University of Pavia

Department of Brain and Behavioral Sciences

Doctoral Program in "Psychology, Neuroscience and Medical Statistics"

Coordinator: Prof. Gabriella Bottini

XXX Cycle

DIAGNOSING AUTISM SPECTRUM DISORDERS IN ADULTS: EXPLORING THE UTILITY OF THE ADOS-2 AND THE ADI-R

Supervisor

Prof. Pierluigi Politi

Doctoral Candidate

Laura Fusar Poli

Academic Year 2016-2017

SUMMARY

INTRODUCTION

"Indeed, in a strange way, most people speak only of autistic children and never of autistic adults, as if the children somehow just vanished from the earth. But though there may indeed be a devastating picture at the age of three, some autistic youngsters, contrary to expectations, may go on to develop fair language, a modicum of social skills, and even high intellectual achievements; they may develop into autonomous human beings, capable of a life that may at least appear full and normal -even though, beneath it, there may remain a persistent and even profound autistic singularity."

When Oliver Sacks wrote these few sentences at the beginning of "An Anthropologist on Mars" (Sacks, 1995), we were still unaware of the "autism pandemic" that is (was?) affecting more than 1% of population worldwide (Centers for Disease Control and Prevention, 2014). After more than twenty years, we are starting to search for the "lost generation" of autistic adults (Lai & Baron-Cohen, 2015) who have been missed because of too stringent diagnostic criteria or because of the limited awareness towards the condition. The challenge seems hard, also considering the scarce knowledge of the scientific community about the evolution of autism spectrum disorders (ASD) in adulthood. Nevertheless, the importance of recognizing ASD symptoms in adults has been acknowledged for the promotion of an adequate support. It is thus essential to improve the diagnostic tools currently available, to facilitate an accurate identification of the diverse autistic phenotypes and the innumerable clinical presentations of ASD along the life span. Through the present thesis, I would like to provide an overview of the reliability of diagnostic instruments in adults, particularly in people with high cognitive abilities and mild symptoms, who often remain unrecognized for a long time.

In *Section I*, a brief overview of ASD will be presented, together with an extensive explanation of the diagnostic criteria and the difficulties connected with a diagnostic assessment in people who are already in adulthood. In this first part, I will resume also some of the papers published during the last three years, regarding the treatment, the outcome and the special talents of people with ASD.

Section II will comprehend the experimental and clinical data collected during my collaboration with the Laboratorio Autismo of the University of Pavia. The first part, will report the preliminary results of a systematic review of the instruments used to confirm ASD diagnoses in clinical trials. Second, I will analyze the accuracy of the ADOS-2 and the ADI-R - the most widely used standardized tools - in diagnosing ASD in 140 adults referred to the Laboratorio Autismo. Part of these data have been already included in a publication (Fusar-Poli et al., 2017c). Predictors of the agreement between diagnostic instruments and clinical diagnosis will also be examined. Finally, some paradigmatic clinical vignettes of adult people seeking for a first formal diagnosis of ASD will be illustrated.

SECTION I

1. AUTISM SPECTRUM DISORDERS: AN OVERVIEW

Definition and epidemiology

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by persistent deficits in communication and social interaction, and by the presence of stereotypic, restricted and repetitive behaviors, causing functional impairment (American Psychiatric Association, 2013).

Recent epidemiological studies have reported that 1 every 68 children in the United States may belong to the autism spectrum (Centers for Disease Control and Prevention, 2014), and the data regarding the prevalence in the adult population are similar. After a community survey in England, Brugha et al. (2011) estimated a prevalence of 9.8 every 1000 people of 16 years and above. However, since the first epidemiological study, which reported a prevalence of the condition minor than 0.5‰ (Lotter, 1966), there has been a dramatic increase of ASD diagnoses. Several factors could explain the so-called "autism epidemic": reasons could be mainly ascribed to the changes occurred in the diagnostic criteria (Hansen, Schendel, & Parner, 2015) and to the greater awareness that general population and clinicians have towards the condition (Elsabbagh et al., 2012). Particularly, after the broadening of the diagnostic criteria, it is acknowledged that autism spectrum conditions might not be recognized in some individuals until adulthood. Researchers are therefore trying to identify the so-called "lost generation" of adults with ASD (Lai & Baron-Cohen, 2015). However, a real growth of risk factors cannot be excluded (Lai, Lombardo, & Baron-Cohen, 2014).

Of note, ASD are more commonly diagnosed in males, with a ratio of about 1 female every 4 males diagnosed (Centers for Disease Control and Prevention, 2014), although

the difference decreases in individuals with intellectual disability (ID) (Elsabbagh et al., 2012).

Etiopathogenesis

Despite the extensive research and the development of several models, the etiology and pathogenesis of ASD remain largely unclear. Nevertheless, it is now evident that ASD has a genetic basis with significant contribution of environmental factors (Lai, Lombardo, & Baron-Cohen, 2014; Yenkoyan, Grigoryan, Fereshetyan, & Yepremyan, 2017). A recent meta-analysis reported that heritability of ASD in twin studies ranged from 64% to 91% (Tick, Bolton, Happe, Rutter, & Rijsdijk, 2016). However, genetics of ASD is characterized by an extreme complexity and remarkable heterogeneity (Geschwind & State, 2015). To date, genetic antecedents have been identified only in a small subgroup of individuals with ASD, where rare and common *de novo* mechanisms seem to be at play (An & Claudianos, 2016). The presence of ASD or autistic characteristics has been associated to a wide variety of genetic syndromes, such as fragile X syndrome, Rett syndrome, tuberous sclerosis complex, Down syndrome, phenylketonuria, CHARGE syndrome, Angelman syndrome, Timothy syndrome and Joubert syndrome. The prevalence of ASD in these conditions ranges from 5% in Down syndrome to 97% in Rett syndrome (Moss & Howlin, 2009).

A variety of known and potential environmental risk factors, both pre- and post-natal, are associated with ASD, potentially influencing the neurodevelopment (Schmidt, Lyall, & Hertz-Picciotto, 2014). A recent review suggested that perinatal trauma or ischemia and hypoxia have a strong link to ASD, as well as advanced parental age. On the contrary, other pregnancy-related factors, such as maternal obesity, diabetes and caesarian

section, have shown a less strong association with risk of ASD. Several environmental factors, including vaccination, maternal smoking, thimerosal exposure, and most likely assisted reproductive technologies are unrelated to risk of ASD. The evidence regarding the negative effects produced by the deficiency of folic acid and omega-3 is inconsistent. There is instead enough evidence for the association between some heavy metals (most important inorganic mercury and lead) and ASD that warrants further investigation (Modabbernia, Velthorst, & Reichenberg, 2017). Several studies have demonstrated a significant increase in ASD risk after exposure to air pollution during the prenatal period, particularly for heavy metals and particulate matter. A few studies suggest also a link with organophosphate pesticides (Schmidt et al., 2014).

Evidence indicates that the combination of genes and environment may cause alterations in brain functioning that in turn could be responsible for the specific behavioral pattern (Lai et al., 2014). Neuropathological research has focused on the study of ASD brain using different neuroimaging techniques and through post-mortem studies. Neuroanatomical examinations found an increased rate of brain growth in infancy and early childhood, mainly in the frontal, temporal and parietal lobes, and cerebellum. This is followed by abnormally slow cerebral and cerebellar growth in later childhood and adolescence. Variable structural abnormalities in the corpus callosum, amygdala, and hippocampus have also been reported (McFadden, 2013). Neurochemical investigations in autistic disorder have focused on several neuromodulators. Serotonin seems strongly linked to autism. On the contrary, there is little evidence supporting a dysfunction of norepinephrine or endogenous opioids. The findings regarding the role of dopaminergic system are conflicting. Promising new areas

of study may include possible dysfunction of the cholinergic system, oxytocin, and amino acid neurotransmitters (Lam, Aman, & Arnold, 2006). There is substantial evidence implicating chronic neurological inflammation and immune dysregulation leading to upregulation of inflammatory cytokines in the ASD brain, probably due to altered blood-brain barrier function (Noriega & Savelkoul, 2014).

In parallel with the evolution of biological models, some cognitive theories of ASD have also been developed to explain the differences in brain functioning compared to healthy controls. In particular, people with ASD seem to present deficits in the theory of mind, the ability to understand the mental states in self and others (Baron-Cohen, 1995). Additionally, they show executive functions deficits (Ozonoff, 1997) and a weak of central coherence, a cognitive style prioritizing details over the global picture (Frith, 1989).

Comorbidities

Intellectual disability (ID) represents one of the most frequent comorbid conditions in individuals with ASD. Recently, the Centers for Disease Control and Prevention (CDC) estimated that 31% of children with ASD had also ID, while 23% were in the borderline range of intelligence (Centers for Disease Control and Prevention, 2014). Overall, literature shows that prevalence of ID ranges from 16.7% to 84% (Postorino et al., 2016). Nevertheless, it is important to underline that such estimates might be highly influenced by the type of intelligence evaluated. In ASD individuals, in fact, a discrepancy between performance and verbal subtests is very common (Lai et al., 2014). Language disorders are also quite frequent. In DSM-IV, language delay was a defining feature of autism, which is no longer included in DSM-5. Attention-deficit hyperactivity disorder (ADHD),

tic disorders, and Tourette's syndrome are other disorders often associated with ASD. Around 80% of ASD people present motor abnormalities (Lai et al., 2014).

Considering medical comorbidities, epilepsy affects between 6 and 37% of individuals with ASD, particularly those with ID or genetic syndromes (Jeste & Tuchman, 2015). A recent meta-analysis showed that also gastrointestinal problems are significantly higher in children with ASD compared to typically developing children, with a symptomatology that may include constipation, chronic diarrhea, abdominal pain and gastro-esophageal reflux (McElhanon, McCracken, Karpen, & Sharp, 2014). Food selectivity is a common problem in children with ASD and is of particular concern because of its negative impact on nutrient intake (Bandini et al., 2017). Sleep disorder, particularly insomnia, have a prevalence of at least 50% among people with ASD. Nocturnal agitation, poor sleep hygiene, co-sleeping, and early final awakening have been often reported (Miano, Giannotti, & Cortesi, 2016).

Both clinical practice and epidemiological research confirm that psychological and psychiatric comorbidities are very common in ASD (Lai et al., 2014). In particular, the prevalence of anxiety disorders and mood disorders appears to be significantly higher in adolescents and adults with ASD and average cognition compared to neurotypical adults (Bruggink, Huisman, Vuijk, Kraaij, & Garnefski, 2016). For anxiety disorders the prevalence rates in high-functioning people with ASD are around 50% (Hofvander et al., 2009; Lugnegård, Hallerbäck, & Gillberg, 2011). In addition, a recent systematic review found that the rates of depression in people with high-functioning ASD varied from 1% to 47% (Wigham, Barton, Parr, & Rodgers, 2017). Psychotic disorders can be also present, mainly in adults. Oppositional behaviors are often a manifestation of anxiety, resistance to change, persevering belief in the correctness of own point of view, and

poor awareness of the consequences of own behavior on others (Lai et al., 2014). On the other hand, aggressive (more frequently directed to caregivers) and self-injurious behaviors are more typical of patients with lower IQ. They could represent a signal frustration in individuals with reduced communication, as well as anxiety, sensory overload, or disruption of routines (Lai et al., 2014).

Interventions

To date, there is no effective treatment for ASD core symptoms. Nevertheless, a wide range of interventions are available for individuals with ASD and their families (Bölte, 2014).

Most interventions are educational or psychosocial. Among comprehensive approaches, the Applied Behavior Analysis (ABA; Sulzer-Azaroff & Mayer, 1977) is mainly targeted at the reduction of aggression, exploiting a functional behavioral assessment to teach alternative behaviors. More recently, the Early Start Denver Model (ESDM; Rogers & Dawson, 2010) and the Early Intensive Behavioral Intervention (EIBI; Reichow, Barton, Boyd, & Hume, 2012) have been developed for very young children, following the principles of ABA with some integrations. The Treatment and Education of Autism and related Communication-handicapped Children (TEACCH; Mesibov, Shea, & Schopler, 2005) can be used for individuals of any age and provides friendly structured environment and activities that can be understood by the patients, considering their interests and strengths. The Picture Exchange Communication System (PECS; Bondy & Frost, 1994) also showed a moderate efficacy in teaching spontaneous social-communication skills by means of pictures or symbols. Early intervention can be also parent- or teacher-mediated in order to apply intervention strategies also at home or in

community settings (Oono, Honey, & McConachie, 2013). For adolescents and adults with higher cognitive abilities, cognitive behavioral therapy (CBT), specifically tailored for people with ASD, may be useful for reducing anxiety and for teaching practical adaptive strategies. Social-skills training interventions, such as the PEERS® program (Laugeson, Frankel, Gantman, Dillon, & Mogil, 2012), appear also useful in teaching social behavior.

Giving the high rate of psychiatric comorbidities and the oppositional and aggressive behaviors characterizing ASD, pharmacological treatments are often necessary. Antipsychotic drugs, such as risperidone and aripiprazole, are mainly used for reducing problem behaviors, even if may present a high rate of adverse events. On the other hand, the Selective Serotonin Reuptake Inhibitors (SSRI) are frequently used for the treatment of comorbid anxiety and depression.

During the doctoral course, a more detailed research on both pharmacological and non-pharmacological treatments for ASD was conducted. In particular, we focused on the potential complementary and alternative therapies for ASD and on the role of the drugs acting on the GABAergic system. The results were presented into two papers (Brondino et al., 2015; Brondino et al. 2016).

Complementary and alternative therapies for ASD

Complementary and alternative medicine (CAM) represents a popular therapeutic option for patients with ASD. We conducted a systematic review to investigate trials of CAM in ASD. We retrieved a total of 80 studies, examining several types of CAM. Among biological treatments, we included diets, nutraceuticals, herbal remedies, hyperbaric oxygen therapy, and chelation. Among non-biologically based CAM therapies, music therapy, auditory integration training, sensory integration

therapy, drama, acupuncture, massage, yoga, pet therapy, and chiropractic care were examined. Our research concluded that there is no evidence supporting the efficacy of CAM therapies in ASD. However, music therapy, sensory integration therapy, acupuncture, and massage showed promising results. The contrast between the wide use of CAM by families of people with ASD and the paucity of scientific results for alternative treatments is interesting. One possible reason for this discrepancy is that CAM therapies are in general considered as "natural," with an optimal safety profile and less side effects than conventional medications (Brondino et al., 2015).

Pharmacological modulation of GABA function in ASD

Among available pharmacological treatment for ASD, we focused mainly on those modulating GABA function. In fact, it has been hypothesized that ASD may result from a disruption of the equilibrium between excitatory glutamatergic and inhibitory GABAergic pathways (Hussman, 2001). In total, 14 studies and five ongoing trials were included in the systematic review. The following GABA modulators were examined: acamprosate, arbaclofen, bumetanide, carnosine, flumazenil, riluzole, valproate. We concluded that evidence is still insufficient to suggest the use of GABA modulators in autistic patients. However, it is important to underline that short-term use of the reviewed drugs appeared free from side effects. Of note, research has focused mainly on children or adolescents and no study has been specifically designed for adults (Brondino et al., 2016).

Outcome in adulthood

A recent meta-analysis reported that the overall outcome of autistic disorders in adulthood seems remarkably impaired. In particular, across the studies about 20% demonstrated a good outcome, close to 30% had a fair outcome, whereas half of the

participants had a poor or even a very poor outcome in adulthood (Steinhausen, Mohr Jensen, & Lauritsen, 2016). Another review reported sparse evidence (Magiati, Tai, & Howlin, 2014). While social functioning, cognitive ability and language skills remained relatively stable in some studies, other papers reported deterioration over time. Adaptive functioning tended to improve in most studies. Diagnosis of autism or ASD was generally stable, although severity of autism-related behavioral symptoms was often reported to improve (Magiati, Tay, & Howlin, 2014). A certainty is that people with ASD need a continuous support throughout the life span (Henninger & Taylor, 2013; Magiati et al., 2014; Smith, Greenberg, & Mailick, 2012). Early intervention is expected to improve outcome (Fein et al., 2013; Reichow, 2012), that is the main reason for promoting early detection and diagnosis.

The needs of adults with autism have been neglected by society for a long time. During the last century, it was almost inevitable to institutionalize people with severe forms of ASD. With the growing knowledge of the condition, there are more possibilities to implement effective behavioral and environmental techniques of treatment. Among the diverse forms of residential facilities, the model of the farm-community represents an innovative concept, built on the theories of normalization, social role valorization, capacity building, and deinstitutionalization (Giddan & Obee, 1996). During the doctoral course, the 10-year adaptive outcome of a cohort of 22 adults living in a farm-community specifically designed for autistic people was evaluated (Fusar-Poli et al., 2017a).

Long-term outcome of a cohort of adults with ASD and ID

We examined the change in adaptive abilities of 22 adults with severe autism. All patients were living in Cascina Rossago (Barale et al., 2016; Fusar-Poli et al., 2016),

a farm-community whose core feature was the choice of a rural environment suitable for a life project for people with autism and ID. The intervention implied careful attention to the environment and a relationship-based approach, through a TEACCH-oriented rehabilitation program (Giddan & Giddan, 1993). This method targeted both cognitive and daily living skills, communication and socialization. All the patients participated in accurately scheduled farm-related activities, such as animal care, gardening and taking care of common spaces for a minimum of five hours a day. In addition, they were assigned to different activities according to their individual preferences for two hours daily. In particular, they could participate to different kinds of physical activity (e.g. hiking, basketball, swimming) and artistic activity (e.g. music, pottery, weaving laboratory). During the laboratories, they were constantly supported by a member of the staff with expertise in the specific field. Subjects were evaluated by means of the Vineland Adaptive Behavior Scales (VABS; Sparrow, Balla, Cicchetti, Harrison, & Doll, 1984) immediately after the admission in the farm-community and after ten years. Results showed no statistically significant improvement neither deterioration according to VABS raw scores. On the contrary, a significant improvement was evident in standard scores of VABS total score and in single domains. These results partially mirrored the findings of Magiati et al. (2012) who observed that adaptive functioning tended to improve. In general, our patients remained stable in adaptive abilities, showing that living in a structured environment specifically designed for ASD patients could be useful despite the severity of autism (Fusar-Poli et al., 2017a).

Special talents in ASD

One of the most under-studied (and under-estimated) aspects of ASD is probably their mysterious and fascinating talent (Boso et al., 2010; Happé & Frith, 2010; Politi et al.,

2016). Indeed, the myth of the autistic "savant" is common in popular thinking (Happé & Frith, 2010). Despite their social deficits, in fact, people with ASD may display unexpected and extraordinary skills in numerous fields, including music, arts, calculation/mathematics and memory (Boso et al., 2010). Several authors have tried to study the prevalence of special talents in autism, with estimates ranging from 1 every 3 (Howlin, Goode, Hutton, & Rutter, 2009) to 1 every 10 individuals with ASD (Treffert, 2009). Interestingly, these peculiar areas of interest, such as musical giftedness, may be positively exploited within rehabilitation programs in autism to promote social interactions, communicative behavior and emotional responsiveness (Boso et al., 2010). The case of a special musical talent in a woman affected by severe autism has been studied during the doctoral course (Fusar-Poli, Rocchetti, Garda, & Politi, 2017).

The invisible talent of Simona

Simona is a 46-year-old woman living in Cascina Rossago, a farm-community located in in the North of Italy. Since the age of three, she has been playing piano in a repetitive and monotonous, but extremely musical, way. She has always refused to learn musical rules. Of note, Simona is completely non-verbal, with an IQ of 36. It is not clear whether Simona's ability is a real talent or a stereotypy. However, piano probably represents her alternative but very efficacious way to communicate with the rest of the world (Fusar-Poli et al., 2017b; Politi et al., 2016).

2. THE DIAGNOSIS OF AUTISM SPECTRUM DISORDERS

Although ASD is a common neurodevelopmental disorder, clear biomarkers are not currently available: ASD is currently defined and diagnosed only on the basis of behavior (Lord, 2010). Since the first description of the condition, the definition of autism has radically changed. Initially considered a disorder characterized by extreme aloofness and repetitive and sensorimotor behaviors, now much more importance is given to the understated socio-communication deficits (Lord, 2010). ASD can be associated with a broad range of intellectual and language skills. Of note, symptoms vary across individuals and within individuals at different ages. A correct identification of well-defined behaviors for an accurate diagnosis is thus a complex task (Lord et al., 2014).

Diagnostic criteria of ASD: an historical perspective

Even though many children who would now have been diagnosed with autism have been seen in the last century, Leo Kanner was the first to provide a detailed clinical description of 11 autistic children in his "Autistic Disturbances of Affective Contact" (Kanner, 1943). Kanner highlighted some core elements of the phenotype: the profound lack of affective contact with others, the absence of a communicative language, a repetition of verbal and motor behaviors, and the intense desire for sameness. Kanner also noticed that autistic children did not show evident congenital abnormalities and presented a variety of cognitive and motor abilities (Kanner, 1943).

Almost simultaneously, Hans Asperger noticed similar characteristics in a group of children from his clinic in Austria. However, Asperger's cases showed higher intellectual abilities, even presenting the same impairing difficulties in socio-communication. Their interests were very circumscribed and they presented unusual sensory responses and

repetitive behaviors. Unfortunately, Asperger's work was written in German, thus being for a long time available only to a small part of the scientific community. His pioneering thesis was re-discovered several years later (Frith & Mira, 1992).

However, following Kanner's description there was a growing body of work on the validity and definition of autism. Influential approaches were in particular those developed by Rutter (Rutter, 1978), and by the National Society of Autistic Children (NSAC; Ritvo & Freeman, 1977). The increase of interest for ASD led to its first recognition in the third edition of the Diagnostic and Statistical Manual (DSM-III; American Psychiatric Association, 1980). DSM-III represented a landmark in psychiatric diagnosis with the adoption of an atheoretical approach that emphasized valid and reliable descriptions of clinical conditions (Volkmar, Reichow, Westphal, & Mandell, 2014). Autism was included in the manual for the first time (as "Infantile autism"), in the new class of the Pervasive Developmental Disorders (PDD), together with other disorders. The core features of the new diagnostic category were a pervasive lack of responsiveness to others, gross deficits in language development, peculiar speech patterns, and bizarre responses to the environment, including resistance to change and fascination with objects, with an onset prior to 30 months of age. Criteria for the diagnosis had all to be present, and a complete developmental history was required. This could potentially represent a problem for adults (Volkmar et al., 2014). Additionally, for the first time, a clear boundary between autism and schizophrenia was created: according to DSM-III, autism could not occur in the presence of psychotic symptoms, such as delusions or hallucinations.

In 1987, DSM-III-R (American Psychiatric Association, 1987) formally separated three core domains (impairment in reciprocal social interaction, communication, and restricted or repetitive behaviors), and age of onset was dropped as an essential feature. Additionally, individuals with autism were no longer excluded from a co-occurring diagnosis of schizophrenia (Volkmar et al., 2014).

The fourth edition of DSM (DSM-IV; American Psychiatric Association, 1994) was closely related to the tenth revision of the International Classification of Diseases (ICD-10; WHO, 1993), with the attempt to have consensus on a robust definition of autism, and a good balance of specificity and sensitivity (Volkmar et al., 2014). At the end of the process, only minor changes were introduced in respect of the previous editions. However, the release of DSM-IV was associated with an enormous increase in research and with the development of new dimensional assessment instruments specifically keyed to it (Lord, Corsello, & Grzadzinski, 2014). DSM-IV recognized three disorders new to DSM: childhood disintegrative disorder, Asperger disorder, and Rett disorder, along with the Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) category, already present in the previous version. Of these conditions, the definition of Asperger was the most problematic: the text appeared radically changed in DSM-IV-TR, but the criteria could not be changed at that point. As already mentioned, DSM-IV and ICD-10 did come to convergent definitions, and the approach has been widely used and highly productive for research. This approach also facilitated the development of new dimensional approaches for screening and diagnosis that further enhanced research (Volkmar & Reichow, 2013) .

DSM-5: from categorical to dimensional

The last edition of DSM (DSM-5; American Psychiatric Association, 2013) was released in May 2013. It addresses the advances made in the last 20 years. Significant changes to the overall structure have been introduced. The major change regards the introduction of the umbrella term "autism spectrum disorder": it emphasizes the dimensional nature of the condition, indicating that symptoms of ASD fall on a continuum, with some individuals showing milder symptoms, while others having more severe symptoms and requiring extensive support. Using DSM-IV, patients could be diagnosed with four separate disorders: autistic disorder, Asperger's disorder, childhood disintegrative disorder, or PDD-NOS. After DSM-5 release, people who were previously diagnosed with one of the four PDD from DSM-IV should meet the criteria for ASD.

The second major change is that the triad of core symptoms has been re-organized into a dyad: (A) difficulties in social communication and social interaction and (B) restricted and repetitive behavior, interests, or activities.

Under the DSM-5 criteria, individuals with ASD must show symptoms from early childhood, even if those symptoms are not recognized until later. This criteria change encourages earlier diagnoses of ASD but also allows people whose symptoms may not be manifest until social demands exceed their capacity to receive the diagnosis. It is an important change from DSM-IV criteria, which was oriented toward the identification of school-aged children with autistic disorders, but was not as useful in diagnosing younger children (Volkmar et al., 2014).

Finally, the DSM-5 requires a specification of the severity of functioning across a three-levels scale. This scale is rated by clinicians separately for each of the two domains. Further specifiers regard the presence of intellectual disability and/or language

impairment; the association with other known medical or genetic conditions; environmental factors; neurodevelopmental, mental, or behavioral disorders; catatonia. More than one specifier can be given at the same time (Volkmar et al., 2014).

DSM-5 Diagnostic Criteria for Autism Spectrum Disorder 299.00 (F84.0)

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interest, emotions, or affect; to failure to initiate or respond to social interactions.

2. Deficits in nonverbal communicative behaviors used to social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of

gestures; to a total lack of facial expressions and nonverbal communication.

3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by

history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat

same food every day).

3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior

C. Symptoms must be present in the early developmental period (but may not become fully manifested until social demands exceed

limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of

autism spectrum disorder and intellectual disability, social communication should be below that expected of general developmental level.

Note: Individuals with a well-established *DSM-IV* diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise need criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

With or without accompanying intellectual impairment

With or without accompanying language impairment

Associated with a known medical or genetic condition or environmental factor (**Coding note:** Use additional code to identify the associated medical or genetic condition.)

Associated with another neurological, mental, or behavioral disorder (**Coding note:** Use additional code[s] to identify the associated neurodevelopmental, mental, or behavioral disorder[s].)

With catatonia (refer to the criteria for catatonia associated with another mental disorder, pp. 119–120, for definition) (**Coding note:** Use additional cost 293.89 [F06.1] catatonia associated with autism spectrum disorder to indicate the presence of the comorbid catatonia).

From the *Diagnostic and Statistical Manual*, 5th edition, pp. 50–55. American Psychiatric Association, 2013, Arlington, VA: American Psychiatric Publishing.

Diagnosing ASD in adults

ASD are long-life conditions, but research has focused mainly on the recognition of ASD and intervention in early childhood (Lai et al., 2014). However, interest in outcome and development in adulthood is growing (Happé & Charlton, 2012; Howlin & Moss, 2012). The clinical picture is usually clearer in individuals with severe symptoms (e.g. extreme social aloneness, no eye contact, motor mannerism) and concurrent developmental difficulties (e.g. cognitive or language delay), who are more easily diagnosed during childhood. On the contrary, ASD in people without an evident developmental delay and with subtler difficulties is more likely to be identified later in life. Additionally, with the broadening of the diagnostic criteria, it is now acknowledged that some forms of ASD might not be recognized until adulthood. Nonetheless, an accurate and timely identification of ASD in adults is important for the provision of support services and the promotion of positive outcomes (IACC, 2012; Lai & Baron-Cohen, 2015; Volkmar & McPartland, 2014).

Guidelines recommend to evaluate adults with suspected ASD through a multistep and multidisciplinary assessment (Pilling et al., 2012; Wolf & Ventola, 2014). It should be undertaken by trained and competent professionals, considering information of current and past behavior, also including early development. It is important to rely on different methodologies to adequately characterize the individual's psychopathology and need for treatment and service (Pilling et al., 2012; Volkmar et al., 2014; Volkmar, Booth, McPartland, & Wiesner, 2014). For more complex assessments, it is recommended to support the clinical judgment with standardized instruments, such as checklists,

interviews and observational methods, which could improve the reliability of diagnosis (Pilling et al., 2012; American Psychiatric Association, 2013).

Challenges in making a diagnosis of ASD in adulthood

Although the diagnosis of ASD usually occurs during early childhood, subjects with average or above-average intellectual abilities might receive a diagnosis later in life. In some cases, diagnosis is not obtained until adulthood (Lai & Baron-Cohen, 2015).

Several reasons for diagnostic delay of ASD have been hypothesized. It could be due to camouflaging of symptoms, or late onset of symptoms that causes the individual to meet criteria for ASD in adulthood (Bargiela, Steward, & Mandy, 2016; Hull, Mandy, & Petrides, 2017; Lai & Baron-Cohen, 2015; Rynkiewicz et al., 2016). Particularly, females tend to suffer more from internalizing (e.g. anxiety, depression) rather than externalizing (e.g. hyperactivity, conduct problems) difficulties (Bargiela et al., 2016). Therefore, impairments may be overshadowed. The DSM-5 reports in fact that "girls without accompanying intellectual disability or language delays may go unrecognized, perhaps because of subtler manifestation of social and communication difficulties" (American Psychiatric Association, 2013).

Additionally, ASD symptoms, even if present since childhood, may not become manifest until social demands exceed the individual's limited capacities. Consequently, some individuals might not meet cut-offs for ASD, in particular those with milder symptoms severity and normal range IQ (Fusar-Poli et al., 2017c). In other cases, problems or relational difficulties can be minimized or even denied by parents or caregivers.

Sometimes comorbid psychiatry conditions may cover ASD symptomatology (Mazefsky et al., 2012). The presence of similarities in symptoms with other psychopathological conditions, such as personality disorders, obsessive–compulsive disorder or social anxiety could represent another potential factor of delay in diagnosis (Wolf & Ventola, 2014). Of note, research has noticed elevated rates of misdiagnosed ASD adults in acute psychiatric wards (Nylander & Gillberg, 2001). Professionals could eventually be misled by previous psychiatric diagnoses in the subjects' medical history (Nicolaidis, Kripke, & Raymaker, 2014).

In general, it is difficult for clinicians to diagnose ASD in adults, also considering the paucity of diagnostic instruments specifically designed for this age group (Bastiaansen et al., 2011). To obtain a clinical diagnosis, in fact, it is necessary not only to present a current symptomatology in line with diagnostic criteria, but also an anamnesis corresponding to the developmental profile of people with ASD. While direct observation or clinical interview can be easily conducted, clinicians may experience difficulties in gaining information about the patient's early development (Lai & Baron-Cohen, 2015). Sometimes, in fact, caregivers or parents are not available, live away or have died. Even when available, they struggle to remember specific details about their children's early development, since many years have passed. To compensate for the lack of information, it is possible to ask to an older brother or sister or to obtain data from alternative sources, such as old school reports.

In conclusion, for a first formal assessment of ASD in adults, it is important to collect a very accurate anamnesis, to examine individual's behavior through semi-structured or structured observations and to directly gain information from the parents or the

relatives of the patient, who are daily in touch with him. All possible differential diagnoses should be considered to provide an accurate evaluation. An assessment combining different instruments and informers in in line with good clinical practice (Wolf & Ventola, 2014).

Differential diagnosis in adults

Several psychiatric disorders are often mistaken for ASD in adults. Differential diagnosis is particularly challenging for psychiatrists who did not receive a specific training on psychiatric psychopathology in adults with neurodevelopmental disorders (Bertelli et al., 2015). A comprehensive evaluation performed by professionals with expertise in ASD is thus essential in making a differential diagnosis (Wolf & Ventola, 2014).

First, anxiety disorders may sometimes be similar to ASD: social phobia, generalized anxiety disorder (GAD) or agoraphobia, for instance, could significantly impact on the social functioning of an individual (Kerns et al., 2016). In addition, obsessive-compulsive disorder (OCD) shares some features with ASD, such as the presence of rituals, the rigid and stereotyped behaviors, or the restrictive interests. However, in OCD the repetitive behaviors are generally linked to anxious or obsessive thoughts, representing a means of calming anxiety. On the contrary, in ASD, repetitive behaviors are not associated with an obsessive thought or anxiety (Russell, Mataix-Cols, Anson, & Murphy, 2005).

Depression may also determine a social withdrawal. However, an accurate evaluation of social skills and cognition, together with a psychiatric interview specifically focused on depressive symptoms, can easily help to determine whether the individual's social realm is due to a depressed mood (Wolf & Ventola, 2014).

Individuals with attention deficit hyperactivity disorder (ADHD) often have impairments in executive functioning, such as autistic subjects; additionally, their socially inappropriate behavior may sometimes lead to difficulties in socialization that can be mistaken for ASD. However, people with ADHD usually do not show neither communication deficits or restricted interests and behaviors (Salley, Gabrielli, Smith, & Braun, 2015).

Psychotic disorders, such as schizophrenia, can also be characterized by social isolation, socially inappropriate behaviors, low social insight. Additionally, thought disorders and the use of an atypical or nonsensical language (e.g. tangentiality, circumstantiality, neologisms) are common to both psychoses and ASD. It is thus fundamental to obtain a detailed clinical history to determine the onset. In fact, while ASD are neurodevelopmental disorders and the onset typically lies during early childhood, psychotic conditions firstly manifest during adolescence or early adulthood. Additionally, some symptoms, such as delusions or hallucinations, are not common in ASD. Some patterns of speech (e.g. the "word salad", in which words are jumbled together without an apparent meaning) are also specific of schizophrenia (Nylander, 2014).

Many personality disorders, particularly those belonging to cluster A or C of DSM-IV (American Psychiatric Association, 1994), share several features with ASD. As for psychotic disorders, a determination of the onset is critical, since personality disorders usually become evident later in life (Wolf & Ventola, 2014).

Schizotypal personality disorder is probably one of the most difficult to distinguish from ASD. It is characterized by preoccupations, odd patterns of speech and thinking, atypical behavioral patterns, flattened affect, and an absence of peer relationships. However, the social impairment is usually greater in ASD than in schizotypal personality disorder. Furthermore, schizotypal individuals may show behaviors related to the psychotic spectrum, such as magical thinking, ideas of reference, paranoid ideation, and perceptual experiences, that are very uncommon in people with ASD (Wolf & Ventola, 2014).

Subjects with schizoid personality disorder show a flattened affect and a strong disinterest in social relationships. This is in contrast with ASD: the majority of ASD individual express the desire to have meaningful social relationships, but do not have sufficient skills to build them. Additionally, schizoid personalities do not present repetitive behaviors or restricted interests (Wolf & Ventola, 2014).

Avoidant personality disorders share with ASD a reduced social participation and the lack of friendships. However, the avoidance of social situations is active and more due to anxiety rather than to impaired social skills, in avoidant personality disorder. Additionally, stereotypies or communication difficulties are not present in this group of patients (Wolf & Ventola, 2014).

Finally, ID is highly prevalent in ASD, and, in some subjects, it can be difficult to determine whether an ASD is also present. In fact, individuals with ID may present stereotypies and language impairments analogously to ASD. However, the two conditions may be discriminated by social interaction features: patients with ID only

usually do not present alterations of eye contact or difficulties in shared enjoyment that are instead typical of ASD individuals. ID also show an homogeneous impairment of cognitive profile, while ASD individuals (also those with an average intellectual functioning) tend to have a higher degree of scatter in their profile, with areas of strengths ("island of abilities") and weaknesses (Matson & Shoemaker, 2009).

3. DIAGNOSTIC INSTRUMENTS FOR AUTISM SPECTRUM DISORDERS

Standard diagnostic instruments were developed initially for research purposes to acquire information both through direct clinical observation and interviews of caregivers. Research on diagnostic instruments for ASD have incredibly flourished during the last 30 years, when we gained more knowledge about the uses and limitations of different approaches. Additionally, the constant use of these instruments in clinical practice has resulted in major improvements and important changes (Lord, 2010).

Some promising questionnaires for the screening of ASD in adults are available. Some examples are the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003), the Social responsiveness Scale (SRS; Constantino & Gruber, 2012), the Autism-Spectrum Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), and the Ritvo Autism Asperger Diagnostic Scale-Revised (RAADS-R; Ritvo et al., 2011). However, even if self-report questionnaires could provide important information, they also need to be critically interpreted in light of the clinical presentation in order to avoid problems of validity (Lord et al., 2014). Because some individuals with ASD may have difficulties in self-referential cognition that affect self-insight and metacognitive processing (Lombardo & Baron-Cohen, 2010, 2011), it is possible that self-report ratings may not accurately measure autistic symptoms for such individuals because of underestimation. Significant discrepancies between self- and parent-reported questionnaires were in fact found (Didehbani et al., 2012; Lopata et al., 2010; Mazefsky, Kao, & Oswald, 2011), showing that children and adolescents with ASD might have difficulties in identifying their own. Reasons could be related to the problems in verbal

and non-verbal communication, and to the difficulties in emotion recognition. In addition, while screening instruments for ASD appear useful in the general population, they might not be reliable in clinical samples, where symptoms of other psychopathological condition could partially overlap those of ASD.

Several standardized instruments are available for a more systematic assessment of ASD, even if they have been developed mainly for children and their accuracy has been limitedly study in adulthood (Bastiaansen et al., 2011). It is worth recognizing that the existence and the continuous improvement of such measures are associated with more accurate diagnoses of ASD. However, as for screening questionnaires, standardized diagnostic tools are often limited by inadequate power to correctly identify individuals with and without ASD (Charman & Gotham, 2013).

Among the most common diagnostic instruments, there are both observational measures and interviews directed to parents or caregivers. The first group include the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2012) and the Childhood Autism Rating Scale (CARS; Schopler, Reichler, DeVellis, & Daly, 1980). Among the second category, the most used are the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), the Diagnostic Interview for Social and Communication Disorders (DISCO; Wing, Leekam, Libby, Gould, & Larcombe, 2002), and the Developmental, Dimensional, and Diagnostic Interview (3Di; Skuse et al., 2004).

Because of their strong discriminant validity, the ADOS and the ADI-R have been translated into several languages and are used worldwide. Even if both instruments have been used to measure severity of autism symptoms and changes over time, it is

important to keep in mind that these measures were developed to differentiate individuals with and without ASD (Charman & Gotham, 2013). The ADOS-2 and the ADI-R are currently considered the "gold standard" tools for the diagnosis of ASD (Falkmer, Anderson, Falkmer, & Horlin, 2013; Ozonoff, Goodlin-Jones, & Solomon, 2005).

However, a moderate amount of evidence shows that standardized tools are less reliable in specific groups of individuals. In particular, ADOS-2 seems to have a minor accuracy in detecting ASD in females (Lai et al., 2011; Rynkiewicz et al., 2016). The ADOS-2, in fact, was developed mainly on male characteristics and may not be able to fully capture the female phenotype (Lai et al., 2015; Rynkiewicz et al., 2016). Recently, Wilson and colleagues (2016) showed that gender influenced diagnostic evaluation in a clinical sample of adults with suspected ASD. Females with ASD, in fact, present similar or better adaptive and social abilities than males (Howe et al., 2015), and are less likely to show externalizing than internalizing behaviors (Bargiela et al., 2016; Mandy et al., 2012). Additionally, the low proportion of ASD females with high cognitive abilities may reflect an under-identification of this particular subsample (Frazier et al., 2014). However, other studies reported no significant relationship between ADOS (Bastiaansen et al. 2011) or ADI-R (Talari et al. 2017) scores and other factors, such as gender, age and IQ.

The Autism Diagnostic Observation Schedule-2 (ADOS-2)

The ADOS-2 is a semi-structured observation of individuals who may belong to the autism spectrum (Lord et al., 2012). It is composed by five different domains: Communication, Reciprocal Social Interaction, Communication+Reciprocal Social Interaction, Imagination/Creativity, and Stereotyped Behaviors and Restricted Interests. The ADOS-2 consists of five modules, addressed to children and adults according to their

developmental and language levels. Adolescents or adults with normal intelligence and good verbal fluency are evaluated by means of Module 4.

The semi-standardized observation should last from 30 to 45 minutes and is composed by some hands-on tasks (i.e. puzzle, description of a fantastic story, invent a story with objects provided by the interviewer), and a part of conversation (i.e. examining social relationships, emotions, daily life, school, job). While some parts are mandatory, other are optional. After the observation, a score ranging from 0 to 2 or 3 is given to the items of the different domain. The sum of the items included the algorithm can collocate the subject into the "autism spectrum" or into "autism".

According to the original algorithm (Lord et al., 2012), Module 4 of ADOS-2 is suggestive of a diagnosis of ASD if the subject met the cut-off values for the "autism spectrum" in the Communication domain (score of 2 or above), Social domain (4 or above), as well as in the Communication + Social domain (7 or above). The subject is instead classified into the "autism" category if the scores exceed the cut-offs of 3 in Communication, 6 in Social Interaction and 10 in the sum of the two domains. The scores for Imagination/Creativity and Stereotyped Behaviors and Restricted Interests domains are not considered for final classification. A revised version of ADOS-2 Module 4 algorithm has been recently proposed by Hus and Lord (2014). In the revised algorithm, a score of 8 or above in the sum of social affect (SA) and restricted and repetitive behaviors (RRB) domains is considered suggestive of a diagnosis of ASD.

The scoring sheet of the original algorithm is reported in Appendix 1.

Reliability of the ADOS in adulthood

It has been extensively demonstrated that ADOS is a reliable and valid instrument to assess the presence of ASD in children, adolescents and adults (Bastiaansen et al., 2011; De Bildt et al., 2004; De Bildt, Sytema, Meffert, & Bastiaansen, 2016; Kamp-Becker et al., 2013; Langmann, Becker, Poustka, Becker, & Kamp-Becker, 2017; Molloy, Murray, Akers, Mitchell, & Manning-Courtney, 2011; Risi et al., 2006). However, Module 4, which has been developed for adolescents and adults with fluent language skills, received less psychometric evaluations. Bastiaansen et al. (2011) examined the psychometric properties of ADOS-2 Module 4 in an independent sample of adults without ID with an established diagnosis of ASD compared to other clinical (schizophrenia and psychopathy) and non-clinical groups. The authors concluded that the ADOS-2 could adequately discriminate ASD from psychopathy and typically developed adults, while discrimination from schizophrenia was more difficult. More recently, De Bildt and colleagues (2016) found an improved sensitivity using the revised algorithm. Langmann et al. retrospectively investigated the utility of ADOS-2 Module 4 in an independent clinical sample of high-functioning adolescents and adults (Langmann et al., 2017). Both original and revised algorithms demonstrated good sensitivity and specificity, with slightly better results for the revised algorithm. Maddox et al. recently evaluated the accuracy of ADOS-2 in identifying ASD among adults with complex psychiatric conditions. Results showed a high rate of false positives, particularly in patients affected by psychoses (Maddox et al., 2017).

The Autism Diagnostic Interview-Revised (ADI-R)

The ADI-R is a semi-structured parent interview that covers all three major areas of impairment in autism (quality of reciprocal social interaction; communication; repetitive, restricted, and stereotyped patterns of behavior) (Lord et al., 1994). A prominent part of the interview focuses on the period between the ages of 4 and 5 years, when differences among individuals with different levels of functioning can be better observed and compared.

The ADI-R is considered suggestive of a diagnosis of ASD if the scores in the three domains exceed the cut-off values, which are different for verbal and non-verbal subjects. The total cut-off scores for the communication and language domain is 8 for verbal subjects. For all subjects, the cut-off for the social interaction domain is 10, and the cut-off for restricted and repetitive behaviors is 3. Additionally, some abnormalities in at least one area should be present by 36 months of age.

The scoring sheet of the ADI-R algorithm is reported in Appendix 2.

Reliability of the ADI-R in adulthood

The ADI-R, a diagnostic interview administered to caregivers, appears as a valid instrument independently from age and level of functioning (De Bildt et al., 2004). Studies reported diagnostic stability of the ADI-R over lifetime in non-ID samples (Mazefsky & Oswald, 2006; Moss, Magiati, Charman, & Howlin, 2008; Soke et al., 2011). However, the interview is focused on early development so the instrument could be not completely reliable in adults: parents are asked to remember events or behaviors of the past. To our knowledge, its utility in adulthood has been examined only by two studies.

In particular, Sappok et al. (2013) investigated the applicability and validity of both ADOS-2 (Modules 1–4) and ADI-R in a sample of adults with ID in a clinical setting. The authors observed that the ADI-R could be a reliable tool for the assessment of ASD in adults with ID, with good specificity (80%) and sensitivity (88%). More recently, Talari, Balaji, & Stansfield (2017) found that ADI-R had a high sensitivity (100%), but a low specificity (37%). Specificity was lower in male than females, and in people with ID compared to those with an average intelligence.

SECTION II

4. INSTRUMENTS USED FOR THE DIAGNOSIS OF ASD IN CLINICAL TRIALS: A SYSTEMATIC REVIEW

OBJECTIVES

The data reported in the present section are part of a wider project implemented by the Laboratorio Autismo of the University of Pavia. The idea was to build a database including all randomized controlled trials (RCT) and controlled clinical trials (CCT) published from 1980 to present. In particular, we aimed to:

(1) review the number and type of instruments used in RCTs and CCTs published from 1980 to December 2016;

(2) trace a temporal overview of the diagnostic tools;

(3) analyze the relationship between diagnostic instruments and age of included population;

(4) analyze the relationship between diagnostic instruments and IQ of included population.

In the present section, the preliminary results of a systematic review of the tools used for the diagnosis of ASD are reported.

METHODS

Search strategies

We conducted a comprehensive search following the guidelines outlined in the PRISMA Statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The Web of Science™ database by Thomson Reuters® (including Web of Science™, BIOSIS Citation Index℠, MEDLINE®, Russian Science Citation Index and SciELO Citation Index) was searched from 1980 until

December 2016, including abstracts in English language only. We adopted the following search string:

(autis OR (developm* AND disorder) OR asperger OR Kanner OR ASD OR PDD) AND (RCT OR trial OR observational OR 'open label' OR prospective OR longitudinal OR randomized OR cohort)*

The electronic searching was then supplemented by hand-searching of reference lists of the included review articles to identify any additional sources.

Selection criteria

All records were extracted to EndNote reference management software. Duplicates were detected and deleted. Titles and abstracts were screened to identify potentially relevant studies and assessed full texts to determine eligible studies. Any doubt was solved through consultation among the researchers.

We included in our database all the studies fulfilling the following inclusion criteria:

(a) original articles, published in a peer reviewed scientific journal, written in English;
(b) including subjects with a PDD or ASD diagnosis;
(c) randomized controlled trials (RCT) or observational longitudinal studies comparing at least two different interventions directed to individuals with ASD or one treatment and placebo;
(d) reporting at least one clinical outcome.

The papers fitting the following exclusion criteria did not enter in our database:

(a) review, meta-analysis, case report, congress abstracts, and articles in languages other than English;

(b) studies with retrospective observational design or longitudinal observational design without a comparison group;
(c) studies investigating the effect of an indirect treatment (i.e. intervention directed to parents);
(d) studies failing to report a clinical outcome measure (i.e. biomarkers and imaging were not considered clinical outcome measures).

Given the purpose of this research we did not exclude papers with overlapping datasets to retain the largest number of assessment tools adopted.

Data extraction

Data extraction and assessment trials for risk of bias following the Cochrane risk of bias tool (Higgins & Green, 2011) were done in duplicate. Any doubt was solved through consultation with the team of reviewers. A standardized form was used to extract data from the included studies, and for the assessment of study quality and evidence synthesis. We extracted the following information: study name; year of publication; active treatment; comparison; study design; analysis; duration of active intervention and follow-up; sample size; diagnostic tools; primary and secondary outcome measures; presence of psychiatric comorbidities (excluding ID); mean age; age range; mean IQ; IQ range; IQ evaluation tools; female proportion; assessment of risk of bias; study location.

In this preliminary systematic review, we only considered the following data: study name; year of publication; type of intervention; diagnostic tools; age; IQ.

Statistical analysis

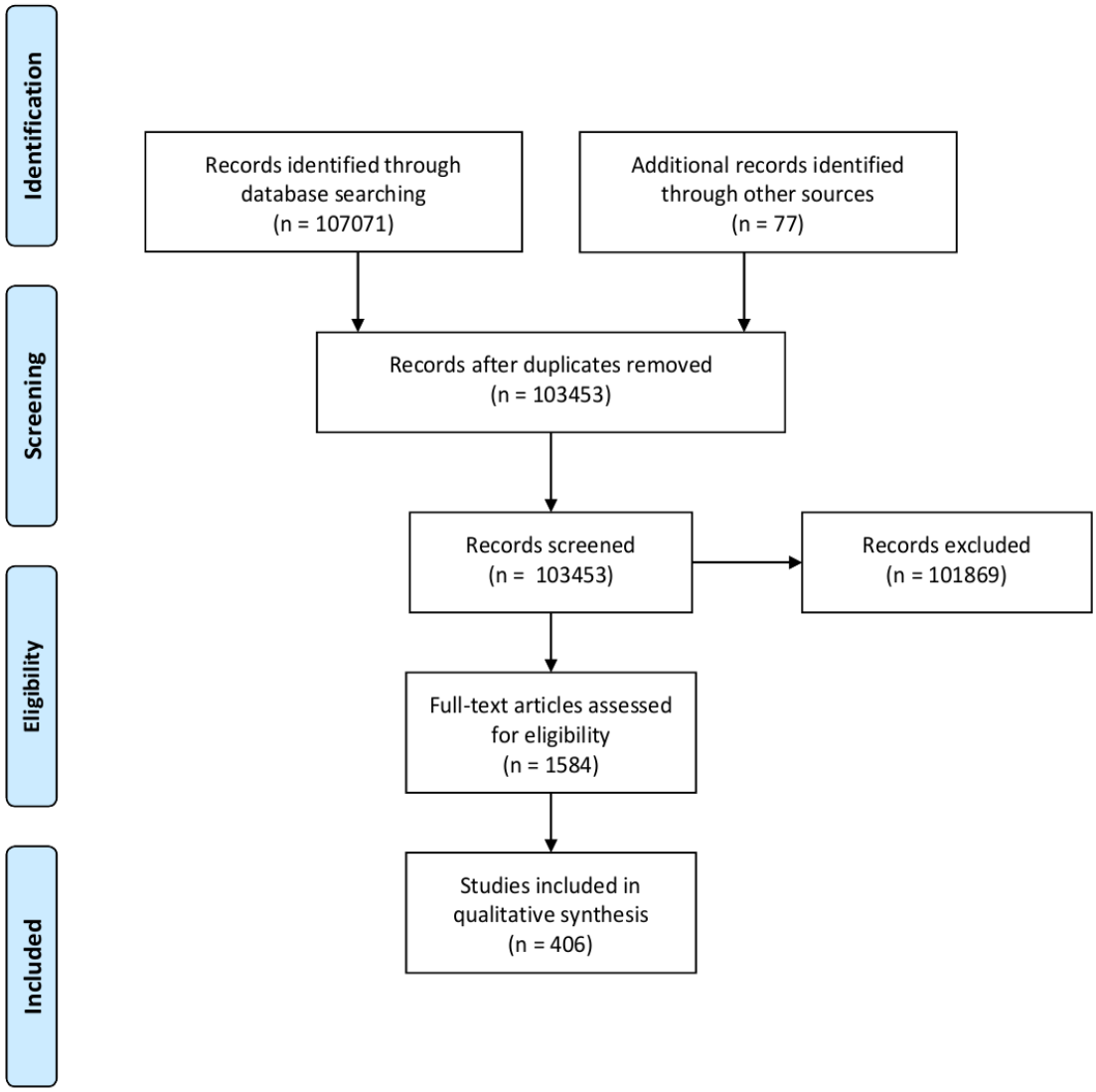
Data are reported as percentages or counts as appropriate. Chi-squared statistics was used to evaluate the relationship between age and diagnostic instruments, and between

IQ and diagnostic tools adopted. Results were considered statistically significant at the $p \leq .05$ level, and all tests were two tailed. Statistical analysis was performed using SPSS 21.0 software packages (SPSS, Chicago, IL).

RESULTS

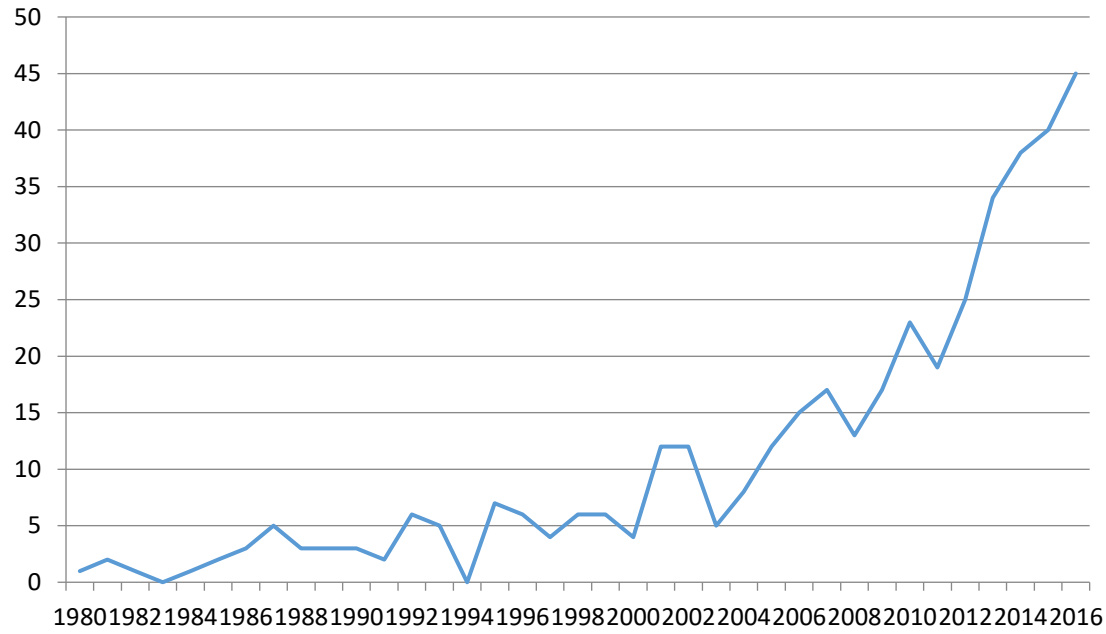
We identified a total of 107071 records from electronic searching and 77 studies from hand-searching. After excluding duplicates and irrelevant references, we obtained 1584 studies to assess for eligibility. The final database was composed by 406 studies, included in 402 publications. A flow diagram of the study selection process is shown in Figure 4.1.

Figure 4.1. PRISMA flow diagram of the selection procedure.



The number of publication per year ranged from zero (1983) to 45 (2016). Figure 4.2 depicts the trend in publications about ASD.

Figure 4.2. Number of publications per year.



Characteristics of the included studies

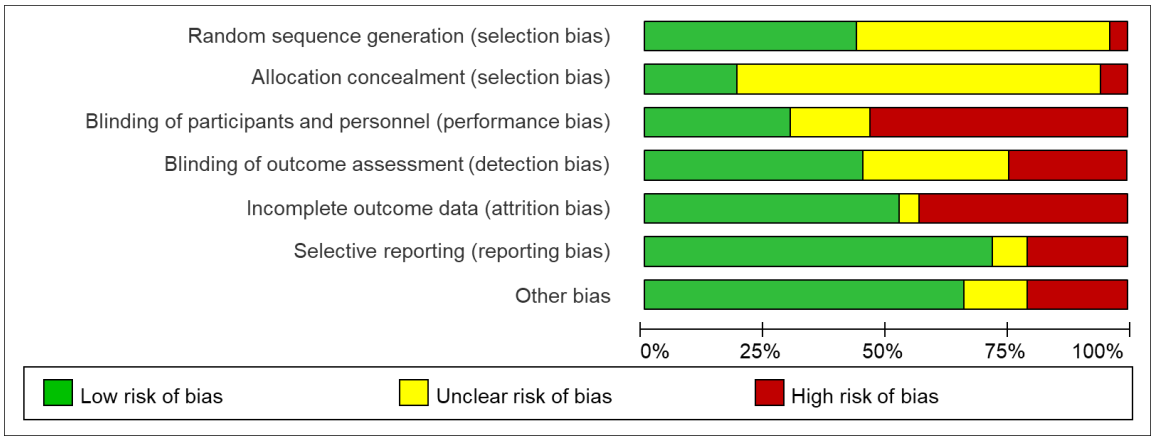
We included 354 RCT (77.2%) and 52 non-randomized trials (12.8%). Primary follow-up length varied from a single administration (one day) to 208 weeks (mean follow-up 17.4 weeks). The active intervention was educational in 137 studies (34%), pharmacological in 132 studies (33%), nutraceutical in 50 (12%), and psychotherapy in 30 (7%). Other types of interventions were adopted in 57 studies (14%). Most of the included studies were conducted in the United States (54% of the studies). See Appendix 3 for a detailed list and characteristics of the included trials.

Approximating for potential overlapping datasets, our database included 17240 participants, of which 11246 were assigned to the active treatment. Recruited samples ranged from 4 to 308. On average, each study included 17.7% of female participants (range 0 - 51%, unclear in 30 studies). 315 studies recruited only children, 19 only adults,

while 39 studies included both children and adults (unclear in 33 studies). Psychiatric comorbidities (excluding ID) were excluded in 56 studies, acknowledged in 52 studies and unclear in 298 studies. IQ characteristics of the sample were not specified in 227 studies, samples with ID only were recruited in 25 studies, while 81 studies included only individuals without ID. In 73 studies, the recruited population was mixed, including both ASD people with and without ID.

According to the Cochrane's collaboration tool (Higgins, 2011), only 11 (3%) studies obtained good quality evaluation, 107 (30%) scored as fair, 235 (66%) had poor quality of reporting. A summary of the quality of included studies is reported in Figure 4.3.

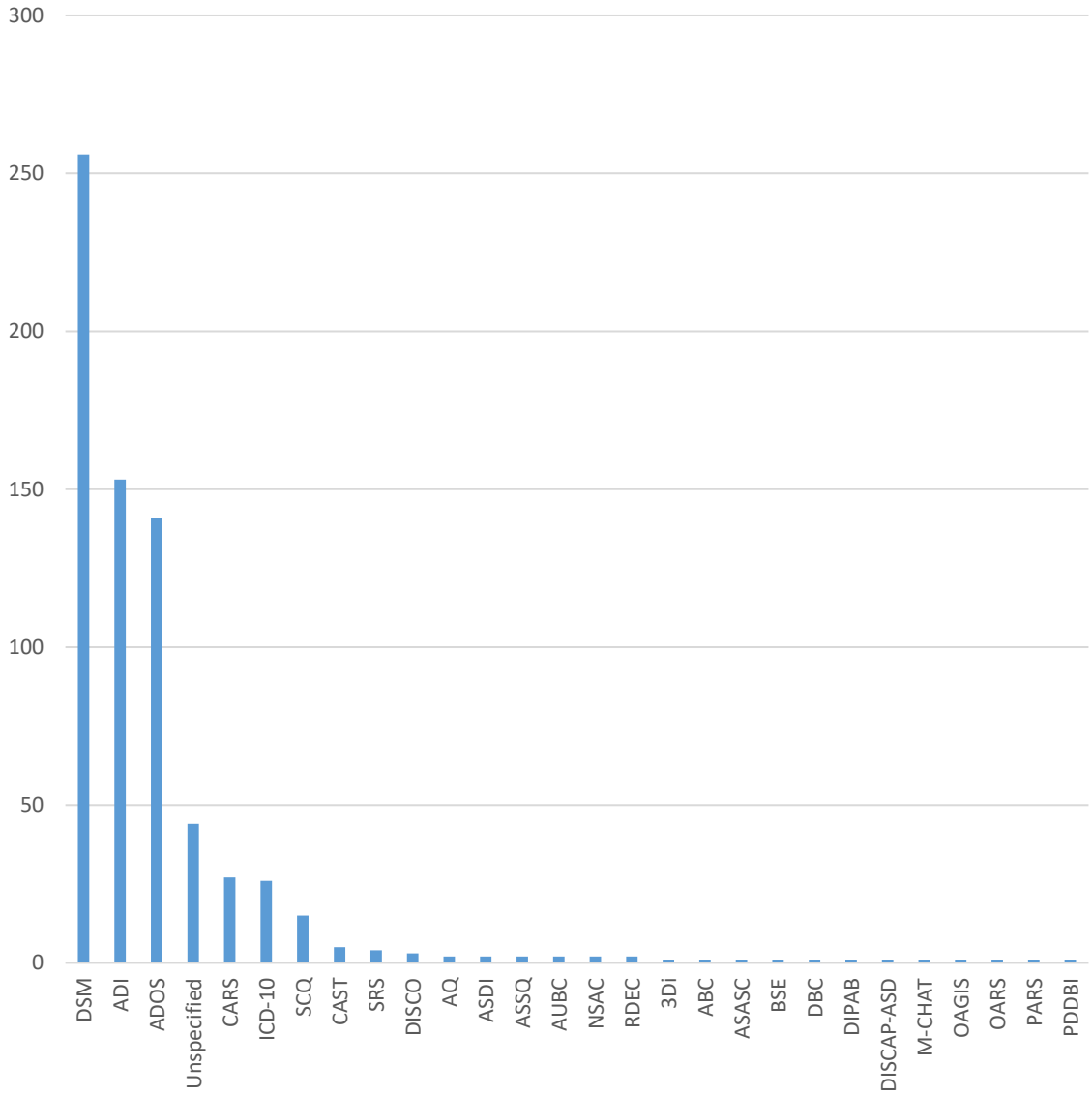
Figure 4.3. Quality assessment of the included studies.



Characteristics of diagnostic instruments

In the included articles, 27 different instruments were used for performing or confirming the diagnosis of ASD of subjects who were recruited (Figure 4.4). Of note, in 44 out or 406 articles (11%) no tools neither diagnostic manuals or guidelines were specified. Among diagnostic instruments, we could find diagnostic manuals or guidelines, direct observation tools, interview to parents/caregivers or questionnaires (Appendix 3).

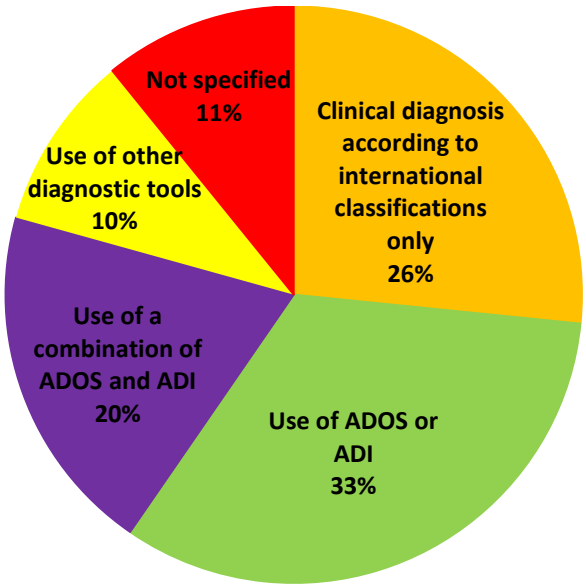
Figure 4.4. Number of studies in which each instrument was used for the diagnostic confirmation.



Legend: *3Di:* Developmental, Dimensional and Diagnostic Interview; *ABC:* Aberrant Behavior Checklist; *ADI*: Autism Diagnostic Interview; *ADOS:* Autism Diagnostic Observation Schedule; *AQ:* Autism-spectrum Quotient; *ASASC:* Australian Scale for Autism Spectrum Conditions; *ASDI:* Autism Spectrum Diagnostic Interview; *ASSQ:* Autism Spectrum Screening Questionnaire; *AUBC:* Autism Behavior Checklist; *BSE:* Behavioral Summarized Evaluation scale; *CARS:* Childhood Autism Rating Scale; *CAST:* Childhood Asperger Spectrum Test; *DBC:* Developmental Behaviour Checklist; *DIPAB:* Diagnosis of Psychotic Behavior in Children; *DISCAP-ASD:* Diagnostic Interview Schedule for Children, Adolescents, and Parents-ASD diagnostic clinical interview; *DISCO:* Diagnostic Instrument for Social and Communication Disorders; *DSM:* Diagnostic and Statistical Manual of mental disorders; *ICD:* International Classification of Diseases; M-*CHAT:* Modified Checklist for Autism Toddlers; *NSAC:* National Society for Autistic Children; *OAGIS:* OSU Autism Global Impression Scale; *OARS:* OSU Autism Rating Scale DSM-IV; *PARS:* PDD-Autism Society Japan Rating Scale; *PDDBI:* PDD Behavior Inventory; *RDEC:* Rimland Diagnostic E-2 Checklist; *SCQ:* Social Communication Questionnaire; *SRS:* Social Responsiveness Scale.

An analysis of the distribution of the use of diagnostic instruments in the included studies revealed that in 26% of the studies the diagnosis was performed only by means of clinical criteria, such as those of DSM, ICD, or NSAC. The 53% of the studies adopted at least one of the two "gold standard" instruments (ADOS and ADI), or both. In 10% of the studies, other diagnostic tools were used, alone or in combination with diagnostic manuals. Finally, as already mentioned, in 11% of the studies no diagnostic tools were reported (Figure 4.5).

Figure 4.5. Distribution of the type of diagnoses.



Use of diagnostic instruments across time

We have analyzed the chronological distribution of the use of the two "gold standard" instruments (ADOS and ADI) across time. Figure 4.6 shows the raw number of studies in which the confirmation of diagnosis was performed with ADOS or ADI. In Figure 4.7, we reported the number of studies weighted for the total number or yearly publications.

Figure 4.6. N of publications which used ADOS and ADI from 1980 to 2016.

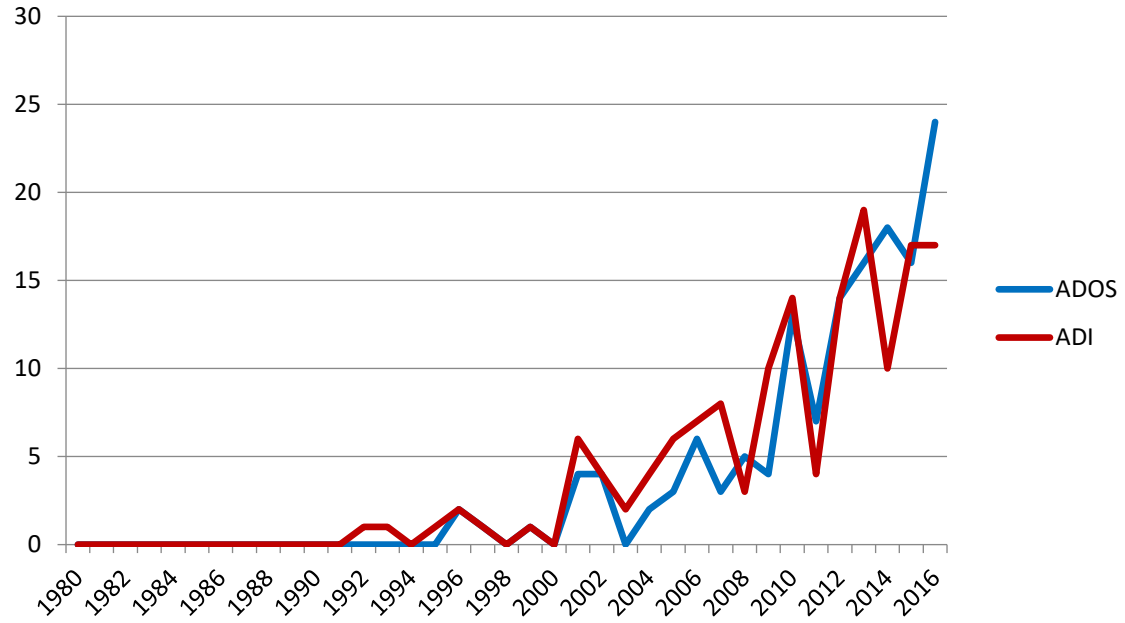
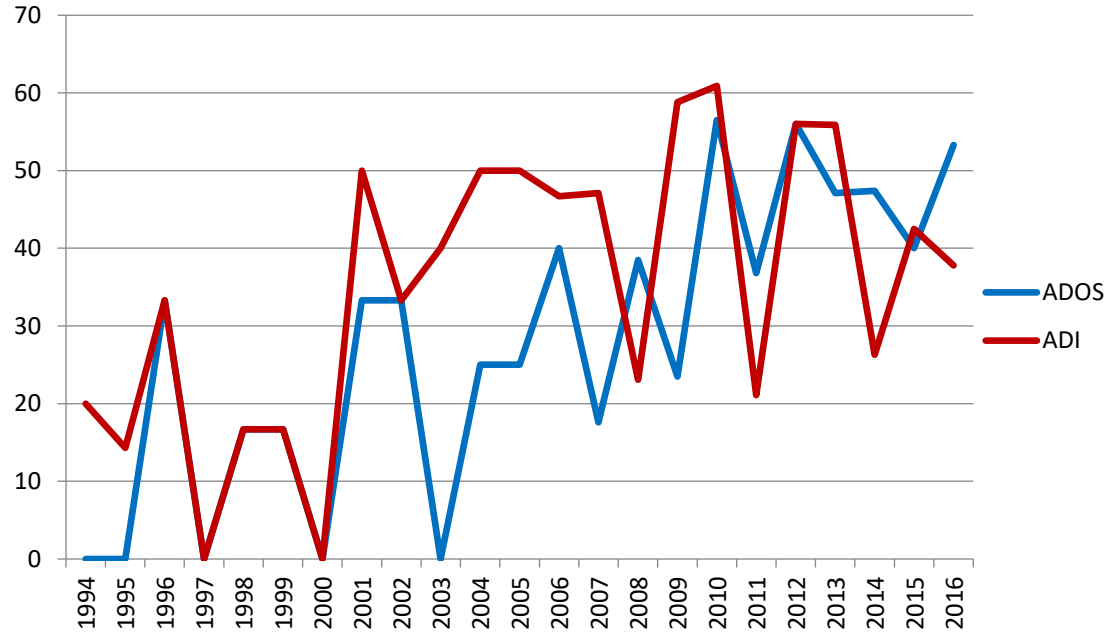


Figure 4.7. Weighted N of publications (%) per year which used ADOS or ADI.



Diagnoses according to age

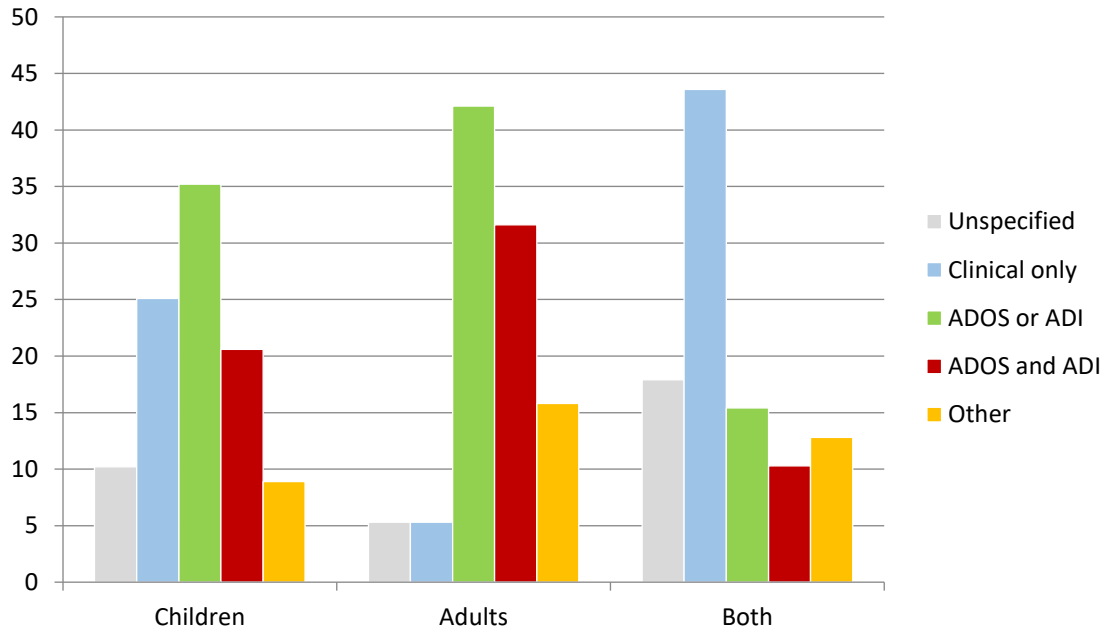
Studies were classified according to the age of participants. Among the 315 studies which involved only children, 35.3% performed the diagnosis by means of clinical criteria only or in an unspecified way. On the other hand, 176 trials (55.8%) used at least one

between ADOS and ADI, or both instruments. In 28 studies (8.9%) other tools were used, alone or in combination with clinical classifications.

Overall, 19 studies involved only adult subjects, of which 14 used ADI, ADOS or both (73.7%). The diagnosis was unspecified or clinical in only two trials, and other tools were used in three studies.

Thirty-nine studies involved people both under and above the age of 18, of which only ten confirmed the diagnosis of participants with at least ADOS or ADI. The diagnosis was in fact unspecified in seven cases, and clinical in 17 cases. Other tools were used in five studies. It is worth mentioning that in 33 studies (8.13%) the age of participants was unclear.

Figure 4.8. Type of diagnosis according to age of participants.



A chi-squared test of independence was performed to examine the relation between age of participants and diagnostic instruments. A significant correlation was found χ^2 (8, n = 373) = 19.434, p = 0.013. In particular, in trials including both children and adults,

ADOS or ADI alone were used less than expected (standardized residual = -2), while clinical criteria alone were used more than expected (standardized residual = 2.2).

Diagnoses according to IQ

Data regarding IQ were reported only in 179 studies (44.08%). Criteria for inclusion in one of the three groups were mainly based on age range. When not available, eligibility criteria were considered.

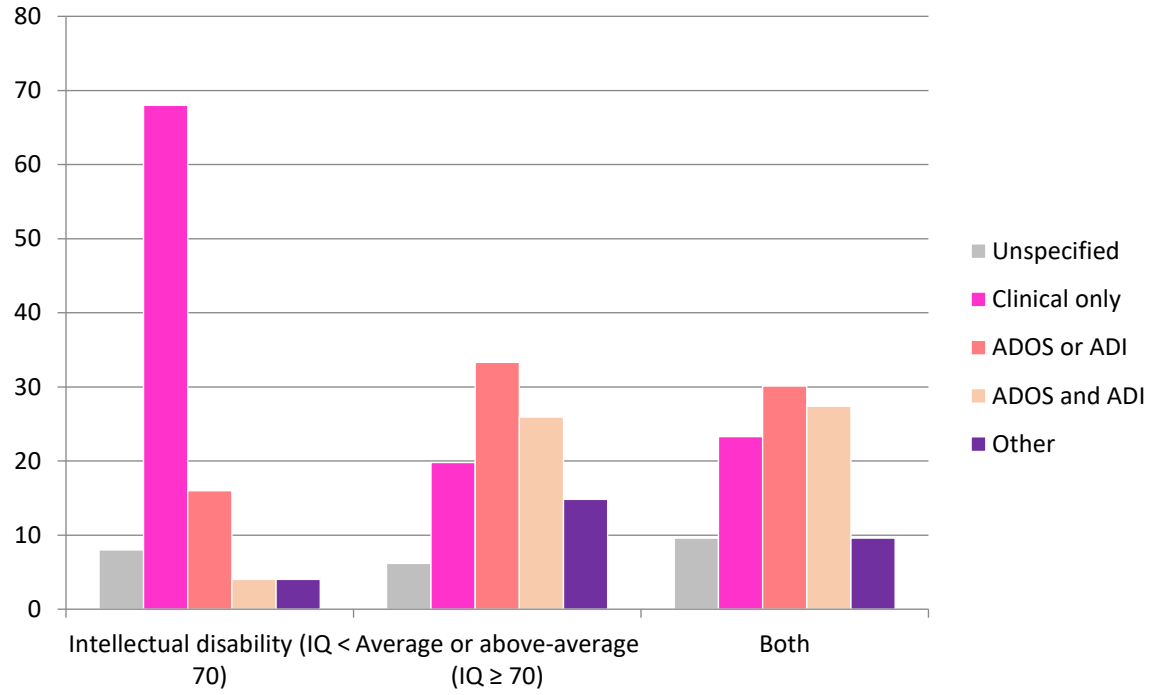
Among the trials reporting IQ, 25 studies (14%) involved only people with ID. In 81 studies (45.3%), only people with IQ of 70 or above were recruited. Finally, in 73 cases (40.8%) a mixed-population was included.

In the first group, participants were mainly diagnosed with clinical criteria only (68%), while in five studies (20%), the diagnosis was performed by means of ADOS, ADI or both. Other tools were used in one study, and diagnostic criteria were unspecified in two studies.

On the other hand, ADOS, ADI or a combination of both was used in 48 of the studies which have included only people with average or above-average intelligence (59.2%). Other tools were used in 12 trials (14.8%) and diagnostic classifications in 16 studies (19.8%). Finally, five studies did not specify any diagnostic criterion.

Considering the trials who recruited both high- and low-functioning people, 57.5% (42 trials) used only ADOS, ADI or both, while in 17 studies (23.3%) the diagnosis was clinical only. In seven studies (9.6% other tools were employed), and in other seven trials no criteria were specified.

Figure 4.9. Type of diagnosis according to IQ of participants.



A chi-squared test of independence was performed to examine the relation between IQ of participants and diagnostic instruments. A significant correlation was found χ^2 (8, n = 179) = 26.400, p = 0.001. In particular, in trials including individuals with ID only, ADOS and ADI in combination were used less than expected (standardized residual = -2), while clinical criteria alone were used more than expected (standardized residual = 3.8).

DISCUSSION

The present systematic review is part of a broad project aimed at summarizing the characteristics of clinical trials published from 1980 to present, and involving people with ASD. The primary aim of our literature search will be to analyze in detail the measures used for the evaluation of outcome that, from a preliminary overview, seem to be extremely heterogeneous and barely evaluating the modification of core symptoms of ASD.

We have reported here a brief synthesis regarding the tools used for the diagnosis in all RCTs and longitudinal studies with at least two comparison groups published from 1980 to 2016. This is a preliminary analysis, since the project is still ongoing and more detailed analyses will be conducted.

At first glance, it is possible to notice that not only the prevalence, but also the body of experimental literature regarding ASD has been impressively growing, especially in the last ten years. In fact, as depicted in Figure 4.2, while until the end of last century less than ten publications per year were released, during 2016, 45 clinical trials involving people with autism were published. This is a proof of the growing interest for ASD among the scientific community and in the general population.

Our data also confirm that ADOS and ADI are the most widely used diagnostic instruments, alone or in combination. In fact, among a total of 406 studies, 153 used the ADI (37.7%) and 141 (34.7%) used the ADOS for confirming participants' diagnoses. Interestingly, the number of studies which adopted the ADI was superior to those which used the ADOS. One possible explanation could rely on the fact that while both were developed in 1989, ADI became available earlier than ADOS. Another possible reason is that most of the studies regard children, and in this age group ADI could be more reliable than in adults. Our results show also evidence of an increasing use of the standardized instruments, which represent a useful support to diagnosis for clinicians. Since 1994 (year of publication of the ADI-R), in fact, the proportion of publications which used ADOS and/or ADI have been progressively increasing.

From our preliminary analysis, it emerged that the use of diagnostic tools varied accordingly to participants' age and IQ. Of note, individuals with ID are less frequently

diagnosed with the support of standardized tools, while more frequently diagnosed by means of clinical criteria only. This is an important issue, since it highlights the lack of diagnostic tools specifically addressed to the diagnosis of ASD in people with ID. ADOS is rarely used in people with ID, particularly adults, since Modules 1 and 2 have been developed mainly for children, while Modules 3 and 4 are mainly directed to children, adolescents or adults with good verbal fluency. Thus, their use is not suggested for adults with ID and severe language impairments. It is also worth mentioning that ASD symptomatology might be more severe and consequently more evident in this last subgroup. Also, standardized instruments were used less than expected in trials involving both adults and children, and in samples including adults only. On the contrary, children are more frequently diagnosed with the support of ADOS or ADI. Of note, in the group of publications which included only participants with an IQ ≥ 70, a moderate number of tools different from ADOS and ADI were used. Such instruments are in some cases questionnaires directed to the parents or to the patient herself. Some examples are the AQ, the CAST (Williams et al., 2005), the SCQ (Rutter, Bailey, & Lord, 2003), the SRS (Constantino & Gruber, 2012), the ASASC (Garnett, Atwood, Peterson, & Kelly, 2013). In other cases, standardized interviews or direct observations, such as the 3Di (Skuse et al., 2004), the ASDI (Asperger Syndrome Diagnostic Interview; Gillberg, Gillberg, Råstam, Wents, 2001), the DISCO (Wing et al., 2002), or the DISCAP (Diagnostic Interview Schedule for Children, Adolescents, and Parents; Holland & Daads, 1997) were used.

It is important to underline that our analyses regarding the relationship between the use of diagnostic instruments, the age and the IQ of participants with ASD is partial and not completely reliable. In fact, the age of participants was unclear in 8.13% of studies;

participants' IQ was not reported in almost 66% of the study. Also, the comorbidities – not considered in the present dissertation – are reported only in a minor proportion of studies. Such data highlights the lack of rigorously designed trials and papers for ASD. ASD in fact is a long-life condition with extremely heterogeneous phenotypical presentations: a "spectrum" of conditions. Therefore, it is important to better characterize and describe the samples recruited in clinical trials, because outcomes could be extremely different in samples with different clinical presentation and characteristics. In this way, research could move towards the development of more specific therapies for the different ASD subgroups.

Despite the research regarding ASD in constantly growing, it is evident that the use of diagnostic tools is still heterogeneous. ADOS and ADI represent the two widest used instruments, but many other questionnaires and non-standardized instruments, or tools which do not measure core symptoms of ASD, are used for the diagnostic confirmation. Auspiciously, scientific community should reach a consensus regarding the standardized instruments needed to confirm the diagnosis of people recruited for clinical trials. It would be also desirable to develop an ideal battery of standardized tests specifically based on age, IQ and other patients' characteristics. As will be reported also in the next chapters, in fact, many screening tools are sometimes inappropriately used for self-diagnoses. The risk is thus to include in clinical trials participants who do not really belong to the autism spectrum, but with only some autism-like traits, who may potentially alter the results of clinical trials, and, in general of scientific research.

5. ACCURACY OF ADOS-2 AND ADI-R AND PREDICTORS OF THE AGREEMENT WITH CLINICAL DIAGNOSIS

OBJECTIVES

ASD diagnosis in adulthood often represents a challenge for clinicians. For this reason, guidelines strongly suggest supporting the clinical evaluation of ASD with standardized instruments, such as the Autism Diagnostic Observation Schedule-2 (ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-R) (Pilling et al., 2012). However, standardized tools have been developed mainly for children and their diagnostic accuracy has been rarely explored in adult individuals (Bastiaansen et al., 2011).

The aims of the present chapter are:

(1) To evaluate the accuracy of ADOS-2 and ADI-R in diagnosing ASD in adults within the normal range of intelligence (IQ ≥70).

(2) To evaluate potential predictors (i.e. age, gender, IQ, severity levels of criteria A and B) of the agreement between clinical diagnosis and instrumental diagnosis in the autistic population.

METHODS

Setting

The Laboratorio Autismo is a research center belonging to the Department of Brain and Behavioral Sciences of the University of Pavia. In more than ten years of scientific activity, the Laboratorio Autismo has developed a specific competence in the diagnosis of ASD in adolescents and adults.

Other fields of research are the following: the evolution of autism spectrum disorders in adulthood; medical and psychiatric comorbidities of the autistic condition; the

evaluation of educational interventions in an ecological context; the quality of life of adults with ASD; the dosage of peripheral biomarkers in ASD; alternative and complementary therapies for people with ASD; scholastic support and employment.

Research staff is composed by licensed medical doctors and psychiatrists. People can be referred to Laboratorio Autismo by professionals, such as physicians or psychologists, relatives, or by means of self-referral.

Clinical evaluation and diagnostic classification

Each person was extensively evaluated by a senior psychiatrist and at least one licensed medical doctor with wide clinical expertise in diagnosing and treating adults with ASD. The staff collected a complete psychopathological and clinical history from the patients and their caregivers, focusing on past and present core symptoms of ASD. In particular, clinicians focused on the following aspects: verbal and nonverbal communicative behaviors, quantity and quality of relationships, social connections, presence of vocal or movement stereotypes, insistence on sameness, restrictive and pervasive interests, rituals, hypo- or hypersensoriality. Based on the psychiatric assessment, additional standardized interviews, such as the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II; First, 1997) or the Comprehensive Assessment of At Risk Mental States (CAARMS; Yung et al., 1996) have been performed to verify the presence of other psychiatric conditions. The diagnostic procedure was completed with the evaluation of the intelligence quotient (IQ) through the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), the Raven's Standard Progressive Matrices (Raven, 1941), or the Leiter International Performance Scale-3 (Roid & Koch, 2017).

Each individual was also independently evaluated by means of the ADOS-2 Module 4 and the ADI-R, if parents or caregivers of the patients were available. The ADOS-2 and the ADI-R were administered by two separate staff members who were blind to the clinical diagnoses. Each interview or direct observation was performed by one assessor; no interrater reliability was then computed.

The definitive clinical diagnoses were finally performed according to the DSM-5 criteria through a consensus meeting among the staff members. Severity levels for criterion A ("Persistent deficits in social communication and social interaction across multiple context") and B ("Restricted, repetitive patterns of behavior, interests, or activities") were specified for those individuals who received an ASD diagnosis. According to DSM-5, individuals with level 1 of severity require support; people with level 2 of severity require substantial support; subjects with level 3 of severity require very substantial support.

Participants

From June 2013 to August 2017, 140 people referring to the Laboratorio Autismo were recruited on the basis of the following inclusion criteria: (1) age of 18 years or above; (2) IQ of 70 or above; (3) good comprehension of spoken and written Italian language. Written informed consent was obtained from all participants. The study was approved by our internal review board and was performed in accordance with the Declaration of Helsinki.

The sample was mainly composed of males (73% of the sample) and the mean age at evaluation was 28.34 ± 10.80 years, while ages ranged from 18 to 58 years. IQ ranged from 75 to 145 and mean IQ was 111.14 ± 17.89. Thirty-seven patients were self-

referred, 56 were referred by relatives, and 47 were referred by a specialist. All individuals underwent ADOS-2 structured observation, while ADI-R could be administered only to 102 parents or caregivers. General characteristics of the sample are depicted in Table 5.1.

Table 5.1. Characteristics of the sample.

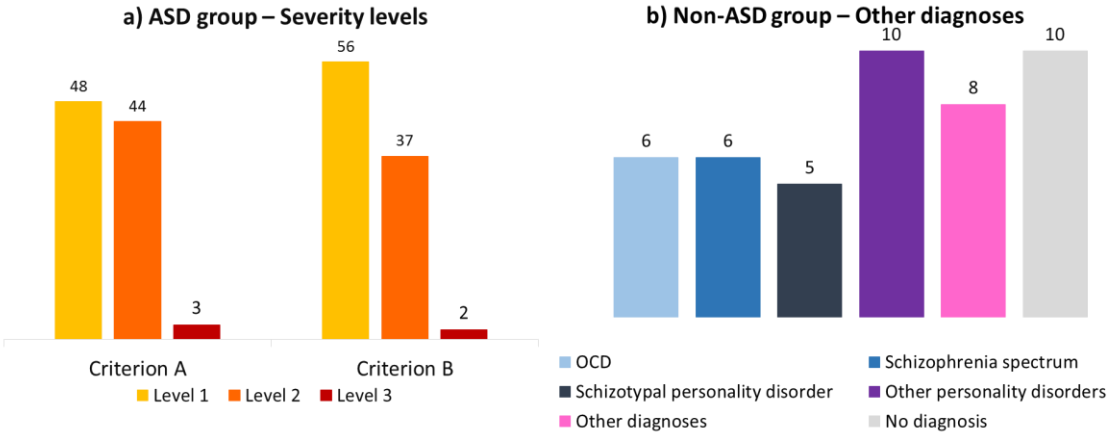
	ASD group n = 95	**Non-ASD group n = 45**	**Total sample n = 140**
Age	25 ± 8.46	35.40 ± 11.85	28.34 ± 10.80
Gender, male (%)	71 (74.7)	31 (68.9)	102 (72.9)
IQ	109.30 ± 17.89	115.02 ± 17.45	111.14 ± 17.89
ADOS-2 (original algorithm)	**n = 95**	**n = 45**	**n = 140**
Communication	3.14 ± 1.50	1.78 ± 1.17	2.51 ± 1.67
Reciprocal Social Interaction	6.62 ± 2.46	3.22 ± 1.99	5.53 ± 2.81
Communication + Reciprocal	9.64 ± 3.80	4.40 ± 2.86	7.96 ± 4.29
Creativity	0.94 ± 0.74	0.67 ± 0.71	0.85 ± 0.74
RRB	1.50 ± 1.23	0.67 ± 1.00	1.24 ± 1.22
ADOS-2 (revised algorithm)	**n = 95**	**n = 45**	**n = 140**
Social affect	9.56 ± 3.78	4.53 ± 3.24	7.94 ± 4.30
Restricted and repetitive behaviors	1.98 ± 1.38	0.80 ± 0.92	1.60 ± 1.36
ADI-R	**n = 81**	**n = 21**	**n = 102**
Qualitative abnormalities in communication	9.80 ± 3.71	5.90 ± 3.87	9.00 ± 4.04

Qualitative abnormalities in reciprocal social interaction	12.73 ± 4.52	6.19 ± 3.29	11.38 ± 5.04
Restricted, repetitive and stereotyped patterns of behavior	4.81 ± 2.31	3.09 ± 1.97	4.46 ± 2.34
Abnormalities of behavior evident at or before 36 months	1.44 ± 1.38	0.09 ± 0.30	1.17 ± 1.35

After the evaluation, 95 people (68% of the sample) received a clinical diagnosis of ASD according to DSM-5 criteria. Severity levels were distributed as follows: as concerns criterion A, 48 individuals had level 1 (50.5%); 44 had level 2 (46.3%) and 3 level 3 (3.2%); as concerns criterion B, 56 individuals had level 1 (58.9%), 37 had level 2 (38.9%) and 2 people had level 3 of severity (2.1%) (Figure 5.1a).

The remaining patients were diagnosed with obsessive–compulsive disorder (6 cases), schizotypal personality disorder (5), attenuated psychosis syndrome (3), schizophrenia (3), avoidant personality disorder (3), schizoid personality disorder (2), borderline personality disorder (2), depressive personality disorders (2), substance abuse (1), narcissistic personality disorder (1), factitious disorder (1), and other diagnoses (6). Of note, 10 patients did not satisfy the criteria for any psychiatric diagnosis (Figure 5.1b).

Figure 5.1. Diagnostic classification of participants.



Statistical analysis

Demographic variables of the studied population are presented as mean and standard deviations, percentages or counts as appropriate. Data were tested for normal distribution and homogeneity of variance using Kolmogorov–Smirnov and Levene's tests before statistical procedures were applied.

Receiver operating characteristic (ROC) analyses were used to evaluate the accuracy of the different diagnostic measures. We used the classification proposed by Hosmer and Lemeshow (Hosmer, Lemeshow, & Sturdivant, 2013) for the interpretation of AUC values (0.5: no discrimination; 0.7–0.79: acceptable; 0.8–0.89: excellent; ≥0.9 outstanding).

Agreement among the assessment tools and between the assessment tools and clinical judgment were computed by means of Cohen's k. We used the Landis's cut-offs (Landis & Koch, 1977) to interpret Cohen's k value (0: no agreement; 0–0.2: slight; 0.21–0.40: fair; 0.41–0.60: moderate; 0.61–0.80: substantial; 0.81–1: almost perfect agreement).

Binary logistic regression analyses using a hierarchical method were conducted to determine independent predictors (age, gender, IQ, and severity at criteria A and B) of

the agreement between the clinical and the positivity to standardized diagnostic instruments in the autistic population. If the model obtained with hierarchical method resulted not significant, a stepwise binary logistic regression was conducted to estimate the best model.

Results were considered statistically significant at the $p \leq 0.05$ level, and all tests were two tailed. Statistical analysis was performed using SPSS 24 software packages (SPSS, Chicago, IL).

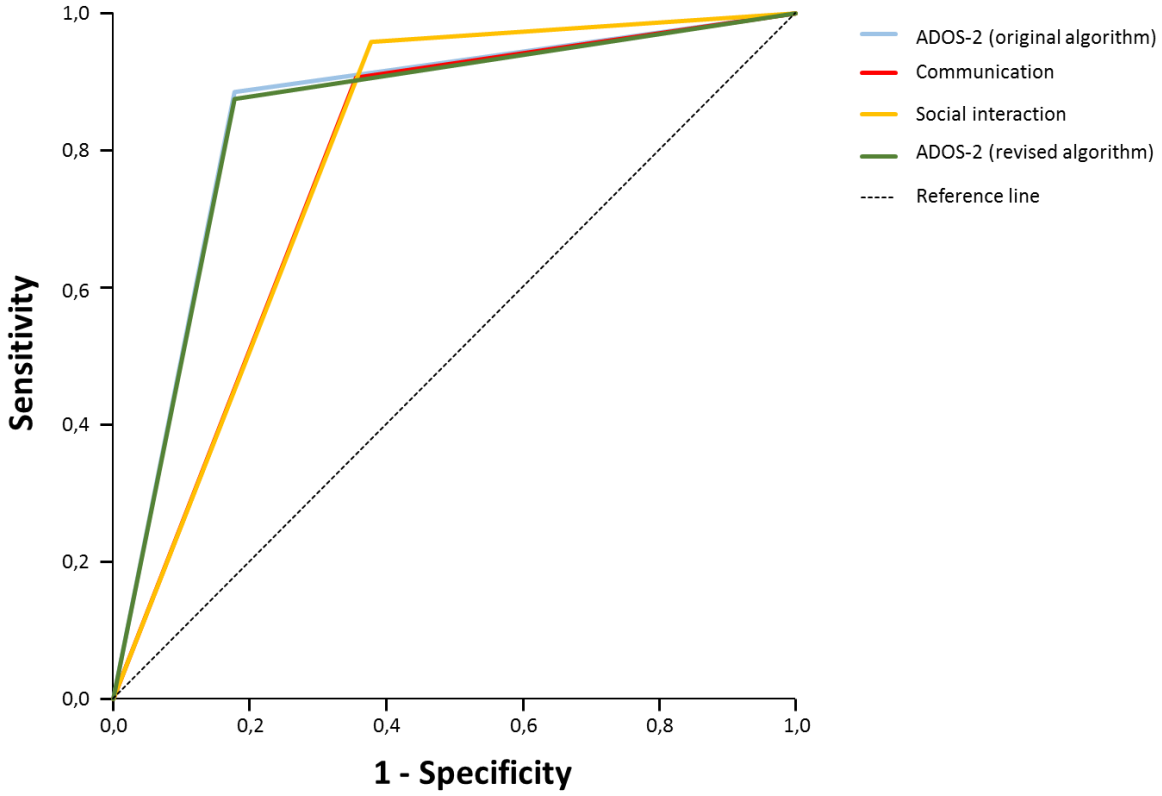
RESULTS

Accuracy of diagnostic instruments and agreement with clinical diagnosis

Accuracy of ADOS-2 and agreement with clinical diagnosis

The diagnostic accuracy of ADOS-2 was tested by means of ROC curves. According to the original algorithm of ADOS-2 Module 4 (Figure 5.2), ROC curves showed an excellent discriminant validity for the Communication + Social domain (AUC = 0.85, SE = 0.04, $p < 0.001$, 95% CI 0.78–0.93). Considering the two domains singularly, they both showed an acceptable accuracy, with an AUC = 0.79 (SE = 0.05, $p < 0.001$, 95% CI 0.70–0.88) for the Social Interaction domain and an AUC = 0.77 (SE = 0.05, $p < 0.001$, 95% CI 0.68–0.87) for the Communication domain. The revised algorithm of ADOS-2 also showed an excellent discriminant validity (AUC = 0.85, SE = 0.04, $p < 0.001$, 95% CI 0.77–0.92).

Figure 5.2. ROC curves of the ADOS-2 and subscales.



Clinical consensus judgment showed a substantial agreement both with traditional (k = 0.69) and revised algorithm (k = 0.68) of ADOS-2. The agreement was substantial also between clinical judgment and Reciprocal social interaction subscale (k = 0.62), while Communication subscale moderately agreed with clinical diagnoses (k = 0.57). All p-values were significant ($p < 0.001$).

Table 2 reports sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of cut-off criteria of the algorithms for ADOS-2 compared to the consensus clinical classification performed according to the DSM-5 criteria. We examined also single subscales.

Table 5.2 ADOS-2 accuracy and agreement with clinical diagnosis.

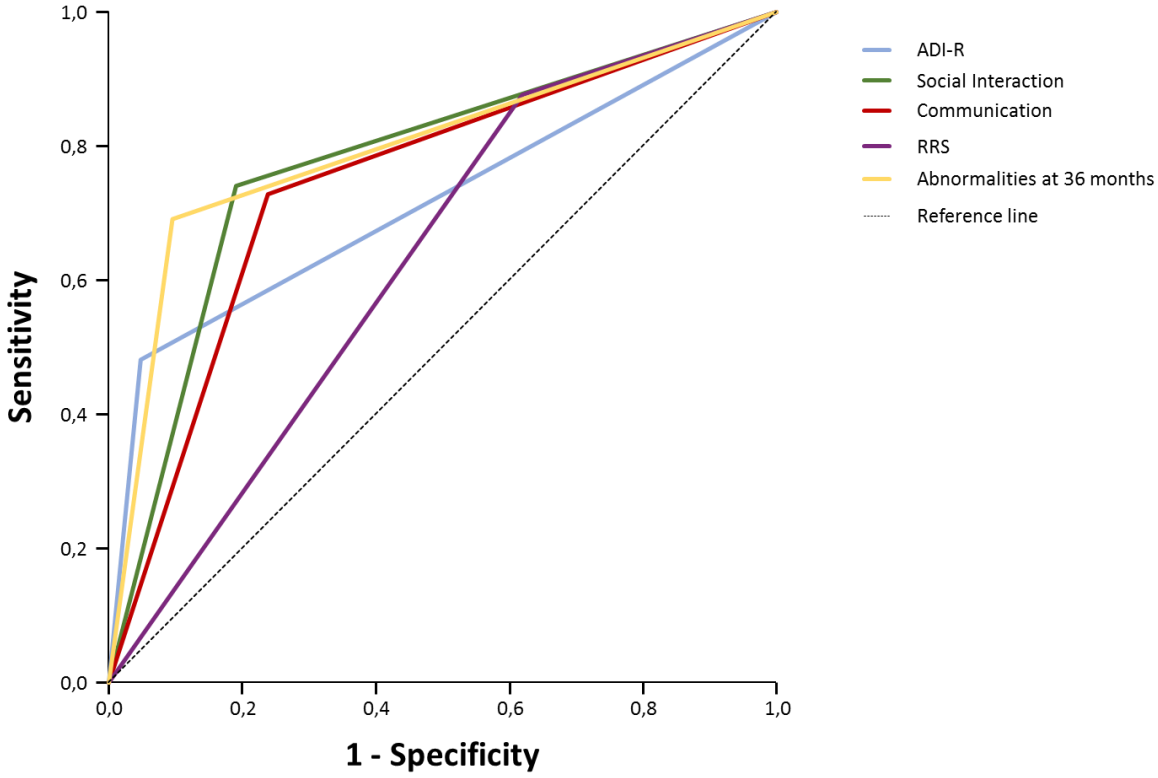
	Sensitivity (%)	Specificity (%)	Correct classification (%)	PPV (%)	NPV (%)	Cohen's k
ADOS-2 (original)	88.4	82.2	86.43	91.3	77.1	0.694*
Communication	90.5	64.4	82.14	84.3	76.3	0.573*
Social interaction	95.8	62.2	85	84.3	87.5	0.628*
ADOS-2 (revised)	87.4	82.2	85.71	91.2	75.5	0.68*

Legend: NPV: Negative Predictive Value; PPV: Positive Predictive Value

Accuracy of ADI-R and agreement with clinical diagnosis

The diagnostic accuracy of the ADI-R was acceptable (AUC = 0.72, SE = 0.05, $p < 0.001$, 95% CI 0.61–0.82). Considering ADI-R single domains (Figure 5.3), ROC curves showed an excellent discriminant validity for the domain regarding the abnormalities of behavior evident at or before 36 months (AUC = 0.80, SE = 0.05, $p < 0.001$, 95% CI 0.70–0.90). An acceptable accuracy was found for qualitative abnormalities in reciprocal social interaction (AUC = 0.77, SE = 0.06, $p < 0.001$, 95% CI 0.66–0.89), and the qualitative abnormalities in communication domain (AUC = 0.75, SE = 0.06, $p < 0.001$, 95% CI 0.63–0.87). On the contrary, we observed a poor accuracy AUC in the restricted, repetitive and stereotyped patterns of behavior domain (AUC = 0.63, SE = 0.07, $p = 0.07$, 95% CI 0.48–0.77).

Figure 5.3 ROC curves of the ADOS-2 and subscales.



Clinical consensus judgment showed a fair agreement with ADI-R (k = 0.25). A fair agreement was found also between final diagnoses and the subscales regarding communication (k = 0.38) and repetitive behaviors (k = 0.27). Finally, the domains of reciprocal social interaction and evidence of abnormalities in the early childhood both moderately agreed with clinical judgment, with a Cohen's k of 0.42 in both cases. All p-values were significant ($p < 0.001$).

Table 5.3 reports sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of cut-off criteria of the algorithms for ADI-R compared to the consensus clinical classification performed according to the DSM-5 criteria. Single subscales were also examined.

Table 5.3. ADI-R accuracy and agreement with clinical diagnosis.

	Sensitivity (%)	Specificity (%)	Correct classification (%)	PPV (%)	NPV (%)	Cohen's k
ADI-R	48.1	95.2	57.84	97.5	32.3	0.252
Qualitative abnormalities in communication	72.8	76.2	73.53	92.2	42.1	0.377
Qualitative abnormalities in reciprocal social interaction	74.1	81	75.49	93.8	44.7	0.423
Restricted, repetitive and stereotyped patterns of behavior	87.7	38.1	77.45	84.5	44.4	0.272
Abnormalities of behavior evident at or before 36 months	69.1	90.5	73.79	96.6	43.2	0.424

Legend: NPV: Negative Predictive Value; PPV: Positive Predictive Value

Predictors of the agreement between standardized instruments and clinical diagnosis in the ASD population

A logistic regression model using a hierarchical method was conducted, including the agreement between clinical diagnosis of ASD and diagnostic instruments as dependent variable, and gender (female=0; male=1), age at evaluation, IQ, and severity at criteria A and B as independent variables. Our aim was to investigate if any of the considered characteristics could differentiate between "true positive" (TP) and "false negative" (FN) for each of the considered diagnostic instruments or subscales.

Predictors of the agreement between ADOS-2 and clinical diagnosis

Among 95 individuals, 84 were collocated in the autism spectrum classification according to the ADOS-2 (TP), while other 11 did not exceed the cut-off scores (FN). The final regression model was significant (p = 0.03) and correctly classified the 88.1% of cases. The logistic regression showed that gender was a significant independent predictor: males were more likely to exceed cut-off values for autism spectrum at the ADOS-2 compared to females (Table 5.4).

Table 5.4. Predictors of the agreement between ADOS-2 (original) and clinical diagnosis.

	B	SE	OR (95% CI)	p-value
Gender	1.592	0.732	4.912 (1.170 to 20.629)	**0.03***
Age	-0.049	0.037	0.952 (0.885 to0 .024)	0.187
IQ	-0.005	0.027	0.995 (0.943 to 1.050)	0.851
Severity A	0.607	0.824	1.835 (0.365 to 9.230)	0.461
Severity B	0.099	0.851	1.104 (0.208 to 5.849)	0.907

Model $\chi^2 = 12.43$, p = 0.03; Cox and Snell pseudo $R^2 = 0.123$; n = 95

The revised algorithm of ADOS-2 correctly classified into the spectrum 83 people (87.4% of the sample) but was not significant and no independent predictors could be identified.

Table 5.5. Predictors of the agreement between ADOS-2 (revised) and clinical diagnosis.

	B	SE	OR (95% CI)	p-value
Gender	1.027	0.709	2.794 (0.696 to 11.211)	0.147
Age	-0.049	0.037	0.953 (0.886 to 1.025)	0.192
IQ	0.025	0.025	1.025 (0.976 to 1.076)	0.320
Severity A	0.557	0.756	1.745 (0.396 to 7.686)	0.462
Severity B	0.777	0.808	2.174 (0.446 to 10.599)	0.337

Model $\chi^2 = 8.02$, $p = 0.15$; Cox and Snell pseudo $R^2 = 0.08$; $n = 95$

Considering ADOS-2 subscales (communication and reciprocal social interaction), no significant models or independent predictors could be identified (Table 5.5).

Predictors of the agreement between ADI-R and clinical diagnosis

Eighty-one parents were interviewed by means of the ADI-R, with 39 ASD patients resulting correctly identified (TP). On the contrary, 42 individuals, despite a clinical diagnosis of ASD, did not exceed cut-off values in all ADI-R subscales (FN). The final regression model fitted 68.3% of the sample. IQ and severity at criterion B were significant predictors of a correct classification according to the ADI-R (Table 5.6). While people with higher IQ had less probability to be recognized as autistic at the ADI-R, those with higher severities in the RRB domain had more probability to be identified at the ADI-R.

Table 5.6. Predictors of the agreement between ADI-R and clinical diagnosis.

	B	SE	OR (95% CI)	p-value
Gender	0.028	0.649	0.973 (0.273 to 3.467)	0.966
Age	-0.015	0.040	0.986 (0.911 to 1.066)	0.715
IQ	-0.033	0.016	0.968 (0.939 to 0.998)	**0.037***
Severity A	-0.323	0.516	0.724 (0.263 to 1.991)	0.531
Severity B	1.202	0.539	3.326 (1.156 to 9.565)	**0.026***

Model $\chi^2 = 15.23$, $p = 0.009$; Cox and Snell pseudo $R^2 = 0.17$; $n = 81$

Predictors of the agreement between ADI-R (Communication) and clinical diagnosis

Twenty-two out of 81 individuals did not exceed cut-offs at the communication domain of ADI-R (FN). In the final regression model (correct classification of 71.6% of the sample), gender and severity at criterion B appeared significant predictors. In particular, males had more probability of agreement than females at this subscale. On the other hand, people with higher severity levels in the RRB domain had more probability to be recognized at the ADI-R communication scale (Table 5.7).

Table 5.7. Predictors of the agreement between ADI-R (Communication) and clinical diagnosis.

	B	SE	OR (95% CI)	p-value
Gender	1.538	0.692	4.654 (1.198 to 18.072)	**0.026***
Age	0.024	0.044	1.024 (0.940 to 1.115)	0.584
IQ	0.008	0.019	1.008 (0.971 to 1.046)	0.676
Severity A	0.297	0.611	1.346 (0.406 to 4.462)	0.627

Severity B	1.912	0.734	6.769 (1.605 to 28.551)	**0.009***

Model $\chi^2 = 18.41$, p = 0.002; Cox and Snell pseudo $R^2 = 0.203$; n = 81

Predictors of the agreement between ADI-R (Reciprocal Social Interaction) and clinical diagnosis

Sixty patients were identified as autistic according to the social interaction subscale (TP). The model was significant and correctly classified the 76.5%, but we did not find any independent predictors.

Table 5.8. Predictors of the agreement between ADI-R (Social interaction) and clinical diagnosis.

	B	SE	OR (95% CI)	p-value
Gender	0.924	0.650	2.520 (0.704 to 9.018)	0.155
Age	-0.020	0.041	0.980 (0.905 to 1.061)	0.616
IQ	-0.012	0.018	0.988 (0.953 to 1.024)	0.510
Severity A	0.224	0.588	1.251 (0.395 to 3.956)	0.703
Severity B	1.203	0.673	3.329 (0.891 to 12.445)	0.074

Model $\chi^2 = 12.99$, p = 0.023; Cox and Snell pseudo $R^2 = 0.148$; n = 81

Predictors of the agreement between ADI-R – (Restricted, repetitive, and stereotyped behaviors and interests – RRB) and clinical diagnosis

Only ten autistic patients did not exceed cut-off scores at the RRB scale (FN). Even if the model was significant (p = 0.002, correct classification = 88.9%), no independent predictors were found at the ADI-R – RRB subscale. Only age at evaluation bordered significance (p = 0.06), with older people being less likely to be classified correctly according to the RRB subscale (Table 5.9).

Table 5.9. Predictors of the agreement between ADI-R (RRB) and clinical diagnosis.

	B	SE	OR (95% CI)	p-value
Gender	0.283	0.897	1.327 (0.229 to 7.698)	0.752
Age	-0.104	0.056	0.902 (0.809 to 1.005)	0.062
IQ	-0.009	0.029	0.991 (0.936 to 1.048)	0.745
Severity A	-1.037	0.836	0.354 (0.069 to 1.824)	0.215
Severity B	20.119	6106.908	546442658.60 (N/A)	0.997

Model $\chi^2 = 19.53$, $p = 0.002$; Cox and Snell pseudo $R^2 = 0.214$; $n = 81$

Predictors of the agreement between ADI-R (Abnormalities at or before 36 months) and clinical diagnosis

Twenty-five out of 81 autistic people showed no abnormalities at or before the age of 36 six months (FN), according to ADI-R interview. The logistic regression including gender, age at evaluation IQ and severity at criteria A and B appeared not significant ($\chi 2 = 10.24$, $p = 0.06$). A stepwise logistic regression method was then applied. The best significant model included only gender, age at evaluation and IQ, correctly classifying the 74.1% of the sample. IQ was as a significant predictor of the agreement between the clinical diagnosis and the subscale regarding early developmental abnormalities. Results are presented in Table 5.10.

Table 5.10. Predictors of the agreement between ADI-R (Abnormalities evident at 36 months) and clinical diagnosis.

	B	SE	OR (95% CI)	p-value
Gender	0.269	0.608	1.309 (0.397 to 4.311)	0.658
Age	-0.012	0.037	0.988 (0.918 to 1.063)	0.749

IQ	-0.040	0.015	0.961 (0.932 to 0.990)	**0.01***

Model $\chi^2 = 8.88$, $p = 0.03$; Cox and Snell pseudo $R^2 = 0.104$; $n = 81$

DISCUSSION

Scientific literature is poor of studies investigating the reliability of the main standardized instruments for diagnosing ASD in adulthood. The present dissertation reported data of the evaluation of adult subjects without ID who have referred to an Italian University center for first formal diagnosis of ASD (Fusar-Poli et al., 2017c). Our first objective was to evaluate the accuracy of ADOS-2 and ADI-R for the diagnosis of ASD in adults, and their agreement with clinical judgment. Secondly, we aimed to evaluate the potential predictors of being collocated into the autism spectrum by diagnostic instruments after a clinical diagnosis of ASD.

Our results provide evidence for substantial agreement between the clinical diagnosis and the ADOS-2 scores (both using the original and the revised algorithm), showing also good sensitivity and specificity. AUC values of the ROC curves for the Communication + Social Interaction domain (original algorithm) and for the SA + RRB domain (revised algorithm) were both suggestive of excellent accuracy. Our findings are in line with previous studies which evaluated the discriminant validity of ADOS-2 Module 4 in samples of adults with average or above-average intelligence (Bastiaansen et al., 2011; De Bildt et al., 2016; Hus & Lord, 2014; Kamp-Becker et al., 2013; Langmann et al., 2017; Pugliese et al., 2015), cautiously suggesting that it could be a reliable instrument also for first evaluations in adults (Fusar-Poli et al., 2017c).

Considering the ASD sample, males were more likely to be diagnosed as autistic by standardized instruments compared to females. This finding confirms literature data,

which reported a minor accuracy of observational instruments in detecting ASD in females. Diagnostic and screening tests, such as the ADOS-2, in fact, rely on the typical male phenotype of ASD, which exclude some of the features of girls with autism (Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2015; Rynkiewicz et al., 2016). The DSM-5 itself specifies that "girls without accompanying intellectual disability or language delays may go unrecognized, perhaps because of subtler manifestation of social and communication difficulties" (American Psychiatric Association, 2013). Lai et al. (2011) alluded to higher camouflaging in women than men with autism based on the observation that, given similar scores at the ADI-R, women with ASD tended to show less pronounced autistic features during the ADOS. More recently, Rynkiewicz et al. (2016) found that girls with autism used gestures more vividly than boys with autism during the ADOS-2. It also worth mentioning that the female autistic phenotype may be more difficult to detect in people with average intelligence and above, such as the subjects included in our sample. However, it is important to mention that considering the revised algorithm, no significant models could be detected.

The ADI-R is a semi-structured interview administered to caregivers. Our sample was composed by adults (mean age = 28.34) and unfortunately in about 27% of cases we were not able to contact parents or caregivers. The agreement between ADI-R and clinical diagnosis was poor, correctly classifying only 58% of our sample. It is worth mentioning that most of the items of the ADI-R focuses on the period between the ages of 4 and 5 years (Lord et al., 1994). For adults, the quality of informant's recall might not be detailed or reliable due to the long time elapsed from subject's childhood to the current assessment (Lai & Baron-Cohen, 2015). Additionally, IQ appeared to be a

negative predictor of the positivity to ADI-R in the ASD sample. It is plausible that individuals with high cognitive abilities may have developed camouflaging or compensating strategies during their childhood, thus being able to mask the core ASD symptoms. For instance, findings from Hus and Lord (2013) associated greater cognitive delays with a more severe impairment on most behavioral measures in samples of children spanning the full range of IQ. Surprisingly, age was not a predictor of the agreement between ADI-R and clinical judgment in our sample. In fact, we could have expected older people to be less likely to agree with clinical diagnosis, due to the long time elapsed from the subjects' childhood to the current assessment.

Our findings are partially in contrast with the study published by Sappok et al. (2013) that examined the accuracy of ADI-R in adults. Sappok and colleagues, in fact, found less specificity (80%), but extremely higher sensitivity (88%) compared to our sample. This discrepancy could be partly explained by the characteristics of Sappok's sample: all patients recruited in the study had a diagnosis of ID and a long history of developmental delay. Consequently, parents or caregivers were probably more prone to recall information about the abnormal developmental history of the patients, and may have undergone through several previous evaluations (Fusar-Poli et al., 2017c). However, our results are in line with the study of Talari, Balaji, & Stansfield (2017) that recently found a low specificity (37.5%) of ADI-R in a clinical sample of adults with diverse cognitive abilities. Additionally, our findings partially mirror the conclusions of recent studies evaluating the discriminant validity of ADI-R in children, which have found high specificity, but moderate to low sensitivity (De Bildt et al., 2015; Zander, Sturm, & Bölte, 2015).

The communication domain fairly agreed with clinical diagnosis in the whole sample (k = 0.38), even if with good sensitivity and specificity. Considering only the ASD sample, gender seemed to influence negatively the ADI-R domain regarding abnormalities in communication. Again, these data support the hypothesis of a different autistic phenotype in females since childhood, with a subsequent tardive recognition of the diagnosis (Lai et al., 2016).

The restricted, repetitive behaviors and interests represented the less specific scale of the ADI-R (38.1). On the contrary, all the other domains presented good discriminant validity. The limited utility of the stereotyped behaviors domain is in line with the findings of Mazefsky and Oswald (2006), who analyzed the agreement between single ADI-R scales and clinical diagnosis in children. The high number of false positive at this scale (13 out of 21 patients) could find an explanation in the characteristics of our sample, which may be considered a general clinical population. Stereotypes and rituals, in fact, may be present also in other psychiatric conditions, such as obsessive-compulsive disorder or psychoses. Finally, previous studies showed an improvement in the RRB domain in adults with ASD, in particular in the repetitive use of objects, complex mannerisms and unusual preoccupations (Seltzer et al., 2003). Even if age at evaluation was not a negative independent predictor of the agreement between ASD diagnosis and RRB subscale, the result bordered significance (p = 0.06). On the other hand, current level of severity at criterion B was a positive independent predictor of the agreement between ADI-R and clinical diagnosis. People with more stereotypes and restricted interests were more likely to exceed cut-off scores in all ADI-R domain. Accordingly, our data confirm the findings of Talari, Balaji, & Stansfield (2017) who have recently

demonstrated the strong predictability of RRB domain for clinical diagnosis of autism. This association is confirmed also by further evidence showing that scores on RRB domain of the ADI-R are more indicative of autism, particularly in males (Duvekot et al., 2017; Jamison, Bishop, Huerta, & Halladay, 2017).

The domain regarding the evidence of abnormalities at or before 36 months deserves to be critically discussed for its poor sensitivity. In 25 out of 81 ASD patients no abnormalities could be detected before three years of age, despite a clinical classification into the autism spectrum. A possible explanation could again rely in the poor trustworthiness of informants. We should consider that the individuals examined in our study belonged to the higher-functioning part of the autistic spectrum, with good general cognitive ability and low severity of symptoms, who were evaluated for the first time between 18 and 55 years; thus, it is unlikely that some early abnormalities could be noticed without a consequent evaluation or that they would not be reported at the moment of the interview. IQ, in fact, resulted to be a negative predictor of the agreement between clinical diagnosis of ASD and the subscale of early developmental abnormalities. This finding confirms that individuals with high IQ, like those included in our sample, may have developed several copying strategies sufficient to cover the presence of abnormalities or delays. Another possible explanation could be related to the changes occurred in the diagnostic criteria. While DSM-IV-TR required an onset of the impairments before the age of 3 years, according to DSM-5 “ASD symptoms must be present in the early developmental period, but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life” (American Psychiatric Association, 2013). Thus, a clinical diagnosis could be

formulated also for those individuals who did not completely show ASD symptoms during their childhood.

The present study has the major strength to take into account the so-called “lost generation” of autistic adults (Lai and Baron-Cohen, 2015), who has been seeking for first diagnosis after the broadening of diagnostic criteria and the increased awareness towards the. In particular, individuals included in our sample represent the part of the spectrum with higher cognitive abilities and milder symptoms. An accurate diagnosis is much more difficult for this population (Lai and Baron-Cohen, 2015). Another strength is that ADOS-2 and ADI-R were administered by personnel blind to the clinical diagnoses and thus unaware of the psychopathological anamnesis of the subject. Professionals, in fact, could sometimes be misled by previous diagnoses. In addition, we have avoided the risk of generating low specificity values due to the naturalistic design of the study, as already suggested by previous studies that evaluated the ADOS in clinical settings (Bastiaansen et al., 2011; Mazefsky & Oswald, 2006; Molloy et al., 2011; Sappok et al., 2013).

Nevertheless, it is important to underline some limitations. First, we are aware that the sample is still relatively small; on the other hand, our sample is rapidly growing and we hope to further validate our analysis considering larger population in the near future. Second, the assessment process was not conducted by a multidisciplinary team, as suggested by guidelines (Pilling et al., 2012). Anyway, assessors were both psychiatrists and medical doctors with a high expertise in diagnosing ASD in adulthood. Third, we limited the analysis to people belonging to the higher-functioning part of the spectrum, thus hampering the generalizability of our findings also to subjects with ID; however,

including ID subjects may have excessively reduced the homogeneity of the sample, leading to a loss of important information. Finally, while we examined possible predictors of “false negative” (people who were not collocated in the autism spectrum by diagnostic instrument, but met DSM-5 criteria for ASD), we could not investigate potential predictors of “false positive”. This was not possible because too few individuals positively scored during the diagnostic questionnaires despite not receiving an ASD diagnosis after the clinical evaluation (0.48% for the ADI-R and 17.78% for the ADOS). Of note, they were all subjects affected by psychosis or personality disorders. In the future, we are planning to specifically recruit non-ASD samples (e.g. schizophrenia andschizophrenia-like disorders, schizoid and schizotypal personality disorders, etc.) to investigate the accuracy of observational tools (i.e. ADOS-2) in patients affected by complex psychiatric conditions. Nevertheless, ADI-R have a specificity that borders 100% and could be considered very reliable in excluding a diagnosis of ASD.

6. CLINICAL VIGNETTES

The aim of the present section is to depict a series of clinical vignettes regarding complex assessments of young and older adults who referred to the Laboratorio Autismo of the University of Pavia for a first formal diagnosis of ASD.

The cases hereafter reported are paradigmatic. First, they demonstrate how the demand for diagnoses of ASD is incredibly increasing also in adults. One motivation undoubtedly relies in the growing awareness towards the disorder. However, we could also hypothesize that ASD might represent a "trendy" condition, a sort of diagnostic etiquette that some people would like to gain in order to explain their eccentricity or the difficulties they have encountered in their life. Second, the clinical vignettes show how the diagnostic assessment in adulthood might be difficult to conduct, necessitating a wide expertise in discriminating among the different psychiatric conditions. During clinical practice, in fact, the risk of facing the "false-positive" or "false-negative" is always imminent. It is not infrequent to encounter people who were misdiagnosed or not recognized as autistic, or people with the false belief to belong to the autism spectrum.

The heterogeneity of phenotypical presentations of ASD in different individuals might be also a confounding element, needing a constant comparison and integration between diagnostic tools and psychopathology. To quote Oliver Sacks in "An Anthropologist on Mars" (1995), "*No two people with autism are the same; its precise form or expression is different in every case. Moreover, there may be a most intricate (and potentially creative) interaction between the autistic traits and the other qualities of the individual. So, while a single glance may suffice for clinical diagnosis, if we hope to understand the autistic individual, nothing less than a total biography will do.*"

Hysteria?

Antonio was a young adult of 20 years who asked a clinical assessment to the research center for personality disorders of the University of Pavia (CIRDIP). Since kindergarten, Antonio was characterized by social isolation, absence of relationships, tendency to concentrate on few restricted interests. However, he had never undergone a mental health evaluation. Psychiatrists working at CIRDIP, suspecting the presence of a neurodevelopmental disorder, contacted the Laboratorio Autismo for a formal evaluation of ASD.

During the assessment, Antonio's parents were interviewed. The developmental history was suggestive of ASD. In fact, the ADI-R exceeded cut-offs in almost all domains, apart from the scale regarding restrictive and repetitive behaviors (*Qualitative Abnormalities in Reciprocal Social Interaction:* 11, *Qualitative Abnormalities in Communication:* 8, *Restricted, Repetitive, and Stereotyped Patterns of Behavior:* 2, *Abnormalities of Development Evident at or Before 36 Months:* 1). In particular, Antonio's parents referred that he had never shown interest in interacting with peers (e.g. he never went to birthday parties) and presented many motor abnormalities. Antonio himself mentioned that he felt like an adult, pretending to act like a child while playing with peers. Antonio showed a good eye and verbal contact with the examiner. Conversation was fluent and reciprocal. However, during the interview and the semi-structured observation, Antonio showed a noticeable rigidity. The comprehension of own and others' emotions was also poor. Antonio had no relationships with peers, with the presence of pervasive interests (i.e. videogames). The patient, in fact, after concluding high school, spent most of the time at the computer playing videogames and chatting with other virtual players. The ADOS-2 also confirmed the presence of an autistic

disorder (*Communication*: 3; *Reciprocal social interaction*: 5; *Communication + social interaction:* 8; *Imagination/creativity*: 0; *Stereotyped behavior and restricted interests*: 1). SCID-II identified narcissistic, obsessive-compulsive and schizotypal traits, which in fact could be connected also to ASD.

Antonio reported several "secondary" problems, of various nature, which complicated the diagnostic process. First, the patient lamented a cognitive and physical decline, apparently begun at the age of 16. He had always been underweight, showing also the tendency to develop recurrent bronchial infections. After several medical evaluations finalized to the assessment of his physical and behavioral disturbs, Antonio started to perceive a deterioration of his cognitive functioning, with loss of memory, attention and logic abilities, accompanied by extreme fatigue and sleepiness. Such problems were pervasive and compromised any kind of activity. It is worth mentioning that from the beginning to the end of the assessment, the sense of fatigue had gone worsening, until Antonio could not get up from bed, go to the bathroom, or have a shower, if not forced to. He also presented a complete inversion of the sleep-wake rhythm. In addition, alterations of sensorial perception (i.e. amplified taste and smell, muffled hearing, tingling in unusual parts of the body) and phenomena described by Antonio as "thought blocking" were reported. Even if part of this psychopathological picture could be ascribed to ASD, the subjective cognitive deterioration (despite an IQ of 126 at the WAIS-R) could not be explained by the neurodevelopmental disorder. Consequently, the patient was administered the CAARMS, which confirmed the presence of alterations compatible with an attenuated psychotic syndrome.

In parallel, Antonio decided to consult a neurologist for the sleep problems. However, after several diagnostic examinations (i.e. polysomnography, EEG, RMN, etc.), no specific medical conditions could be detected, and a therapy to re-establish his circadian rhythm was prescribed. Other medical conditions also led Antonio to ask for innumerable medical evaluations. He was also taking cannabis for the treatment of an irritable bowel syndrome.

Another problem of psychopathological nature regarded the sexual orientation. Antonio did not have a specific position at the regard. He never had sexual relationships with men or women and he reported to consider valuing the personality over the physical aspect. After chatting with another videogame player, who had just changed their sex, he began to mature worries regarding his sexual identity and started to search information about sex transition. However, it is probable that those identity problems did not represent a real gender dysphoria, but rather the desire to be facilitated in socialization. According to Antonio's beliefs, in fact, social interaction would be easier for women. Probably, the difficulties in emotional comprehension typical of ASD did not help Antonio in the research of his own identity.

In conclusion, the case of Antonio was challenging and despite a clinical history suggestive for ASD, it was not totally clear if the presence of psychotic symptomatology could be referred to a comorbid attenuated psychotic syndrome or not. Other possible differential diagnoses, or comorbidities, have been considered. For instance, given the extreme underweight of Antonio (BMI = 16), we hypothesized also the presence of a restrictive eating disorder. Nevertheless, diagnostic criteria were not satisfied, and both Antonio and his parents confirmed that, despite the low weight, the nutritional intake

was adequate, without the presence of food selectivity. Since Antonio had consulted several medical professionals, a diagnosis of hypochondria was also taken into account. During the assessment, he reported several times his worries to be affected by some kind of genetic or rare disease. Finally, we could not exclude the presence of a somatoform disorder (the so-called "hysteria"), a mental disorder characterized by the manifestation of physical symptoms suggesting illness or injury, but which cannot be explained fully by a general medical condition or by the direct effect of a substance, and are not attributable to another mental disorder (American Psychiatric Association, 2013).

The woman who wanted to be adopted from native American Indians

Cecilia was 51 when she was sent to the Laboratorio Autismo for a formal confirmation of an ASD diagnosis, received by a psychiatrist working in public mental health services. Unfortunately, Cecilia's parents lived away and it was not possible to perform a standardized assessment regarding her developmental history. Cecilia reported that, when she was a child, she refused physical contact and did not want to play with other children. At the age of 16, she abandoned her family to move to a Hindu community. Reasons for this decision relied mainly in the intolerance towards some impositions of her family. For instance, her father did not want her to be vegetarian. During her permanence in the community, Cecilia got married with a stranger, who was 15 years older than the girl. The relationship was very problematic, and Cecilia reported physical abuses from her husband. Four years later, she managed to leave him and the community. She started to travel and to live in different communities around the world. Twelve years later, "like a newborn" she decided to establish in Italy after becoming "the fiancée of a famous musician, a psychopath". In the meanwhile, Cecilia was working as

a translator and art performer. After breaking up with the musician, she spent the period between her late thirties and forties in a sort of "wondering". She finally established in the United States to satisfy the desire of being adopted by a community of native Indian American. She returned to Italy for a brief period to undergo some medical examinations. Here, she received a presumptive diagnosis of Asperger's syndrome, for which she asked a formal confirmation.

The history of Cecilia was very peculiar and she shared some clinical features with ASD. The patient presented preoccupations, odd patterns of speech and thinking, atypical behavior patterns and difficulties in the relationship with other people. In fact, some characteristics of autism emerged also during the semi-structured observation, with an ADOS-2 that exceed the cut-off in the socio-communicative domain (*Communication*: 2; *Reciprocal social interaction*: 6; *Communication + social interaction:* 8; *Imagination/creativity*: 2; *Stereotyped behavior and restricted interests*: 1). However, at the SCID-II, criteria for schizotypal personality disorder were completely satisfied, with the presence also of passive-aggressive and depressive traits. Cecilia was finally diagnosed with a schizotypal personality disorder, which is probably one of the most difficult conditions to distinguish from ASD.

The girl who desired to become a boy

Eleonora entered in contact for the first time with child psychiatry at the age of 5, after the suggestion of her teachers, who described her as "a little shy". She was thus evaluated and followed psychomotricity for two years without a specific diagnosis. While Eleonora had no problems with peers during primary school, also participating to social activities, she became more introvert during high school. After obtaining a professional

qualification, Eleonora struggled to find a job, only completing a few brief and unpaid traineeships. At the age of 18, after referring to an employment center, she was assessed by a psychiatrist for the evaluation of adaptive abilities. In that occasion, Eleonora received a diagnosis of Asperger's syndrome. However, after requesting a certification of disability, this condition was not formally recognized.

In parallel with social and occupational problems, Eleonora since primary school experienced also a discomfort due to the non-acceptance of her biological gender. Since childhood, Eleonora used to wear male clothes and secretly played with male toys. From high school, she also presented hair on her face, probably due to a hormonal disequilibrium. Unfortunately, the patient had never had a friend or a meaningful relationship that could led her to disclose her distress. At the age of 27, she decided to reveal her feelings to her parents with the purpose of starting the sex transition. After the beginning of the assessment for gender dysphoria, the psychologist who had taken Eleonora in charge decided to send her to our diagnostic center for a re-evaluation. The presence of ASD in fact could significantly influence the process of sex transition, due to the scarce insight and comprehension of emotions typical of people with ASD.

During the semi-structured observation, Eleonora's speech was almost absent, and limited to responses to the examiner. She also presented a monotonous speech. However, according to her parents' account, this way of communicating was limited to unfamiliar contexts. Eye contact was reduced in frequency and no emphatic or descriptive gestures were used. Eleonora's parents reported the presence of routines and rigidities in daily living. However, during ADOS-2 no motor or verbal stereotypes were noticed. Intelligence was in the average range (IQ = 107).

Both ADOS-2 (*Communication*: 6, *Social Interaction*: 7, *Communication + Social Interaction total*: 13, *Creativity*: 2, *Stereotyped behaviors and restricted interests*: 0) and ADI-R (*Qualitative Abnormalities in Reciprocal Social Interaction* 10, *Qualitative Abnormalities in Communication* 9, *Restricted, Repetitive, and Stereotyped Patterns of Behavior*, *Abnormalities of Development Evident at or Before 36 Months* 1) confirmed that Eleonora was affected by ASD. In the case of Eleonora, ASD was associated with gender dysphoria. This emerging topic is very interesting and deserves to be elucidated in future research.

The "uniformologist"

Emilio was a 55-year-old man living in Trentino Alto-Adige, who had been in charge to the local psychiatric services for several years with a diagnosis of personality disorder not otherwise specified in comorbidity with bipolar disorder. A relative working in the psychiatric field started to suspect that he could belong to the autism spectrum, and sent him to our diagnostic center. Emilio was living alone in a flat next to his old father, but was not able to attend in autonomy to daily living activities. The municipality daily provided the lunch to Emilio, while the dinner was usually prepared by his father. Additionally, a housekeeper helped him cleaning the house. The patient did not have a stable job, but only a seasonal employment as cultural operator and tour guide. He had obtained a master's degree in History and, in the past, he had worked as a teacher in some high schools, never being able to maintain the job for long periods and with several problems in the management of the classrooms.

Emilio was a funny and lively man, with a scarcely modulated eye contact. The way of speaking was polished and verbose. It was possible to get in contact with Emilio, even if

it was very difficult to stop him while talking about his special interests. Emilio, in fact, showed an overpowering passion for history, knowing almost every detail of historical events. In particular, he was fascinated by uniforms ("I am an expert in uniformology", he said). Such pervasive passions caused difficulties to Emilio in the management of daily life, since he spent much time of the day pursuing his interests. Additionally, the patient had several problems in the interaction with other people, not always interested in these topics. In this regard, he had very limited relationships, in the majority of cases related to his seasonal job. Emilio presented also a specific phobia for fires: in particular, he was afraid that historical books or documents may go lost after a fire. According to the ADOS-2 Emilio was collocated into the autism spectrum (*Communication*: 3; *Reciprocal social interaction*: 5; *Communication + social interaction*: 8; *Imagination/creativity*: 0; *Stereotyped behavior and restricted interests*: 3).

Emilio's old father and sister were also involved in the assessment process. Given to the poor physical conditions of the parent and to the long time passed since the patient's childhood, a formal assessment by means of the ADI-R was not possible. However, Emilio's relatives gave precious information regarding his early development and his current behavior. They reported complications during birth (a cephalohematoma), but a regular development, without noticeable delays. They also referred that during childhood Emilio was diagnosed with epilepsy for which he was still taking medication (gabapentin). Additionally, they reported that during several years, the patient had personally written dozens of books regarding historical themes of his interest, collecting information from different sources. However, such masterpieces were hidden and no one had access to them.

The case of Emilio represents a clear example of an older adult with ASD who has been misdiagnosed for several years by clinicians, but with a number of special abilities and interests that could be exploited for his and others' advantages.

"The Aspie quiz told me I am neurodiverse"

Manuela was a 58 years old woman, living only with her daughter after divorcing from her husband. Her psychopathological history was silent. Manuela had a conflictual relationship with her parents and sister which caused anxiety and depressive symptoms to the patient. She started then to become retired, isolated, avoiding any social contact. After reading some characteristics of the Asperger's syndrome on the web, she completed the Aspie quiz, an online questionnaire, which deposed for neurodiversity. She then decided to go to a private child psychiatrist specialized n ASD for an assessment. After administering the RAADS-R, a screening tool, the child psychiatrist diagnosed Manuela with ASD. She also advised the patient to start a psychotherapy specifically addressed to autism and to consult adult psychiatric services for the administration of an appropriate medication for his symptomatology. Consequently, Manuela consulted our diagnostic center for a formalization of the diagnosis and for the medication.

During both the clinical interview and the standardized observation, Manuela showed no peculiar features of ASD. She had a good and communicative eye contact, and the prosody was extremely varied. Also, emphatic and descriptive gestures were appropriate and related to the content of the discourse. Additionally, Michela reported that, even if quite reserved, she had never had problems in relationships with other people. After working for several years as architect and urban planner, Michela was not

working at the moment of the evaluation, having the possibility to live off private income. She had the dream of writing a book.

The semi-standardized observation (ADOS-2) did not highlight any characteristics typical of the autism spectrum (*Communication*: 0; *Reciprocal social interaction*: 0, *Communication + social interaction*: 0; *Imagination/creativity*: 0; *Stereotyped behavior and restricted interests*: 0). However, Manuela was experiencing an important anxious symptomatology. An appropriate medication with antidepressant and benzodiazepines was then suggested.

The case of Manuela is paradigmatic. First, Manuela represents the typical adult who performed a self-diagnosis of ASD. It is important to underline that self-diagnoses are not always reliable and need to be confirmed by a psychiatrist or a psychologist. The second moral is that only competent professionals with a wide expertise in diagnosing adolescents and adults with ASD should perform diagnoses within this age range. Several other psychiatric conditions in fact - some of which are not typical of child psychopathology – could imitate ASD symptoms. Consequently, it is important to be aware of any possible differential diagnosis without focusing only on the specific evaluation of ASD traits.

Father of an autistic son

Mario was the father of an autistic boy of 6 years. After the diagnosis of his child, he hypothesized to share some peculiar characteristics with him. He decided to refer to the same center that had evaluated the son. After a clinical assessment, a child psychiatrist confirmed that Michele was affected by ASD.

During the clinical interview, Michele reported no particular problems in his

relationships with peers during school, being able to maintain some friendships until adulthood. He was bulled during high school, which he however abandoned for poor performance. During that period, he presented also some suicidal thoughts, that led him to follow a brief psychotherapy cycle. After obtaining a professional qualification, he started working in several fields, both as employee and independently. All business collaborations were interrupted because of the meticulousness of Michele and his scarce tolerance towards other errors and methodology. He also referred to be particularly slow in finishing his tasks. However, it is important to underline that he was never dismissed. The last job (window manufacturer) had terminated because of incomprehension with Michele's business partner. After the conclusion of this work collaboration, Michele started to take antidepressants and benzodiazepines. The ADOS-2 did not exceed cut-offs for ASD (*Communication*: 0; *Social Interaction*: 4; *Communication + Social Interaction total*: 4; *Creativity*: 0; *Stereotyped behaviors and restricted interests*: 1). SCID-II evidenced the presence of an obsessive-compulsive personality disorder, with passive-aggressive, narcissistic, and depressive traits.

The case of Michele was quite complex, since he had already received a diagnosis of ASD from another professional and in fact shared some common characteristics with autism. In addition, no specific developmental history was available. Michele referred a precocious development of language and logorrhea (which it was noticed also during the clinical evaluation, with difficulties in containing his discourse). He also reported that when he was a child, he underwent a hearing evaluation, because of the absence of response to name. During the assessment, eye contact was adequately modulated and communicative. Facial mimicry was varied and correctly accompanied the discourse. No stereotypes or rituals could be detected. Michele also showed a good insight and an

efficacious communication of emotions. In conclusion, the diagnosis of ASD was disconfirmed by our center and Michele was diagnosed with an obsessive-compulsive personality disorder.

"Idiotic" gaze

Rachele was a 46-year-old woman, married with two children. Her marriage was passing through a problematic period due to her obsessiveness in daily life. She had just been diagnosed with a personality disorder from a private psychiatrist. However, Rachele felt that such diagnostic etiquette did not fulfil her person and spontaneously referred to the Laboratorio Autismo for an assessment specifically focused on ASD. Some characteristics of her personality, in fact, had led her to think to belong to the autism spectrum. For instance, Rachele tended to literally interpret every sentence, having troubles with metaphors, sarcasm, and figures of speech. She did not completely comprehend social rules, particularly during work (she was working in the show business, but in an "unexposed" position). She could not distinguish friendships from working relationships. Additionally, she was not able to modify the conversation register during the different occasions (formal vs. non-formal). She presented a hypersensoriality, with even difficulties in touching some particular materials, and an acute sense of hearing. She also reported to have absolute pitch. Rachele presented also complex daily rituals that, when interrupted, could cause psychomotor agitation and crises. During the standardized observation with ADOS-2, Rachele showed some abnormal features that could related to the autism spectrum, but did not exceed the cut-off in the original algorithm (*Communication:* 2; *Reciprocal social interaction:* 4; *Communication + social interaction:* 6; *Imagination/creativity:* 2; *Stereotyped behavior and restricted interests:* 3).

Also, the ADI-R was not suggestive of a history of developmental disorder (Qualitative Abnormalities in Reciprocal Social Interaction: 4; Qualitative Abnormalities in Communication 6; Restricted, Repetitive, and Stereotyped Patterns of Behavior; Abnormalities of Development Evident at or Before 36 Months 0). It is however important to underline that Rachele's father lived in a different city when she was young, and her mother stayed rarely with her because of her job. For this reason, the interview cannot be considered completely reliable. Rachele grew up in a college. The patient started to read at the age of three, learning in autonomy in the library were her mother was working. The mother referred that Rachele used to speak like a "small adult" and showed a noticeably food selectivity, later disappeared. The patient also reported several misunderstandings with her teacher during the primary school. The child, in fact, often presented agitation and anger crises, attributed by Rachele to the difficulties in comprehending what the teacher was explaining. On the contrary, her mother tended to underestimate this oppositional behavior, attributing it to a challenging attitude of her daughter. During the period of the college, Rachele was frequently deputed to the organization of intellectual games, while she was often excluded from motor activities. The patient also reported that she was often blamed for her restlessness and for the difficulty in maintaining eye contact, a behavior that her mother used to define "idiotic" or "lying".

In conclusion, in the case of Rachele, despite both standardized diagnostic instruments did not depose for ASD, a clinical diagnosis was formulated. Rachele may represent the typical example of woman with ASD that have developed camouflaging strategies since childhood, but that is not able to completely face social demands during adulthood.

Furry headphones for Christmas

Stefano was a 23-year-old boy, living with his mother and his grandfather. His parents divorced when he was a child. Stefano was sent to the Laboratorio Autismo for an assessment specifically focused on ASD after consulting another third level center, specialized in psychoses.

The psychopathological history of Stefano began when he was 12. The boy presented aggressiveness and impulsivity, probably because of the difficult relationship with his father, described as a violent man. During a Christmas lunch, Stefano received a pair of furry headphones. That gift triggered him to obsessively think that people could perceive him as a homosexual. After a gradual increase of delusional ideas and perceptions, Stefano was then admitted to a psychiatric inpatient ward. During the recovery, neuropsychological evaluations indicated an intelligence in the normal range (IQ = 100), while Stefano "showed difficulties in the regulation of emotional situations, also with problems related to his personal identity". The patient received a diagnosis of "emotional disturbance" and "identity disturbance", beginning a therapy with risperidone, subsequently modified with olanzapine and valproic acid.

During the clinical interview at our center, Stefano described the presence of rituals, stereotyped behaviors and thoughts that were progressively increasing in intensity. Thoughts and rituals (i.e. counting the position of letters within the words, following rigid routines) were described as "something to do with the purpose to contain delusional ideas".

At the standardized direct observation (ADOS-2), Stefano exceeded the cut-offs for ASD considering the original algorithm (*Communication:* 3; *Reciprocal social interaction:* 6

Communication + social interaction: 9; *Imagination/creativity:* 0*; Stereotyped behavior and restricted interests;* 0). Eye contact was present, but abnormal and poorly communicative. Stefano stared at the interlocutor without modulation. He often smiled, but in an incongruent way. During the standardized observation, no stereotypes or rituals could be observed. On the contrary, ADI-R was not suggestive of an autistic disorder overall, even if the scale regarding stereotypes and rituals exceeded the cut-off (*Qualitative Abnormalities in Reciprocal Social Interaction:* 7; *Qualitative Abnormalities in Communication:* 5; *Restricted, Repetitive, and Stereotyped Patterns of Behavior:* 5: *Abnormalities of Development Evident at or Before 36 Months:* 0).

Symptomatology evident during the direct observation was not specific of ASD. Abnormalities observed were in fact compatible with a schizophrenia spectrum disorder, congruent also with the clinical history reported by Stefano's mother and the psychopathological anamnesis. In conclusion, Stefano was diagnosed with a psychotic disorder not otherwise specified. Stefano's history demonstrates how the use of standardized instruments need to be integrated with a comprehensive anamnesis and psychopathological evaluation, in order to avoid false positive.

CONCLUSIONS

The diagnosis of ASD is a complex and time-consuming process, which should involve different professionals. In adults with high cognitive abilities, in particular, it may be challenging for clinicians to discriminate ASD from other conditions with similar symptomatology and to collect information about the early development of the patients (Lai & Baron-Cohen, 2015).

Our results drew attention to the critical points of the diagnostic assessment of ASD in adults, especially in the mildest form of the spectrum, when information about subjects' developmental profile are not always reliable. It appears desirable to carefully consider the possible evolution of core symptoms of ASD in adulthood. From our results, in fact, it is possible to confirm the reliability of ADOS-2 Module 4 for the diagnosis of ASD in clinical practice. On the contrary, it could be cautiously asserted that the ADI-R algorithm lacks of accuracy in the diagnosis of adults seeking first formal diagnosis of ASD (Fusar-Poli et al., 2017c). In particular, women and individuals with higher IQ, seem to develop more camouflaging strategies and less pronounced symptoms. Consequently, it is more difficult to correctly identify ASD by means of standardized instruments. On the contrary, higher severities in repetitive behaviors and the presence of restricted interest tend to facilitate the classification into the autism spectrum.

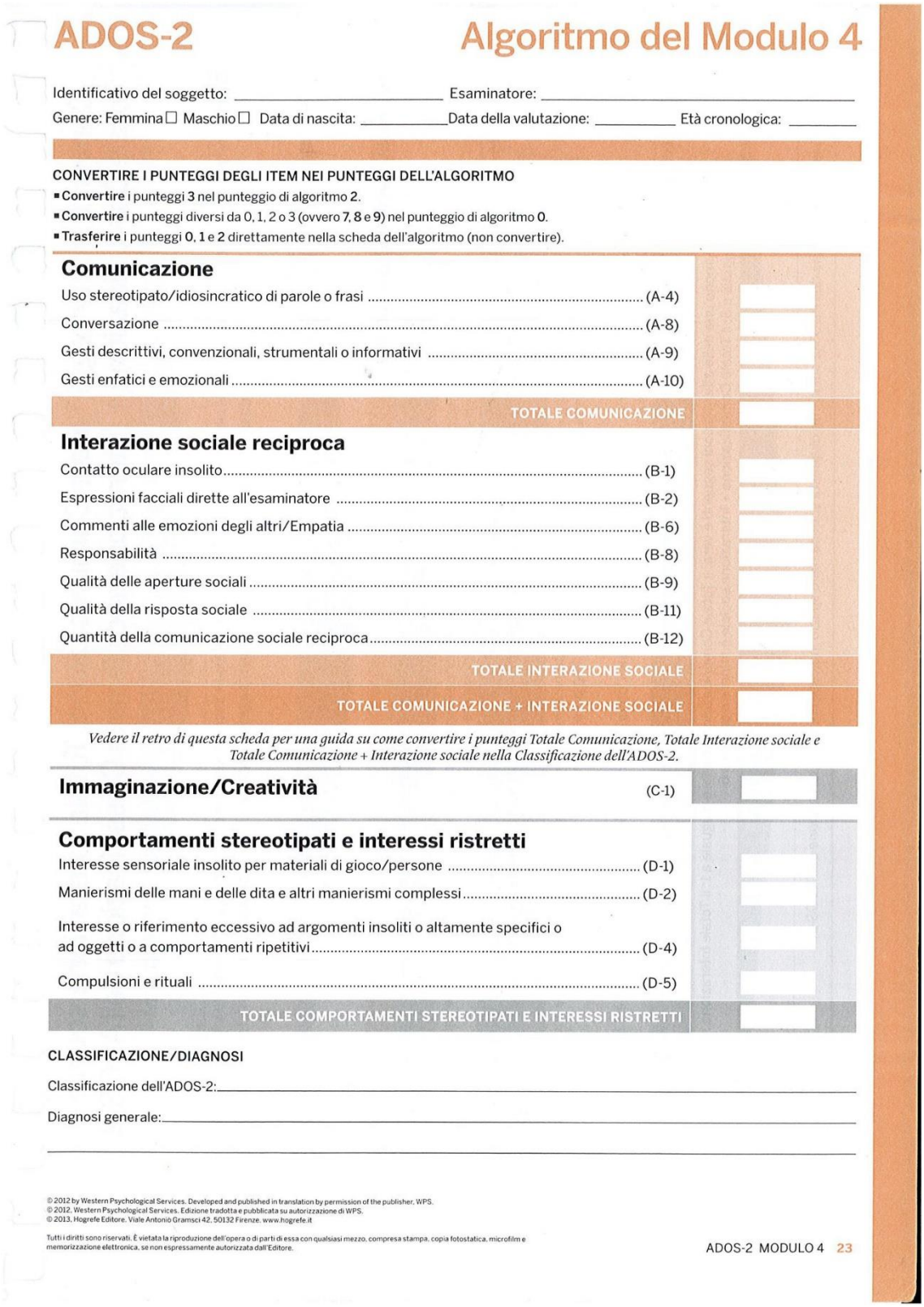
The use of standardized diagnostic instruments could be useful in the evaluation of adults with ASD without ID. This is confirmed also by the increasing number of experimental literature using standardized tools – in particular ADOS and ADI-R – for the confirmation of ASD diagnosis. Nevertheless, given our findings, it is also crucial to consider their possible limitations to efficiently profit of their useful information.

Training and experience remains of primary importance while assessing an adult who could potentially belong to the autism spectrum (Fusar-Poli et al., 2017c).

It is desirable to dedicate future research to the improvement of the observational diagnostic instruments currently available, which already have shown a reasonable accuracy in detecting ASD in adults. In particular, a customization based on age and IQ would be useful. Unfortunately, structured interviews directed to caregivers seems not always reliable in adults, also because detailed information about past behavior are often difficult to recall. In addition, our data showed that people with higher IQ tend to show less developmental abnormalities. In this particular group of people, it would be probably more important to focus on current symptomatology, consulting not only parents or caregivers, but also other figures (i.e. spouses, children, colleagues, friends…) whose account could be extremely important for better understanding the nature of the condition.

In conclusion, an accurate identification of ASD also in the adult population is fundamental to guarantee an adequate support and to promote well-being (Lai & Baron-Cohen, 2015). Additionally, research regarding adults with ASD is gradually expanding, as shown by the systematic review included in the present dissertation. Consequently, there is the necessity to include in clinical trials only people whose diagnosis has been confirmed by professionals with specific expertise, and not self-diagnosed individuals. This issue is important to avoid distorted results that could be damaging for people with ASD.

APPENDIX 1



ADOS-2 Algoritmo del Modulo 4

Identificativo del soggetto: _____ Esaminatore: _____

Genere: Femmina ☐ Maschio ☐ Data di nascita: _____ Data della valutazione: _____ Età cronologica: _____

CONVERTIRE I PUNTEGGI DEGLI ITEM NEI PUNTEGGI DELL'ALGORITMO

- **Convertire** i punteggi **3** nel punteggio di algoritmo **2**.
- **Convertire** i punteggi diversi da 0, 1, 2 o 3 (ovvero **7**, **8** e **9**) nel punteggio di algoritmo **0**.
- **Trasferire** i punteggi **0**, **1** e **2** direttamente nella scheda dell'algoritmo (non convertire).

Comunicazione

Uso stereotipato/idiosincratico di parole o frasi (A-4)	
Conversazione (A-8)	
Gesti descrittivi, convenzionali, strumentali o informativi (A-9)	
Gesti enfatici e emozionali (A-10)	
TOTALE COMUNICAZIONE	

Interazione sociale reciproca

Contatto oculare insolito (B-1)	
Espressioni facciali dirette all'esaminatore (B-2)	
Commenti alle emozioni degli altri/Empatia (B-6)	
Responsabilità (B-8)	
Qualità delle aperture sociali (B-9)	
Qualità della risposta sociale (B-11)	
Quantità della comunicazione sociale reciproca (B-12)	
TOTALE INTERAZIONE SOCIALE	
TOTALE COMUNICAZIONE + INTERAZIONE SOCIALE	

Vedere il retro di questa scheda per una guida su come convertire i punteggi Totale Comunicazione, Totale Interazione sociale e Totale Comunicazione + Interazione sociale nella Classificazione dell'ADOS-2.

Immaginazione/Creatività

(C-1)	

Comportamenti stereotipati e interessi ristretti

Interesse sensoriale insolito per materiali di gioco/persone (D-1)	
Manierismi delle mani e delle dita e altri manierismi complessi (D-2)	
Interesse o riferimento eccessivo ad argomenti insoliti o altamente specifici o ad oggetti o a comportamenti ripetitivi (D-4)	
Compulsioni e rituali (D-5)	
TOTALE COMPORTAMENTI STEREOTIPATI E INTERESSI RISTRETTI	

CLASSIFICAZIONE/DIAGNOSI

Classificazione dell'ADOS-2: _____

Diagnosi generale: _____

_____

APPENDIX 2

ADI-R Autism Diagnostic Interview-Revised
Ann Le Couteur, Catherine Lord, Michael Rutter
Versione italiana a cura di R. Faggioli, M. Saccani, A.M. Persico, R. Tancredi, B. Parrini e R. Igliozzi

età da 4.0 anni e oltre

Algoritmo diagnostico

Nome del soggetto

Data di nascita | Data dell'intervista | Età cronologica | Sesso (F / M)

Nome dell'informatore

Relazione con il soggetto

Esaminatore

Servizio/Scuola

Conversione della codifica degli item dell'algoritmo in punteggio

CODIFICA	PUNTEGGIO
0	0
1	1
2	2
3	2
7	0
8	0
9	0

GIUNTI O.S. Organizzazioni Speciali

A. Anomalie qualitative nell'interazione sociale reciproca

Valutare "Molto anomalo tra i 4.0 e i 5.0 anni" per tutti gli item da A1 a A4 (eccetto 31, 58 e 65).

		CODIFICA	PUNTEGGIO
A1. Difficoltà nell'uso di comportamenti non verbali per regolare l'interazione sociale			
Sguardo diretto	(50)		
Sorriso sociale	(51)		
Varietà delle espressioni facciali usate per comunicare	(57)		
Totale A1			
A2. Difficoltà a sviluppare relazioni con i coetanei			
Gioco immaginativo con i coetanei	(49)		
Interesse nei confronti di altri bambini	(62)		
Risposta agli approcci degli altri bambini	(63)		
Gioco di gruppo fra coetanei *[valutare se da 4.0 a 9.11 anni]*	(64)		
OPPURE *[scegliere 64 o 65, in rapporto all'età del soggetto]*			
Amicizia *[valutare se ha 10.0 anni o più]* "Molto anomalo tra i 10.0 e i 15.0 anni"	(65)		
Totale A2			
A3. Difficoltà a condividere il divertimento			
Mostrare e attirare l'attenzione	(52)		
Offrire per condividere	(53)		
Cercare di condividere il proprio divertimento con altri	(54)		
Totale A3			
A4. Difficoltà nella reciprocità socioemotiva			
Uso del corpo dell'altro per comunicare	(31)		RISCONTRATO
Offrire conforto	(55)		
Qualità delle aperture sociali	(56)		
Espressioni facciali inappropriate	(58)		RISCONTRATO
Risposte sociali appropriate	(59)		
Totale A4			
Totale A = A1 + A2 + A3 + A4		**TOTALE A (*cut-off* = 10)**	

B. Anomalie qualitative nella comunicazione

Valutare "Molto anomalo fra i 4.0 e i 5.0 anni" in tutti gli item in B1 e B4.
Valutare B2 (V) e B3 (V) solo per i soggetti verbali (item 30 = "0"), usando "Riscontrato".
Valutare solo B1 e B4 per i soggetti non verbali (item 30 = "1" o "2").

		CODIFICA	PUNTEGGIO
B1. Assenza o ritardo di linguaggio e difficoltà a compensare attraverso l'uso di gesti			
Pointing per esprimere interesse	(42)		
Annuire	(43)		
Scuotere la testa per dire "NO"	(44)		
Gesti convenzionali/strumentali	(45)		
Totale B1			
B4. Difficoltà nella varietà di giochi spontanei di far finta o nel gioco imitativo			
Imitazione spontanea di azioni	(47)		
Gioco immaginativo	(48)		
Gioco sociale di imitazione	(61)		
Totale B4			

Solo per soggetti verbali:

		CODIFICA	PUNTEGGIO
B2 (V). Difficoltà relative a iniziare o sostenere la conversazione reciproca			
Verbalizzazione sociale/chiacchiera	(34)		RISCONTRATO
Conversazione reciproca	(35)		RISCONTRATO
Totale B2 (V)			
B3 (V). Verbalizzazioni stereotipate, ripetitive o idiosincratiche			
Espressioni stereotipate ed ecolalia differita	(33)		RISCONTRATO
Domande o affermazioni inappropriate	(36)		RISCONTRATO
Inversione dei pronomi	(37)		RISCONTRATO
Neologismi/linguaggio idiosincratico	(38)		RISCONTRATO
Totale B3 (V)			
Totale B verbale = B1 + B2 (V) + B3 (V) + B4	**TOTALE B (V) (*cut-off* = 8)**		
Totale B non verbale = B1 + B4	**TOTALE B (NV) (*cut-off* = 7)**		

C.M. 93510-N

C. Modelli di comportamento ristretti, ripetitivi e stereotipati

Valutare "Riscontrato" per gli item da C1 a C4.

		CODIFICA	PUNTEGGIO
C1. Preoccupazioni circoscritte o modelli limitati di interessi			
Preoccupazioni insolite	(67)		
Interessi circoscritti	(68)		
Totale C1			
C2. Apparente adesione compulsiva a routine o rituali non funzionali			
Rituali verbali *[valutare solo se item 30 = 0]*	(39)		
Compulsioni/rituali	(70)		
Totale C2			
C3. Stereotipie e manierismi ripetitivi del corpo			
Manierismi delle mani e delle dita	(77)		
OPPURE *[registrare la più alta delle due valutazioni]*			
Altri manierismi complessi o movimenti stereotipati del corpo	(78)		
Totale C3			
C4. Preoccupazione per parti di oggetti o elementi non funzionali del materiale			
Uso ripetitivo di oggetti o interesse per parti di oggetti	(69)		
OPPURE *[registrare la più alta delle due valutazioni]*			
Interessi sensoriali insoliti	(71)		
Totale C4			
Totale C = C1 + C2 + C3 + C4	**TOTALE C (*cut-off* = 3)**		

D. Anomalie dello sviluppo evidenti a/o prima dei 36 mesi

Età della prima valutazione dei genitori *[se <36 mesi, punteggio 1]*	(2)		
Età delle prime parole singole *[se >24 mesi, punteggio 1]*	(9)		
Età delle prime frasi *[se >33 mesi, valutare 1]*	(10)		
Età in cui le prime anomalie risultano evidenti *[se codificato "3" o "4", punteggio 1]*	(86)		
Opinione dell'esaminatore sull'epoca in cui si sono manifestati i primi sintomi *[se <36 mesi, punteggio 1]*	(87)		
Totale D (*cut-off* = 1)			

APPENDIX 3

Reference	Intervention	Design	Total ASD sample	Diagnostic tool	Study location
Adams, 2004	Nutr	RCT-P	20	Unspecified	USA
Adams, 2011	Nutr	RCT-P	104	Unspecified	USA
Adkins, 2012	Edu	RCT-P	36	DSM-IV-TR, ADOS	USA
Akhondzadeh, 2004	Pharm	RCT-P	40	DSM-IV	Iran
Akhondzadeh, 2008	Pharm	RCT-P	40	DSM-IV	Iran
Akhondzadeh, 2010	Pharm	RCT-P	40	DSM-IV-TR	Iran
Al-Ayadhi, 2013	Nutr	RCT-H2H	60	DSM-IV-TR	Saudi Arabia
Al-Ayadhi, 2015	Nutr	RCT-H2H	65	DSM-IV-TR	Saudi Arabia
Aldred, 2004	Edu	RCT-P	28	ADI, ADOS	UK
Allam, 2008	Misc	RCT-P	20	DSM-IV-TR, CARS	Egypt
Almirall, 2016	Edu	RCT-SMART	61	ADOS	USA
Aman, 2010	Pharm	RCT-P	308	DSM-IV-TR, ADI	USA
Amatachaya, 2014	Misc	RCT-C	20	DSM-IV-TR	Thailand
Amatachaya, 2015	Misc	RCT-C	20	DSM-IV-TR	Thailand
Amminger, 2007	Nutr	RCT-P	12	DSM-IV, ADI, ADOS	Austria
Anagnostou, 2012	Pharm	RCT-P	19	DSM-IV, ADI, ADOS	USA
Anderson, 1984	Pharm	RCT-C	40	DSM-III	USA
Anderson, 1989	Pharm	RCT-C	45	DSM-III	USA
Andrews, 2013	Psy	RCT-P	58	ASDI	Australia
Anninos, 2016	Misc	RCT-C	10	Unspecified	Greece
Arnold, 2006	Pharm	RCT-C	16	DSM-IV, ADI	USA
Arnold, 2012	Pharm	RCT-P	20	DSM-IV, ADI	USA
Asadabadi, 2013	Pharm	RCT-P	40	DSM-IV-TR, ADI	Iran
August, 1987	Pharm	RCT-C	10	DSM-III	USA
Baghdadli, 2013	Edu	RCT-P	14	ICD-10, ADI, ADOS	France
Barthelmey, 1981	Nutr	RCT-C	21	DSM-III	France
Barthelmey, 1981	Nutr	RCT-C	35	DSM-III	France
Barthelmey, 1981	Nutr	RCT-C	37	DSM-III	France
Bass, 2009	Misc	RCT-P	34	DSM-IV-TR	USA
Beaumont, 2008	Edu	RCT-P	49	DSM-IV-TR, CAST	Australia
Beaumont, 2015	Edu	Non-RCT	69	Unspecified	Australia
Beeghly, 1987	Pharm	RCT-C	7	DSM-III	USA
Begeer, 2011	Edu	RCT-P	36	DSM-IV-TR	Netherlands
Begeer, 2015	Edu	RCT-P	97	DSM-IV-TR	Netherlands
Beisler, 1986	Pharm	RCT-C	6	DSM-III	USA
Belsito, 2001	Pharm	RCT-P	28	ADI	USA
Bent, 2011	Nutr	RCT-P	25	DSM-IV-TR, ADI, SCQ	USA

Bent, 2014	Nutr	RCT-P	57	SCQ	USA
Bernard-Opitz, 2004	Edu	Non-RCT	8	ADI	Singapore
Bertoglio, 2010	Nutr	RCT-C	30	DSM-IV-TR, ADOS, ADI	USA
Bettison, 1996	Misc	RCT-P	80	Unspecified	Australia
Birnbrauer, 1993	Edu	Non-RCT	14	DSM-III-R	Australia
Bolman, 1999	Nutr	Non-RCT	8	DSM-III-R	USA
Borgi, 2016	Misc	RCT-P	26	ICD-10, DSM-IV-TR	Italy
Bouvard, 1995	Pharm	RCT-C	10	DSM-III-R, ADI	France
Boyd, 2014	Edu	Non-RCT	198	ADOS, SCQ	USA
Buchsbaum, 2001	Pharm	RCT-C	6	DSM-IV, ADI	USA
Buday, 1995	Misc	RCT-C	10	Unspecified	USA
Buitelaar, 1990	Pharm	RCT-C	14	DSM-III	Netherlands
Buitelaar, 1992	Pharm	RCT-C	14	DSM-III-R	Netherlands
Buitelaar, 1996	Pharm	RCT-P	47	DSM-III-R	Netherlands
Campbell, 1982	Pharm	RCT-C	33	DSM-III	USA
Campbell, 1988	Pharm	RCT-P	28	DSM-III	USA
Campbell, 1990	Pharm	RCT-P	18	DSM-III-R	USA
Campbell, 1993	Pharm	RCT-P	41	DSM-III-R	USA
Carey, 2002	Pharm	RCT-C	8	DSM-IV	USA
Carminati, 2016	Pharm	RCT-P	13	CARS, ADI, ICD-10	Switzerland
Casenhiser, 2013	Edu	RCT-P	51	ADOS, ADI	Canada
Chalfant, 2007	Psy	RCT-P	47	Unspecified	Australia
Chan, 2009	Misc	RCT-P	32	Unspecified	Hong Kong
Chan, 2012	Nutr	RCT-P	24	DSM-IV-TR, ADI	Hong Kong
Chan, 2013	Misc	RCT-H2H	40	DSM-IV-TR, ADI	Hong Kong
Chez, 2000	Pharm	RCT-C	25	DSM-IV	USA
Chez, 2002	Nutr	RCT-P	31	DSM-IV-TR	USA
Chez, 2003	Pharm	RCT-P	43	DSM-IV	USA
Chugani, 2016	Pharm	RCT-P	142	DSM-IV-TR, ADI, ADOS	USA
Coben, 2007	Misc	Non-RCT	49	Unspecified	USA
Coggins, 1988	Pharm	RCT-C	5	Unspecified	USA
Cohen, 1980	Pharm	RCT-C	10	DSM-III	USA
Cohen, 2006	Edu	Non-RCT	37	ADI	USA
Coniglio, 2001	Pharm	RCT-P	57	DSM-IV	USA
Corbett, 2001	Pharm	RCT-C	12	DSM-IV, ADI, ADOS	USA
Corbett, 2008	Misc	RCT-C	11	DSM-IV, ADOS	USA
Corbett, 2016	Misc	RCT-P	30	DSM-5, ADOS	USA
Cortesi, 2012	Pharm	RCT-P	134	DSM-IV-TR, ADI, ADOS	Italy
Dadds, 2014	Pharm	RCT-P	38	DSM-IV-TR, CARS, DISCAP-ASD, OARS, OAGIS	Australia

Danfors, 2005	Nutr	RCT-C	12	DSM-IV	Sweden
Dawson, 2010	Edu	RCT-P	45	DSM-IV, ADI, ADOS	USA
Dawson, 2012	Edu	RCT-P	29	DSM-IV, ADI, ADOS	USA
de Vries, 2015	Misc	RCT-P	90	DSM-IV-TR, SRS, ADI	Netherlands
D'Elia, 2014	Edu	Non-RCT	30	DSM-IV-TR, ADI, ADOS	Italy
DeRosier, 2011	Edu	RCT-H2H	52	ASSQ, CAST, SCQ	USA
Dollfus, 1992	Pharm	RCT-H2H	18	DSM-III	France
Dolske, 1993	Nutr	RCT-C	18	DSM-III-R	USA
Domes, 2014	Pharm	RCT-C	14	DSM-IV, ADI, ADOS	Germany
Drahota, 2011	Psy	RCT-P	40	Unspecified	USA
Duker, 1991	Pharm	Non-RCT	22	DSM-III-R	Netherlands
Dunn-Geier, 2000	Pharm	RCT-P	95	DSM-IV, CARS	Canada
Edelson, 1999	Misc	RCT-P	19	RDEC	USA
Edelson, 1999	Misc	RCT-P	12	Unspecified	USA
Eikeseth, 2002	Edu	Non-RCT	25	ICD-10, ADI	Norway
Eikeseth, 2007	Edu	Non-RCT	25	ICD-10, ADI	Norway
Ekman, 1989	Pharm	RCT-C	20	DSM-III-R	Sweden
Elder, 2006	Nutr	RCT-C	15	DSM-IV, ADI	USA
Enticott, 2014	Misc	RCT-P	30	DSM-IV	Australia
Escalona, 2001	Misc	RCT-P	20	DSM-III-R	USA
Fahmy, 2013	Nutr	RCT-P	30	Unspecified	Egypt
Fankhauser, 1992	Pharm	RCT-C	9	DSM-III-R	USA
Fazlioğlu, 2008	Edu	RCT-P	30	DSM-IV	Turkey
Feldman, 1999	Pharm	RCT-C	24	DSM-III-R, CARS	USA
Fernell, 2011	Edu	Non-RCT	198	DSM-IV	Sweden
Findling, 1997	Nutr	RCT-C	10	DSM-III-R	USA
Fletcher-Watson, 2016	Edu	RCT-P	54	ADOS	UK
Flores, 2014	Edu	RCT-H2H	13	Unspecified	USA
Frankel, 2010	Edu	RCT-P	68	ADOS, ADI, ASSQ	USA
Freitag, 2016	Psy	RCT-P	209	ICD-10, ADI, ADOS	Germany
Frye, 2016	Nutr	RCT-P	48	ADOS, ADI, DSM-5	USA
Fujii, 2013	Psy	RCT-P	12	ADOS, ADI	USA
Gabriels, 2015	Misc	RCT-H2H	116	ADOS	USA
Gantman, 2012	Edu	RCT-P	17	AQ	USA
Garstang, 2006	Pharm	RCT-C	7	Unspecified	UK
Gattino, 2011	Misc	RCT-P	24	DSM-IV-TR, ADI, CARS	Brazil
Geier, 2011	Nutr	RCT-P	27	Unspecified	USA
Geretsegger, 2016	Misc	RCT-P	15	ICD-10, ADOS, ADI	Austria
Gev, 2016	Misc	RCT-P	67	DSM-IV-TR, ADOS	Israel
Ghaleiha, 2013	Pharm	RCT-P	40	DSM-IV-TR, ADI	Iran

Ghaleiha, 2014	Pharm	RCT-P	40	DSM-IV-TR, ADI	Iran
Ghaleiha, 2015	Pharm	RCT-P	40	DSM-IV-TR, ADI	Iran
Ghaleiha, 2016	Pharm	RCT-P	46	DSM-IV-TR, ADI	Iran
Ghalichi, 2016	Nutr	RCT-P	76	ADI	Iran
Ghanizadeh, 2013	Nutr	RCT-P	31	DSM-IV-TR, ADI	Iran
Ghanizadeh, 2014	Pharm	RCT-H2H	59	DSM-IV-TR, ADI	Iran
Ghanizadeh, 2015	Pharm	RCT-P	34	DSM-IV-TR, ADI	Iran
Ghasemtabar, 2015	Misc	Non-RCT	27	CARS	Iran
Gillberg, 1986	Nutr	RCT-C	4	DSM-III	Sweden
Golan, 2006	Misc	Non-RCT	26	DSM-IV	UK
Golan, 2006	Misc	RCT-P	41	DSM-IV	UK
Golan, 2010	Misc	RCT-P	38	ADI, CAST	UK
Goods, 2013	Edu	RCT-H2H	11	ADOS	USA
Gordon, 1992	Pharm	RCT-H2H	14	DSM-III-R, ADI	USA
Gordon, 1993	Pharm	RCT-C	12	DSM-III-R, ADI	USA
Gordon, 1993	Pharm	RCT-C	12	DSM-III-R, ADI	USA
Gordon, 2011	Edu	RCT-P	83	ADOS	UK
Gordon, 2015	Edu	RCT-P	48	3Di	UK
Granpeesheh, 2010	Misc	RCT-P	29	DSM-IV, ADOS	USA
Green, 2010	Edu	RCT-P	152	ADOS, ADI	UK
Gringras, 2014	Misc	RCT-C	67	ADI, ADOS	UK
Groden, 1987	Pharm	Non-RCT	8	DSM-III, NSAC	USA
Guastella, 2010	Pharm	RCT-C	15	DSM-IV-TR	Australia
Guastella, 2015	Pharm	RCT-P	50	DSM-IV-TR, ADOS	Australia
Gulsrud, 2010	Edu	RCT-P	38	DSM-IV, ADI	USA
Handen, 2000	Pharm	RCT-C	12	CARS	USA
Handen, 2005	Pharm	RCT-C	8	ADOS, ADI	USA
Handen, 2009	Pharm	RCT-P	111	DSM-IV-TR, ADI	USA
Handen, 2011	Pharm	RCT-P	34	ADI, ADOS	USA
Handen, 2015	Pharm	RCT-P	64	DSM-IV-TR, ADI	USA
Hardan, 2012	Nutr	RCT-P	29	DSM-IV-TR, ADOS, ADI	USA
Hardan, 2015	Edu	RCT-H2H	47	DSM-IV-TR, ADI, ADOS	USA
Harfterkamp, 2012	Pharm	RCT-P	97	ADI	Netherlands
Hasanzadeh, 2012	Nutr	RCT-P	47	DSM-IV-TR, ADI	Iran
Hayward, 2009	Edu	Non-RCT	44	ICD-10, ADI	UK
Hellings, 2005	Pharm	RCT-P	30	DSM-IV, ADI, ADOS	USA
Hendren, 2016	Nutr	RCT-P	50	ADI, ADOS	USA
Hesselmark, 2014	Psy	RCT-H2H	68	ADOS	Sweden
Hildebrandt, 2016	Misc	RCT-P	43	ICD-10	Germany
Hochhauser, 2016	Edu	RCT-P	61	SCQ	Israel
Hollander, 2003	Pharm	RCT-C	15	DSM-IV, ADI	USA

Hollander, 2005	Pharm	RCT-C	39	DSM-IV-TR, ADI, ADOS	USA
Hollander, 2006	Pharm	RCT-P	13	DSM-IV, ADI, ADOS	USA
Hollander, 2006	Pharm	RCT-P	11	DSM-IV, ADOS, ADI	USA
Hollander, 2007	Pharm	RCT-C	15	DSM-IV, ADI	USA
Hollander, 2010	Pharm	RCT-P	27	DSM-IV-TR, ADI, ADOS	USA
Hollander, 2012	Pharm	RCT-P	34	DSM-IV, ADOS, ADI	USA
Honomichl, 2002	Pharm	RCT-C	14	DSM-IV, ADOS, ADI	USA
Hopkins, 2011	Edu	RCT-P	49	DSM-IV, CARS	USA
Howard, 2005	Psy	Non-RCT	61	DSM-IV	USA
Howlin, 2007	Misc	RCT-P	84	ADOS	UK
Hyman, 2016	Nutr	RCT-C	14	DSM-IV-TR, ADI, ADOS	USA
Ichikawa, 2013	Edu	RCT-P	11	ICD-10	Japan
Ichikawa, 2016	Pharm	RCT-P	92	DSM-IV-TR	Japan
Ingersoll, 2010	Edu	RCT-P	21	DSM-IV-TR, ADOS	USA
Ingersoll, 2012	Edu	RCT-P	27	DSM-IV-TR, ADOS	USA
Ingersoll, 2016	Edu	RCT-P	19	DSM-IV-TR, ADOS	USA
Isong, 2014	Edu	RCT-P	69	Unspecified	USA
Iwanaga, 2014	Edu	Non-RCT	20	DSM-IV	Japan
Jarusiewicz, 2002	Misc	RCT-P	24	Unspecified	USA
Jaselskis, 1992	Pharm	RCT-C	8	DSM-III-R	USA
Jocelyn, 1998	Edu	RCT-P	35	DSM-III-R	Canada
Johnson, 2010	Nutr	RCT-P	23	DSM-IV-TR, ADOS	USA
Kaale, 2012	Edu	RCT-P	61	ICD-10, ADI, ADOS	Norway
Kalyva, 2005	Edu	Non-RCT	5	Unspecified	UK
Kamps, 2015	Edu	RCT-P	94	Unspecified	USA
Kaplan, 1998	Misc	RCT-C	18	Unspecified	USA
Kasari, 2006	Edu	RCT-P	58	ADOS, ADI	USA
Kasari, 2010	Edu	RCT-P	38	DSM-IV, ADI	USA
Kasari, 2012	Edu	RCT-P	60	ADOS, ADI	USA
Kasari, 2014	Edu	RCT-SMART	61	ADOS	USA
Kasari, 2014	Edu	RCT-H2H	107	ADOS	USA
Kasari, 2015	Edu	RCT-H2H	83	ADOS, ADI	USA
Kasari, 2016	Edu	RCT-H2H	133	ADOS, SCQ	USA
Keehn, 2013	Psy	RCT-P	22	DSM-IV-TR, ADI, ADOS	USA
Kent, 2013	Pharm	RCT-P	92	DSM-IV-TR, ADI	USA
Kenworthy, 2014	Edu	RCT-H2H	60	DSM-IV-TR, ADOS	USA
Kern, 2001	Nutr	RCT-P	37	DSM-IV	USA
Kern, 2002	Pharm	RCT-C	19	DSM-IV	USA
Kern, 2013	Edu	RCT-C	10	CARS, M-CHAT	USA
Khorshid, 2006	Misc	RCT-H2H	14	Unspecified	USA

Kim, 2008	Misc	RCT-C	10	DSM-IV, CARS, ADOS	South Korea
King, 2001	Pharm	RCT-P	39	DSM-IV, ICD-10, ADI, ADOS	USA
King, 2009	Pharm	RCT-P	149	DSM-IV-TR, ADOS, ADI	USA
Klaiman, 2013	Nutr	RCT-P	46	DSM-IV-TR, ADI, ADOS	USA
Knivsberg, 2002	Nutr	RCT-P	20	DIPAB	Norway
Koch, 2015	Misc	Non-RCT	31	ICD-10	Germany
Koehne, 2016	Misc	RCT-P	51	DSM-IV, ICD-10, ADOS, ADI	Germany
Koenig, 2010	Edu	RCT-P	41	ADOS, SCQ, PDDBI	USA
Kok, 2002	Edu	Non-RCT	8	AUBC	Singapore
Kolmen, 1995	Pharm	RCT-C	13	DSM-III-R, CARS	USA
Kolmen, 1997	Pharm	RCT-C	11	DSM-III-R, CARS	USA
Koning, 2013	Psy	RCT-P	15	DSM-IV-TR, ADOS	Canada
Kosaka, 2016	Pharm	RCT-P	60	DSM-IV-TR, DISCO	Japan
Kouijzer, 2013	Misc	RCT-P	38	DSM-IV-TR, ADI, SCQ	Netherlands
Kretzmann, 2015	Edu	RCT-P	24	DSM-IV-TR, ADOS	USA
Kroeger, 2007	Edu	Non-RCT	25	Unspecified	USA
Kuriyama, 2002	Nutr	RCT-P	8	DSM-IV	Japan
Lamberti, 2016	Pharm	RCT-H2H	44	DSM-5, ADOS, ADI	Italy
Landa, 2011	Edu	RCT-H2H	48	ADOS	USA
Langdon, 2016	Psy	RCT-C	45	ADO	UK
Laugeson, 2009	Edu	RCT-P	33	Unspecified	USA
Laugeson, 2014	Edu	Non-RCT	73	DSM-IV-TR	USA
Laugeson, 2015	Edu	RCT-P	17	AQ	USA
Lawton, 2012	Edu	RCT-P	16	ADO	USA
Layton, 1988	Edu	RCT-H2H	60	CARS	USA
Leboyer, 1992	Pharm	RCT-C	4	DSM-III-R	France
LeGoff, 2004	Edu	Non-RCT	47	Unspecified	USA
Lelord, 1981	Nutr	RCT-C	21	Unspecified	France
Lemonnier, 2012 #218	Pharm	RCT-P	54	ICD-10, ADOS, ADI, CARS	France
Lerna, 2012	Edu	Non-RCT	18	DSM-IV-TR, ADOS	Italy
Lerna, 2014	Edu	Non-RCT	14	DSM-IV-TR, ADOS	Italy
Lerner, 2012	Edu	RCT-H2H	13	SRS, SCQ	USA
Levine, 1997	Nutr	RCT-C	9	DSM-III-R	Israel
Levy, 2003	Pharm	RCT-P	61	ADI	USA
Loebel, 2016	Pharm	RCT-P	148	DSM-IV-TR, ADI	USA
Lopata, 2008	Edu	RCT-H2H	54	DSM-IV-TR	USA
Lopata, 2010	Edu	RCT-P	35	Unspecified	USA
Lopata, 2015	Edu	RCT-H2H	47	ADI	USA

Lopata, 2016	Edu	RCT-P	36	ADI	USA
Lovaas, 1987	Edu	Non-RCT	38	DSM-III	USA
Luby, 2006	Pharm	RCT-P	23	DSM-IV	USA
Maddox, 2016	Psy	RCT-P	25	ADOS, ADI	USA
Magiati, 2007	Edu	Non-RCT	44	ADI	UK
Malone, 2001	Pharm	RCT-H2H	12	DSM-I	USA
Mandell, 2013	Edu	RCT-P	119	ADOS	USA
Mankad, 2015	Nutr	RCT-P	38	DSM-IV-TR, ADI, ADOS	Canada
Marcus, 2009	Pharm	RCT-P	178	DSM-IV-TR, ADI	USA
Marshall, 2016	Edu	RCT-P	37	ICD-10, DSM-IV-TR	UK
Martineau, 1985	Nutr	RCT-C	60	DSM-III	France
McConachie, 2014	Psy	RCT-P	32	ADOS	UK
McCracken, 2002	Pharm	RCT-P	101	DSM-IV, ADI	USA
McDougle, 1996	Nutr	RCT-C	17	DSM-III-R, ICD-10, ADOS, ADI	USA
McDougle, 1996	Pharm	RCT-P	30	DSM-III-R, ICD-10, ADI, ADOS	USA
McDougle, 1998	Pharm	Non-RCT	31	DSM-IV, ADI, ADOS	USA
McGillivray, 2014	Psy	Non-RCT	42	Unspecified	Australia
McKeel, 2015	Edu	RCT-P	27	Unspecified	USA
McNally Keehn, 2013	Psy	RCT-P	22	ADOS, ADI, DSM-IV-TR	USA
McVey, 2016	Edu	RCT-P	47	ADOS	USA
Minshawi, 2016	Pharm	RCT-P	66	ADOS, ADI, DSM-IV-TR	USA
Miral, 2008	Pharm	RCT-H2H	28	DSM-IV	Turkey
Miyajima, 2016	Misc	RCT-P	14	DSM-5, PARS	Japan
Mohammadi, 2013	Pharm	RCT-P	40	DSM-IV-TR, ADI	Iran
Mohammadzaheri, 2014	Edu	RCT-H2H	30	DSM-IV-TR	Iran
Molloy, 2002	Pharm	RCT-C	42	DSM-IV	USA
Morgan, 2014	Edu	RCT-P	28	DSM-IV-TR, ADOS	USA
Mudford, 2000	Misc	RCT-C	16	DSM-IV, ICD-10	UK
Munasinghe, 2010	Nutr	RCT-C	43	DSM-IV-TR	Australia
Munesue, 2016	Pharm	RCT-C	29	DSM-IV-TR, DISCO	Japan
Nagaraj, 2006	Pharm	RCT-P	39	DSM-IV	India
Navarro, 2015	Nutr	RCT-P	12	DSM-IV, ADI, ADOS	USA
Nazni, 2008	Nutr	Non-RCT	20	Unspecified	India
Niederhofer, 2003	Pharm	RCT-C	12	ICD-10	Austria
Niederhofer, 2004	Pharm	RCT-C	14	ICD-10	Italy
Nikoo, 2015	Nutr	RCT-P	40	DSM-IV-TR, ADI, ABC	Iran
Owen, 2009	Pharm	RCT-P	98	DSM-IV-TR, ADI	USA
Owens, 2008	Edu	RCT-P	47	ADI, SCQ	UK

Owley, 1999	Pharm	RCT-C	20	ADI, ADOS, DSM-IV	USA
Owley, 2001	Pharm	RCT-C	56	DSM-IV, ADOS, ADI	USA
Ozonoff, 1998	Edu	Non-RCT	22	Unspecified	USA
Pahnke, 2014	Psy	RCT-P	28	DSM-IV	Sweden
Pajareya, 2011	Edu	RCT-P	31	DSM-IV	Thailand
Panerai, 2009	Edu	Non-RCT	34	DSM-IV-TR, CARS, ADI	Italy
Pearson, 2013	Pharm	RCT-C	24	DSM-IV-TR, ADI, ADOS	USA
Peters-Scheffer, 2010	Edu	Non-RCT	34	DSM-IV	Netherlands
Peters-Scheffer, 2013	Edu	Non-RCT	40	ICD-10, DSM-IV-TR, CARS, ADOS	Netherlands
Pfeiffer, 2011	Misc	RCT-H2H	37	DSM-IV-TR	USA
Pineda, 2008	Misc	RCT-P	19	ADI, ADOS	USA
Piravej, 2009	Misc	RCT-P	60	DSM-IV	Thailand
Porges, 2014	Misc	RCT-P	114	ICD-10, DSM-IV-TR, ADI	USA
Posey, 2004	Pharm	Non-RCT	20	DSM-IV-TR, ADI	USA
Poslawsky, 2015	Edu	RCT-P	77	DSM-IV-TR, ADOS	Netherlands
Pusponegoro, 2015	Nutr	RCT-P	50	DSM-IV	Indonesia
Quintana, 1995	Pharm	RCT-C	10	DSM-III-R, CARS	USA
Quirmbach, 2009	Edu	RCT-H2H	45	ADOS	USA
Ratcliffe, 2014	Edu	Non-RCT	217	DSM-IV-TR	Australia
Ratliff-Schaub, 2005	Pharm	RCT-C	15	DSM-IV	USA
Realmuto, 1986	Pharm	RCT-C	12	DSM-III	USA
Reaven, 2009	Psy	Non-RCT	31	ADOS, SCQ	USA
Reaven, 2012	Psy	RCT-P	50	ADOS, SCQ, DSM-IV-TR	USA
Reed, 2007	Edu	Non-RCT	27	Unspecified	UK
Reitzel, 2013	Edu	RCT-P	15	DSM-IV-TR, ADI, ADOS	Canada
Remington, 2001	Pharm	RCT-C	36	DSM-IV	Canada
Remington, 2007	Edu	Non-RCT	44	ADI	UK
Research Units on Pediatric Psychopharmacology Autism, 2005	Pharm	RCT-C	66	DSM-IV, ADI	USA
Rezaei, 2010	Pharm	RCT-P	40	DSM-IV-TR, ADI	Iran
Rice, 2015	Edu	RCT-P	31	Unspecified	USA
Rickards, 2007	Edu	RCT-P	59	DSM-IV, ADI, ADOS	Australia
Rimland, 1995	Misc	RCT-P	16	RDEC	USA
Roberts, 2001	Pharm	RCT-P	64	ADI, ADOS, DSM-IV	Canada
Roberts, 2011	Edu	RCT-P	56	DSM-IV, ADOS	Australia
Rodgers, 2015	Edu	RCT-P	60	ADI	USA
Roeyers, 1996	Edu	RCT-P	85	DSM-III-R	Belgium

Rogers, 2006	Edu	RCT-H2H	10	ADOS, SCQ, DSM-IV	USA
Rossignol, 2009	Misc	RCT-P	56	DSM-IV, ADI, ADOS	Australia
Russell, 2013	Psy	RCT-H2H	40	ADI, ADOS	UK
Saad, 2015	Nutr	RCT-P	92	DSM-IV-TR	Egypt
Sallows, 2005	Psy	RCT-H2H	23	DSM-IV, ADI	USA
Sampanthavivat, 2012	Misc	RCT-P	58	DSM-IV-TR	Thailand
Sandler, 1999	Pharm	RCT-P	52	DSM-IV, CARS, AUBC	USA
Santomauro, 2016	Psy	RCT-P	20	ASDI, ASASC	Australia
Scahill, 2015	Pharm	RCT-P	62	DSM-IV, SCQ, ADOS	USA
Scarpa, 2011	Psy	RCT-P	11	ADOS	USA
Schaaf, 2014	Edu	RCT-P	31	ADI, ADOS	USA
Schohl, 2014	Edu	RCT-P	58	ADOS	USA
Schreibman, 2014	Edu	RCT-H2H	39	DSM-IV, ADI, ADOS	USA
Schwartzberg, 2013	Edu	RCT-H2H	30	Unspecified	USA
Schwartzberg, 2016	Edu	RCT-H2H	29	Unspecified	USA
Scifo, 1991	Pharm	RCT-C	11	DSM-III-R, CARS, BSE	Italy
Shea, 2004	Pharm	RCT-P	77	DSM-IV, CARS	Canada
Sheinkopf, 1998	Edu	Non-RCT	22	Unspecified	USA
Sherman, 198	Pharm	RCT-C	15	DSM-III, NSAC	Canada
Silva, 2007	Misc	RCT-P	15	DSM-IV	USA
Silva, 2009	Misc	RCT-P	46	Unspecified	USA
Silver, 2001	Edu	RCT-P	22	Unspecified	UK
Singh, 2014	Nutr	RCT-P	36	ADOS, DSM-IV	USA
Smith, 1985	Misc	RCT-C	14	Unspecified	USA
Smith, 1997	Edu	Non-RCT	21	DSM-III	Norway
Smith, 2014	Edu	RCT-P	26	SRS	USA
Smith, 2016	Pharm	RCT-P	22	DSM-IV-TR, ADI	USA
Sofronoff, 2005	Psy	RCT-P	71	DSM-IV, CAST	Australia
Sofronoff, 2007	Psy	RCT-P	45	DSM-IV, CAST	Australia
Solomon, 2004	Edu	RCT-P	18	DSM-IV, ADI, ADOS	USA
Solomon, 2008	Edu	RCT-P	19	DSM-IV-TR, ADI, ADOS	USA
Solomon, 2014	Edu	RCT-P	121	DSM-IV, ADOS, SCQ	USA
Soorya, 2015	Edu	RCT-H2H	67	DSM-IV-TR, ADOS, ADI	USA
Spek, 2013	Edu	RCT-P	41	DSM-IV-TR, ADI	Netherlands
Spjut Jansson, 2016	Edu	Non-RCT	71	ADOS, DISCO	Sweden
Sponheim, 2002	Pharm	RCT-C	6	ADI, ICD-10	Norway
Srinivasan, 2015	Misc	RCT-P	33	ADOS	USA
Srinivasan, 2016	Misc	RCT-P	33	ADOS	USA
Stern, 1990	Pharm	RCT-C	19	DSM-III	Australia

Storch, 2013	Psy	RCT-P	45	ADI, ADOS	USA
Storch, 2015	Psy	RCT-P	31	ADI, ADOS, CARS	USA
Strain, 2011	Edu	RCT-H2H	294	Unspecified	USA
Strickland, 2013	Edu	RCT-P	22	Unspecified	USA
Sugie, 2005	Pharm	RCT-C	18	DSM-IV	Japan
Sun, 2016	Nutr	Non-RCT	66	DSM-IV	China
Sung, 2011	Psy	RCT-H2H	70	DSM-IV, ADOS	Singapore
Tanaka, 2010	Edu	RCT-P	79	DSM-IV, ADI, ADOS	Canada
Thomeer, 2012	Edu	RCT-P	34	ADI	USA
Thomeer, 2015	Edu	RCT-P	43	ADI	USA
Thomeer, 2016	Edu	RCT-P	57	SCQ	USA
Thompson, 2014	Misc	RCT-P	21	DSM-IV-TR	Australia
Tolbert, 1993	Nutr	RCT-C	15	DSM-III-R	USA
Troost, 2005	Pharm	RCT-P	24	DSM-IV-TR, ADI	Netherlands
Tsang, 2007	Edu	Non-RCT	34	DSM-IV	Hong Kong
Unis, 2002	Pharm	RCT-P	85	DSM-IV, ADOS	USA
Urbano, 2014	Pharm	RCT-H2H	20	DSM-IV-TR	USA
Urbano, 2015	Pharm	RCT-H2H	20	DSM-IV-TR	USA
Van Bourgondien, 2003	Edu	Non-RCT	32	Unspecified	USA
Van Hecke, 2015	Edu	RCT-P	57	ADOS,	USA
van Steensel, 2014	Psy	Non-RCT	49	DSM-IV-TR, ADI	Netherlands
van Steensel, 2015	Psy	Non-RCT	79	DSM-IV-TR, ADI	Netherlands
Veenstra-VanderWeele, 2016	Pharm	RCT-P	150	DSM-IV-TR, ADOS	USA
Voigt, 2014	Nutr	RCT-P	48	DSM-IV-TR, CARS	USA
Wasserman, 2006	Pharm	RCT-P	20	DSM-IV, ADOS, ADI	USA
Watanabe, 2015	Pharm	RCT-C	9	DSM-IV-TR, ADI, ADOS	Japan
Wehman, 2014	Edu	RCT-P	40	Unspecified	USA
Welterlin, 2012	Edu	RCT-P	20	Unspecified	USA
Wetherby, 2014	Edu	RCT-H2H	82	ADOS	USA
White, 2013	Edu	RCT-P	30	ADOS, ADI	USA
White, 2016	Edu	RCT-H2H	8	ADOS	USA
Whiteley, 2010	Edu	RCT-P	59	ICD-10, ADOS, ADI	Denmark
Willemsen-Swinkels, 1995	Pharm	RCT-C	24	DSM-III	Netherlands
Willemsen-Swinkels, 1995	Pharm	RCT-C	17	DSM-III-R	Netherlands
Willemsen-Swinkels, 1996	Pharm	RCT-C	20	DSM-III-R	Netherlands
Williams, 2012	Edu	RCT-P	55	ADOS, DSM-IV-TR	Australia
Wink, 2014	Pharm	Non-RCT	142	DSM-IV-TR	USA
Wink, 2016	Nutr	RCT-P	25	DSM-IV, ADI	USA

Wong, 2007	Edu	RCT-H2H	41	ADOS, ADI	USA
Wong, 2010	Misc	RCT-P	55	DSM-IV, ADI, ADOS	Hong Kong
Wong, 2010	Edu	RCT-P	17	ADI, ADOS, DSM-IV-TR	Hong Kong
Wong, 2010	Misc	RCT-P	50	DSM-IV, ADI, CARS	Hong Kong
Wong, 2013	Edu	RCT-P	33	CARS	USA
Woo, 2013	Misc	RCT-P	28	ADOS	USA
Woo, 2015	Misc	RCT-P	50	DSM-IV-TR, ADOS	USA
Wood, 2009	Psy	RCT-P	40	ADI, ADOS	USA
Wood, 2015	Psy	RCT-P	33	ADI, ADOS	USA
Wright, 2011	Pharm	RCT-C	17	ICD-10, ADI, ADOS	UK
Wu, 2016	Edu	RCT-P	20	DSM-IV	Taiwan
Yarbrough, 1987	Pharm	RCT-C	20	DSM-III	USA
Yatawara, 2016	Pharm	RCT-C	31	DSM-IV-TR, ADOS, SRS, DBC	Australia
Yoder, 2006	Edu	RCT-H2H	36	ADOS	USA
Yoo, 2014	Edu	RCT-P	47	DSM-IV, ADI, ADOS	South Korea
Young, 2016	Edu	RCT-P	255	CARS	USA
Yui, 2012	Nutr	RCT-P	13	DSM-IV, ADI	Japan
Zachor, 2007	Edu	Non-RCT	39	DSM-IV, ADI	Israel
Zachor, 2010	Edu	Non-RCT	78	DSM-IV, ADI	Israel
Zhang, 2012	Misc	Non-RCT	76	DSM-IV, CARS	China

Legend: *Edu:* Educational; *Misc:* Miscellaneous; *Non-RCT*: Non-randomized trial; *Nutr:* Nutraceutical: *Pharm:* Pharmacological; *Psy:* Psychotherapy; *RCT-C*: Randomized controlled trial - Crossover; *RCT-H2H*: Randomized controlled trial – Head-to-head; *RCT-P*: Randomized controlled trial – Parallel group; *RCT-SMART:* Randomized controlled trial – SMART design.

REFERENCES

An, J. Y., & Claudianos, C. (2016). Genetic heterogeneity in autism: From single gene to a pathway perspective. *Neuroscience & Biobehavioral Reviews, 68* (Supplement C), 442-453.

American Psychiatric Association (1980). *Diagnostic and Statistical Manual of Mental Disorders (DSM-III).* Washington (DC): American Psychiatric Association.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Health Disorders (DSM-III-R)*. Washington (DC): American Psychiatric Association.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Health Disorders (DSM-IV)*. Washington (DC): American Psychiatric Association.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. Washington (DC): American Psychiatric Association.

Bandini, L. G., Curtin, C., Phillips, S., Anderson, S. E., Maslin, M., & Must, A. (2017). Changes in Food Selectivity in Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders, 47*(2), 439-446.

Barale F., Brondino N., Fusar-Poli L., Orsi P., Politi P., & Ucelli Di Nemi S. (2016). Residenzialità nell'autismo. In: Binetti P. *Lo spettro autistico. La legge n. 134/15 e i suoi risvolti clinici e sociali* (pp.343-358). Magi Edizioni.

Bargiela, S., Steward, R., & Mandy, W. (2016). The Experiences of Late-diagnosed Women with Autism Spectrum Conditions: An Investigation of the Female Autism Phenotype. *Journal of Autism and Developmental Disorders, 46*(10), 3281-3294.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, malesand females, scientists and mathematicians. *Journal of Autism and Developmental Disorders, 31*(1), 5-17.

Baron Cohen, S. (1995). Mindblindness, Cambridge, MA, Bradford Book. In: MIT Press.

Bastiaansen, J. A., Meffert, H., Hein, S., Huizinga, P., Ketelaars, C., Pijnenborg, M., et al. (2011). Diagnosing autism spectrum disorders in adults: the use of Autism

Diagnostic Observation Schedule (ADOS) module 4. *Journal of Autism and Developmental Disorders, 41*(9), 1256-1266.

Bertelli, M. O., Piva Merli, M., Bradley, E., Keller, R., Varrucciu, N., Del Furia, C., & Panocchia, N. (2015). The diagnostic boundary between autism spectrum disorder, intellectual developmental disorder and schizophrenia spectrum disorders. *Advances in Mental Health and Intellectual Disabilities, 9*(5), 243-264.

Bölte, S. (2014). Is autism curable? *Developmental Medicine & Child Neurology, 56*(10), 927-931.

Boso, M., & Emanuele, E., Prestori, F., Politi, P., Barale, F., & D'Angelo, E. (2010). Autism and genius: is there a link? The involvement of central brain loops and hypotheses for functional testing. *Functional Neurology*, *25*(1), 15.

Brondino, N., Fusar-Poli, L., Rocchetti, M., Provenzani, U., Barale, F., & Politi, P. (2015). Complementary and alternative therapies for autism spectrum disorder. *Evidence-Based Complementary and Alternative Medicine*, *2015*.

Brondino, N., Fusar-Poli, L., Panisi, C., Damiani, S., Barale, F., & Politi, P. (2016). Pharmacological modulation of gaba function in autism spectrum disorders: A systematic review of human studies. *Journal of Autism and Developmental Disorders*, *46*(3), 825-839.

Bondy, A. S., & Frost, L. A. (1994). The picture exchange communication system. *Focus on Autistic Behavior, 9*(3), 1-19.

Bruggink, A., Huisman, S., Vuijk, R., Kraaij, V., & Garnefski, N. (2016). Cognitive emotion regulation, anxiety and depression in adults with autism spectrum disorder. *Research in Autism Spectrum Disorders, 22* (Supplement C), 34-44.

Brugha, T. S., McManus, S., Bankart, J., Scott, F., Purdon, S., Smith, J., et al. (2011). Epidemiology of autism spectrum disorders in adults in the community in England. *Archives of General Psychiatry, 68*(5), 459-465.

Charman, T., & Gotham, K. (2013). Measurement Issues: Screening and diagnostic instruments for autism spectrum disorders – lessons from research and practice. *Child and Adolescent Mental Health, 18*(1), 52-63.

Constantino, J. N., & Gruber, C. P. (2012). *Social responsiveness scale (SRS)*. Western Psychological Services Torrance, CA.

De Bildt, A., Sytema, S., Ketelaars, C., Kraijer, D., Mulder, E., Volkmar, F., & Minderaa, R. (2004). Interrelationship between autism diagnostic observation schedule-generic (ADOS-G), autism diagnostic interview-revised (ADI-R), and the diagnostic and statistical manual of mental disorders (DSM-IV-TR) classification in children and adolescents with mental retardation. *Journal of Autism and Developmental Disorders, 34*(2), 129-137.

De Bildt, A., Sytema, S., Meffert, H., & Bastiaansen, J. A. (2016). The Autism Diagnostic Observation Schedule, Module 4: application of the revised algorithms in an independent, well-defined, Dutch sample (n= 93). *Journal of Autism and Developmental Disorders, 46*(1), 21-30.

De Bildt, A., Sytema, S., Zander, E., Bölte, S., Sturm, H., Yirmiya, N., et al. (2015). Autism Diagnostic Interview-Revised (ADI-R) algorithms for toddlers and young preschoolers: application in a non-US sample of 1,104 children. *Journal of Autism and Developmental Disorders, 45*(7), 2076-2091.

Centers for Disease Control and Prevention (CDC) (2014). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill Summ, 63*(2), 1-21.

Didehbani, N., Shad, M. U., Kandalaft, M. R., Allen, T. T., Tamminga, C. A., Krawczyk, D. C., & Chapman, S. B. (2012). Brief report: Insight into illness and social attributional style in Asperger's syndrome. *Journal of Autism and Developmental Disorders, 42*(12), 2754-2760.

Duvekot, J., van der Ende, J., Verhulst, F. C., Slappendel, G., van Daalen, E., Maras, A., & Greaves-Lord, K. (2017). Factors influencing the probability of a diagnosis of autism spectrum disorder in girls versus boys. *Autism*, *21*(6), 646-658.

Elsabbagh, M., Divan, G., Koh, Y. J., Kim, Y. S., Kauchali, S., Marcín, C., et al. (2012). Global prevalence of autism and other pervasive developmental disorders. *Autism Research, 5*(3), 160-179.

Falkmer, T., Anderson, K., Falkmer, M., & Horlin, C. (2013). Diagnostic procedures in autism spectrum disorders: a systematic literature review. *European Child & Adolescent Psychiatry, 22*(6), 329-340.

Fein, D., Barton, M., Eigsti, I. M., Kelley, E., Naigles, L., Schultz, R. T., et al. (2013). Optimal outcome in individuals with a history of autism. *Journal of Child Psychology and Psychiatry, 54*(2), 195-205.

First, M. B., Gibbon, M., Spitzer, R. L., & Benjamin, L. S. (1997). *User's guide for the structured clinical interview for DSM-IV axis II personality disorders: SCID-II*. American Psychiatric Publications.

Frazier T. W., Georgiades S., Bishop S. L., et al. (2014). Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. *Journal of the American Academy of Child & Adolescent Psychiatry* 53: 329-340. e323.

Frith, U. (1989). *Autism: Explaining the enigma* (Vol. 1989): Wiley Online Library.

Frith, U., & Mira, M. (1992). Autism and Asperger syndrome. *Focus on Autistic Behavior, 7*(3), 13-15.

Fusar-Poli L., Brondino N., Orsi P., Damiani S., Provenzani U., Ucelli di Nemi S., Barale F. & Politi P. (2016). Cascina Rossago: un modello «ecologico» di intervento per adulti affetti da autismo a basso funzionamento. In: Keller R. *I disturbi dello spettro autistico in adolescenza e i*n età adulta. Aspetti diagnostici e proposte di intervento (pp. 223-232). Erickson.

Fusar-Poli, L., Brondino, N., Orsi, P., Provenzani, U., De Micheli, A., di Nemi, S. U., et al. (2017a). Long-term outcome of a cohort of adults with autism and intellectual disability: A pilot prospective study. *Research in Developmental Disabilities*, *60*, 223-231.

Fusar-Poli, L., Rocchetti, M., Garda, M., & Politi, P. (2017b). 'Aut'-sider: the invisible talent of Simona Concaro. *Epidemiology and Psychiatric Sciences*, *26*(2), 119-121.

Fusar-Poli, L., Brondino, N., Rocchetti, M., Panisi, C., Provenzani, U., Damiani, S., & Politi, P. (2017c). Diagnosing ASD in Adults Without ID: Accuracy of the ADOS-2 and the ADI-R. *Journal of Autism and Developmental Disorders*, 47(11), 3370-3379.

Garnett, M. S., Attwood, T., Peterson, C., & Kelly, A. B. (2013). Autism spectrum conditions among children and adolescents: a new profiling tool. *Australian Journal of Psychology*, *65*(4), 206-213.

Geschwind, D. H., & State, M. W. (2015). Gene hunting in autism spectrum disorder: on the path to precision medicine. *Lancet Neurology, 14*(11), 1109-1120.

Giddan, J. J., & Giddan, N. S. (1993). *European farm communities for autism*. Medical College of Ohio Press.

Giddan, J. J., & Obee, V. L. (1996). Adults with autism: Habilitation challenges and practices. *Journal of Rehabilitation*, *62*(1), 72.

Gillberg, C., Gillberg, C., Råstam, M., & Wentz, E. (2001). The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI): a preliminary study of a new structured clinical interview. *Autism*, *5*(1), 57-66.

Hansen, S. N., Schendel, D. E., & Parner, E. T. (2015). Explaining the increase in the prevalence of autism spectrum disorders: the proportion attributable to changes in reporting practices. *JAMA Pediatrics, 169*(1), 56-62.

Happé, F., & Charlton, R. A. (2012). Aging in autism spectrum disorders: A mini-review. *Gerontology, 58*(1), 70-78.

Happé, F., & Frith, U. (Eds.). (2010). *Autism and talent* (Vol. 364, No. 1522). OUP Oxford.

Henninger, N. A., & Taylor, J. L. (2013). Outcomes in adults with autism spectrum disorders: A historical perspective. *Autism, 17*(1), 103-116.

Higgins, J. P., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions* (Vol. 4). John Wiley & Sons.

Holland, D., & Dadds, M. R. (1997). The diagnostic interview schedule for children, adolescents, and parents. *Unpublished manuscript, Griffith University, Brisbane*.

Hofvander, B., Delorme, R., Chaste, P., Nydén, A., Wentz, E., Ståhlberg, O., et al. (2009). Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BMC psychiatry, 9*(1), 35.

Hosmer Jr, D. W., Lemeshow, S., & Sturdivant, R. X. (2013). *Applied logistic regression* (Vol. 398): John Wiley & Sons.

Howe Y.J., O'Rourke J.A., Yatchmink Y., et al. (2015). Female autism phenotypes investigated at different levels of language and developmental abilities. *Journal of Autism and Developmental Disorders,* 45, 3537-3549.

Howlin, P., Goode, S., Hutton, J., & Rutter, M. (2009). Savant skills in autism: psychometric approaches and parental reports. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *364*(1522), 1359-1367.

Howlin, P., & Moss, P. (2012). Adults with autism spectrum disorders. *The Canadian Journal of Psychiatry, 57*(5), 275-283.

Hull, L., Mandy, W., & Petrides, K. V. (2017). Behavioural and cognitive sex/gender differences in autism spectrum condition and typically developing males and females. *Autism, 21*(6), 706-727.

Hus, V., & Lord, C. (2013). Effects of child characteristics on the Autism Diagnostic Interview-Revised: Implications for use of scores as a measure of ASD severity. *Journal of Autism and Developmental Disorders, 43*(2), 371-381.

Hus, V., & Lord, C. (2014). The autism diagnostic observation schedule, module 4: revised algorithm and standardized severity scores. *Journal of Autism and Developmental Disorders, 44*(8), 1996-2012.

Hussman, J. P. (2001). Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *Journal of Autism and Developmental Disorders, 31*, 247–248.

Interagency Autism Coordinating Committee (2012). IACC strategic plan for autism spectrum disorder research: 2012 update. *US Department of Health and Human Services Interagency Autism Coordinating Committee*.

Jamison, R., Bishop, S. L., Huerta, M., & Halladay, A. K. (2017). The clinician perspective on sex differences in autism spectrum disorders. *Autism*, 1362361316681481.

Jeste, S. S., & Tuchman, R. (2015). Autism spectrum disorder and epilepsy: Two sides of the same coin? *Journal of Child Neurology, 30*(14), 1963-1971.

Kamp-Becker, I., Ghahreman, M., Heinzel-Gutenbrunner, M., Peters, M., Remschmidt, H., & Becker, K. (2013). Evaluation of the revised algorithm of Autism Diagnostic Observation Schedule (ADOS) in the diagnostic investigation of high-functioning children and adolescents with autism spectrum disorders. *Autism, 17*(1), 87-102.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child, 2*(3), 217-250.

Kerns, C. M., Rump, K., Worley, J., Kratz, H., McVey, A., Herrington, J., & Miller, J. (2016). The differential diagnosis of anxiety disorders in cognitively-able youth with autism. *Cognitive and Behavioral Practice, 23*(4), 530-547.

Lai, M.-C., & Baron-Cohen, S. (2015). Identifying the lost generation of adults with autism spectrum conditions. *The Lancet Psychiatry, 2*(11), 1013-1027.

Lai, M.-C., Lombardo, M. V., Auyeung, B., Chakrabarti, B., & Baron-Cohen, S. (2015). Sex/gender differences and autism: setting the scene for future research. *Journal of the American Academy of Child & Adolescent Psychiatry, 54*(1), 11-24.

Lai, M. C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. *The Lancet, 383*(9920), 896-910.

Lai, M. C., Lombardo, M. V., Pasco, G., Ruigrok, A. N., Wheelwright, S. J., Sadek, S. A., et al. (2011). A behavioral comparison of male and female adults with high functioning autism spectrum conditions. *PLoS One, 6*(6), e20835.

Lai, M.-C., Lombardo, M. V., Ruigrok, A. N., Chakrabarti, B., Auyeung, B., Szatmari, P., et al. (2016). Quantifying and exploring camouflaging in men and women with autism. *Autism*, 1362361316671012.

Lai, M. C., & Baron-Cohen, S. (2015). Identifying the lost generation of adults with autism spectrum conditions. *Lancet Psychiatry, 2*(11), 1013-1027.

Lai, M. C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. *Lancet, 383*(9920), 896-910.

Lam, K. S., Aman, M. G., & Arnold, L. E. (2006). Neurochemical correlates of autistic disorder: a review of the literature. *Research in Developmental Disabilities, 27*(3), 254-289.

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, 159-174.

Langmann, A., Becker, J., Poustka, L., Becker, K., & Kamp-Becker, I. (2017). Diagnostic utility of the autism diagnostic observation schedule in a clinical sample of adolescents and adults. *Research in Autism Spectrum Disorders, 34*, 34-43.

Laugeson, E. A., Frankel, F., Gantman, A., Dillon, A. R., & Mogil, C. (2012). Evidence-based social skills training for adolescents with autism spectrum disorders: The UCLA PEERS program. *Journal of Autism and Developmental Disorders, 42*(6), 1025-1036.

Lombardo, M. V., & Baron-Cohen, S. (2010). Unraveling the paradox of the autistic self. *Wiley Interdisciplinary* Reviews: *Cognitive Science, 1*(3), 393-403.

Lombardo, M. V., & Baron-Cohen, S. (2011). The role of the self in mindblindness in autism. *Conscious and Cognition, 20*(1), 130-140.

Lopata, C., Toomey, J. A., Fox, J. D., Volker, M. A., Chow, S. Y., Thomeer, M. L., et al. (2010). Anxiety and Depression in Children with HFASDs: Symptom Levels and Source Differences. *Journal of Abnormal Child Psychology, 38*(6), 765-776.

Lord, C., Corsello, C., & Grzadzinski, R. (2014). Diagnostic instruments in autistic spectrum disorders. *Handbook of Autism and Pervasive Developmental Disorders, Fourth Edition*.

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. (2012). *Autism diagnostic observation schedule: ADOS-2*. Western Psychological Services Los Angeles, CA.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with

possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24*(5), 659-685.

Lord, C. E. (2010). Autism: from research to practice. *American Psychologist, 65*(8), 815.

Lotter, V. (1966). Epidemiology of autistic conditions in young children. *Social Psychiatry and Psychiatric Epidemiology, 1*(3), 124-135.

Lugnegård, T., Hallerbäck, M. U., & Gillberg, C. (2011). Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. *Research in Developmental §Disabilities, 32*(5), 1910-1917.

Maddox, B. B., Brodkin, E. S., Calkins, M. E., Shea, K., Mullan, K., Hostager, J., et al. (2017). The Accuracy of the ADOS-2 in Identifying Autism among Adults with Complex Psychiatric Conditions. *Journal of Autism and Developmental Disorders, 47*(9), 2703-2709. doi:10.1007/s10803-017-3188-z

Magiati, I., Tay, X. W., & Howlin, P. (2014). Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: a systematic review of longitudinal follow-up studies in adulthood. *Clinical Psychology Review, 34*(1), 73-86.

Mandy W., Chilvers R., Chowdhury U., et al. (2012). Sex differences in autism spectrum disorder: evidence from a large sample of children and adolescents. *Journal of Autism and Developmental Disorders,* 42, 1304-1313.

Matson, J. L., & Shoemaker, M. (2009). Intellectual disability and its relationship to autism spectrum disorders. *Research in Developmental Disabilities, 30*(6), 1107-1114.

Mazefsky, C. A., Kao, J., & Oswald, D. P. (2011). Preliminary evidence suggesting caution in the use of psychiatric self-report measures with adolescents with high-functioning autism spectrum disorders. *Research in Autism Spectrum Disorders, 5*(1), 164-174.

Mazefsky, C. A., & Oswald, D. P. (2006). The discriminative ability and diagnostic utility of the ADOS-G, ADI-R, and GARS for children in a clinical setting. *Autism, 10*(6), 533-549.

Mazefsky, C. A., Oswald, D. P., Day, T. N., Eack, S. M., Minshew, N. J., & Lainhart, J. E. (2012). ASD, a psychiatric disorder, or both? Psychiatric diagnoses in adolescents with high-functioning ASD. *Journal of Clinical Child & Adolescent Psychology, 41*(4), 516-523.

McElhanon, B. O., McCracken, C., Karpen, S., & Sharp, W. G. (2014). Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis. *Pediatrics, 133*(5), 872-883.

McFadden, K. (2013). Neuroanatomy. In *Encyclopedia of Autism Spectrum Disorders* (pp. 2009-2014): Springer.

Mesibov, G. B., Shea, V., & Schopler, E. (2005). *The TEACCH approach to autism spectrum disorders*: Springer Science & Business Media.

Miano, S., Giannotti, F., & Cortesi, F. (2016). Sleep disorders and autism spectrum disorder. In *Psychiatric symptoms and comorbidities in autism spectrum disorder* (pp. 111-128): Springer.

Modabbernia, A., Velthorst, E., & Reichenberg, A. (2017). Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Molecular Autism, 8*(1), 13.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*, 6(7), e1000097.

Molloy, C. A., Murray, D. S., Akers, R., Mitchell, T., & Manning-Courtney, P. (2011). Use of the Autism Diagnostic Observation Schedule (ADOS) in a clinical setting. *Autism, 15*(2), 143-162.

Moss, J., & Howlin, P. (2009). Autism spectrum disorders in genetic syndromes: implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. *Journal of Intellectual Disability Research*, *53*(10), 852-873.

Moss, J., Magiati, I., Charman, T., & Howlin, P. (2008). Stability of the Autism Diagnostic Interview—Revised from pre-school to elementary school age in children with

autism spectrum disorders. *Journal of Autism and Developmental Disorders, 38*(6), 1081-1091.

Nicolaidis, C., Kripke, C. C., & Raymaker, D. (2014). Primary care for adults on the autism spectrum. *The Medical clinics of North America, 98*(5), 1169.

Noriega, D. B., & Savelkoul, H. F. (2014). Immune dysregulation in autism spectrum disorder. *European Journal of Pediatrics, 173*(1), 33-43.

Nylander, L. (2014). Autism and schizophrenia in adults: clinical considerations on comorbidity and differential diagnosis. In *Comprehensive Guide to Autism* (pp. 263-281): Springer.

Nylander, L., & Gillberg, C. (2001). Screening for autism spectrum disorders in adult psychiatric out-patients: a preliminary report. *Acta Psychiatrica Scandinavica, 103*(6), 428-434.

Oono, I. P., Honey, E. J., & McConachie, H. (2013). Parent-mediated early intervention for young children with autism spectrum disorders (ASD). *Evidence-Based Child Health: A Cochrane Review Journal, 8*(6), 2380-2479.

Ozonoff, S. (1997). Components of executive function in autism and other disorders.

Ozonoff, S., Goodlin-Jones, B. L., & Solomon, M. (2005). Evidence-based assessment of autism spectrum disorders in children and adolescents. *Journal of Clinical Child and Adolescent Psychology, 34*(3), 523-540.

Pilling, S., Baron-Cohen, S., Megnin-Viggars, O., Lee, R., Taylor, C., & Group, G. D. (2012). Recognition, referral, diagnosis, and management of adults with autism: summary of NICE guidance. *British Medical Journal, 344*, e4082.

Politi P., Fusar-Poli L., Ancona N., Pozzato E., Rocchetti M., & Garda M. (2016). Fra talenti invisibili e stereotipie manifeste. In: Keller R. *I disturbi dello spettro autistico in adolescenza e in età adulta. Aspetti diagnostici e proposte di intervento* (pp. 211-222). Erickson.

Postorino, V., Fatta, L. M., Sanges, V., Giovagnoli, G., De Peppo, L., Vicari, S., & Mazzone, L. (2016). Intellectual disability in Autism Spectrum Disorder: Investigation of

prevalence in an Italian sample of children and adolescents. *Research in Developmental Disabilities, 48*, 193-201.

Pugliese, C. E., Kenworthy, L., Bal, V. H., Wallace, G. L., Yerys, B. E., Maddox, B. B., et al. (2015). Replication and comparison of the newly proposed ADOS-2, module 4 algorithm in ASD without ID: A multi-site study. *Journal of Autism and Developmental Disorders, 45*(12), 3919-3931.

Raven, J. C. (1941). Standardization of progressive matrices, 1938. *Psychology and Psychotherapy: Theory, Research and Practice, 19*(1), 137-150.

Reichow, B. (2012). Overview of meta-analyses on early intensive behavioral intervention for young children with autism spectrum disorders. *Journal of autism and developmental disorders, 42*(4), 512-520.

Reichow, B., Barton, E. E., Boyd, B. A., & Hume, K. (2012). Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). *The Cochrane Library*.

Risi, S., Lord, C., Gotham, K., Corsello, C., Chrysler, C., Szatmari, P., . . . Pickles, A. (2006). Combining information from multiple sources in the diagnosis of autism spectrum disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 45*(9), 1094-1103.

Ritvo, E. R., & Freeman, B. (1977). National Society for Autistic Children definition of the syndrome of autism. *Journal of Pediatric Psychology, 2*(4), 146-148.

Ritvo, R. A., Ritvo, E. R., Guthrie, D., Ritvo, M. J., Hufnagel, D. H., McMahon, W., et al. (2011). The Ritvo Autism Asperger Diagnostic Scale-Revised (RAADS-R): a scale to assist the diagnosis of autism spectrum disorder in adults: an international validation study. *Journal of Autism and Developmental Disorders, 41*(8), 1076-1089.

Rogers, S. J., & Dawson, G. (2010). *Early start Denver model for young children with autism: Promoting language, learning, and engagement*: Guilford Press.

Roid, G. H., & Koch, C. (2017). Leiter-3: Nonverbal Cognitive and Neuropsychological Assessment. In *Handbook of Nonverbal Assessment* (pp. 127-150): Springer.

Russell, A. J., Mataix-Cols, D., Anson, M., & Murphy, D. G. (2005). Obsessions and compulsions in Asperger syndrome and high-functioning autism. *The British Journal of Psychiatry, 186*(6), 525-528.

Rutter, M. (1978). Diagnosis and definition of childhood autism. *Journal of Autism and Developmental Disorders, 8*(2), 139-161.

Rutter, M., Bailey, A., & Lord, C. (2003). *The social communication questionnaire: Manual*: Western Psychological Services.

Rynkiewicz, A., Schuller, B., Marchi, E., Piana, S., Camurri, A., Lassalle, A., & Baron-Cohen, S. (2016). An investigation of the 'female camouflage effect' in autism using a computerized ADOS-2 and a test of sex/gender differences. *Molecular Autism, 7*, 10.

Rynkiewicz, A., Schuller, B., Marchi, E., Piana, S., Camurri, A., Lassalle, A., & Baron-Cohen, S. (2016). An investigation of the ‘female camouflage effect’in autism using a computerized ADOS-2 and a test of sex/gender differences. *Molecular Autism, 7*(1), 10.

Sacks, O. (1995). *An Anthropologist on Mars.* New York, NY: Knopf

Salley, B., Gabrielli, J., Smith, C. M., & Braun, M. (2015). Do communication and social interaction skills differ across youth diagnosed with autism spectrum disorder, attention-deficit/hyperactivity disorder, or dual diagnosis? *Research in Autism Spectrum Disorders, 20* (Supplement C), 58-66.

Sappok, T., Diefenbacher, A., Budczies, J., Schade, C., Grubich, C., Bergmann, T., et al. (2013). Diagnosing autism in a clinical sample of adults with intellectual disabilities: How useful are the ADOS and the ADI-R? *Research in Developmental Disabilities, 34*(5), 1642-1655.

Schmidt, R. J., Lyall, K., & Hertz-Picciotto, I. (2014). Environment and Autism: Current State of the Science. *Cutting edge psychiatry in practice, 1*(4), 21-38.

Schopler, E., Reichler, R. J., DeVellis, R. F., & Daly, K. (1980). Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). *Journal of Autism and Developmental Disorders, 10*(1), 91-103.

Seltzer, M. M., Krauss, M. W., Shattuck, P. T., Orsmond, G., Swe, A., & Lord, C. (2003). The symptoms of autism spectrum disorders in adolescence and adulthood. *Journal of Autism and Developmental Disorders, 33*(6), 565-581.

Skuse, D., Warrington, R., Bishop, D., Chowdhury, U., Lau, J., Mandy, W., & Place, M. (2004). The developmental, dimensional and diagnostic interview (3di): a novel computerized assessment for autism spectrum disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 43*(5), 548-558.

Smith, L. E., Greenberg, J. S., & Mailick, M. R. (2012). Adults with autism: Outcomes, family effects, and the multi-family group psychoeducation model. *Current Psychiatry Reports, 14*(6), 732-738.

Soke, G. N., Philofsky, A., Diguiseppi, C., Lezotte, D., Rogers, S., & Hepburn, S. (2011). Longitudinal changes in scores on the Autism Diagnostic Interview—Revised (ADI-R) in pre-school children with autism: Implications for diagnostic classification and symptom stability. *Autism, 15*(5), 545-562.

Steinhausen, H. C., Mohr Jensen, C., & Lauritsen, M. B. (2016). A systematic review and meta-analysis of the long-term overall outcome of autism spectrum disorders in adolescence and adulthood. *Acta Psychiatrica Scandinavica, 133*(6), 445-452.

Sulzer-Azaroff, B., & Mayer, G. R. (1977). *Applying behavior-analysis procedures with children and youth*: Harcourt School.

Talari, S., Balaji, K., & Stansfield, A. J. (2017). What is the association between ADI-R scores and final diagnsois of autism in an all IQ Adult Autism Diagnostic Service? *Advances in Autism*. doi:10.1108/AIA-05-2017-0012

Tick, B., Bolton, P., Happe, F., Rutter, M., & Rijsdijk, F. (2016). Heritability of autism spectrum disorders: a meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry, 57*(5), 585-595.

Treffert, D. A. (2009). The savant syndrome: an extraordinary condition. A synopsis: past, present, future. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *364*(1522), 1351-1357.

Sparrow, S. S., Balla, D. A., Cicchetti, D. V., Harrison, P. L., & Doll, E. A. (1984). *Vineland adaptive behavior scales*. American Guidance Service.

Volkmar, F., Siegel, M., Woodbury-Smith, M., King, B., McCracken, J., & State, M. (2014). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 53*(2), 237-257.

Volkmar, F. R., Booth, L. L., McPartland, J. C., & A Wiesner, L. (2014). Clinical evaluation in multidisciplinary settings. *Handbook of Autism and Pervasive Developmental Disorders, Fourth Edition*.

Volkmar, F. R., & McPartland, J. C. (2014). From Kanner to DSM-5: autism as an evolving diagnostic concept. *Annual Review of Clinical Psychology*, *10*, 193-212.

Volkmar, F. R., & Reichow, B. (2013). Autism in DSM-5: progress and challenges. *Molecular Autism, 4*(1), 13.

Volkmar, F. R., Reichow, B., Westphal, A., & Mandell, D. S. (2014). Autism and the autism spectrum: Diagnostic concepts. *Handbook of Autism and Pervasive Developmental Disorders, Fourth Edition*.

Wechsler, D. (1981). *WAIS-R manual: Wechsler adult intelligence scale-revised*. Psychological Corporation.

Wigham, S., Barton, S., Parr, J. R., & Rodgers, J. (2017). A Systematic Review of the Rates of Depression in Children and Adults With High-Functioning Autism Spectrum Disorder. *Journal of Mental Health Research in Intellectual Disabilities, 10*(4), 267-287.

Wilson C.E., Murphy C.M., McAlonan G., et al. (2016). Does sex influence the diagnostic evaluation of autism spectrum disorder in adults? *Autism,* 20, 808-819.

Wing, L., Leekam, S. R., Libby, S. J., Gould, J., & Larcombe, M. (2002). The diagnostic interview for social and communication disorders: Background, inter-rater reliability and clinical use. *Journal of Child Psychology and Psychiatry, 43*(3), 307-325.

Wolf, J. M., & Ventola, P. (2014). Assessment and Treatment Planning in Adults with Autism Spectrum Disorders. In F. R. Volkmar, B. Reichow, & J. C. McPartland (Eds.), *Adolescents and Adults with Autism Spectrum Disorders* (pp. 283-298). New York, NY: Springer New York.

World Health Organization (1993). ICD-10, the ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research. *Geneva: World Health Organization*.

Yenkoyan, K., Grigoryan, A., Fereshetyan, K., & Yepremyan, D. (2017). Advances in understanding the pathophysiology of autism spectrum disorders. *Behavioral Brain Research, 331*, 92-101.

Yung, A. R., Phillips, L. J., McGorry, P. D., Ward, J. L., & Thompson, K. (1996). *The Comprehensive Assessment of At-risk Mental States (CAARMS). Manual.* Melbourne: University of Melbourne.

Zander, E., Sturm, H., & Bölte, S. (2015). The added value of the combined use of the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observation Schedule: Diagnostic validity in a clinical Swedish sample of toddlers and young preschoolers. *Autism, 19*(2), 187-199.

Williams, J., Scott, F., Stott, C., Allison, C., Bolton, P., Baron-Cohen, S., & Brayne, C. (2005). The CAST (Childhood Asperger Syndrome Test) test accuracy. *Autism*, *9*(1), 45-68.

ACKNOWLEDGMENTS

All'inizio di questo percorso, cominciato un po' per caso, non avrei mai immaginato che così tante persone mi avrebbero arricchita sia professionalmente che umanamente. Anche se può sembrare una banalità, è davvero difficile ringraziare tutti quelli che hanno contribuito alla realizzazione del lavoro di questi tre anni.

Grazie Natascia per avermi insegnato il 99% di quello che adesso so, per avermi trasmesso l'energia e l'entusiasmo per la ricerca di nuove idee, per la sensibilità verso i pazienti, per la compagnia quotidiana, per tutti i pranzi, gli aperitivi e le cene. Grazie Matteo per avermi supportata e spesso sopportata, sempre pronto a darmi una mano quando ce n'è stato bisogno, per aver cercato invano di insegnarmi la statistica e di rendermi più ossessiva di quanto già sono. Grazie Prof. Politi per aver saputo intuire la mia passione per la ricerca, dandomi l'opportunità di esprimerla al meglio attraverso questo percorso formativo, per avermi sempre coinvolta valorizzando il mio pensiero, grazie per tutto. Grazie Stefano e Umberto per l'amicizia sincera, per avermi sempre ascoltata e consigliata con pazienza, per la serietà del vostro lavoro, e soprattutto per tutte le birre che abbiamo condiviso e che spero condivideremo. Siete stati senza dubbio i miei migliori compagni di scrivania, anche se per poco, purtroppo. Grazie Marco per tutti i pomeriggi passati a leggere articoli ed estrarre dati, per i passaggi del venerdì con annessi pettegolezzi, e grazie anche a Federico per avermi liberata dal tavolino di De Martis, che in fondo era la collocazione naturale dello Jaspers. Grazie a tutti voi, a Gianluca e Francesca, per le pizze ed i caffè del mercoledì, per le chiacchierate ed i consigli reciproci: sono certa che con la dovuta calma riusciremo a concludere tutto quello che abbiamo iniziato, non disperate. Grazie anche a Giansanto, Alessia, Maria, Martina, Cristina e a tutto il LabAut. Grazie Prof. Barale per avermi inconsapevolmente

lasciato in eredità il suo studio, per la sua immensa gentilezza e capacità di valorizzare le persone e i loro talenti. Grazie Jasmine perché ci sei sempre stata, perché hai dovuto sopportare tutti i miei momenti no, che sono stati più di quelli sì, perché sei sempre riuscita a trovare le parole giuste e ad avere un effetto ansiolitico che nemmeno l'En. Mi duole dirtelo ma sei sprecata come dermatologa: fossi in te, ritornerei sui miei passi. Grazie mamma e papà che non mi avete mai fatto mancare il vostro sostegno in questo percorso un po' "alternativo", e mi avete sempre incoraggiata a seguire le mie aspirazioni. Grazie Francesco per esserci sempre stato, anche quando non c'eri (so che non c'è due senza tre, ma spero di non dover ripetere questa frase anche nella prossima tesi). Grazie a Christian e a tutto il GAMUT per tutti gli insegnamenti, per aver scommesso su di me ed avermi coinvolta in progetti che non avrei nemmeno lontanamente immaginato di poter realizzare. Grazie a tutti i ragazzi dell'Orchestra Invisibile, ad Enrico, Alice, Cristina, per aver riempito i miei venerdì pomeriggio, facendomi arrivare a casa ogni volta esausta, ma più consapevole.

Una pagina è davvero riduttiva per spiegare che il contributo di tutti voi è stato più fondamentale del mio. Grazie.