female with ASD and the rate was notably greater compared to sex difference observed in non-ASD subjects. The findings from the research are provided below:

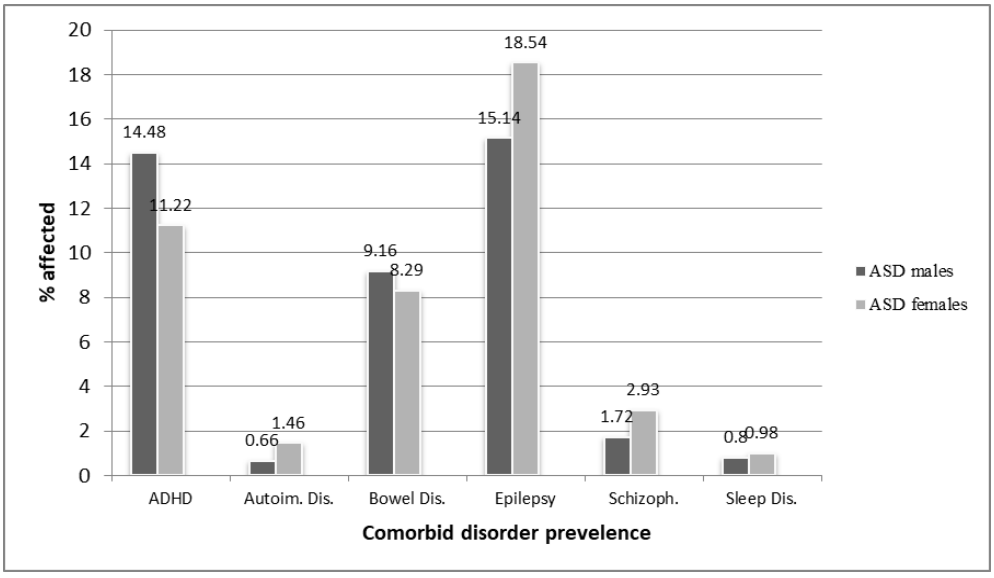

Fig 2: Comorbid disorder prevalence in males and females *(Supekar et al., 2017)*

These findings raise the question of whether there are any phenotypic indications differences between ASD and epilepsy in male and female. It was observed that neurological phenotypes such as - microcephaly, developmental regression, neurological deficits etc had a higher affinity for females compared to males which in turn increases the female ratio of epilepsy (Ben-Itzchak et al., 2013). This information can further awaken the interest regarding sex specific treatment considerations for comorbid epilepsy.

- **Responsible phenotypic traits**

One of the main causes of epilepsy prevalence in autistic females is assumed to be comorbid intellectual disability. From our observation, we have deduced that ID is rampant in females to some certain extent. This increases the risk of epilepsy occurrence as well. Different meta-analysis found evidence for ID and epilepsy correlation and children with both ASD and ID is at a greater risk for epilepsy (25%) than children without comorbid ID (8%) (Woolfenden et al., 2012a). It was

also noted that epilepsy and seizure severity also depended on the cognitive impairment severeness.

Other than presence of comorbid ID, another contributing factor for high epilepsy rate is presumed to be increased genetic or etiological burden in females. Novel findings from Jacquemont et al. (2014) prove that Females with ASD carry a higher mutational burden for deleterious autosomal copy-number variants (CNVs). This is because of X-inactivation mechanism which is known as "female protective effect" against ASD. Because of this mechanism, a greater percentage of gene mutation is required for females to cross the threshold into ASD disease expression. This higher level of gene mutation ultimately results in elevated amount of autosomal copy-number variants (CNVs) and different neurologic abnormalities. Many of these rare CNV's and higher degree of neurologic abnormalities are known to initiate epilepsy symptoms (Blackmon et al., 2015).

Nevertheless, it is not entirely attested weather presence of ID, increased neurologic burden or any other genetic mutations and abnormalities surely gives rise to epilepsy prevanalne in females. Also, is severity of epilepsy symptoms in autism dependent on gender or not is yet to be investigated.

3.2.3. Anorexia Nervosa (AN) in male and female with ASD

In accordance with the epidemiological research, women are more likely than men to suffer from eating disorders, with figures ranging from 3:1 to 18:1 female to male ratio (Adamson et al., 2020). Some researchers even argue that AN is a female manifestation of ASD for its predominance in women and commonalities in attributes with ASD (Kerr-Gaffney et al., 2021).

Margari et al. (2019) investigated 159 high functioning autistic patients to determine which gender is more likely to have distinct AN comorbidity characteristics (100 male and 59 female). They compared data to neurotypical males and females and assessed the gender distribution of the comorbidity using DSM-5 criteria for a diagnosis. Anorexia Nervosa was shown to be more common in female respondents with a statistically significant difference, according to the findings. This result corroborates to the epidemiological rate of AN. To counter the result of this study, the large statistical difference for certain gender prevalence could be due to misdiagnosis, as symptoms that appear to be related to AN could be caused by the patient's severe ASD. Because the diagnosis of Anorexia Nervosa is skewed toward women due to epidemiological findings, many men may receive a "false negative" diagnosis of AN. However, it is also true that there is a higher rate of missed or delayed diagnosis of ASD in females during childhood. This might leave them vulnerable to secondary diseases such as Anorexia, which can be a reason for this comorbidity frequency in women (Westwood et al., 2015).

- **Mechanism related to specific gender prevalence**

Despite the fact that there is a correlation between the behavioral phenotypes seen in ASD and anorexia nervosa (AN), and these disorders may share a common neurobiological basis, the gender difference in AN prevalence may not be linked to ASD. Both genetic and psychological risk factors are thought to play a role in the gender gap in AN prevalence.

Firstly, puberty can moderate genetic effects on problematic eating attitudes and behaviors. As hypothesized by Klump et al. (2010), ovarian hormones such as estrogen, progesterone can affect changes in food intake in both animals and humans. These ovarian hormones become prominent

in girls during puberty which can be a reason for the prevalence of AN in adolescent girl. Estradiol is one of the ovarian hormones that is raised early in puberty and gradually increases throughout the pubertal phase. The genetic changes associated with disordered eating were found to increase as hormone levels rose during puberty. Estradiol is a prominent regulator of gene transcription in the central nervous system, and it seems to be a key mediator of genetic influences on eating problems in women during adolescence. Furthermore, it has been proven that higher ovarian hormone levels regulate numerous transmission systems that are disturbed in eating disorders, such as the serotoninergic system (Timko et al., 2019). On the other hand, a few studies have shown that higher testosterone levels are linked to fewer disordered eating behaviors, which suggests that testosterone may be a biological factor that helps males avoid eating disorders to some extent (Culbert et al., 2014).

Secondly, adolescent females are much more vulnerable than young boys to sociocultural elements that can increase the likelihood of AN development, including peer pressure, thinness, and cultural influences. Increased exposure to certain risk factors in the environment can trigger hereditary concerns. Many studies believe that psychosocial risk factors alone are insufficient to explain the onset of AN because girls can be exposed to these sociocultural variables before puberty, yet AN is more common during puberty (Cafri et al., 2005; Klump et al., 2011). It is hypothesized that a combination of both hormonal activation and psychosocial factors plays a major role in the increasing incidence of AN in girls (Margari et al., 2019).

3.2.4. Sex difference in Psychiatric Comorbidity

As per Gjevik et al. (2010), gender differences and psychological comorbidities have no significant correlation. Solomon et al. (2011), on the other hand, claim that boys with ASD are more prone to develop externalizing abnormalities like ADHD and oppositional defiant disorder, whereas girls with ASD are at an increased risk of developing internalizing psychopathology. Externalizing disorders, such as ADHD, oppositional defiant disorder (ODD), and behavioral disorder, are defined by outwardly directed actions and emotions. Internalizing disorders, on the other hand, are described by inwardly directed behaviors and emotions that include mood disorders (e.g., major depressive disorder, dysthymic disorder) and anxiety disorders (e.g., separation anxiety disorder, social anxiety, obsessive–compulsive disorder or OCD, particular phobias).

(i) Behavioral Problems

A number of recent studies have found that males with comorbid behavioral disorders exhibit more frequent externalizing behavior problems such as violence and hyperactivity, whereas women report greater internalizing complexities but more prevalent nonverbal communication and social interaction (Mayes et al., 2012; Rynkiewicz et al., 2016). This theory is somewhat supported by Cohen et al. (2009) as they revealed that self-injurious behavior (PASLF) is more extreme in adult females with autism, while aggressive attitudes (PAOTH) are more common among men. Self-injury and self-deprecating remarks were found to be more common in female sample groups.

(ii) ADHD

Among autistic individuals, ADHD is the most frequent psychiatric comorbidity. According to a recent survey, about 37–85% of children with ASD have both ASD and ADHD at the same time. However, there are some disagreements in opinion among researchers concerning whether there is a statistically significant difference in the prevalence rate between male and female patients. Margari et al. (2019), for example, conducted a retrospective study of 159 HFA (high functioning autism) individuals (100 male and 59 female) to determine the gender distribution rate of ADHD. They discovered that the prevalence of ADHD was nearly equal in both male and female participants. In comparison, Posserud et al. (2021) discovered that ADHD was at least 1.44% more frequent in adult males and about 1.6% in adolescent males. In addition, children had a greater male-to-female ratio (5.45:1) for this comorbidity. This research included information from a large study population (2,486,088 people) of various ages. Based on the findings of this experiment, it can be concluded that ADHD as a comorbidity is more common among males with autism than females. The results of this investigation are summarized in the table below.

Group		N (%)	MFR	PR (95% CI)
ADULTS, born 1967–1997				
Reference pop.	M	864,856 (51.1)	1.05	Reference
	F	827,355 (48.9)		
Any ASD	M	6,474 (72.0)	2.57	1.41 (1.39–1.42)
	F	2,521 (28.0)		
ASD (no ADHD)	M	4,617 (71.2)	2.47	1.39 (1.37–1.41)
	F	1,866 (28.8)		
ASD+ADHD	M	1,857 (73.9)	2.83	1.44 (1.41–1.48)
	F	655 (26.1)		
ALL CHILDREN, born 1998–2011				
Reference pop.	M	406,063 (51.0)	1.04	Reference
	F	390,027 (49.0)		
Any ASD	M	6,332 (78.6)	3.67	1.54 (1.53–1.56)
	F	1,724 (21.4)		
ASD (no ADHD)	M	4,229 (77.5)	3.44	1.52 (1.50–1.54)
	F	1,230 (22.5)		
ASD+ADHD	M	2,103 (81.0)	4.26	1.59 (1.56–1.62)
	F	494 (19.0)		
CHILDREN, aged 4–10, born 2005–2011				
Reference pop.	M	209,374 (51.1)	1.05	Reference
	F	200,104 (48.9)		
Any ASD	M	2,170 (81.7)	4.46	1.60 (1.57–1.63)
	F	487 (18.3)		
ASD (no ADHD)	M	1,669 (80.9)	4.23	1.58 (1.55–1.62)
	F	395 (19.1)		
ASD+ADHD	M	501 (84.5)	5.45	1.65 (1.60–1.71)
	F	92 (15.5)		

Table 5: Male/female ratio (MFR) and male prevalence ratio (PR) in ASD and comorbid ADHD *(Posserud et al., 2021)*

(iii) Anxiety

Few researches have looked into the potential connection between gender and various types of anxiety symptoms, and no significant differences have been found thus far (Kirkovski et al., 2013). Some studies with a small sample size have yielded encouraging results on this topic, however the results vary from study to study. For instance, Solomon et al. (2011) found that high functioning autistic girls have more anxiety symptoms than boys, especially during adolescence, but Margari et al. (2019) refutes this finding by demonstrating that anxiety is

prevalent in a high proportion of both male and female HF patients, with no statistically significant difference.

(iv) Depression

Depressive disorders are commonly observed in children, with rates considerably higher in teenage girls (Oswald et al., 2016.) These findings are consistent with Wijnhoven et al. (2019) who reveled that females with ASD and anxiety had considerably greater child-rated symptoms of depression than boys with ASD and anxiety. However, no significant difference in the prevalence of suicide ideation was found in their study between boys and girls. Unfortunately, because some studies demonstrate opposite outcomes, it is still unclear whether or not girls with ASD are at a higher risk for depression or not. According to Menezes et al. (2018) and Pezzimenti et al. (2019), girls with ASD are at the same, greater, or lower risk for developing depression as boys with ASD.

- **Diagnostic issues of Psychiatric Comorbidity:**

The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria have been the most widely used method for detecting comorbid psychopathologies until recently. But often time, DSM criteria have been found to be the origin of misdiagnosis or underdiagnosis of females for autism and its comorbidities. According to Ratto et al. (2017), women sometimes show camouflage effects in which they successfully mask core symptoms through rehearsed mimicry of socially normative behaviors. Because the phenotypes of these conditions are so similar, those who effectively camouflage their ASD are frequently misdiagnosed as having borderline personality disorder, bipolar disorder, or depressive disorder (Takara & Kondo, 2015). In these circumstances, indicators associated with psychiatric comorbidities often divert attention away

from the core diagnosis of ASD. High functioning autistic females, for example, are the most difficult to discover, due to milder symptomatology or methodological bias such as a absence of adequate diagnostic instruments. (Hull et al., 2016).

It's also hard to ascertain whether anxiety symptoms or repetitive behaviors are seen in individuals are evidence of a comorbid condition like anxiety disorders and obsessive-compulsive disorder, or if they're signs of core ASD symptoms (Matson & Cervantes, 2014). There is an ongoing debate of whether the studies measuring anxiety in ASD are genuinely detecting anxiety disorders and not just characteristics of ASD. A large percentage of the research assessed anxiety disorders in autistic patients using tools designed for children with typical development. There is clearly diagnostic overlap between anxiety subtypes and ASD criteria, particularly between ASD and OCD or ASD and social anxiety disorder. Also, severity in ASD pathogenesis may also affect the expression of anxiety symptoms which might not be easily diagnosed (Postorino et al., 2017b).

Because of limitations in speech or face-to-face communication regarding feelings, many studies have demonstrated that identifying depression in children with ASD and impaired cognitive functioning can be difficult (Casanova et al., 2020).

It's crucial to carefully investigate comorbidity in clinical samples since it can affect the symptoms of the core ASD diagnosis, treatment approaches, and prognosis. Furthermore, having a good understanding of the rate at which certain comorbidities occur can lead to immediate detection and the implementation of prevention initiatives.

Chapter 4

Conclusion

Despite the lack of literature, we discovered sex differences in comorbid conditions in the ASD population—ADHD was more common in males with ASD than women, while epilepsy, eating disorders, and intellectual disability were more prevalent among women than boys with ASD. Even though males are still overrepresented across the spectrum, a few studies have found that affected females diagnosed with ASD have more severe cognitive impairment. Altered presentation of clinical symptoms of both ASD and comorbidities were observed. More research is required to explore into comorbidity patterns in both men and women, as well as the genetic, epigenetic, and neurological origins of sex differences and age-related alterations in comorbidity. While researchers have yet to discover a definitive etiology for the reported gender differences, it may be interesting to look into sex-specific treatments for some of these comorbidities.

4.1 Limitations of the study:

There are certain limitations regarding our literature that we should have taken into consideration. First, while collecting data and statistics, we did not inquire whether the participants were taking any kind of medication that can result in certain comorbidities. Second, Age range of the participants and if they had any underlying medical condition unrelated to ASD also should have taken into consideration. Also further research regarding the comorbidities and combined therapeutic strategy should be performed to ensure that the best possible level of treatment is provided to all individuals affected by this debilitating disorders and that future treatment options are more directed and suitable for all who are affected.

4.2 Future research plan:

There are few research prospects that we can focus on in future. Firstly, the relationship between age, gender and comorbidity prevalence of the subject can be taken into consideration. Secondly, Further study into the comorbidities and integrated therapy strategy should be carried out in order to guarantee that the best possible quality of treatment is delivered to all those affected by these debilitating conditions. Moreover, thorough research should be conducted on sex-specific medication for these comorbidities in attempt to implement treatment choices that are more targeted and appropriate for all persons who are impacted.

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