Life Span and Disability XXII, 1 (2019), 55-75

# Systematic review protocol of measures for early detection of risk for Autism Spectrum Disorders in toddlers

*Annalisa Levante*[1], *Serena Petrocchi*[2, 3] *& Flavia Lecciso*[1, 3]

## Abstract

*Several studies have developed and validated measures for early detection of signs of risk for Autism Spectrum Disorders in toddlers. This protocol systematically reviews aims and methods to evaluate validity and psychometric properties of these measures.*
*Method: The systematic review will be drawn up according to the PRISMA guidelines and the eligible papers will be evaluated using the COSMIN checklist. The search strategy will be applied to six electronic databases following pre-specified inclusion and exclusion criteria.*
*Discussion: Evidence from the review would inform on the state-of-the-art measures, limits, and future development. The findings will have practical implications for health care providers, families, policy and public health.*

*Keywords:* Early risk for ASD; Measures; Protocol; Systematic review; PRISMA; COSMIN.

*Received*: June 6, 2018; *Revised:* February 21, 2019; *Accepted*: March 15, 2019


[1] Department of History, Society and Human Studies, Università del Salento.
[2] Institute of Communication and Health, Università della Svizzera italiana.
[3] Lab of Applied Psychology and Intervention, Università del Salento.

Correspondence to: Annalisa Levante, Università del Salento, Department of History, Society and Human Studies, Edificio 5 – Complesso Studium 2000, Via Valesio 73100, Lecce, Italy. Phone+39 0832 294869; E-mail: annalisa.levante@unisalento.it.

# 1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction areas across multiple contexts and by restricted and repetitive patterns of behavior or restricted interests and activities (American Psychiatric Association, 2013). The symptoms appear during early childhood and significantly compromise the individual's social functioning (Frith, 1989; Frith & Happé, 1999; Rutter, 2011; World Health Organization, 2012; American Psychiatric Association, 2013).

According to the Centers for Disease Control and Prevention (2019), ASD prevalence is 1 in 59 children at age 4 and it occurs 4.5 fold more among boys (1 in 42) than among girls (1 in 189) (Christensen, Maenner, Bilder, Costantino, Daniel, Durkin, *et al.*, 2019). The ratio seems to vary according to the IQ, thus in subjects with severe intellectual dysfunction male to female gender ratio is 2:1 while in subjects with average IQ, gender ratio is 4:1 (Wing & Gould, 1979; Ehlers & Gillberg, 1993; Bryson, 1997). Several studies (Fombonne, 1999; 2003; 2009; Croen, Grether, Hoogstrate, & Selvin, 2002; Madsen, Hviid, Vestergaard, Schendel, Wohlfahrt, Thorsen *et al.*, 2002; Chakrabarti & Fombonne, 2005) reveal that there has been a dramatic 7% increase in the prevalence of ASD in the last decade.

The *gold standard* measures for the ASD diagnosis are the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord, Risi, Lambrecht, Cook, Leventhal, DiLavore *et al.*, 2000; Lord, Luyster, Gotham, & Guthrie, 2013), the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), and the Childhood Autism Rating Scale (CARS; Schopler, Reichler, DeVellis, & Daly, 1980; Schopler, Reichler, & Renner, 2002). These measures are reliable (Gilchrist, Green, Cox, Burton, Rutter, & Le Couteur, 2001) and standardized (Schopler *et al.*, 1980; Lord *et al.*, 1994; Lord *et al.*, 2000).

Currently, ASD is diagnosed starting from the age of 3-4 years (Siegel, Pliner, Eschler, & Elliott, 1988; Howlin & Moore, 1997; Mandell, Novak, & Zubritsky, 2005; Christensen, Bilder, Zahorodny, Pettygrove, Durkin, Fitzgerald *et al.*, 2016), but various studies found that parents report their concerns to the health care providers during their children's first year of life (Adrien, Faure, Perrot, Hameury, Garreau, Barthelemy *et al.*, 1991; Adrien, Barthelemy, Perrot, Roux, Lenoir, Hameury *et al.*, 1992; Adrien, Lenoir, Martineau, Perrot, Hameury, Larmande *et al.*, 1993; Osterling & Dawson, 1994; 1999; Stone, Hoffman, Lewis, & Ousley, 1994; Baranek, 1999;

Werner, Dawson, Osterling, & Dinno, 2000; Werner & Dawson, 2005). Retrospective studies (Siegel *et al.*, 1988; Mandell *et al.*, 2005; Siklos & Kerns, 2007; Ozonoff, Young, Steinfeld, Hill, Cook, Hutman *et al.*, 2009; Chamak, Bonniau, Oudaya, & Ehrenberg, 2011; Ryan & Salisbury, 2012) found that parents of children with a diagnosis of ASD started to notice that something was wrong in their children's development at the age of 15-18 months. For example, some parents perceived that their children were less able to perform specific behaviors, as compared to their peers, while others reported a regression or a loss of abilities (Osterling & Dawson, 1994; Bristol, Cohen, Costello, Denckla, Eckberg, Kallen *et al.*, 1996; Tuchman & Rapin, 1997; Maestro, Muratori, Cavallaro, Pecini, Cesari, Paziente *et al.*, 2005; Werner & Dawson, 2005).

Nevertheless, there is still a delay between the first signs of concern, the first consultation and the diagnosis (Young, Brewer, & Pattison, 2003; Stone, Coonrod, Turner, & Pozdol, 2004; Renty & Roeyers, 2006; Wiggins, Baio, & Rice, 2006; Zwaigenbaum, Bryson, Lord, Rogers, Carter, Carver *et al.*, 2009; Daniels & Mandell, 2014; Zablotsky, Colpe, Pringle, Kogan, Rice, & Blumberg, 2017). There are many factors that may influence this delay: poor knowledge of ASD (Knafl, Ayres, Gallo, Zoeller, & Breitmayer, 1995), the tendency of pediatricians to take their time in referring families to a diagnostic assessment by professionals (Shah, 2001; Shevell, Majnemer, Rosenbaum, & Abrahamowicz, 2001) and the non-availability of well-validated measures for young children that can be administered to the general population.

Recently, several researchers have developed measures for the early detection of signs of risk for ASD (Reznick, Baranek, Reavis, Watson, & Crais, 2007; Allison, Baron-Cohen, Wheelwright, Charman, Richler, Pasco *et al.*, 2008). The early detection of the risk for ASD represents a quick step in the full diagnostic process, to establish whether a toddler is at risk of developing ASD and whether a deeper diagnostic assessment should be made (Baer & Blais, 2010; Sappok, Heinrich, & Underwood, 2015). In this vein, measures for the detection of the first signs of ASD would help health professionals to make their first evaluation of a child and then, if appropriate, refer the family to a diagnostic process (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Baird, Charman, Baron-Cohen, Cox, Swettenham, Wheelwright *et al.*, 2000; Baron-Cohen, Wheelwright, Cox, Baird, Charman, Swettenham *et al.*, 2000; Wetherby, Woods, Allen, Cleary, Dickinson, & Lord, 2004; Canal-Bedia, Garcia-Primo, Martin-Cilleros, Santos-Borbujo, Guisuraga-Fernandez, Herraez-Garcia *et al.*, 2011; Allison,

Auyeung, & Baron-Cohen, 2012). The American Academy of Pediatrics itself (Johnson & Myers, 2007) recommends that pediatricians evaluate early signs of ASD.

The early detection of risk and the subsequent early diagnosis of ASD could improve the prognosis (Dawson & Osterling, 1997; Corsello, 2005; Kasari, Freeman, & Paparella, 2006). Early diagnosis could lead to earlier intervention for children, which would enhance their adaptation (Lovaas, 1987; Sallows & Graupner, 2005; Perry, Cummings, Geier, Freeman, Hughes, LaRose *et al.*, 2008; Dawson, Rogers, Munson, Smith, Winter, Greenson *et al.*, 2010), prevent secondary developmental disturbances (Daniels & Mandell, 2014; Renty & Roeyers, 2006; Wiggins *et al.*, 2006), and lead to better outcomes (Anderson, Liang, & Lord, 2014; Robins & Dumont-Mathieu, 2006; Sutera, Pandey, Esser, Rosenthal, Wilson, Barton *et al.*, 2007). Early diagnosis would also help parents to cope with the diagnosis (Lecciso, Petrocchi, Savazzi, Marchetti, Nobile, & Molteni, 2013; Marvin & Pianta, 1996) and would reduce family stress (Dawson, 2008; Mundy, Sullivan, & Mastergeorge, 2009; Reichow, Barton, Boyd, & Hume, 2012).

### *1.1. Previous systematic reviews and research questions of the present protocol*

There are several published reviews of measures of early detection of ASD (Daniels, Halladay, Shih, Elder, & Dawson, 2014; Garcia-Primo, Hellendoorn, Charman, Roeyers, Dereu, Roge *et al.*, 2014; McPheeters, Weitlauf, Vehorn, Taylor, Sathe, Krishnaswami *et al.*, 2016; Sappok *et al.*, 2015; Zwaigenbaum, Bauman, Fein, Pierce, Buie, Davis *et al.*, 2015). Garcia-Primo and colleagues (2014) and Sappok and colleagues (2015) conducted no-systematic reviews on both measures for the early detection of risk for ASD and relevant diagnosis. The study by Garcia-Primo's research group (2014) was limited to measures used in Europe, published up until 2012, and restricted to two databases (PubMED and PsycINFO). The review by Sappok and colleagues (2015) was limited to one database (PubMED) and it considered measures developed for German and English speakers. Zwaigenbaum's no-systematic review (Zwaigenbaum *et al.*, 2015) was limited to one database (PubMED) and the research strategies included papers published up until December 2013.

The paper by Daniels, Halladay and colleagues (2014) focused on studies investigating approaches aiming at improving of the early detection of ASD.

This was a systematic review using five databases, although the authors chose to include only studies published up until 2013 and conducted in the United States.

McPheeters and colleagues (2016) made a valuable systematic review of ASD screening tools for children under 36 months of life for low-risk populations, administered in primary care settings. Nevertheless, their search strategies were extended to four databases and they considered studies published since 2000.

None of those studies analyzed the psychometric properties of the measures applying a standardized protocol. The purpose of our review is (a) to propose an up-to-date systematic research strategy to identify measures for the early detection of signs of ASD in children under the age of 2, and (b) to analyze the psychometric properties and validity of the measures. Specifically, the research questions are: (RQ1) What are the measures to detect early signs of risk for ASD in children under 24 months? (RQ2) What are their psychometric and validity properties? (RQ3) Is there one (or more) "best instrument" for the early detection of risk for ASD?

## 2. Method

The systematic review will be reported according to the Preferred Reporting Item for Systematic Review and Meta-analyses guidelines (PRISMA; Moher, Liberati, Tetzlaff, Altman, & Prisma Group 2009), whereas psychometric and validity properties will be evaluated according to the COSMIN checklist (Mokkink, Terwee, Patrick, Alonso, Stratford, Knol *et al.*, 2010), as previously done for ASD measures for adults (Baghdadli, Russet, & Mottron, 2017).

### *2.1. Population*

All studies involving children who have completed evaluation for the early signs of risk for ASD before their second birthday will be included.

The basic keywords guiding the systematic search will be: "early diagnosis or diagnos*", "ASD screen*", "ASD detect*", "ASD or autism or autist*", "Assessment tool", "assess*", "instrument*", "measure*", "psychometric properties", "standardiz*", "tool*", "validat*". The record of keywords will be applied to all databases.

### *2.2. Study selection criteria*

According to the research questions of the systematic review, a list of inclusion and exclusion criteria have been developed (see Tab. 1).

Table 1 - *Inclusion and exclusion criteria of the systematic search*

| Inclusion criteria | Exclusion criteria |
|---|---|
| Measures of the early signs of risk of ASD designed to be used with children under 24 months of life | Papers on measures of the diagnosis of ASD or on measures of risk detection/diagnosis of others developmental disorders |
| Validation studies, standardization of measures, cross cultural comparisons | Retrospective studies |
| Published papers | Papers explaining early diagnosis procedures other than questionnaires, interviews and observation procedure (i.e., biological markers, fMRI, blood test) |
| Paper written in English | Epidemiological studies and guideline for experts with or without any reference on measures |
| Publications between 1990 and 2017 | Publications that are not in peer-reviewed journals |
| | Other systematic reviews of measures |
| | Papers without the specific aim to evaluate psychometric properties or validity properties of the measures |
| | Dissertation thesis or conference papers |

Two researchers will independently screen the eligible papers in two steps. In step 1, they will screen the papers according to titles and abstracts. In step 2, they will select and include in or exclude from the review the papers according to the full-length version. At the end of the process, the consistency between the two coders will be evaluated using the kappa coefficient. The number of articles included and excluded at the various stages and reasons will be reported. In case of discordance between the two coders, a third reviewer will arbitrate and the reasons for the discordance will be discussed.

### *2.3. Search and strategy*

The final number of eligible papers will be obtained through a multistep strategy. First, we will conduct an electronic search into six databases, such as Ebsco, PsycINFO, CINAHL, Scopus, ERIC and MEDLINE. Second, we will conduct a manual search of other eligible papers analyzing the reference lists of each included paper and of other systematic reviews. Finally, experts and leading authors in the field of autism research will be contacted.

### *2.4. Data extraction procedure*

The final list of papers included in the systematic review will be organized in a table and basic information will be extracted. Table 2 shows the structure of the data collected.

The next step will be the extraction of the descriptive data of each sample including source (i.e., general population, children with diagnosis, high-risk population), gender distribution, age range, means, standard deviations, children's cognitive functioning and parental socio-demographic information. Table 3 shows the structure of the data that will be collected.

### *2.5. Quality assessment of the studies*

The COSMIN Checklist (Mokkink *et al.*, 2010) will be used to evaluate the methodological characteristics of the papers. This instrument allows the most important psychometric and validity properties of a study or a measure to be evaluated and enables studies to be rated as poor, fair, good or excellent (see Tab. 4). It includes eleven boxes, nine of which assess whether the standard of a study is of good methodological quality. These eleven boxes allow five kinds of validity to be assessed: content validity, structural validity, construct validity, cross-cultural validity, and criterion validity. COSMIN was also used for the evaluation of the test-retest, inter-rater, and intra-rater reliability, internal consistency, measurement error, and the responsiveness in terms of the measure's ability to identify the change of the construct over time. The checklist includes also a box which evaluates the interpretability of a study or a measure and another box which evaluates the generalizability of the results.

Table 2 - *Details of the papers included in the systematic review*

| Author(s), (year) | Study design | Measure name (short name) | Short description | Admin. Age (months) | Item | Type of Answer | Admin. Time (min.) | Admin. Method | Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

Table 3 - *Overview of the samples of each study*

| Source | Gender distribution | Age range, *M (SD)* | Children's cognitive functioning | Parental socio-demographic info |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |

Table 4 - *COSMIN psychometric properties of each study*

| Measures | Author(s), (Years) | Psychometric properties | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | A | B | C | D | E | F | G | H | I |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

*Note:* COSMIN psychometric property boxes: A = internal consistency, B = reliability, C = measurement error, D = content validity, E = structural validity, F = hypotheses testing, G = cross-cultural validity, H = criterion validity, I = responsiveness.

4-point scale rating: +++ = excellent, ++ = good, + = fair, 0 = poor; - = Property not evaluated in study.

# 3. Discussion

Our study will allow to define a systematic review of measures for the early detection of risk for ASD in toddlers. The PRISMA guidelines will be followed to report results of the review and COSMIN checklist will be used to evaluate papers.

The systematic review will include validation studies of screening tools published until 2017 and the electronic search will be extended to six databases. Furthermore, we will not limit our search to validation studies of measures conducted or used in a specific geographic area.

The review will provide a contribution to the existing literature. Evidence from our systematic review will inform research regarding the state-of-the-art of the measures for the early detection of ASD, their limits, and future development in this field. The review will provide valuable information regarding the existing measures for the detection of the early signs of ASD in children under the age of 2. The evidence will assist in the identification of the psychometric and validity properties of each study and measure. Consequently, it will help in the identification of the "best instrument(s)" for the early detection of risk for ASD or give pointers for further development of existing measures.

As mentioned before, several studies (Adrien *et al.*, 1991; 1992; 1993; Osterling & Dawson, 1994; 1999; Stone *et al.*, 1994; Baranek, 1999; Werner *et al.*, 2000; Werner & Dawson, 2005) underlined a delay between parents' first concerns and pediatrician's referral to diagnostic assessment. In this vein, the delay highlights the crucial role played by professionals in primary

care settings, especially pediatricians and nurses, in the early detection of ASD.

Findings from the systematic review will also have substantial practical implications for health care providers, families, policy-makers and for public health. Our systematic review will help health care providers to choose the most valid measure(s) for the early ASD risk detection in their patients. This early detection and the resulting early diagnosis will facilitate well-timed interventions, leading to better prognosis (Dawson & Osterling, 1997; Corsello, 2005; Kasari *et al.*, 2006; Zwaigenbaum *et al.*, 2009) and more successful family adaptation (Howlin & Moore, 1997; Rogers & Vismara, 2008).

In the long term, this will also be of use to health policy makers. The findings will help in the creation of guidelines for health providers to support them in the early detection of signs of ASD risk during scheduled well-child visits. Evidence would also help policy makers in their decisions on allocation of scarce resources for the prevention and detection of ASD.

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