Artículo II

Referencia: Lugo-Marín, J., Alviani, M., Mahtani-Chugani, V., Magan-Maganto, M., Díez-Villoria, E., & Canal-Bedia, R. (2018). Prevalence of Schizophrenia Spectrum Disorders in Average-IQ Adults with Autism Spectrum Disorders: A Meta-analysis. *Journal of autism and developmental disorders*, *48*(1), 239-250.

Título: Prevalencia de Trastornos del Espectro de la Esquizofrenia en personas adultas con Trastorno del Espectro Autista sin discapacidad intelectual asociada: un metaanálisis

Resumen

Introducción: Desde su separación como entidades diagnósticas independientes, el Trastorno del Espectro Autista (TEA) y los Trastornos del Espectro de la Esquizofrenia (TEE) han sido considerados mutuamente excluyentes. Sin embargo, el solapamiento de algunas de las características mostradas por las personas afectadas por estos trastornos cuestiona esta separación, dificultando establecer el límite entre ambas condiciones, llevando esto a una posible confusión a la hora de realizar el diagnóstico.

Objetivo: el objetivo del presente estudio fue revisar la prevalencia diagnóstica de TEE en adultos con TEA y capacidad intelectual preservada.

Método: se realizó una búsqueda electrónica en bases de datos (PsycInfo, Medline, Embase, CINAHL), así como una búsqueda manual a través de las referencias de estudios potencialmente elegibles para ser incluidos en la revisión. Únicamente se incluyeron aquellos estudios que reportasen datos de prevalencia de TEE en población adulta (18 años o mayor)

con diagnóstico de TEA. Se excluyeron diagnósticos de psicosis afectiva y psicosis inducida por sustancias.

Resultados: Un total de 278 referencias fueron identificadas, de las cuales 12 fueron incluidas en la síntesis cualitativa y 10 fueron incluidas en el metaanálisis. La prevalencia ponderada de TEE en adultos con TEA y capacidad intelectual en rango normativo fue cercana al 6%, señalando una elevada concurrencia de ambas condiciones.

Conclusiones: la prevalencia diagnóstica de TEE en población adulta con TEA sin discapacidad intelectual asociada es casi seis veces superior a la prevalencia en población general. Este resultado se puede deber a una vulnerabilidad superior en esta población de desarrollar un TEE, o bien una confusión diagnóstica entre ambas condiciones, sobreestimando la ocurrencia de TEE en población con TEA. Se hace necesaria una mayor investigación de las características discriminatorias de cada entidad diagnóstica, así como el desarrollo de instrumentos diagnósticos que permitan diferenciar entre ambos trastornos en la etapa adulta.

Palabras clave: Trastorno del Espectro Autista; Psicosis; Comorbilidad; Metaanálisis.

Dear M.Sc. Lugo Marín,

We have completed our review of your revised manuscript: "Prevalence of schizophrenia spectrum disorders in average-IQ adults with autism spectrum disorders: a meta-analysis". We appreciate your careful attention to the reviewers' concerns and feel that the manuscript is now ready for publication.

You will be contacted about proofs and offprints by Springer. Please remember to quote the manuscript number, JADD-D-17-00263R3, whenever inquiring about your manuscript.

Thank you for this interesting contribution. We are pleased that you chose to submit your work to the Journal of Autism and Developmental Disorders. We wish you the very best in your research and look forward to hearing from you again soon.
Sincerely,
Marc Woodbury-Smith, PhD, MRCPsych (UK)
Associate Editor
Journal of Autism and Developmental Disorders

Prevalence of schizophrenia spectrum disorders in average-IQ adults with autism spectrum disorders: a meta-analysis

Abstract

Since their separation as independent diagnoses, autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) have been conceptualized as mutually exclusive disorders. Similarities between these disorders can lead to misdiagnosis, especially when it comes to average-IQ adults who were not identified during childhood. The aim of this review was to examine the occurrence of SSD in average-IQ adults with ASD. Electronic and manual searches identified a total of 278 references, of which 10 were included in a meta-analysis. The pooled prevalence of SSD in the total ASD sample was close to 6%, pointing to a high co-occurrence of the two conditions. Further research is needed to determine the factors that predispose members of this population to the emergence of psychotic disorders.

Keywords: Autism Spectrum Disorders; Psychosis; Comorbidity; Meta-analysis.

Prevalence of schizophrenia spectrum disorders in average-IQ adults with autism spectrum disorders: a meta-analysis

Autism spectrum disorders (ASD) are neurodevelopmental conditions characterized by deficits in two areas of global functioning: social communication and restricted, repetitive behaviors (American Psychiatric Association, 2013). The worldwide prevalence of ASD was set at 7.6 per 1000 in recent years (Baxter et al., 2015). First symptoms usually appear before 3 years of age, but sometimes they appear later. Although ASD co-occur often with associated intellectual disability (ID), average-IQ cases are also frequent. These particular forms of ASD may cause the disorder to remain masked, as the person learns skills that compensate for ASD's core difficulties. Also, parental protection during childhood can help those with ASD to manage in the social world. It is then, when they should go into this unpredictable environment full of implicit norms and rules that problems arise, usually impairing their academic and social functioning. Despite often having a normal IQ, sometimes even above average, they often have difficulty understanding many of the social conventions that most people intuitively learn. This causes misunderstandings that can lead to conflicts with their peers. In addition, the naivety with which they confront most social contexts makes them vulnerable to other people's tricks and lies. As a result of their difficulties in social cognition, they begin to distrust others, isolating themselves and being socially withdrawn. This can lead to the emergence of psychiatric disorders such as anxiety, social phobia, affective disorders and, in some cases, psychosis (Hofvander et al., 2009; Unenge Hallerbäck, Lugnegård, & Gillberg, 2012).

Schizophrenia spectrum disorders (SSD) are characterized by the presence of so-called positive symptoms, i.e., delusions and hallucinations. Emil Kraepelin first described the syndrome that he called "dementia praecox," differentiating it from the "manic-depressive psychosis" which

co-occurs with affective symptoms (Kraepelin, 1896). Later, Eugen Bleuler introduced the concept of "schizophrenia" in his work "Dementia Praecox; Or, The Group of Schizophrenias" (Bleuler, 1911). Today, the global burden of schizophrenia and other psychotic disorders is established at 1.1% (Rössler, Salize, van Os, & Riecher-Rössler, 2005).

SSD and ASD have been seen as related throughout the last century. Bleuler (1911) first described the term “autism” as a withdrawal from reality, with a pathological predominance of inner life. Later, Leo Kanner (1943) used the term to refer to a group of children with deficits in communication, social interaction and imagination (Kanner, 1943). In the first edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1952), “autism” was classified within the group of childhood psychoses. It was not until the third edition of the manual (American Psychiatric Association, 1980), after studies by Kolvin (1971) and Rutter (1972), that “autism” was conceptualized as an independent disorder. In subsequent editions, the group of autistic disorders was expanded to include several discrete categories: Rett disorder, Childhood disintegrative disorder, Asperger Syndrome (AS) and pervasive developmental disorder not otherwise specified (PDD-NOS). DSM 5 has removed this categorical classification, establishing one generic dimensional category named “Autism Spectrum Disorder” with varying degrees of severity depending on the deficits in the areas of social communication and restricted, repetitive behaviors (American Psychiatric Association, 2013).

Despite the perceived relationship between ASD and SSD, the International Classification of Mental and Behavioural Disorders (ICD-10), in its description of AS, describes the co-occurrence of psychotic disorders during adolescence, but excludes a comorbid diagnosis of AS with childhood schizophrenia (World Health Organization, 1992). Paradoxically, the direct

consequence of the polarization of both diagnoses was the increase in the probability of confusing both diagnoses. This became very likely, since the two diagnoses can be confused with great ease. First, the idiosyncratic beliefs of a person with ASD can be confused with the delusional ideas of a person with psychosis. However, delusions do not follow logical reasoning, whereas in the person with ASD, rationality can be glimpsed within their speech. Also, the cognitive (and behavioral) inflexibility of people with ASD can be confused with the typically delusional conviction of psychosis. Secondly, the sensory disorders that often co-occur with ASD can be mistaken for hallucinations. Difficulties in social communication make it difficult to know the real nature of these perceptual phenomena. Finally, as SSD onset frequently takes place during adolescence or young adulthood, it could be hypothesized that those with ASD who were not diagnosed during childhood could have been wrongly diagnosed with any of the SSD, thus not receiving the appropriate intervention.

In order to analyze the evidence on comorbidity between ASD and SSD, a review of the literature was carried out. The aim of this review was to describe the actual evidence on the prevalence of SSD in average-IQ adults with ASD in the literature. Thus, questions regarding similarities between both disorders at biological levels, as well as possible explanations for the common co-occurrence, if yet pointed out, are definitely out of the scope of this study.

METHODS

The review was registered at PROSPERO (reference number CRD42016039448) and it was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009).

Search of studies

The search strategies used were (1) an electronic search where four databases were investigated to identify related studies: PsycINFO, Medline, CINAHL, and Embase; (2) screening of reference lists of original articles; and (3) Google Alert to identify recently published studies that addressed the subject of the review. Table 1 shows the details of the electronic search.

[Insert Table 1 about here]

Inclusion and exclusion criteria

Inclusion criteria were: (1) Observational studies that investigate the comorbidity of ASD and SSD; (2) Sample mean IQ above 70; (3) Sample mean age above 18 years old; (4) Clinical diagnoses had been established on the basis of diagnostic classifications in DSM (any version) and/or ICD-10; (5) Studies reported in English, Spanish or German languages; and (6) Peer-reviewed journal articles.

Studies were excluded that included participants with: (1) medical conditions (seizures, delirium, medication toxicity, metabolic or subtle co-occurring neurodevelopmental disorders), (2) psychiatric disorders due to a general medical condition, or (3) psychiatric disorders due to substance intoxication. Also excluded were studies that focused on genetic issues.

Only diagnoses of non-affective psychosis disorders were included (ICD-10/DSM F.20-F.29). Diagnoses included in the category “Mood Disorders” (ICD-10 / DSM F.30-F39) that may present associated psychotic symptoms (e.g., bipolar disorder, depression and manic episodes)

were excluded, as psychotic symptoms are here secondary and there is not such a potential risk of overlap with the core features of ASD as in the case of SSD.

References screening

Two independent reviewers assessed the studies taking into account both inclusion and exclusion criteria. A first screening was performed based on the articles' title and abstract. Kappa coefficient (k) was applied to assess interrater agreement. In those studies, in which discrepancies took place an agreement was reached between both reviewers. If agreement was still not reached, a third reviewer was consulted. The criteria that led to greater discrepancies were related to ID and age. For this reason, initial agreement was below the significance threshold (k = 0.36, CI 95% = 0.18, 0.55). In order to solve this, it was decided to include those studies that clearly indicated an average-IQ mean score above 70 in the ASD sample or, in those cases where IQ scores were not reported, studies conducted with participants whose diagnostics implied an absence of ID. As well, the age criterion raised some discrepancies since numerous studies included participants both under and above 18 years old. In these cases, it was agreed to take into account the average age of the whole sample. As a result of making these changes, after the full-text screening it was found that interrater agreement had improved considerably (k = 0.94, CI 95% = 0.82, 1).

Data extraction and quality assessment

The variables recorded were as follows: first author, year of study, country, number of total ASD participants, male ratio, mean age, mean IQ score, diagnostic criteria, ASD subtype, ASD measure, SSD measure and number of participants with SSD. Methodological quality was assessed with the Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) guidelines (Von Elm et al., 2007), which provide general recommendations for descriptive observational studies in epidemiology.

Statistical analysis

The extraction of selected variables was conducted with Microsoft Excel 2013. Comprehensive Meta-analysis v3 was used for conducting the quantitative synthesis.

RESULTS

The electronic search strategy initially identified 230 studies, with 195 remaining after duplicate removal. Once title/abstract screening was finished, 155 references were excluded. The full-text of the remaining 40 references was screened and 7 of them were included in the review. Forty-eight additional references were found through the reference lists of the included studies and those reported from a Google alert on the topic. Eventually, five of these studies were included in the review. Thus, as shown in Figure 1, twelve studies were ultimately included in the review. The main reasons for exclusion were as follows: type of study (not observational studies), studies that did not address the comorbidity between both disorders, studies with participants averaging under 18 years old and/or had ID, and studies including fewer than 10 subjects. As well, we contacted the authors of the studies included in the review asking them for unpublished material on this subject. One of them reported unpublished material on the topic covered by this review, but retrieval of quantitative data was not possible. Table 2 shows a summary of the quality assessment of selected studies.

[Insert Figure 1 about here]

[Insert Table 2 about here]

Qualitative synthesis

All the included studies were English-language papers and half of them took place in Sweden. Only one study conducted before the year 2000 was included. The whole sample comprised a total of 713 participants with ASD, 73.49% of whom were males. Mean age and IQ ranged from 21.5 to 36.46 years and 83.5 to 107.6, respectively. The most frequent ASD diagnosis was AS (62.69%), followed by PDD-NOS (15%), Autistic Disorder (AD) (10.52%), Atypical Autism (AA) (9.4%) and High-Functioning Autism (HFA) (2.38%). Regarding diagnostic measures, the Diagnostic Interview for Social and Communication Disorders (DISCO) and the Asperger Syndrome Screening Questionnaire (ASSQ) (16.7%) were the most used instruments to diagnose ASD. The SSD diagnoses were established using the Structured Clinical Interview for DSM-IV – Axis I disorders (SCID-I) in most of the cases (41.7%). Both diagnoses were based on DSM-IV diagnostic criteria in practically all cases (91.7%). Table 3 shows the results of the qualitative synthesis.

[Insert Table 3 about here]

Quantitative synthesis (meta-analysis)

Two studies were excluded from the meta-analysis. Szatmari et al. (1989) was excluded because it did not provide quantitative data on the prevalence of SSD in the ASD sample. Also, Raja et al. (2010) was excluded after normality tests were conducted. Thus, a total of 10 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 17.884, p = 0.04), pointing to a high degree of heterogenity in the included studies (I2 = 49%). Because of that, we decided to conduct a random effects model meta-analysis. Figure 2 shows the results derived from the meta-analysis. The pooled prevalence of SSD in ASD adults was 6.4%. Publication bias was addressed by visual inspection of the funnel plot (Figure 3) that showed an asymmetrical pattern and was also confirmed by an Egger's regression test (Eggers r = -2.3, p = 0.001), thus suggesting a high probability of publication bias. However, Eggers et al. (1997) recommended taking into account other possible explanations when analyzing a funnel plot (poor methodological design, true heterogeneity, chance). In this case, the funnel plot suggests missing studies in the right side of the diagram, making publication bias highly plausible.

[Insert Figure 2 about here]

[Insert Figure 3 about here]

DISCUSSION

To the extent of our knowledge this is the first meta-analysis on the prevalence of SSD in average-IQ adults diagnosed with ASD.

Co-occurrence of SSD and ASD

Concerning the research question posed at the beginning of this review, we have found strong evidence of the occurrence of SSD in people with ASD during adulthood. These results are in line with studies suggesting that both conditions can coexist (Konstantareas & Hewitt, 2001; Waris, Lindberg, Kettunen, & Tani, 2013) and involve some overlapping genetic predispositions (Crespi, Stead, & Elliot, 2010; Sporn et al., 2004). In her review on comorbidity and differential diagnosis between the two types of disorders, Nylander (2014) points to the possibility of comorbid diagnosis, concluding that in that case both disorders would present mild forms that would overlap in a dimensional continuum. A significant contribution of this review is to describe symptoms similar to psychosis (psychosis-like symptoms) which would occur in a person with ASD as a result of unexpected stress factors (changes in the environment, sensory overstimulation), causing behavioral shifts that would trigger first contact with mental health services. Similarly, Abell and Hare (2005) have developed a cognitive model for the emergence of delusional beliefs in people with ASD. Fundamental to these beliefs are cognitive deficits (in executive functions, autobiographical memory and theory of mind) that would likely result in awkward social interactions and, as a consequence, social exclusion. This would adversely affect the person's self-esteem, and, being aware of these deficits, they might develop delusional thoughts that would protect them from the subjective perception of lack of control. Furthermore, the authors found that these beliefs had a component of grandiosity or, in cases where there is a processing bias, a component of injury and/or threat. In clinical practice,

Bakken and Hoidal (2014) reported the assessment of 12 cases set in a psychiatric unit for an adult population diagnosed with both AS and Schizophrenia. They concluded that those symptoms that best discriminated between the disorders were the age of onset, the presence of hallucinations, disorganized speech and behavior, and the occurrence of relapses in relation to psychotic symptoms. In this connection, it has been observed that formal thought disorders (FTDs) are very common in the ASD population. Solomon et al. (2008) found that executive control and anxiety were related to illogical thinking and loose associations, respectively. Also, Eussen et al. (2015) found FTD were also prevalent in adolescents and young adults on the autism spectrum and that these correlate with severity of autistic features and do not predict prodromal symptoms of psychosis. Table 4 shows a comparison between FTD and typically ASD thought and speech features, thus reflecting the high probability of misdiagnosing both disorders.

[Insert Table 4 about here]

Although not included in the present review, studies relating the presence of autistic-like traits in people with SSD were identified (Davidson, Greenwood, Stansfield, & Wright, 2014; Hallerbäck, Lugnegård, & Gillberg, 2012; Matsuo et al., 2015). These studies point to a high prevalence of autistic traits in the SSD population. If we consider that many people with average-IQ forms of ASD have not been diagnosed during childhood (Lai & Baron-Cohen, 2015), it is not unreasonable to think that they have received a misdiagnosis of SSD during adulthood. It is noteworthy that many of these studies only used screening tools to explore the presence of ASD, which have low specificity in the diagnosis of ASD. Another limitation, implicit in any retrospective assessment, is the influence of a memory bias that might distort the

results of the procedure, which rests mainly on the testimony of relatives who often cannot accurately remember specific aspects of relevant developmental events.

Global burden of SSD/ASD

A constant in all studies is the high prevalence of SSD in people with ASD, much higher than in the general population. This supports the vulnerability argument for people with ASD to develop a psychotic disorder. One possible explanation for this phenomenon is a common genetic source shared by both disorders (Canitano & Pallagrosi, 2017; Crespi & Crofts, 2012; Guilmatre et al., 2009; Owen, O'Donovan, Thapar, & Craddock, 2011). The very high occurrence of psychotic symptomatology in this population suggests a shared biological etiology of both disorders. The neurodevelopmental hypothesis of schizophrenia proposes this as the end state of abnormal events occurring in early developmental stages (Owen et al., 2011; Rapoport, Giedd, & Gogtay, 2012). Thus, schizophrenia would share a common genetic origin with other neurodevelopmental disorders, such as ID, attention deficit and hyperactivity disorder, and ASD (Waltereit, Banaschewski, Meyer-Lindenberg, & Poustka, 2014).

Limitations

When addressing limitations of this study, it is first important to note that the original scope was to examine the prevalence of SSD in average-IQ adults with ASD, stating clearly the rationale for the criteria for study selection, and examining the results for evidence of publication bias. Other methodologies could be more appropriate for dealing with research questions more directly related to the similarities and differences between ASD and SSD (Chisholm, Lin, Abu-Akel, & Wood, 2015; Li et al., 2015) or for explaining and understanding in more detail the co-occurrence rate.

Among the most frequent diagnoses, it is curious to find a high proportion of “catchall" diagnoses. For example, in the case of ASD, a high percentage of studies included the diagnostic category "PDD-NOS” which refers to those developmental disorders that do not meet all criteria of a pervasive developmental disorder, in which ASD were included until recently. Similarly, the generic diagnostic "Psychotic disorder not otherwise specified" was reported in a large number of studies. This suggests a particular manifestation of both disorders when they occur simultaneously, making it difficult to conceptualize under the criteria established in standard diagnostic classifications.

Regarding the IQ criterion, it is known that a large percentage of people diagnosed with ASD present a comorbid intellectual deficit and for this reason they are not excluded in the studies relating comorbid mental disorders. Nevertheless, this could make it hard to establish a direct link between ASD and SSD, since the origin of psychotic symptoms could be explained for the ID rather than the ASD (Guilmatre et al., 2009; Morgan, Leonard, Bourke, & Jablensky, 2008). In our review, we decided to include only those studies that reported an above average mean IQ score for the total ASD sample. Nevertheless, as can be seen in the data synthesis, participants scoring below average were included. Although these subjects do not represent the majority of individuals, their results could be a source of bias, probably increasing considerably the prevalence of SSD in this population. In that case, an above-average IQ score would be considered a protective factor against the emergence of psychosis. More research in this field is needed.

In general, the results of the quality assessment are positive. However, there are some limitations that could affect the generalizability of these findings. First, the high heterogeneity of research methodology in each of the studies should be noted. Second, most of the studies took place in Sweden, which could raise questions about their external validity. Similarly, it could be argued that there is gender bias in the samples. Most of the studies had

overwhelmingly male samples, in some cases 100% male. This can be explained by a higher prevalence of ASD in males (Kim et al., 2011; Newschaffer et al., 2007). Still, we must highlight the importance of in-depth research concerning the presentation of ASD in female population, which has shown particular characteristics not shared by males with ASD (Werling & Geschwind, 2013).

Similarly, diagnostic tools used to evaluate the presence of ASD and SSD differ greatly between studies. Some studies include diagnostic tests that are usually used for screening assessments (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004), which are insufficient to establish a diagnosis of ASD. Only Ketelaars et al. (2008) used "gold standard" measures for ASD (Le Couteur, Lord, & Rutter, 2003; Rühl & Delmo, 1998). Interestingly, this was the only study not reporting any SSD in the ASD sample.

One of the limitations of the samples in most of the studies is that practically all of them involved assessments of a clinical population, i.e., subjects that, for one reason or another, have contacted a mental health service. These subjects could present a vulnerability to developing comorbid psychiatric disorders, which could bias the results in the direction of an overestimate of the prevalence of SSD in this population. Future studies should address this issue.

Finally, it seems particularly important to highlight follow-up studies, as these are the only observational studies that establish a sequence within the onset of SSD in a person previously diagnosed with ASD. Only three follow-up studies were identified in this review (Cederlund, Hagberg, Billstedt, Gillberg, & Gillberg, 2008; Gillberg, I. C., Helles, A., Billstedt, E., & Gillberg, 2016; Szatmari, Bartolucci, Bremner, Bond, & Rich, 1989). Future studies must be done and more refined assessments of genetic defects and biomarkers should be used. It would be useful to include a range of known variables (i.e. advanced paternal age and maternal infection/immune activation during pregnancy) that have been reported to increase the risk of

both ASD and SSD (Hommer & Swedo, 2015).These variables could help to clarify the causes of the association between ASD and SSD. Notwithstanding that, we hope that this study motivates other researchers to perform future epidemiological studies with in depth information that can add value for future meta-analyses.

Clinical implications

The findings support the idea of comorbidity between both disorders, although the limitations noted above regarding the nature of the sample and diagnostic methods suggest that caution regarding this conclusion is warranted. More research on this topic is needed, especially follow-up studies. This will result in improved intervention with this particular population, for which psychopharmacological treatment, while necessary, is insufficient until now. It is also necessary to treat those deficits relating communication, social interaction and sensory processing, thus preventing the recurrence of psychotic episodes. Also, a review of diagnostic classifications is imperative. It should take into account the possible emergence of psychotic symptoms in ASD individuals, without thereby developing a schizophrenic disorder. Finally, it is necessary to develop screening and diagnostic tools that allow early detection, thus improving intervention in this population.

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Figure 1. PRISMA flow diagram

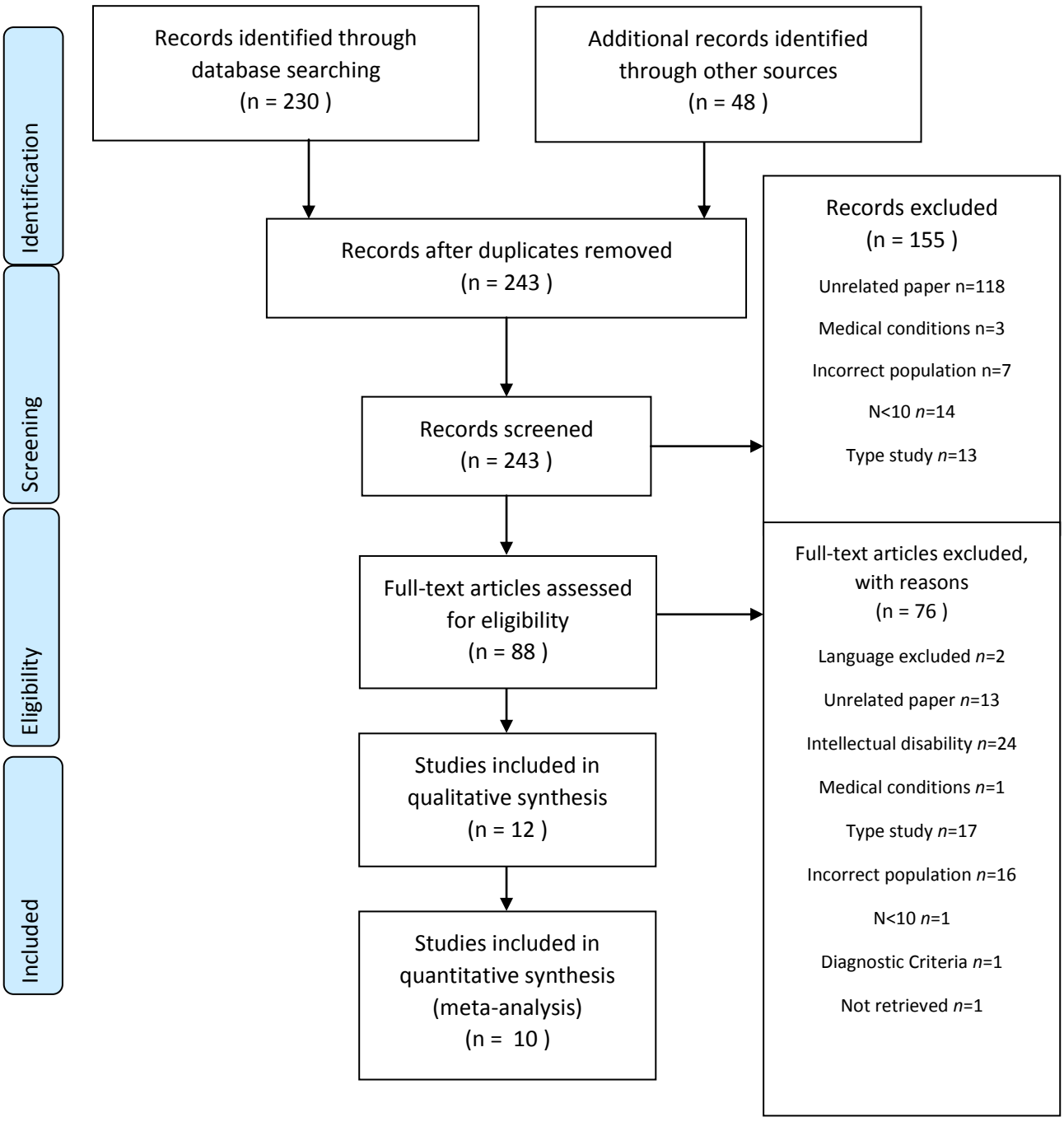

Figure 2. Forest plot of the pooled prevalence of SSD in average-IQ adults with ASD.

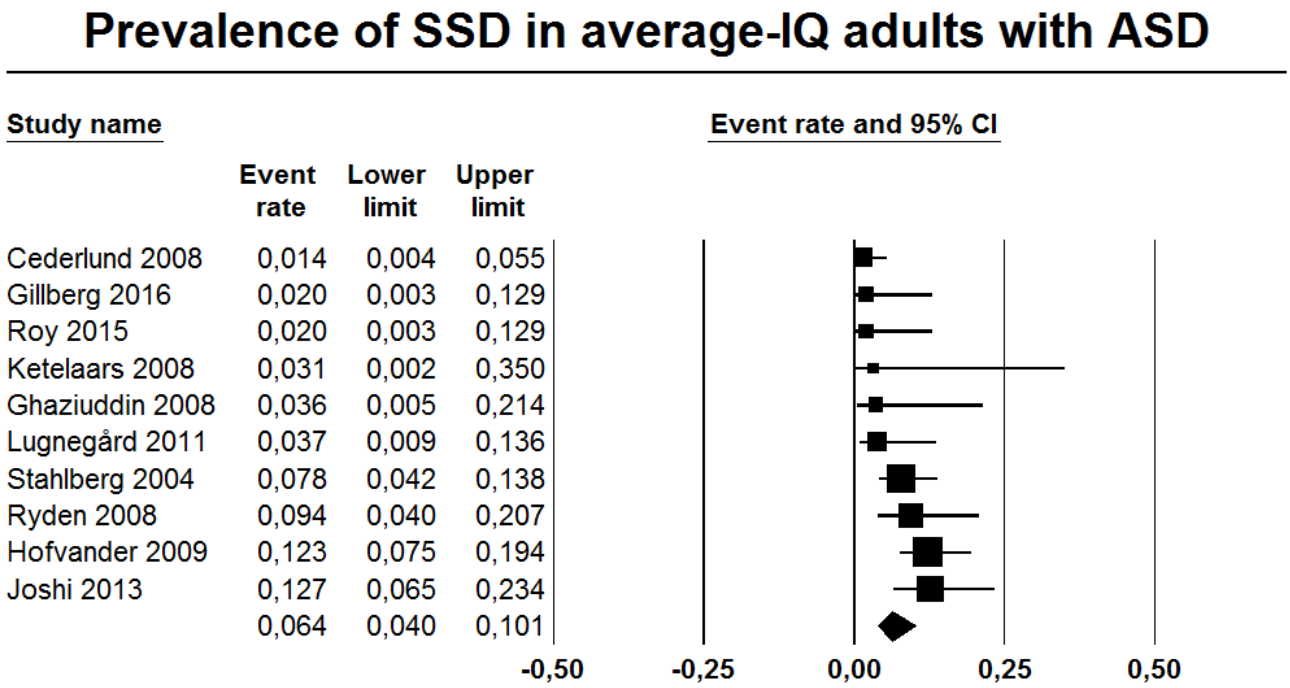

Figure 3. Funnel plot of Standard Error by Logit event rate. Large standard errors are indicative of a small sample size. A logit event rate that is negative in sign corresponds to an actual event rate that is smaller than 0.5 (50%), and vice versa.

Table 1. Search strategy summary

Source	Date (MM/DD/YY)	Search Strategy	Filters	Results
PsycINFO	03/09/16	((DE "Autism Spectrum Disorders") OR autism) AND ((DE "Schizophrenia") OR Schizophrenia) AND ((DE "Comorbidity" OR Comorbidity))	Publication year: 1980[a]-2016 Type: Academic journal Language: english, spanish; german Age: adulthood (18 years & older)	82
Medline	03/09/16	("Child Development Disorders, Pervasive"[Mesh] OR "pervasive developmental disorders"[All Fields]) AND ("Schizophrenia Spectrum and Other Psychotic Disorders"[Mesh] OR ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields])) AND ("Comorbidity"[Mesh] OR ("comorbidity"[MeSH Terms] OR "comorbidity"[All Fields]))		43
Embase	03/07/16	'autism'/exp OR autism AND ('schizophrenia'/exp OR schizophrenia) AND ('comorbidity'/exp OR comorbidity)		101
CINAHL	03/09/16	(MH "Child Development Disorders, Pervasive+") AND (MH "Schizophrenia+") AND (MM "Comorbidity")		4
TOTAL				230

[a] The start date was set in 1980 as this was the moment when autism was conceptualized as an independent category, separated from psychotic disorders.

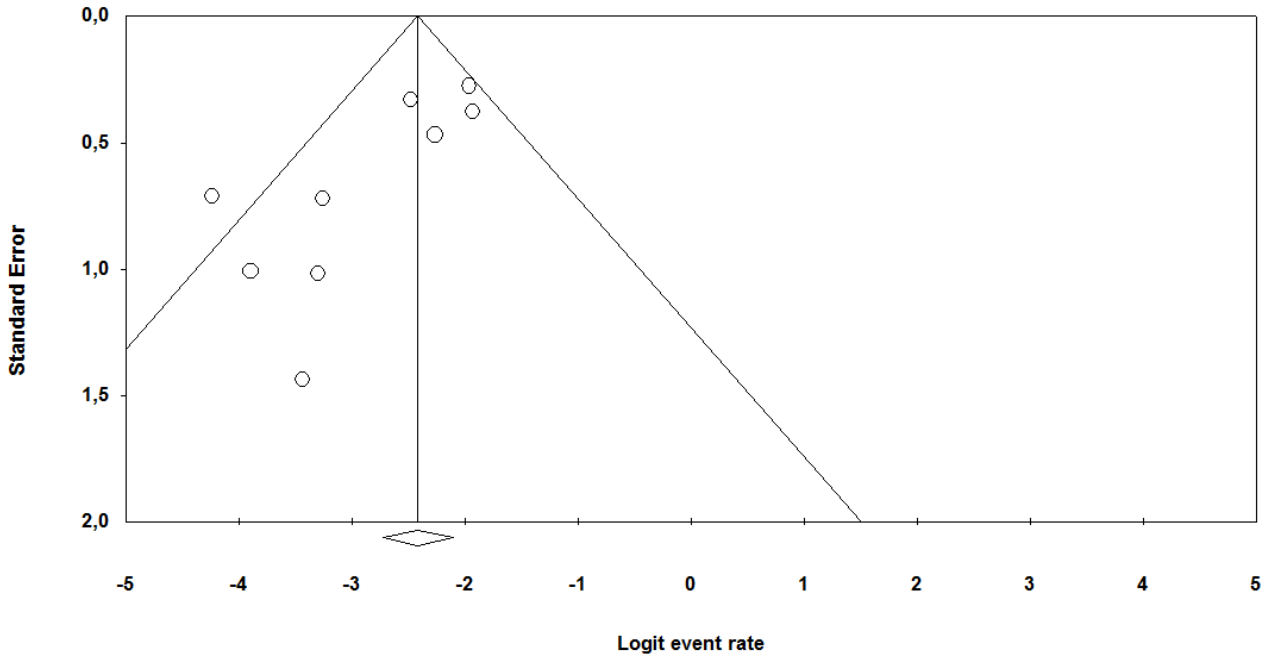

Table 2. Quality assessment of included studies

First Author (Year)	STROBE	LIMITATIONS
Szatmari (1989)	17/22	It does not report conducted statistical analyzes.
Stahlberg (2004)	12/22	It does not address the risk of bias. It does not report conducted statistical analyzes. It does not address the limitations of the study.
Cederlund (2008)	16/22	The risk of bias was not addressed. It does not report confidence intervals. It does not address the external validity of the results.
Ghaziuddin (2008)	15/22	It does not report conducted statistical analyzes. It does not report tools used in neuropsychological and language assessment. The diagnosis of ASD and comorbid psychiatric disorders is based on the clinical interview.
Ketelaars (2008)	14/22	It does not provide information on the risk of bias. It does not report confidence intervals. It does not address the external validity of the results.
Rydén (2008)	17/22	It does not report confidence intervals.
Hofvander (2009)	17/22	It does not provide information on the socio-demographic data of the sample.
Raja (2010)	16/22	It does not provide information on potentially eligible participants.
Lugnegård (2011)	17/22	It does not report conducted statistical analyzes.
Joshi (2013)	18/22	It does not report confidence intervals. It does not address the external validity of the results.
Roy (2015)	18/22	Use a self-made diagnostic tool for diagnosing Asperger Syndrome. It does not report conducted statistical analyzes. It does not justify the sample size. It does not address the risk of bias.
Gillberg (2016)	16/22	It does not report confidence intervals. It does not address the external validity of the results.

Table 3. Characteristics of included studies in the review

First Author (Year)	Country	N (% Male)	Mean Age (SD) (Range)	Mean IQ (SD) (Range)	Diagnostic Criteria	ASD diagnosis	SSD Measure	ASD Measure	Results
Szatmari (1989)*	Canada	16 (75)	26.1 (NR) (17-34)	92.4 (14.2) (68-110)	DSM-III	HFA 16	Diagnostic Interview for Children and Adolescents	Clinical records	Several people reported hearing voices and paranoid ideation. An individual diagnosed with chronic schizophrenia was under injectable antipsychotic treatment.
Stahlberg (2004)	Sweden	129 (56.02)	32 (9.4) (NR)	86.2 (21.3) (42-134)	DSM-IV	AD 13; AS 49; AA 67	SCID-I	ASSQ. ASDI.	10 participants (7.75%) with ASD diagnosis met criteria for schizophrenia or other SSD.
Cederlund (2008)	Sweden	76 (100)	21.5 (4.4) (16-33.9)	103.0 (14.8) (66-143)	DSM-IV ICD-10	AS 76	Clinical records	DISCO-10	2 participants (2.63%) with AS diagnosis met criteria for SSD. None had received a diagnosis of schizophrenia.
Ghaziuddin (2008)	USA	28 (64.29)	26.5 (11.3) (18-57)	NR (Only 2 had mild ID)	DSM-IV	AD 6; AS 14; PDD-NOS 8	Clinical records	Autism Behaviour Checklist.	1 participant (3.57%) met SSD criteria.
Ketelaars (2008)	Netherlands	15 (80)	22 (5) (18-24)	104 (10) (NR)	DSM-IV	AS 4; HFA 1; PDD-NOS 10	SCAN-2.1	ADI-R. ADOS-G	None ASD group participant met SSD criteria.
Rydén (2008)	Sweden	84 (53.57)	30 (10) (NR)	NR (IQ<70 excluded)	DSM-IV	AD 5; AS 51; PDD-NOS 28	Clinical records	ASSQ	5 ASD group participants (9.43%)* met criteria for SSD.
Hofvander (2009)	Sweden	122 (67.21)	29 (NR) (16-60)	NR (IQ<70 excluded)	DSM-IV	AD 5; AS 67; PDD-NOS 50	SCID-I	ADI	15 participants (12.2%) met SSD criteria (4 Schizophrenia, 3 Brief psychotic disorder, 1 DD).
Raja (2010)*	Italy	26 (96.15)	30.2 (9.8) (NR)	33.5 (18.2) (NR)	DSM-IV-TR	AD 5; AS 16; PDD-NOS 5	BPRS. SAPS. SANS	Clinical records. Family interview	16 participants (61.54%) met SSD criteria.
Lugnegård (2011)	Sweden	54 (51.85)	27 (3.9) (NR)	102 (12) (NR)	DSM-IV	AS 54	SCID-I	DISCO-11	2 participants (3.7%) with AS diagnosis met SSD criteria.
Joshi (2013)	USA	63 (100)	29.2 (11) (18-63)	104.4 (17.3) (55-136)	DSM-IV	AD 41; AS 16; PDD-NOS 6	SCID-I	Clinical interview	8 participants (12.6%) with ASD met SSD lifetime criteria, while 5 participants (8%) met SSD current criteria.
Roy (2015)	Germany	50 (68)	36.46 (NR) (20-65)	NR	DSM-IV	AS 50	SCID-I Clinical Interview	Diagnostic Interview: Asperger Syndrome in Adults. AQ. EQ.	1 participant (2%) met SSD criteria.
Gillberg (2016)	Sweden	50 (100)	30.2 (5) (23-43)	107.6 (IQ<70 excluded)	DSM-IV ICD-10	AS 50	MINI	Gillberg Criteria	1 participant (2%) with ASD met criteria for SSD.

ASD – Autism spectrum disorders; SSD – Schizophrenia spectrum disorders; AD – Autistic Disorder; AS – Asperger Syndrome; HFA – High-Functioning Autism; AA – Atypical Autism; PDD-NOS – Pervasive developmental disorder not otherwise specified; SCID-I- The *Structured Clinical Interview for DSM-IV* Axis I Disorders; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; BPRS - Brief Psychiatric Rating Scale; SAPS - Scale for the Assessment of Positive Symptoms; SANS - Scale for the Assessment of Negative Symptoms; MINI - The *Mini*-international neuropsychiatric *interview*; ASSQ – Asperger Syndrome Screening Questionnaire; ASDI – Asperger Syndrome Diagnostic Interview; ADI-R – Autism Diagnostic Interview Revised; ADOS-G – Autism Diagnostic Observation Schedule Generic; ADI – The Asperger Syndrome Diagnostic Interview; DISCO – Diagnostic Interview for Social and Communication Disorders; AQ – Autism Quotient; EQ – Empathy Quotient; BPD-PS – Bipolar disorder with psychotic symptoms; NR – Not reported.

* Studies excluded from the meta-analysis
* Only provided clinical data for 53 participants

Table 4. Comparison between FTD and typically ASD communication features.

FORMAL THOUGHT DISORDERS	ASD THOUGHT/SPEECH FEATURES
Alogia / Blocking	High latency response
Circumstantiality	Excessive and unnecessary details
Distractible speech	Attention to details
Echolalia	Echolalia
Illogicality / Incoherence / Neologisms	Stereotyped / Idiosyncratic speech
Perseveration / Pressure of speech / Tangentiality	Restricted interests
Self-reference	Lack of reciprocity
Stilted speech / Word approximations	Old-fashioned speech
Clanging / Flight of ideas	Attention to patterns
Evasive interaction	Contact avoidance