Tesis doctoral por compendio de publicaciones

Características psicopatológicas en adultos con Trastorno del Espectro Autista

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Dedicatoria

A la persona que se sentía *azul*.

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Autorización de los directores para la presentación en formato por compendio de publicaciones

El Dr. D. Ricardo Canal Bedia, Profesor Titular de Universidad, del Departamento de Personalidad, Evaluación y Tratamiento Psicológicos en la Universidad de Salamanca y el Dr. D. Emiliano Díez Villoria, Profesor Titular de Universidad, del Departamento de Psicología Básica, Psicobiología y Metodología de las ciencias del comportamiento

CERTIFICAMOS:

Que el presente trabajo de investigación titulado "CARACTERÍSTICIAS PSICOPATOLÓGICAS EN ADULTOS CON TRASTORNO DEL ESPECTRO AUTISTA" constituye el trabajo de investigación que bajo nuestra dirección ha realizado D. Jorge Lugo Marín, Especialista en Psicología Clínica, para optar al Grado de Doctor por la Universidad de Salamanca. La presente Tesis Doctoral se presenta en la modalidad de Tesis por Compendio de Artículos, optando a la mención de Doctor Internacional.

Para que así conste, y tenga los efectos oportunos, firmamos este certificado en Salamanca, a uno de junio de dos mil diecinueve.

Prof. Dr. Ricardo Canal Bedia

Prof. Dr. Emiliano Díez Villoria

Tesis doctoral por compendio de publicaciones

De acuerdo con el Real Decreto 99/2011, de 28 de enero, por el que se regulan las enseñanzas oficiales de doctorado, la Comisión de Doctorado y Posgrado de la Universidad de Salamanca (sesión de 15 de febrero de 2013) establece como posible formato de presentación de Tesis Doctoral, la modalidad de Tesis por Compendio de Artículos/Publicaciones. La presente Tesis Doctoral se presenta en esta modalidad, optando a la mención de Doctor Internacional.

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Indice

Resumen

El Trastorno del Espectro Autista (TEA) es una condición del neurodesarrollo cuyas características se extienden a lo largo de todo el ciclo vital. Las dificultades a las que se enfrentan estas personas se relacionan con dos áreas del funcionamiento global: la comunicación social y la flexibilidad cognitiva y comportamental. El conocimiento sobre la naturaleza del TEA ha aumentado considerablemente en las últimas décadas, si bien ha sido recientemente cuando ha comenzado a identificarse a las formas más leves del TEA. Esto se ha traducido en una mejora de la detección precoz y una intervención temprana que contribuye a mejorar la trayectoria de desarrollo de la persona con TEA. Sin embargo, son muchas las personas con TEA leve, esto es, capacidad intelectual en rango normativo y ausencia de alteraciones en el lenguaje verbal, que no fueron diagnosticadas en sus primeros años de vida, enfrentándose a las exigencias del entorno sin un conocimiento explícito de sus dificultades. Así pues, la investigación en TEA se ha centrado de manera intensiva en el estudio de las dificultades en las primeras etapas del desarrollo, quedando en un segundo plano el estudio de las dificultades específicas de la etapa adulta. En este sentido, es conocida la alta probabilidad de desarrollar sintomatología psiquiátrica relacionada con las dificultades en la adaptación al entorno en personas con TEA en la adultez. Sin embargo, hasta la actualidad son pocos los trabajos llevados a cabo sobre la ocurrencia de estas patologías en personas adultas con TEA. El primer objetivo de este trabajo fue cubrir esta necesidad a través de la revisión y síntesis cuantitativa de la literatura sobre prevalencia de trastornos psiquiátricos en personas adultas (18 años o mayor) con diagnóstico de TEA. Los resultados mostraron una elevada prevalencia de trastornos del neurodesarrollo (trastorno por déficit de atención e hiperactividad), trastornos afectivos (depresión) y trastornos del espectro de la ansiedad (fobia social, trastornos adaptativos y trastorno obsesivo-compulsivo). En general, se encontró una mayor prevalencia de trastornos psiquiátricos en población adulta con TEA en relación a los datos

reportados en población general. Esto señala al TEA como un posible factor de vulnerabilidad para el desarrollo de patología psiquiátrica. Si tenemos en cuenta el solapamiento entre algunas de las características relacionadas con el TEA y los diagnósticos psiquiátricos más prevalentes, los resultados encontrados podrían sobreestimar la prevalencia real de estos diagnósticos en esta población. Este es el caso de los trastornos del espectro de la esquizofrenia (TEE), los cuales comparten algunas de las características típicamente relacionadas con el TEA (síntomas negativos de la esquizofrenia vs. dificultades en comunicación social y flexibilidad cognitiva en el TEA). Por este motivo, se decidió explorar la relación entre ambos trastornos. Se llevó a cabo una revisión y síntesis cuantitativa de la evidencia sobre prevalencia de TEE en personas adultas con TEA y capacidad intelectual preservada. Los resultados encontrados apuntaban a una elevada concurrencia de ambos trastornos, estableciéndose la prevalencia de TEE en personas adultas con TEA sin discapacidad intelectual asociada en un 6%, siendo este dato muy superior a la prevalencia reportada en población general (1% - 2%). Debido al alto riesgo de confusión entre ambos diagnósticos, se decidió llevar a cabo la validación de una prueba diagnóstica que sirviese de apoyo en el proceso de evaluación diagnóstica de personas adultas con TEA y en el diagnóstico diferencial de los TEE. Para ello, se decidió utilizar el instrumento de evaluación para personas adultas con TEA 'Cociente Autista' en su forma abreviada, ya que este había mostrado su utilidad en la evaluación de características relacionadas con el TEA en población adulta en la literatura previa. Se realizó el proceso de traducción y adaptación de la prueba a lengua española. Esta se administró a cuatro grupos de participantes con edad igual o superior a 18 años y capacidad intelectual preservada (46 personas con TEA, 17 personas con TEE, 41 familiares de primer grado de personas con TEA, y 190 participantes sin historia previa de patología psiquiátrica). De igual modo, se estudió la convergencia de este instrumento con la prueba de evaluación gold-standard para el TEA en población adulta: ADOS-2 (Módulo 4). Los resultados del análisis estadístico mostraron buenas propiedades psicométricas del

instrumento, con una estructura factorial similar a la encontrada en estudios previos y buena consistencia interna y fiabilidad test-retest. El análisis de la validez convergente mostró una alta correlación con las puntuaciones en la medida gold-standard. Las puntuaciones en la prueba Cociente Autista abreviada fueron significativamente superiores en el grupo TEA en comparación a los otros grupos. Los grupos TEE y familiares de personas con TEA mostraron puntuaciones más elevadas en comparación al grupo de participantes sin historia de patología psiquiátrica. De esta manera, se concluye que el instrumento Cociente Autista abreviado permite discriminar entre personas con TEA y personas con diagnóstico de TEE. De igual modo, se confirma la estructura dimensional de características TEA, con una manifestación progresiva de los rasgos TEA a lo largo de un continuo, con una mayor expresión en poblaciones específicas.

Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition whose characteristics extend throughout the life cycle. The difficulties faced by these people are related to two areas of global functioning: social communication and cognitive/behavioral flexibility. Knowledge about the nature of ASD has increased considerably in recent decades, although it has been only recently that it has begun to identify the milder forms of ASD. This has resulted in an improvement in early detection and intervention that contributes to improve the developmental trajectory of the person with ASD. However, there are many people with mild ASD, that is, intellectual capacity in normative range and absence of alterations in verbal language, which were not diagnosed in their first years of life, facing the demands of the environment without an explicit knowledge of their difficulties. Thus, research in ASD has focused intensively on the study of difficulties in the early stages of development, leaving aside the study of the specific difficulties in the adult stage. In this sense, the high probability of developing psychiatric symptoms related to the difficulties in adapting to the environment in people with ASD in adulthood is quite known. However, until now there has not been an extensive review of the occurrence of these pathologies in adults with ASD. The first objective of this work was to cover this need through the review and quantitative synthesis of the literature on prevalence of psychiatric disorders in adults (18 years or older) diagnosed with ASD. The results showed a high prevalence of neurodevelopmental disorders (Attention Deficit and Hyperactivity Disorder), affective disorders (depression) and anxiety spectrum disorders (social phobia, adaptive disorders and obsessive-compulsive disorder). In general, a higher prevalence of psychiatric disorders was found in the adult population with ASD in relation to the data reported in the general population. This points to ASD as a possible factor of vulnerability for the development of psychiatric pathology. If we consider the overlap between some of the characteristics related to ASD and the most prevalent psychiatric diagnoses, the

results found could overestimate the real prevalence of some of these diagnoses in this specific population. This is the case of Schizophrenia Spectrum Disorders (SSD), which share some of the characteristics typically related to ASD (negative symptoms in SSD vs. difficulties in social communication and cognitive flexibility in ASD). For this reason, it was decided to explore the relationship between both disorders. A review and quantitative synthesis of the evidence on the prevalence of SSD in adults with ASD without intellectual disability was carried out. The results found pointed to a high co-occurrence of both disorders, establishing the prevalence of SSD in adults with ASD without intellectual disability by 6%, being this much higher than the estimated prevalence reported in general population (1% - 2%). Due to the high risk of confusion between both diagnoses, it was decided to carry out the validation of a diagnostic test that would serve as support in the process of diagnostic evaluation of adults with ASD and in the differential diagnosis of the SSD. For this, it was decided to use the evaluation tool for adults with ASD 'Autism Quotient' in its abbreviated form, since it has shown previously its usefulness in the evaluation of characteristics related to ASD in the adult population. The process of translation and adaptation of the test to Spanish language was carried out. This was administered to four groups of participants aged 18 years or older and preserved intellectual capacity (46 people with ASD, 17 people with SSD, 41 ASD first-degree relatives, and 190 participants without a previous history of psychiatric pathology). Likewise, the convergence of this with a gold-standard instrument for ASD in the adult population was studied. The results of the statistical analysis showed good psychometric properties of the instrument, with a factorial structure similar to that found in previous studies and good internal consistency and test-retest reliability. The analysis of the convergent validity showed a high correlation with the gold-standard instrument. Scores on the abbreviated Autism Quotient were significantly higher in the ASD group compared to the other groups. SSD groups and relatives of people with ASD showed higher scores compared to the group of participants with no prior history of psychiatric pathology. In this way, it is concluded that the abbreviated

Autism Quotient allows to discriminate between people with ASD and people diagnosed with SSD. Likewise, the dimensional structure of ASD features is confirmed, with a progressive manifestation of ASD features along a continuum, with greater expression in specific populations.

Introducción

El Trastorno del Espectro Autista (TEA) es una condición del neurodesarrollo con un gran impacto en el funcionamiento global de la persona. Los criterios diagnósticos incluyen alteraciones en el área de la comunicación social y dificultades en flexibilidad cognitiva y comportamental (American Psychiatric Association, 2013). La comunicación social se refiere a aquellos procesos que tienen lugar en la interacción entre personas. Las personas con TEA muestran un déficit para establecer inferencias sobre los pensamientos, las intenciones y las emociones propias y de los otros (Baron-Cohen, Leslie, & Frith, 1985; Baron-Cohen, 1989). Esto provoca un funcionamiento menoscabado a nivel social, ya que muchas de estas personas requieren de un elevado esfuerzo cognitivo para manejarse en entornos sociales. La flexibilidad cognitiva se refiere a la capacidad para adaptarse a los cambios y a las situaciones nuevas. Esto se traduce en una preferencia por situaciones ya conocidas, desarrollando patrones de conducta e intereses repetitivos altamente resistentes al cambio. Como ocurre en el caso de las dificultades en el área de la socialización, esta rigidez cognitiva genera una gran interferencia en el funcionamiento habitual de la persona, precisando de una anticipación previa a los cambios y situaciones nuevas que, en la mayoría de las ocasiones, no resulta posible llevar a cabo.

Como se ha comentado al inicio de esta introducción, el TEA es una condición del neurodesarrollo, esto es, se encuentra presente desde el nacimiento y se prolonga a lo largo de todo el ciclo vital. Desde su conceptualización como entidad independiente a principios de la década de los años 80 (American Psychiatric Association, 1980), la identificación diagnóstica del TEA ha ido en aumento, estableciéndose una prevalencia actual de 1 de cada 59 personas (Baio et al., 2018). Esto ha supuesto una mejora en las intervenciones dirigidas a mejorar el funcionamiento de las personas con TEA, especialmente en los primeros años de vida en los que se ha demostrado que una detección e intervención tempranas mejoran la trayectoria de

desarrollo de la persona con TEA (Bryson, Rogers, & Fombonne, 2003; Dawson & Bernier, 2013). Sin embargo, muchas de las personas que presentan las formas más leves de TEA, no han sido identificadas en los primeros años de vida (Lai & Baron-Cohen, 2015). Esto es debido principalmente a la tardía inclusión de las formas más leves de TEA en las clasificaciones diagnósticas. Hasta los años 80, el autismo era considerado un síntoma específico de la esquizofrenia (Bleuler, 1911). No fue hasta los trabajos de Lorna Wing, psiquiatra inglesa y madre de una niña con TEA, que la comunidad científica comenzó a identificar al TEA en su forma leve (Wing, 1981; Wing & Gould, 1979). Wing re-descubrió los trabajos del psiquiatra austríaco Hans Asperger, quien en los años 40 ya describió una forma de autismo que, contrariamente a lo que se pensaba en los años setenta, podía presentar una capacidad intelectual y lenguaje verbal preservados (Asperger, 1944). Fue gracias a esto que el autismo se separó de los trastornos del espectro de la esquizofrenia (TEE) en los manuales diagnósticos (American Psychiatric Association, 1980). En los años 90, comenzó a extenderse el conocimiento sobre esta forma de autismo más leve que presentaba un nivel intelectual dentro del rango normativo, así como una ausencia de alteraciones en la adquisición del lenguaje verbal (American Psychiatric Association, 1994). A esta forma leve de autismo se la denominó Síndrome de Asperger, categoría que se mantuvo hasta la última edición del Manual Diagnóstico y Estadístico de los Trastornos Mentales de la Asociación Americana de Psiquiatría (American Psychiatric Association, 2013), en la que se incluyó una nueva categoría general denominada Trastorno del Espectro Autista, con tres niveles de gravedad en base a los apoyos requeridos (Tablas 1 y 2).

Tabla 1. Criterios diagnósticos DSM-5 para el Trastorno del Espectro Autista (American Psychiatric Association, 2013)

A. Deficiencias persistentes en la comunicación social y en la interacción social en diversos contextos, manifestado por lo siguiente, actualmente o por los antecedentes: • Deficiencias de reciprocidad socioemocional • Deficiencias en las conductas comunicativas no verbales empleadas en la interacción social • Deficiencias en el desarrollo, mantenimiento y comprensión de las relaciones
B. Patrones restrictivos y repetitivos de comportamiento, intereses o actividades, que se manifiestan en dos o más de los siguientes puntos, actualmente o por los antecedentes: • Movimientos, utilización de objetos o habla estereotipados o repetitivos • Insistencia en la monotonía, excesiva inflexibilidad de rutinas o patrones ritualizados de comportamiento verbal o no verbal • Intereses muy restringidos y fijos que son anormales en cuanto a su intensidad o foco de interés • Hiper- o hiporreactividad a los estímulos sensoriales o interés inhabitual por aspectos sensoriales del entorno
C. Los síntomas han de estar presentes en las primeras fases del período de desarrollo (pero pueden no manifestarse totalmente hasta que la demanda social supera las capacidades limitadas, o pueden estar enmascarados por estrategias aprendidas en fases posteriores de la vida).
D. Los síntomas causan un deterioro clínicamente significativo en lo social, laboral u otras áreas importantes del funcionamiento habitual.
E. Estas alteraciones no se explican mejor por la discapacidad intelectual (trastorno del desarrollo intelectual) o por el retraso global del desarrollo. La discapacidad intelectual y el trastorno del espectro del autismo con frecuencia coinciden; para hacer diagnósticos de comorbilidades de un trastorno del espectro del autismo y discapacidad intelectual, la comunicación social ha de estar por debajo de lo previsto para el nivel general de desarrollo.
Especificar si: • Se acompaña o no de discapacidad intelectual • Se acompaña o no de deterioro del lenguaje • Está o no asociado a afección médica o genética, o un factor ambiental conocido • Está asociado a otro trastorno del desarrollo neurológico o del comportamiento

Tabla 2. Clasificación DSM-5 basada en niveles de apoyo del TEA (American Psychiatric Association, 2013)

Nivel de gravedad	**Comunicación social**	**Comportamiento restringidos y repetitivos**
Grado 3: "Necesita ayuda muy notable"	Las deficiencias graves de las aptitudes de comunicación social verbal y no verbal causan alteraciones graves del funcionamiento, inicio muy limitado de las interacciones sociales y respuesta mínima a la apertura social de otras personas. Por ejemplo, una persona con pocas palabras inteligibles que raramente inicia interacción y que, cuando lo hace, realiza estrategias inhabituales sólo para cumplir con las necesidades y únicamente responde a aproximaciones sociales muy directas.	La inflexibilidad de comportamiento, la extrema dificultad de hacer frente a los cambios u otros comportamientos restringidos/repetitivos interfieren notablemente con el funcionamiento en todos los ámbitos. Ansiedad intensa/dificultad para cambiar el foco de acción.
Grado 2: "Necesita ayuda notable"	Deficiencias notables de las aptitudes de comunicación social verbal y no verbal; problemas sociales aparentes incluso con ayuda *in situ*; inicio limitado de interacciones sociales; y reducción de respuesta o respuestas no normales a la apertura social de otras personas. Por ejemplo, una persona que emite frases sencillas, cuya interacción se limita a intereses especiales muy concretos y que tiene una comunicación no verbal muy excéntrica.	La inflexibilidad de comportamiento, la dificultad de hacer frente a los cambios u otros comportamientos restringidos/repetitivos aparecen con frecuencia claramente al observador casual e interfieren con el funcionamiento en diversos contextos. Ansiedad y/o dificultad para cambiar el foco de acción.
Grado 1: "Necesita ayuda"	Sin ayuda *in situ*, las deficiencias en la comunicación social causan problemas importantes. Dificultad para iniciar interacciones sociales y ejemplos claros de respuestas atípicas o insatisfactorias a la apertura social de otras personas. Puede parecer que tiene poco interés en las interacciones sociales. Por ejemplo, una persona que es capaz de hablar con frases completas y que establece comunicación, pero cuya conversación amplia con otras personas falla y cuyos intentos de hacer amigos son excéntricos y habitualmente sin éxito.	La inflexibilidad de comportamiento causa una interferencia significativa con el funcionamiento en uno o más contextos. Dificultad para alternar actividades. Los problemas de organización y de planificación dificultan la autonomía.

Dificultades relacionadas con el TEA en la etapa adulta

Si bien el conocimiento sobre el TEA ha aumentado significativamente en las últimas dos décadas, aún queda mucho por conocer sobre su manifestación en las etapas más avanzadas del ciclo vital. La investigación científica se ha centrado en el estudio de las características del trastorno en la etapa infantil y adolescente, dejando en un segundo plano el estudio de las dificultades específicas de aparición en la edad adulta. Si tenemos en cuenta que se trata de una condición que se extiende desde el nacimiento hasta el final de la vida de la persona, se hace necesario un conocimiento profundo de su manifestación en todos los momentos del ciclo vital, ya que las dificultades relacionadas con el trastorno pueden ser diferentes en cada etapa del desarrollo humano.

A lo largo del desarrollo vital, las personas nos enfrentamos a desafíos que son específicos de cada una de las etapas del desarrollo. Estos hitos evolutivos serán alcanzados en la medida que la persona cuente con las habilidades para adaptarse a los cambios y sea capaz de establecer vínculos positivos con el entorno. Como se puede deducir de esto, las personas con TEA se enfrentarán a desafíos cada vez más exigentes a medida que avancen a través del ciclo vital.

De este modo, el final de la etapa adolescente y principio de la vida adulta parece ser un momento crítico para las personas con TEA. Estos son años de grandes cambios, con un incremento de las exigencias en el área de la socialización y el inicio del proceso de individuación de la persona, disminuyendo progresivamente la protección que ofrece el núcleo de apoyo primario. En estos momentos en los que las personas damos forma a nuestro auto-concepto, estableciendo las bases de nuestra personalidad, se inicia la búsqueda de un grupo de pertenencia externo, que conforme una red social de apoyo y facilitadora de oportunidades para el desarrollo de la persona. Los estudios llevados a cabo señalan que en la edad adulta las personas con TEA, a pesar de presentar un elevado deseo por relacionarse con otras personas, fracasan en sus intentos, provocando situaciones de aislamiento y malestar psicológico

(Müller, Schuler, & Yates, 2008; Orsmond, Shattuck, Cooper, Sterzing, & Anderson, 2013; Sperry & Mesibov, 2005; Tobin, Drager, & Richardson, 2014). Igualmente, la necesidad de aprender a manejarse en entornos cambiantes, así como de adaptarse a situaciones nuevas que permitirían avanzar en nuestros proyectos vitales (formación académica, búsqueda de empleo, etc.), suponen un obstáculo difícilmente salvable para estas personas. Las dificultades en el área de la interacción social, así como la falta de habilidades para flexibilizar y la rigidez en los intereses y conductas provocan que muchas de estas personas fracasen en sus intentos por conseguir una formación académica o puesto de trabajo acorde a su capacidad intelectual (Baldwin, Costley, & Warren, 2014; Hendricks, 2010; Roux et al., 2013; Taylor & Seltzer, 2011).

Patología psiquiátrica concomitante en personas adultas con TEA

En este sentido, las personas con TEA experimentan en esta etapa una gran carga de estrés, ya que no consiguen cumplir con los hitos evolutivos, quedándose un paso por detrás de sus iguales a nivel cronológico (Billstedt, Gillberg, & Gillberg, 2005; Cederlund, Hagberg, Billstedt, Gillberg, & Gillberg, 2008; Howlin, 2000; Stewart, Barnard, Pearson, Hasan, & O'Brien, 2006). Esto es especialmente relevante en aquellas personas que presentan formas leves de TEA que no han sido previamente identificadas, las cuales se enfrentan a estas exigencias evolutivas sin un conocimiento explícito de sus dificultades, desarrollando en muchas ocasiones sintomatología psiquiátrica que puede enmascarar las características TEA (Lehnhardt et al., 2013; van Elst, Pick, Biscaldi, Fangmeier, & Riedel, 2013). Las investigaciones llevadas a cabo en este sentido señalan una alta prevalencia de trastornos afectivos y del espectro de la ansiedad en personas adultas con TEA (Hofvander et al., 2009; Lugnegård, Hallerbäck, & Gillberg, 2011; Tantam, 2000). En relación a los trastornos afectivos, la depresión presenta una elevada ocurrencia en personas adultas con TEA, relacionándose con experiencias de victimización (Shtayermman, 2007) con la intensidad de las características TEA (Sterling, Dawson, Estes, &

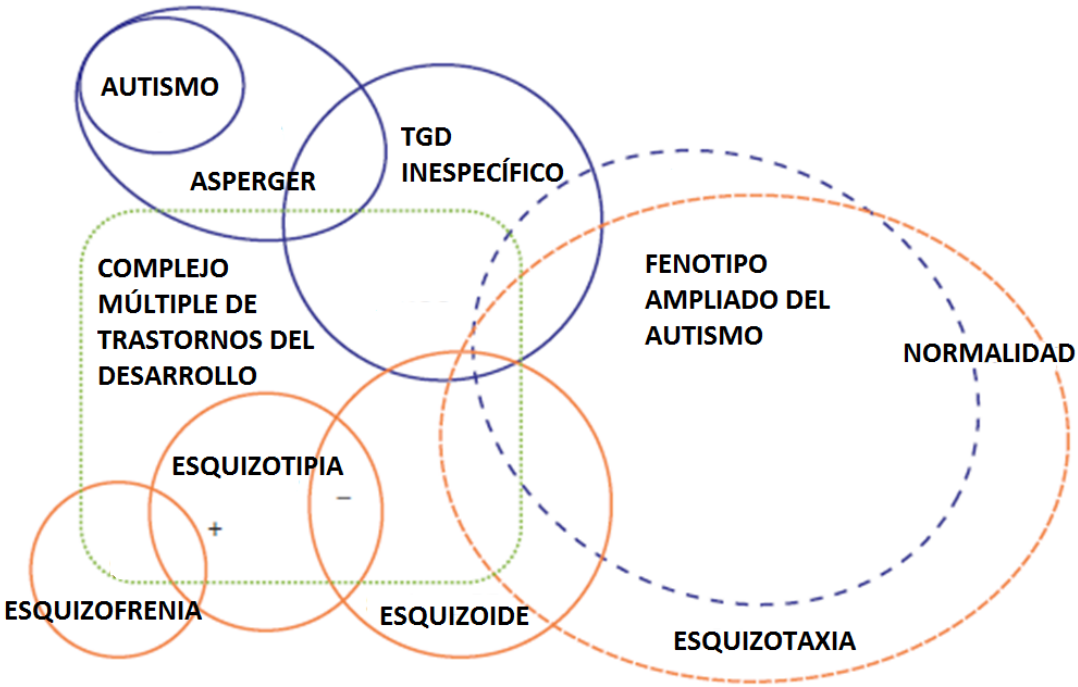
Greenson, 2008) y con un incremento en el riesgo de llevar a cabo una tentativa de suicidio (Cassidy et al., 2014; Kato et al., 2013; Paquette-Smith, Weiss, & Lunsky, 2014). La ocurrencia de trastornos del espectro de la ansiedad conforma la otra patología psiquiátrica de mayor prevalencia en población adulta con TEA, entre los cuales sobresale el trastorno de ansiedad social (Bejerot, Eriksson, & Mörtberg, 2014), el cual se encuentra intrínsecamente relacionado con las dificultades específicas del TEA en el área de la comunicación social (Gillott & Standen, 2007). Otros de los trastornos psiquiátricos de aparición en la etapa adulta incluyen los trastornos por el consumo de sustancias (Kronenberg, Goossens, van Busschbach, van Achterberg, & van den Brink, 2015; Sizoo et al., 2009), los trastornos de personalidad (Lugnegård, Hallerbäck, & Gillberg, 2012; Strunz et al., 2015) y los trastornos del espectro de la esquizofrenia (Hallerbäck, Lugnegård, & Gillberg, 2012; Hofvander et al., 2009; Lugnegård, Hallerbäck, & Gillberg, 2015), si bien el solapamiento entre los criterios diagnósticos de algunos de estos trastornos podría resultar en la sobreestimación de estas patologías en los adultos con TEA (Lugnegård et al., 2012; Spek & Wouters, 2010; Woodbury-Smith, Boyd, & Szatmari, 2010).

La relación entre el TEA y los Trastornos del Espectro de la Esquizofrenia

Desde la primera conceptualización de Bleuler del autismo como un síntoma central del trastorno esquizofrénico (Bleuler, 1911), la relación entre ambos trastornos ha sido ampliamente discutida en la literatura científica. Tras la diferenciación del autismo como categoría independiente en el DSM-III (American Psychiatric Association, 1980), las diferencias clínicas parecían superadas. Sin embargo, estudios posteriores todavía apuntan a una gran brecha en la comprensión de la relación entre los dos trastornos, con una cantidad considerable de literatura que aborda la superposición diagnóstica de los síntomas clínicos (Fitzgerald, 2012; Hallerbäck et al., 2012; King & Lord, 2011; Nylander, Lugnegård, &

Hallerbäck, 2008; Stone & Iguchi, 2011) (Figura 1). Los estudios sobre marcadores neurobiológicos buscan una relación compartida entre los dos trastornos (Abu-Akel, Apperly, Wood, & Hansen, 2017; Cheung et al., 2010; Hirjak et al., 2014; Parellada et al., 2017; Radeloff et al., 2014). De igual manera, otros estudios se han centrado en el estudio de diferencias basadas en el funcionamiento neuropsicológico, obteniendo resultados que sugieren una afectación similar en ambos trastornos (de Boer, Spek, & Lobbestael, 2014; Eack et al., 2013; Goldstein, Minshew, Allen, & Seaton, 2002; Marinopoulou, Lugnegård, Hallerbäck, Gillberg, & Billstedt, 2016).

Figura 1. Complejo Múltiple de Trastornos del Desarrollo (tomado de Nylander, 2014)



Con respecto al estudio del solapamiento a nivel de sintomatología clínica, numerosos estudios han mostrado interés en explorar empíricamente este problema. Al medir la presencia de rasgos similares al TEA (TEA-like) en adultos con trastornos del espectro de la esquizofrenia (TEE), los estudios reportaron una alta prevalencia de estos, lo que sugiere una relación directa entre ambos trastornos (Barlati, Deste, Gregorelli, & Vita, 2018; Lugnegård et al., 2015; Spek &

Wouters, 2010). De la misma manera, muchas personas con TEA desarrollan síntomas similares a los TEE (Blackshaw, Kinderman, Hare, & Hatton, 2001; Craig, Hatton, Craig, & Bentall, 2004; Jänsch & Hare, 2014), considerando las características autistas como un factor de riesgo para recibir un diagnóstico que se incluye dentro del espectro de la esquizofrenia. Debido a la inclusión tardía de las formas más leves de TEA (con capacidad intelectual y lenguaje verbal preservados) en las clasificaciones diagnósticas, las personas con un posible TEA, que presentan graves dificultades adaptativas, están siendo identificadas cada vez más en el entorno clínico. Es muy probable que estas personas no fueran identificadas en los primeros años de vida (Lai & Baron-Cohen, 2015). Por lo tanto, cuando se considera la superposición entre los criterios diagnósticos para el TEA y los TEE, no es difícil darse cuenta que muchos de ellos pueden haber sido diagnosticados erróneamente, sobreestimando la prevalencia de TEE en personas con TEA.

Evaluación del TEA en personas adultas

En la actualidad, se cuenta con herramientas diagnósticas para la evaluación del TEA que han mostrado ser altamente útiles en el proceso de evaluación diagnóstica (Le Couteur, Lord, & Rutter, 2003; Lord et al., 2012). Si bien estas pruebas han mostrado su validez en la detección de casos de TEA en población adulta, la mayoría de ellas se concibieron para su uso en población infanto-juvenil. En este sentido, en los últimos años se han venido desarrollando algunos instrumentos diseñados específicamente para la evaluación de características relacionadas con el TEA en población adulta. En una revisión sobre instrumentos de evaluación de TEA en personas adultas, se encontró una escasez en la disponibilidad de pruebas que hubiesen mostrado buenas propiedades en el proceso de evaluación de personas adultas con TEA (Baghdadli, Russet, & Mottron, 2017). Los autores de la revisión señalan al instrumento 'Cociente Autista' (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) como uno de

los que mejores resultados ha reportado en su uso como instrumento en la evaluación de personas adultas con TEA. Se trata de un cuestionario autoinformado de 50 ítems que evalúa características relacionadas con el TEA. La persona debe responder en una escala Likert de cuatro puntos (desde Totalmente de acuerdo hasta Totalmente en desacuerdo) con una puntuación que varía de 0 hasta 50 puntos. En el estudio de validación original se encontró que la puntuación media del grupo TEA fue de 35, mientras que una puntuación de 32 haría sospechar de la posible presencia de un TEA (Baron-Cohen et al., 2001). En 2011, Hoekstra et al. elaboraron una versión abreviada del instrumento. Este estaba formado por 28 ítems tomados del cuestionario original y una puntuación distribuida en cinco factores: habilidades sociales, rutinas, flexibilidad, imaginación y números/patrones.

Características TEA en poblaciones específicas medidas a través del Cociente Autista

Este instrumento ha mostrado su utilidad en el estudio de características relacionadas con el TEA en población general (Murray, McKenzie, Kuenssberg, & Booth, 2017; Ruzich et al., 2015), y poblaciones clínicas (Kuenssberg, Murray, Booth, & McKenzie, 2014; Lugnegård et al., 2015; Naito, Matsui, Maeda, & Tanaka, 2010; Sizoo et al., 2009; Wakabayashi, Baron-Cohen, Wheelwright, & Tojo, 2006; Westwood et al., 2016). En relación a los TEE, los estudios llevados a cabo con el Cociente Autista han encontrado puntuaciones elevadas en este instrumento, sugiriendo una alta prevalencia de rasgos TEA-like en esta población (Hallerbäck et al., 2012; Lugnegård et al., 2015; Naito et al., 2010; Spek & Wouters, 2010).

Este instrumento se ha empleado también en el estudio de rasgos TEA-like en familiares de primer grado de personas con TEA (Bishop et al., 2004; Wheelwright, Auyeung, Allison, & Baron-Cohen, 2010). Estos estudios han reportado mayores puntuaciones en el Cociente Autista en familiares de personas con TEA en comparación con muestras de población general. A esta expresión subclínica del TEA se le ha denominado ‘Fenotipo Ampliado del Autismo’,

concepto que hace referencia a una manifestación de las características relacionadas con el TEA superior a la que presenta la población general, si bien esta no alcanzaría el rango de interferencia a nivel adaptativo para establecer un diagnóstico de TEA (Bishop et al., 2004; Klusek, Losh, & Martin, 2014; Losh, Childress, Lam, & Piven, 2008; Micali, Chakrabarti, & Fombonne, 2004).

Objetivos

Objetivo general

Estudiar los perfiles psicopatológicos más frecuentes en personas adultas con diagnóstico de TEA.

Objetivos específicos

- Realizar una revisión y síntesis cuantitativa de los estudios publicados sobre prevalencia de trastornos psiquiátricos en personas adultas con TEA.
- Realizar una revisión y síntesis cuantitativa de los datos de prevalencia de TEE en personas adultas con TEA con capacidad intelectual en rango normativo.
- Validar un instrumento de evaluación diagnóstica en lengua española para personas adultas con TEA con capacidad intelectual en rango normativo.
- Estudiar la fiabilidad a través del análisis de la consistencia interna y el análisis test-retest.
- Estudiar la estructura factorial del instrumento.
- Estudiar la convergencia con medidas de evaluación diagnóstica gold-standard en personas adultas con TEA.
- Estudiar las propiedades discriminativas y predictivas del instrumento.
- Estudiar las diferencias en las puntuaciones en el instrumento en participantes con TEE, familiares de personas con TEA y población sin historia conocida de patología psiquiátrica.

Hipótesis

Hipótesis general

Los resultados encontrados en este trabajo permitirán establecer perfiles psicopatológicos específicos de personas adultas con TEA.

Hipótesis específicas

- La revisión y posterior síntesis cuantitativa de la literatura científica resultará en una elevada prevalencia de trastornos psiquiátricos en personas con TEA, siendo esta superior a la reportada en población general.
- La revisión y posterior síntesis cuantitativa de la literatura científica resultará en una elevada prevalencia de TEE en personas con TEA, siendo esta superior a la reportada en población general.
- El instrumento de evaluación diagnóstica de TEA mostrará buenas propiedades psicométricas en población adulta de habla española y capacidad intelectual preservada.
    - El instrumento permitirá discriminar entre personas adultas con diagnóstico de TEA y aquellas con diagnóstico de TEE.
    - El instrumento presentará una alta convergencia con la medida gold-standard de evaluación de TEA.
    - Las personas con TEA presentarán puntuaciones más elevadas en comparación a los otros grupos de participantes. El grupo de pacientes con diagnóstico de TEE y el grupo de familiares de personas con TEA presentarán puntuaciones más elevadas en comparación a al grupo de participantes sin historia de patología psiquiátrica.

Método

Los materiales y métodos empleados en el presente trabajo se pueden consultar en los artículos de este compendio de Tesis Doctoral. Se presentarán por separado los estudios de revisión/metaanálisis y el estudio de validación del instrumento diagnóstico para personas adultas con TEA y capacidad intelectual en rango normativo. En los respectivos artículos se describió el diseño, las características de la muestra, los procedimientos, los instrumentos de medida y los análisis estadísticos de cada estudio.

Presentación de los trabajos que comprende la tesis

Justificación de la unidad temática y coherencia de la línea de investigación

El objetivo principal de este trabajo consistió en explorar perfiles de patología psiquiátrica frecuente en personas adultas con diagnóstico de TEA. Para ello, comenzamos por realizar una revisión sistemática y metaanálisis de la evidencia sobre trastornos psiquiátricos diagnosticados en población adulta con TEA. Se encontró una elevada frecuencia de trastornos afectivos (depresión), así como trastornos del espectro de la ansiedad (trastorno obsesivo-compulsivo, trastornos adaptativos, fobia social). Tras analizar los trastornos psiquiátricos más prevalentes en esta población, se concluyó la elevada prevalencia de diagnósticos psiquiátricos en personas adultas con TEA. Si bien estos resultados coinciden con lo encontrado en la literatura previa, se detectó un probable solapamiento entre las características del TEA y los síntomas de otros trastornos psiquiátricos, lo cual puede haber sobreestimado la prevalencia de patología psiquiátrica presentada por esta población. En este sentido, se identificó un área aun no cubierta por la literatura existente. La alta prevalencia diagnóstica de TEE en adultos con TEA nos llevó a cuestionar la relación entre ambos trastornos. Para ello, se realizó una nueva revisión sobre la relación entre TEA y esquizofrenia, esta vez centrada en adultos con nivel intelectual preservado, concluyendo una prevalencia de TEE en población adulta con TEA significativamente superior a la identificada en población general. Tras esto, se exploró la metodología empleada en el diagnóstico diferencial entre ambas condiciones, concluyendo que no existía ningún instrumento diagnóstico que permitiese distinguir entre ambas condiciones. Por esta razón, se decidió validar un instrumento de evaluaciónque permitiese diferenciar entre ambos trastornos. Para ello, se eligió la escala ‘Cociente Autista’ en su forma abreviada. Las razones para su elección se basaron en las adecuadas propiedades

psicométricas mostradas por el instrumento en la literatura previa, así como el bajo coste en términos de tiempo y esfuerzo cognitivo para el evaluado. Además de las dos muestras de participantes clínicos, se decidió incluir un grupo de familiares de personas con TEA, así como un grupo de población sin antecedentes de patología psiquiátrica. Estos grupos comparativos permitían comprobar la hipótesis dimensional de los rasgos TEA, la cual se encuentra en la base de los criterios diagnósticos para el TEA de la última versión del Manual Diagnóstico y Estadístico de la Asociación Americana de Psiquiatría (DSM-5), y que defiende un continuo de intensidad en la manifestación de las características TEA desde la no manifestación o manifestación leve hasta la expresión extrema del trastorno. En ese sentido, se hipotetizó que las muestras clínicas (TEA y TEE) presentarían puntuaciones más elevadas en el instrumento diagnóstico en comparación a la muestras no clínicas (familiares de personas con diagnóstico de TEA y población sin historia de patología psiquiátrica). En relación a los grupos no clínicos, se hipotetizó que los familiares de personas con diagnóstico de TEA presentarían puntuaciones más elevadas en el instrumento de evaluación de rasgos TEA en comparación con el grupo de participantes sin historia previa de patología psiquiátrica, coincidiendo con la evidencia de una expresión superior de las características relacionadas con el TEA en familiares de primer grado de personas con diagnóstico de TEA. Por último, se incluyó una comparación con la medida de evaluación gold-standard en TEA con el objetivo de explorar la relación entre esta y el instrumento objeto de validación.

Presentación de los artículos que comprende la tesis

A continuación, se incluye una copia completa de las publicaciones que conforman la Tesis Doctoral junto con sus respectivo anexos y el material suplementario publicado en la versión online de la revista en caso de existir. De igual modo, se presenta un resumen en castellano de

cada artículo con los siguientes apartados: introducción, objetivos del estudio, método, resultados y conclusiones. El formato de las publicaciones (referencias, anexos, material suplementario) respeta las normas de la revista en las que fue publicado.

Artículo I

Referencia:

Lugo-Marín, J., Magán-Maganto, M., Rivero-Santana, A., Cuellar-Pompa, L., Alviani, M., Jenaro-Rio, C., Díez-Villoria, E., & Canal-Bedia, R. (2019). Prevalence of psychiatric disorders in adults with autism spectrum disorder: A systematic review and meta-analysis. *Research in Autism Spectrum Disorders*, *59*, 22-33.

Título: Prevalencia de trastornos psiquiátricos en adultos con Trastorno del Espectro Autista: una revisión sistemática y metaanálisis

Resumen

Introducción: las dificultades relacionadas con el Trastorno del Espectro Autista (TEA) en su intento de adaptación al entorno pueden provocar la aparición de sintomatología psiquiátrica concomitante. Esta concurrencia de trastornos psiquiátricos en personas con TEA se hace especialmente evidente en la etapa adulta, cuando las exigencias del ambiente aumentan y la persona no puede responder a las mismas, estableciendo contacto con servicios de salud mental con el objetivo de reducir el malestar asociado. Sin embargo, la mayoría de los estudios se han centrado en explorar la frecuencia de los trastornos psiquiátricos concomitantes en la edad infanto-juvenil, dejando en un segundo plano el estudio de estos trastornos en la población adulta con TEA.

Objetivo: el objetivo del presente trabajo es llevar a cabo una revisión sistemática y metaanálisis de la evidencia disponible sobre la concurrencia de trastornos psiquiátricos en personas adultas con TEA.

Método: Se realizó una búsqueda electrónica en cuatro bases de datos (PubMed, PsycInfo, Web of Science y CINAHL), así como una búsqueda manual a través de listas de referencias y editoriales altamente susceptibles de contener trabajos sobre el tema de revisión (Science Direct, Wiley, Springer, Taylor & Francis, SAGE Publishing y BioMed Central). Se incluyeron estudios observacionales que reportaran datos de prevalencia de trastornos psiquiátricos en población adulta (18 años o más) con diagnóstico de TEA.

Resultados: Un total de 1288 y 24 referencias fueron detectadas en las búsquedas electrónica y manual, respectivamente. Los resultados mostraron una mayor prevalencia de trastornos del neurodesarrollo (Trastorno por déficit de atención e hiperactividad), afectivos (depresión, distimia), y ansiedad (fobia social, trastorno adaptativo y trastorno obsesivo-compulsivo). Los trastornos con menor prevalencia en esta población son los trastornos por consumo de sustancias y los trastornos de la conducta alimentaria.

Conclusiones: La prevalencia de trastornos psiquiátricos en adultos con TEA es superior a la reportada en población general, estableciéndose de este modo el TEA como un posible factor de vulnerabilidad para el desarrollo de un trastorno psiquiátrico concomitante. Son necesarios estudios longitudinales para establecer relaciones de causalidad, así como identificar factores de riesgo/protección frente al desarrollo de patología psiquiátrica. Igualmente, el solapamiento de las características relacionadas con los TEA con síntomas de otras entidades diagnósticas, especialmente los trastornos del espectro de la esquizofrenia), obligan a profundizar en la descripción de características discriminatorias que permitan realizar una buena aproximación diagnóstica en la edad adulta.

Palabras clave: Trastorno del Espectro Autista; Trastornos psiquiátricos; Adultos; Revisión Sistemática; Metaanálisis.

Ms. Ref. No.: RASD-D-18-00018R2
Title: Prevalence of psychiatric disorders in adults with autism spectrum disorder: a systematic review and meta-analysis
Research in Autism Spectrum Disorders

Dear Professor Canal-Bedia,

Thank you for submitting your revised manuscript to Research in Autism Spectrum Disorders. I have reviewed your paper and believe that you have carefully addressed all of the reviewers' comments. I am therefore pleased to inform you that your paper is now ready for publication and will be passed to the production team.

Thank you for your valuable contribution to Research in Autism Spectrum Disorders.

Kind Regards

Grace Iarocci, Ph.D
Associate Editor
Research in Autism Spectrum Disorders

Prevalence of psychiatric disorders in adults with autism spectrum disorder: a systematic review and meta-analysis.

Abstract

Some challenges faced by people with autism spectrum disorder (ASD) when adapting to a neurotypical environment are related with the risk of suffering a psychiatric disorder. The aim of the present study is to conduct a systematic review on the prevalence of psychiatric disorders in adults with ASD (PROSPERO's reference number CRD42016041948). Four databases (PubMed, PsycINFO, Web of Science and CINAHL) were used for the electronic search, while six editorials (Science Direct, Wiley, Springer, Taylor & Francis, SAGE Publishing and BioMed Central) were manually searched for studies not previously identified. Study eligibility criteria were observational studies on psychiatric comorbidity in adults (18 years or older) with ASD, based on standard diagnostic classifications (DSM/ICD), reported in English peer-reviewed journals. A total of 1288 and 24 references were identified by electronic and manual searches, respectively. Results showed that attention deficit and hyperactivity disorder is the most prevalent psychiatric disorder in adults with ASD. Mood and anxiety disorders are also very frequent among this population. The lowest comorbidity prevalence rates of all diagnostic categories are the ones related to substance use and eating disorders. These results show a need for a greater production of studies in this field, especially follow-up studies that focus on risk and protective factors for the emergence of psychiatric problems in adults with ASD. For this reason, it is imperative to create specific diagnostic tools that allow the assessment of mental pathology, attending to the particularities of its manifestation in people with ASD.

Keywords: Autism Spectrum Disorder; Psychiatric Disorders; Adults; Systematic Review.

Prevalence of psychiatric disorders in adults with autism spectrum disorder: a systematic review and meta-analysis

Autism spectrum disorder (ASD) is a neurodevelopmental disorder of early onset, characterized by persistent difficulties in social communication along with restrictive and repetitive patterns of behaviour and interests that have a significant effect on daily routines. About 70% of people with ASD may have a comorbid psychiatric disorder and about 40% have two or more comorbid psychiatric disorders (American Psychiatric Association, 2013). The fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) describes a psychiatric disorder as a "syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning" (American Psychiatric Association, 2013 p.20). Furthermore, the International Classification of Diseases (ICD-10) states that a mental disorder "implies the existence of a clinically recognizable set of symptoms or behaviors associated in most cases with distress and with interference with personal functions" (World Health Organization, 1992, page 11).

Initial studies that reported data on psychiatric comorbidity made more references to specific symptoms and not so many to diagnostic categories. For example, papers published by Rutter, Greenfield & Lockyer (1967) Simons, (1974), Ando & Yoshimura, (1979) and Rumsey, Rapoport & Sceery (1985), highlighted compulsive behaviour, self-injury, or anxiety. The most important debate was focused on whether the observed psychiatric symptoms represent true comorbid psychiatric disorders or are isolated symptoms (Frazier et al., 2001). Most of these published studies were based on children and adolescents clinical samples, contributing to better describe the difficulties that clinicians had to distinguish ASD from other comorbid mental disorders (Clarke, Littlejohns, Corbett, & Joseph, 1989; Ghaziuddin, Tsai, & Ghaziuddin, 1992;

Kobayashi & Murata, 1998; Volkmar & Cohen, 1991). These studies, as a whole, highlight that psychiatric comorbidity significantly increases the adaptive difficulties of these persons in daily life, interfering with activities such as eating or sleeping, accentuating problems such as passivity, social isolation, restlessness, irritability, aggressiveness, or self-injury. The general conclusion from the studies was that the presence of these concurrent behavioural alterations leads to an increase in ASD severity (Lainhart, 1999), as well as leading to confusion for clinicians when differentiating ASD from other psychiatric disorders.

However, there have been very few studies published addressing adults with ASD, to the point that there is a huge disproportion in the number of publications focused on children with respect to those focused on adults. Figure 1 shows the result of a PubMed search on studies about psychiatric problems in people with ASD. The considerable discrepancy in number of publications between children and adults reflects the lack of knowledge about psychiatric problems in adulthood.

[Insert Figure 1 about here]

During the last 10 years there has been a notable increase in the number of publications about comorbid psychiatric disorders in ASD. This indicates the interest that this issue is raising. The studies are mainly focused on investigating the comorbidity of ASD with a specific psychiatric disorder. However, there are not many that have made efforts to systematically analyze and synthesize information with meta-analyses techniques. A scarce number of systematic studies apply a meta-analytical methodology in the results found. Nevertheless, numerous reviews focus on specific psychiatric disorders (Hollocks, Lerh, Magiati, Meiser-Stedman, & Brugha, 2018; Huke, Turk, Saeidi, Kent, & Morgan, 2013; Kalyva, Kyriazi, Vargiami, & Zafeiriou, 2016; Marín et al., 2018; Skokauskas & Gallagher, 2010; Stewart, Barnard, Pearson, Hasan, & O'Brien,

2006; van Steensel, Bögels, & Perrin, 2011; Vannucchi et al., 2014). The largest number of studies are focused on depression and anxiety disorders, which are generally considered to be the most frequent comorbidity (Howlin, 2000) which can be associated with other problems such as maladaptive behaviors, self-injurious aggression and oppositional behaviour (Stewart et al., 2006). A recent meta-analysis (Hollocks et al., 2018) estimates a combined prevalence of 27% to 42% for any anxiety disorder, and from 23% to 37% for depressive disorders. This study reveals a high degree of heterogeneity in the methodology used in different studies and excessive dependence on clinical samples, highlighting the need to conduct studies with well characterized samples. Methodological heterogeneity and limitations in the process of sample selection are aspects mentioned in most of the reviews that address comorbid psychopathology (Gillberg and & Billstedt, 2000; Mannion & Leader, 2013; Matson & Cervantes, 2014; Matson & Goldin, 2013; Underwood, McCarthy, & Tsakanikos, 2010). The reviews provide a wide range of prevalence rates for the different disorders and behavioral problems analyzed. To the knowledge of authors, there are no reviews that integrate meta-analyses results from systematic reviews analyzing the prevalence of different comorbid mental disorders in adults with ASD. For this reason, there is a need for an integrative effort that could bring a better understanding of mental comorbidity in adults with ASD.

The purpose of this work is to systematically collect all the information available on comorbidity of psychiatric disorders in adults with ASD and to provide relevant information to improve clinical practice in terms of diagnosis and treatment.

METHODS

The review was registered at PROSPERO (reference number CRD42016041948, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=41948) and the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009) was used as a guideline.

Search of studies

An electronic search was conducted from 01/01/2000 to 05/31/2016 in four databases: PsycINFO, PubMed, CINAHL Full-Text and Web of Science. The search strategy included terms relating to all psychiatric disorders as they are classified in the standard classifications (DSM-5 and/or ICD-10). The same strategy was used in all databases (see Appendix A's Table 1). In order to find those studies not detected by the electronic search, a manual search was performed reviewing references lists of eligible studies, as well as searching in the "most-likely to publish" editorial webs (Science Direct, Wiley, Springer, Taylor & Francis, SAGE Publishing and BioMed Central).

Inclusion and exclusion criteria

The inclusion criteria were: 1) observational studies focusing on psychiatric comorbidity in ASD; 2) clinical diagnoses which had been established on the basis of diagnostic classifications in DSM (any version) and/or ICD-10; 3) english-written studies; 4) peer reviewed articles. Exclusion criteria were: 1) studies related to genetic / medical conditions; 2) studies based on children and youth population samples (<18 years); 3) small samples (N <10). See Appendix A's Table 2 for rationale on some of the inclusion/exclusion criteria.

References screening

Title, abstract and full text screenings were conducted by three independent reviewers. The selection strategy was the following: 1) One of the raters reviewed all references and the other two reviewed one half of the studies, randomly assigned to each one; 2) When a discrepancy occurred, a fourth independent rater was consulted. To assess the interrater agreement between reviewers, Kappa coefficient (k) was applied. Regarding discrepancies, age criterion raised some doubts, as several of the selected studies included participants both under and above 18 years old. In these cases, it was agreed to include those studies where the average age of the whole sample was equal or greater than 18 years.

Quality assessment and data extraction

The quality assessment was conducted for the five first authors, who independently assessed risk of bias on the included studies. For this, a specific instrument based on standard criteria was used (Berra, Elorza-Ricart, Estrada, & Sánchez, 2008). Disagreements between authors were solved by discussion. An external judge was involved when necessary.

A standardized form was used to extract data from the eligible studies. The collected variables were: first author, year of study, country, context (clinical or community), total of ASD participants, male-to-female ratio, age mean, intellectual quotient (IQ) mean score, intellectual disability (ID) percentage, DSM/ICD version, ASD diagnostic measures, ASD subtype, psychiatric disorders diagnostic measures and main outcomes. When an inter-group comparison was made, the diagnostic nature of this comparison group was recorded, as well as the number of included subjects and the main outcomes.

Statistical analysis

The extraction of selected variables was made with Microsoft Excel 2013. Analyses were conducted with Meta, an R package for meta-analysis (Schwarzer, 2007).

RESULTS

The electronic and manual searches identified 1.288 and 24 studies, respectively. A total of 891 studies remained after duplicates were removed. 112 references were selected for full-text screening. 65 references were considered for inclusion in the review. In the quality assessment stage, 4 studies were excluded. During the data extraction, 14 studies were also excluded because they did not report quantitative data. Thus, a total of 47 studies were included in the review. Figure 2 shows the PRISMA Flow-diagram of the conducted search.

[Insert Figure 2 about here]

Qualitative synthesis

From all the included studies, 26% were conducted in Sweden, while 18% and 13% took place in England and USA, respectively. A total of 87% of the studies were performed in a clinical context. The whole sample was comprised of 26,679 adults with ASD, 74.35% of whom were male, ranging from 16 to 84 years old. IQ scores, when reported, ranged from 46 to 143. When regarding ASD measures, Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview (ADI-R) were found to be chosen as diagnostic instruments in only 17% and 15% of the studies, respectively. DSM diagnostic criteria were the most frequent among

the included studies (55%), while ICD criteria were 34%. Both diagnostic criteria were taken into account in 11% of the included studies. A qualitative synthesis of the results on the prevalence for each psychiatric disorder category can be found in Appendix B. A summary of the quality assessment results for the included studies is described in Appendix C.

Quantitative synthesis (meta-analysis)

We conducted a meta-analysis for each general psychiatric category (substance use disorders, schizophrenia spectrum disorders, mood disorders, anxiety disorders, eating disorders, personality disorders and ADHD). In addition, a general meta-analysis was performed with those studies reporting prevalence for any psychiatric disorder. Only studies reporting prevalence in the main diagnosis category were considered. Consequently, a total of 8 random effects model meta-analyses were conducted. In all analyses, an overall prevalence rate from studies reporting a single proportion was calculated using an inverse variance method, with Clopper-Pearson confidence interval for individual studies and continuity correction of 0.5 in studies with zero cell frequencies. Cochran's Q and I2 were used to assess heterogeneity. Publication bias was explored by way of visual inspection of funnel plots (Appendix D).

Substance use disorders (SUD)

A total of 16 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 360.05, $p < 0.001$), pointing to a high heterogeneity in the included studies (I2 = 96%, 95% CI [94.4-96.9]). The pooled prevalence of SUD in ASD adults was 8.3% (4.1-16.1, CI 95%). When considering the specific categories, alcohol abuse/dependence disorder was the most frequent SUD reported throughout the studies. Cannabis use is also prevalent among adults with ASD. Other drugs, such as cocaine, heroin or

stimulants, were not found as prevalent in these samples. Figure 3 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 12.9% (8.9 – 18.4, CI95%) (I2 = 43%, p = 0.08).

[Insert Figure 3 about here]

Schizophrenia spectrum disorders (SSD)

A total of 17 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 306.76, p < 0.001), pointing to a high heterogeneity in the included studies (I2 = 95%, 95% CI [92.9-96.1]). The pooled prevalence of SSD in ASD adults was 11.8% (95% CI [7.7-17.6]). When considering the specific categories, Schizophrenia was the most frequent SSD reported throughout all the studies. Other categories, such as delusional disorder, schizoaffective disorder and brief psychotic disorder, were not diagnosed as often among these samples. Figure 4 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 10.5% (5.8 – 18.5, CI95%) (I2 = 76%, p = 0.01).

[Insert Figure 4 about here]

Mood disorders (MD)

A total of 14 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 565.98, p = 0.00), pointing to a high heterogeneity in the included studies (I2 = 98%, CI 95% [97-98.2]). The pooled prevalence of MD in ASD adults was

18.8% (95% CI [10.6-31.1]). Depression spectrum disorders were the most frequent MD described throughout the studies when considering the specific categories. Bipolar disorder was also relatively frequent among adults with ASD. Single manic episodes were not so prevalent in these samples. Figure 5 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 21.2% (9.7 – 40.3, CI95%) (I2 = 98%, p = 0.01).

[Insert Figure 5 about here]

Anxiety disorders (ANX)

A total of 17 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 451.13, $p < 0.001$), pointing to a high heterogeneity in the included studies (I2 = 96%, 95% CI [95.4-97.3]). The pooled prevalence of ANX in ASD adults was 17.8% (95% CI [12.3-25.2]). Social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and adjustment disorder (ADJ), were the most frequent ANX reported in all the studies when considering the specific categories. Agoraphobia (AGO), panic disorder (PAN) and generalized anxiety disorder (GAD) were also prevalent among adults with ASD. Other categories, such as post-traumatic stress disorder (PTSD), dissociative disorder (DIS) and somatoform disorder (SMF), were found to be lessprevalent in these samples. Figure 6 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 27.2% (17.2 – 40.2, CI95%) (I2 = 91%, p = 0.01).

[Insert Figure 6 about here]

Eating disorders (ED)

A total of 8 studies were included for quantitative synthesis. The Q analysis showed non-significant results (Chi square = 8.23, p = 0.23), pointing to a low heterogeneity in the included studies (I2 = 21.6%, 95% CI [0.0-63.7]). The pooled prevalence of ED in ASD adults was 3.6% (95% CI [2.1-6.1]). When considering the specific categories, anorexia nervosa (AN) seems to be slightly more prevalent than bulimia nervosa (BM) among these samples. Figure 7 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 3.6% (2.1 – 6.1, CI95%) (I2 = 22%, p = 0.26).

[Insert Figure 7 about here]

Personality disorders (PD)

A total of 13 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 858.83, p < 0.001), pointing to a high heterogeneity in the included studies (I2 = 99% 95% CI [98.2-98.9]). The pooled prevalence of PD in ASD adults was 12.6% (95% CI [4.8-29.3]). When considering the specific categories, schizoid (SCHZ), antisocial (ANT) and obsessive-compulsive (OBS) were the most frequent PD reported throughout the studies. Avoidant (AVD), paranoid (PAR), borderline (BOR) and schizotypal (SCHZT) personality disorders, were also prevalent among adults with ASD. Other PD categories, such as narcissistic (NAR), dependent (DEP) and histrionic (HIS), were found to be less common in these samples. Figure 8 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 20.8% (7.3 – 46.7, CI95%) (I2 = 93%, p = 0.01).

[Insert Figure 8 about here]

Attention deficit and hyperactivity disorder (ADHD)

A total of 18 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 769.07, $p < 0.001$), pointing to a high heterogeneity in the included studies ($I2 = 98\%$, 95% CI [97.2-98.2]). The pooled prevalence of ADHD in ASD adults was 25.7% (95% CI, [18.6-34.3]). Figure 9 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 27.4% (19.3 – 37.2, CI95%) ($I2 = 91\%$, $p = 0.01$).

[Insert Figure 9 about here]

Any psychiatric disorder

A total of 18 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 241.62, $p < 0.001$), pointing to a high heterogeneity in the included studies ($I2 = 93\%$, 95% CI [90.3-94.9]). The pooled prevalence of any psychiatric disorder in ASD adults was 54.8% (95 CI, [46.6-62.7]). Figure 10 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 60.5% (47.3 – 72.4, CI95%) ($I2 = 93\%$, $p = 0.01$).

[Insert Figure 10 about here]

DISCUSSION

To the extent of our knowledge, this is the first systematic review and meta-analysis conducted on the prevalence of psychiatric disorders in adults with ASD. The results suggest a very high prevalence of several psychiatric conditions in adults with ASD, including ADHD, depression and anxiety disorders as the most prevalent. Results suggest that adults with autism are more likely to have a psychiatric disorder than the general population.

SUD is one of the psychiatric categories less frequently diagnosed in adults with ASD. However, looking closely at the specific categories, a high prevalence in the abuse/dependence of two specific substances, alcohol and cannabis, was found (Kronenberg, Goossens, van Busschbach, van Achterberg, & van den Brink, 2015; Sizoo et al., 2009). The anxiolytic effect derived from the abuse/dependence of both substances is quite well-known, especially with alcohol; these are also easily accessible, without often requiring highly-demanding social skills for their purchase. This could explain their use in this population, while typically recreational and social-consumed substances (cocaine, amphetamines and hallucinogens) have a lower prevalence.

The SSD prevalence in general population is approximately 1% (NIMH, 2018). Results found in this review are much higher than this number. This is not surprising as both SSD and ASD have been related since the beginning of modern psychiatry. Regarding research evidence, numerous studies have found similarities between SSD and ASD symptomatology (Konstantareas & Hewitt, 2001; Lugnegård, Hallerbäck, & Gillberg, 2015; Spek & Wouters, 2010) and biological shared structures (Burbach & van der Zwaag, 2009; Crespi, Stead, & Elliot, 2010). In the studies included in this review, schizophrenia is postulated as the most prevalent SSD in adults with ASD, showing a much higher prevalence than that found in the general population (Rössler, Salize, van Os, & Riecher-Rössler, 2005). A possible explanation for this result can be found in the ease of confusing both diagnoses (Nylander, 2014; Raja & Azzoni, 2010). Also, the late inclusion of less severe forms of autism may have led to misdiagnosis of

people with ASD who have psychosis-like symptoms. As a matter of fact, follow-up studies with children with ASD have not found a similar outcome (Howlin, 2000; Volkmar & Cohen, 1991). It is the opinion of the authors that, indeed the ASD population seems more vulnerable to suffer from psychotic symptoms at any given time, although this does not necessarily have to mean the first manifestations of schizophrenia.

The one-year and lifetime prevalence of MD in general population have been observed at 9.7% and 21.4%, respectively (NIMH, 2018). The results found in this study suggest a greater than average prevalence of MD in ASD adult population. Two of the most frequent psychiatric categories in the adult population with ASD are mood and anxiety disorders. Regarding the first, people with ASD show a high prevalence of depressive disorders. The occurrence of depressive disorders could be related to the awareness of the core social difficulties of ASD. The person would be aware of their difficulties in the social environment, which would lead to a loss of self-esteem. After several unsuccessful attempts to fit into the social world, the person with ASD would suffer the rejection of their peers, precipitating the onset of depressive disorder and, in some cases, suicide attempts (Kato et al., 2013; Raja, Azzoni, & Frustaci, 2011).

Regarding anxiety, an estimated of 19.1% of adults in a general population have experienced ANX in the last year, and approximately 31.1% have experienced ANX in their lives (NIMH, 2018). When comparing with ASD participants, the prevalence rate seems greater in the general population. Three specific categories can be found as the most frequently diagnosed ANX in adults with ASD. Firstly, social phobia presents a high prevalence in adults with ASD, although this is not a direct outcome from adult transition (Kuusikko et al., 2008). The explanation for this result seems clear, as people with ASD present difficulties in social communication that may precipitate the emergence of a phobic disorder. Secondly, OCD is one of the most typically anxiety diagnoses found in adults with ASD. There seems to be a relation between the repetitive behaviors and the compulsive rituals. Due to the overlap in the

manifestation of symptoms, it is a challenge to establish a differential diagnosis between both behaviors. A differentiating factor that seems to discriminate well between both diagnoses is the cognitive component. The repetitive behaviors of a person with ASD are not performed as a response to the presence of an obsessive thought, whereas in OCD a person performs the ritual in order to neutralize an obsessive thought. Also, the egodystonic nature of the rituals in OCD is not reflected in the repetitive behaviors of the person with ASD. It is for this reason that the results found here should be taken with caution, since it could be a confusion between diagnoses. Finally, adjustment disorder is the diagnostic category that presents the highest dispersion in its results, with only one study yielding results of high prevalence (Kato et al., 2013). The remaining diagnostic categories of the spectrum of anxiety, although elevated, do not present a frequency as striking as those mentioned above.

ED are, along with substance use disorders, those with the lowest prevalence in people with ASD. General population prevalence of ED is observed at around 1% (NIMH, 2018). In this study, the results found in the ASD group suggest a greater risk of developing ED in this population. The most striking case may be that of anorexia, with some studies finding prevalence rates of up to 13% in the population with ASD (Rydén & Bejerot, 2008). There are some studies on the prevalence of eating disorders in childhood and adolescence (Huke et al., 2013; Oldershaw, Treasure, Hambrook, Tchanturia, & Schmidt, 2011; Zucker et al., 2007), which have found similar results. Among the possible explanations for this phenomenon may be the low cognitive flexibility in anorexia, or the repetitive behaviors of people with bulimia. In any case, there does not seem to be a direct relation between the two conditions.

When it comes to PER, general population prevalence is 9.1% (NIMH, 2018), slightly lower than the results found in this study. When it comes to ASD adult population, three specific personality disorders stand out over the rest. It is not surprising to see the high prevalence of the schizoid personality disorder in adult population with ASD. Although some of its

characteristics coincide with those shown by people with ASD (preference for solitary activities, low emotionality, few friends), others do not seem to be explained solely by the presence of ASD (little enjoyment in social relations, indifference to the praises or criticism from others, little interest in having sex). Furthermore, obsessive personality disorder is also frequently found as axis-II disorder in adults with ASD. An explanation can be easily found for this result, because people with ASD have a high need for control and structuring of the environment, with low flexibility to change and frustration with interruptions of their routine. Finally, having a look at the defining characteristics of the antisocial personality disorder, it is not surprising to find a high prevalence of this diagnosis in ASD adults. This result could be explained by a diagnostic overlap, since the difficulties in social communication characteristic of ASD predispose the emergence of antisocial behaviors, without being associated with the intention to carry out these behaviors. This issue will be addressed by the authors in greater depth in the "Limitations" section.

ADHD is the most frequent psychiatric diagnosis found in adults with ASD. The prevalence in children that have ever been diagnosed with ADHD is 11% (NIMH, 2018), suggesting a greater risk of having an ADHD diagnosis in ASD population. They are neurodevelopmental disorders that have been closely linked in the scientific literature ever since their definition. Regarding this issue, Gillberg (2010) has proposed a multidimensional diagnostic category, which reflects this relation between both conditions, but also as a part of a cluster of syndromes with a high co-occurrence in early developmental stages. In any case, a risk of symptom overlapping should be taken into consideration. ADHD symptoms may well be explained by the existence of an ASD. Attention deficit could be a result of the executive-dysfunction frequently observed in ASD. Another possible explanation is related to the preference for focusing on detail in people with ASD. This could be a deficit in sustained attention, concerning problems with keeping focused and avoiding distractions. Furthermore, hyperactivity can be triggered by

sensory overstimulation, which is often described in people with ASD. The challenge here is to correctly describe both conditions, not only at a behavioral, but also at a neurological level.

Limitations

There are some limitations that could engage the validity of the results. Only a small percentage of the studies used gold standard diagnostic instruments for ASD (ADOS, ADI-R). Also, few studies used self-developed interviews or screening instruments to establish the diagnosis (Munesue et al., 2008; Roy, Prox-Vagedes, Ohlmeier, & Dillo, 2015), thus increasing the likelihood of including false positives in the ASD group. Furthermore, most of the selected studies have recruited the ASD sample in clinical settings (hospitals, health centers). This may bias the results, as these samples may be more vulnerable to develop mental disorders. More studies are needed in ecological contexts to be able to discern the real prevalence of psychiatric problems and the factors that prevent the development of mental pathology in this population.

Regarding the diagnostic approach, two limitations can be considered. Firstly, a great proportion of the included studies reported diagnosis as being based on medical records and/or clinical judgement. These were considered relevant as they reflected a more ecological approach on how the diagnosis was made in real clinical practice. That is, the results found in this review reflect the probability of being diagnosed with a mental disorder when ASD is present. The concept of prevalence should be considered here as a reflection of this probability. Secondly, when systematically assessed, the diagnostic tools chosen to assess the presence of mental disorders in the ASD population may not be sensitive to the particularities in the expression of mental disorders in people with ASD. Although specific instruments have been developed for people with ASD (Bolton & Rutter, 1994; Helverschou, Bakken, & Martinsen, 2009), these tools are unfortunately not widely known in clinical practice. In fact,

only a small percentage of the studies included in this review, have used them for the psychiatric evaluation of the ASD sample (Bakken et al., 2010; Hutton, Goode, Murphy, Le Couteur, & Rutter, 2008). Likewise, the development of specific tests implies rethinking about the diagnostic categories as they are currently described. Moreover, most disorders are described in behavioral terms, which eliminates the possibility of assessing the etiology of that behavior. One good example is the category "antisocial personality disorder". In the included studies, this disorder has one of the highest prevalence, which in some cases may reach 33% (Esan, Chester, Gunaratna, Hoare, & Alexander, 2015). This is not surprising, as antisocial personality disorder (APD) is described as a pattern of violation of social norms, aggression, lack of repentance, irresponsibility, inability to plan and inattention. All these behaviors can easily be found when assessing an ASD adult's personality. However, if these behaviors are compared with those of a person with a APD, it would be agreed that this person is aware of the damage that can be caused, being unlike for the person with ASD to realize the final consequences of their actions. Even so, both would meet criteria for antisocial personality disorder.

Another issue that should be addressed is related to the characteristics of the sample. Approximately 75% of the sample were male. This is consistent with the typical higher prevalence of ASD in men. However, several studies have found differences in the manifestation of ASD characteristics in relation to gender (Rivet & Matson, 2011; Van Wijngaarden-Cremers et al., 2014). This suggests the need to carry out comparative studies that describe gender differences concerning psychiatric pathology in ASD. Similarly, a high percentage of the ASD sample presented ID. People with ID present a potential risk to develop mental disorders (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011), so it is logical to think this factor has increased the prevalence of psychiatric disorders in adults with ASD.

A final limitation is the high heterogeneity found in the meta-analysis results. This could be explained by the variables mentioned above (e.g. gender, IQ, diagnostic measures). Nevertheless, the data reported for the included studies was inconsistent and often did not report the specific data needed to carry out meta-regression analyses. Also, as mean age was available in most of the studies, a set of meta-regression analyses were conducted to explore the heterogeneity explained by the age of the sample. Results showed a meaningful amount of variance (although small and not reaching significance) in the case of eating disorders (44.03%), anxiety disorders (21.43%) and ADHD (19.62%), pointing to the possible relevance of age when estimating the prevalence of these psychiatric disorders.

In addition, an extra pool of meta-analysis was performed with those studies reporting a systematic psychiatric assessment, based on a clinical interview and/or standardized measures. These analyses showed no differences in the heterogeneity when compared with the prior meta-analysis, except in the cases of SUD and SSD, thus suggesting an effect of diagnostic methodology on the prevalence results of these two categories.

Clinical implications

More research is needed on the factors that predispose people to the development of mental disorders, as well as those that protect against their emergence. For this, follow-up studies including psychiatric disorders among their variables, should be conducted. Also, diagnostic tools that present a high discriminative capacity between mental disorders and the core ASD features are necessary. Finally, the approach to psychiatric pathology should be one of the fundamental pillars of intervention in adulthood. As this population deals with communication problems, psychiatric demands can remain masked. As a consequence, professionals should be familiarized with the manifestation of psychiatric disorders within this population.

Ultimately, the insight gathered by meta-analyses like these is imperative for future advances in diagnosis and treatment. The opportunity arises to develop specific diagnostic tools of mental pathology that cater for the distinctive patterns found in people with ASD. Future studies could identify risk and protective factors integral for the development of treatment options that could improve the quality of life of adults with ASD and comorbid psychiatric disorders.

Conflict of interest.

None of the authors have any conflict of interest.

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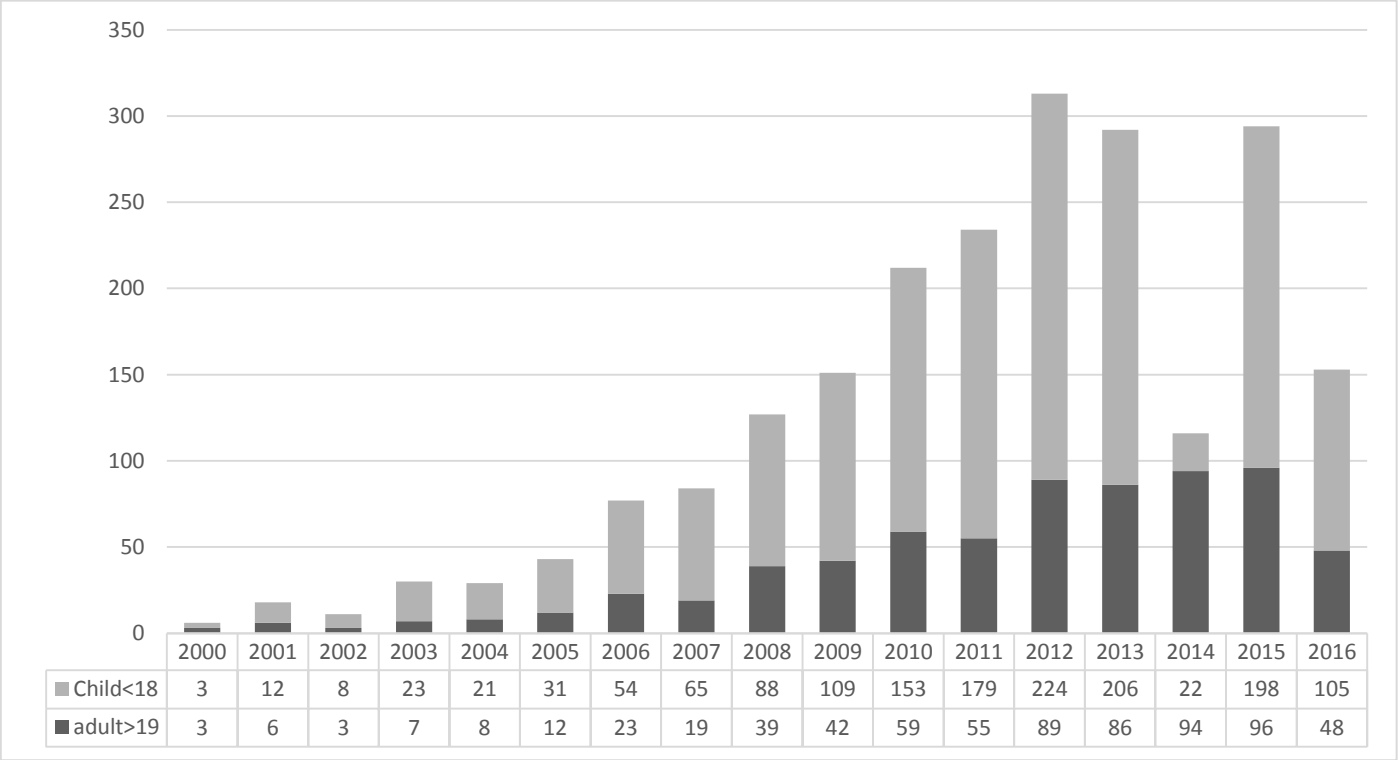
Figure 1. Published studies regarding psychiatric disorders on ASD infants vs. adults.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Child<18	3	12	8	23	21	31	54	65	88	109	153	179	224	206	22	198	105
adult>19	3	6	3	7	8	12	23	19	39	42	59	55	89	86	94	96	48

Figure 2. PRISMA flow diagram

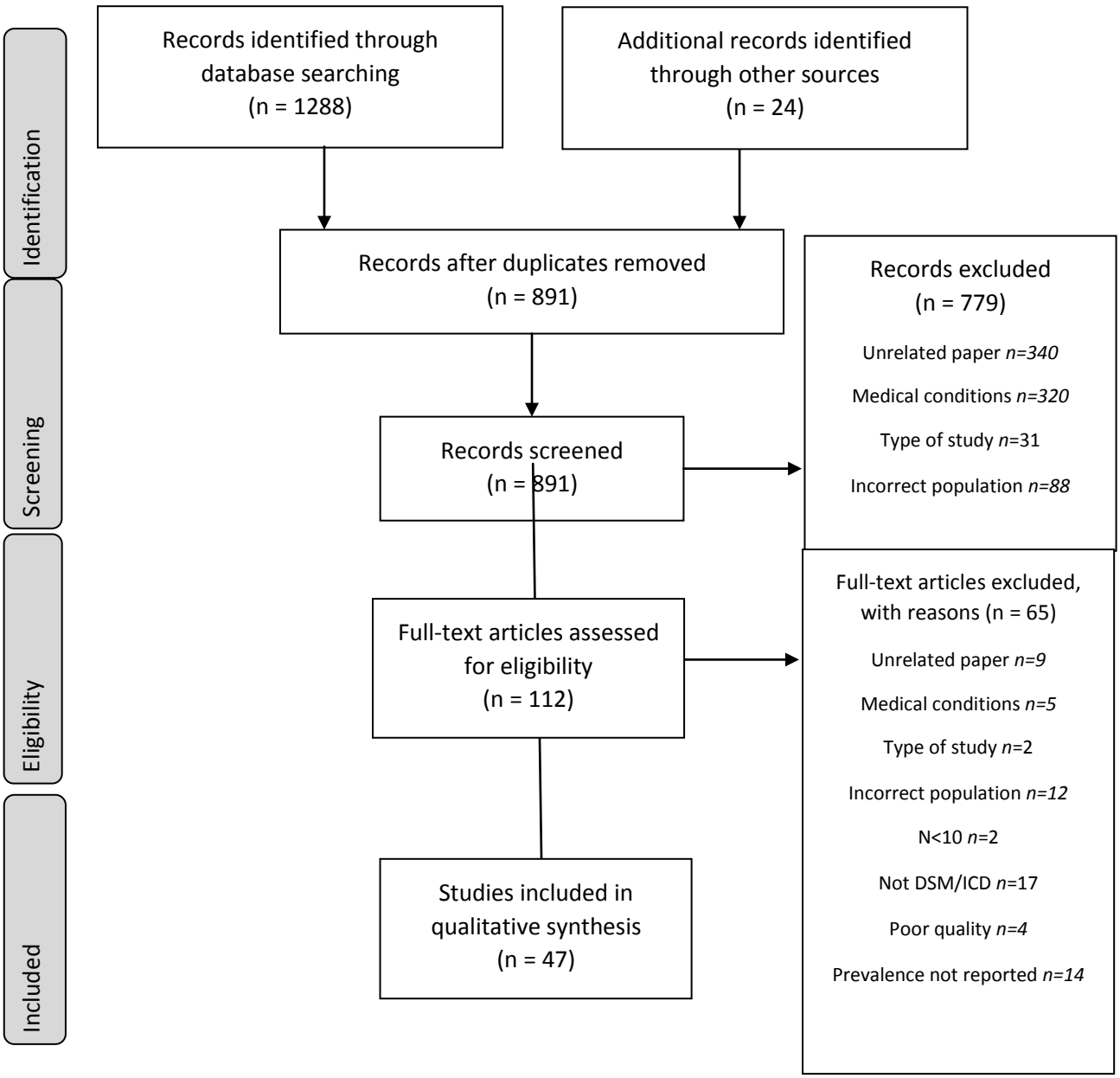


Figure 3. Forest plot of the pooled prevalence of SUD in adults with ASD.

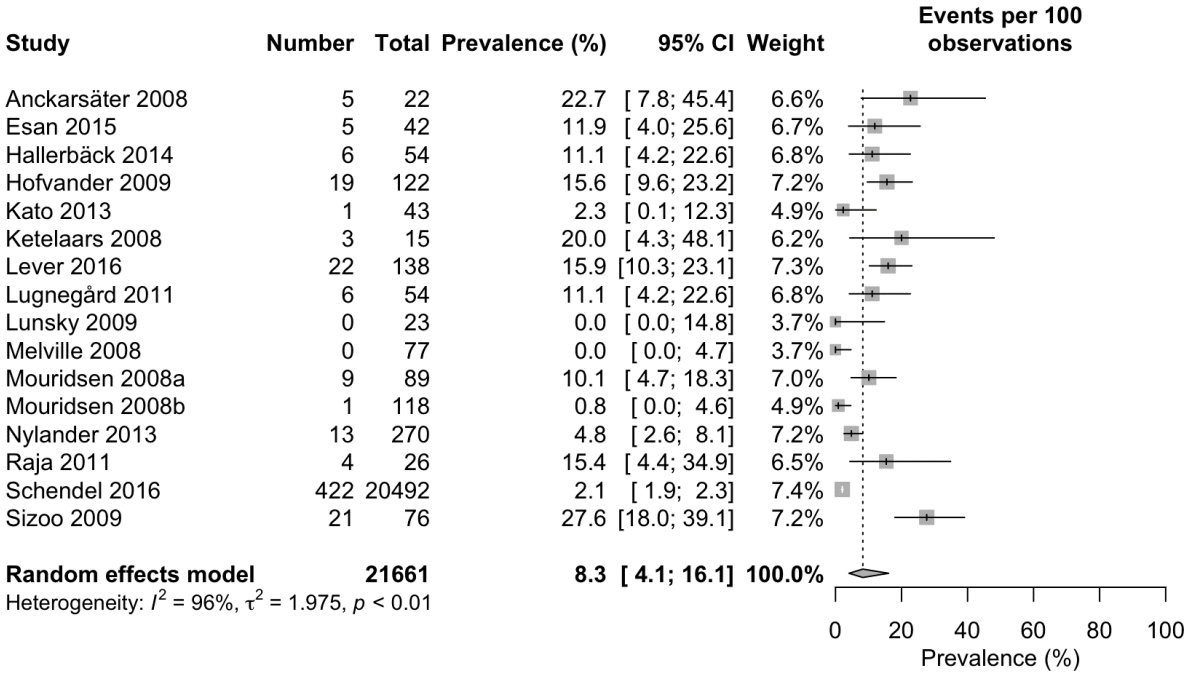


Figure 4. Forest plot of the pooled prevalence of SSD in adults with ASD.

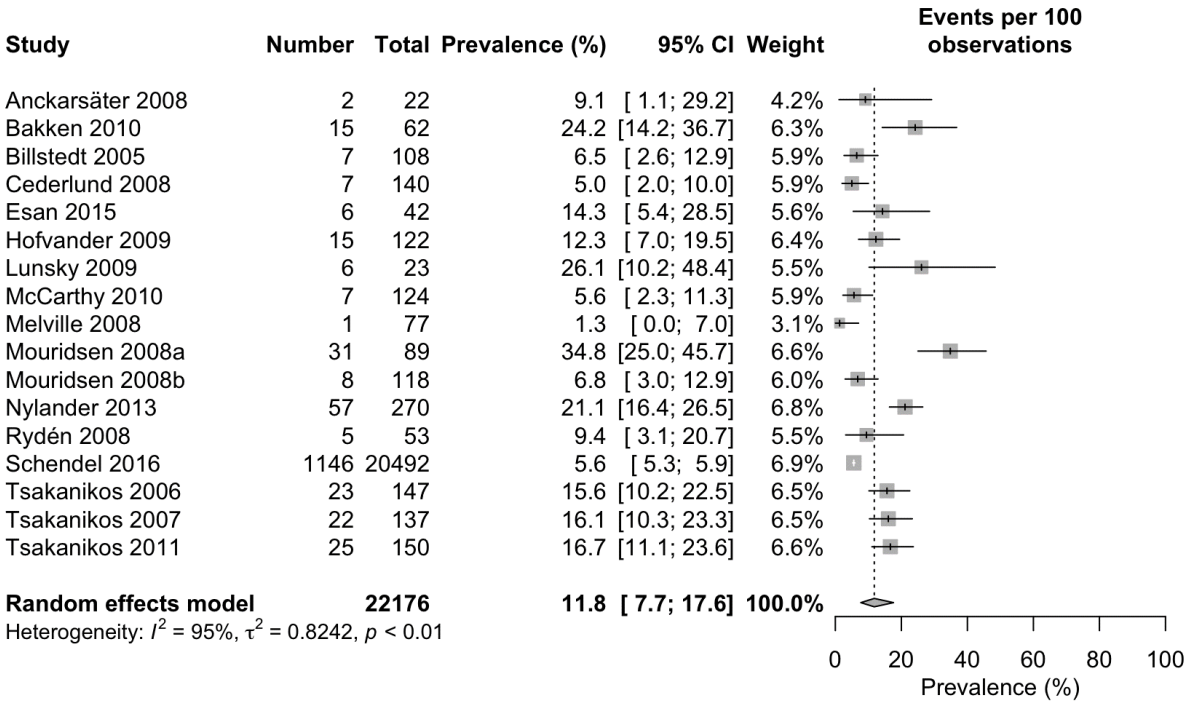


Figure 5. Forest plot of the pooled prevalence of MD in adults with ASD.

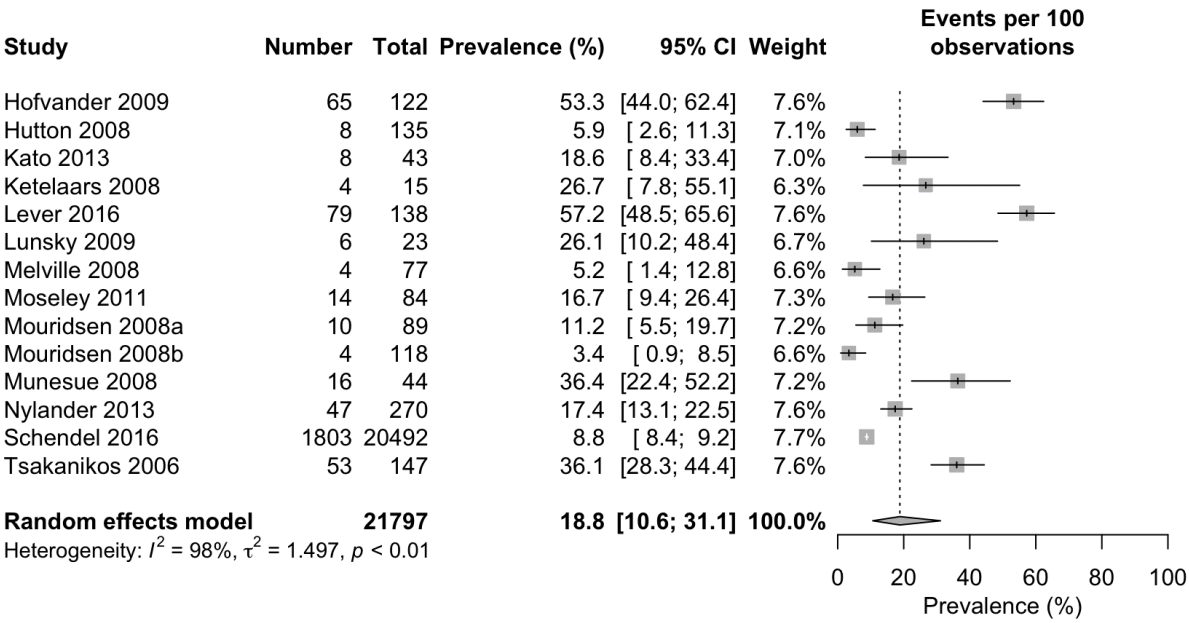


Figure 6. Forest plot of the pooled prevalence of ANX in adults with ASD.

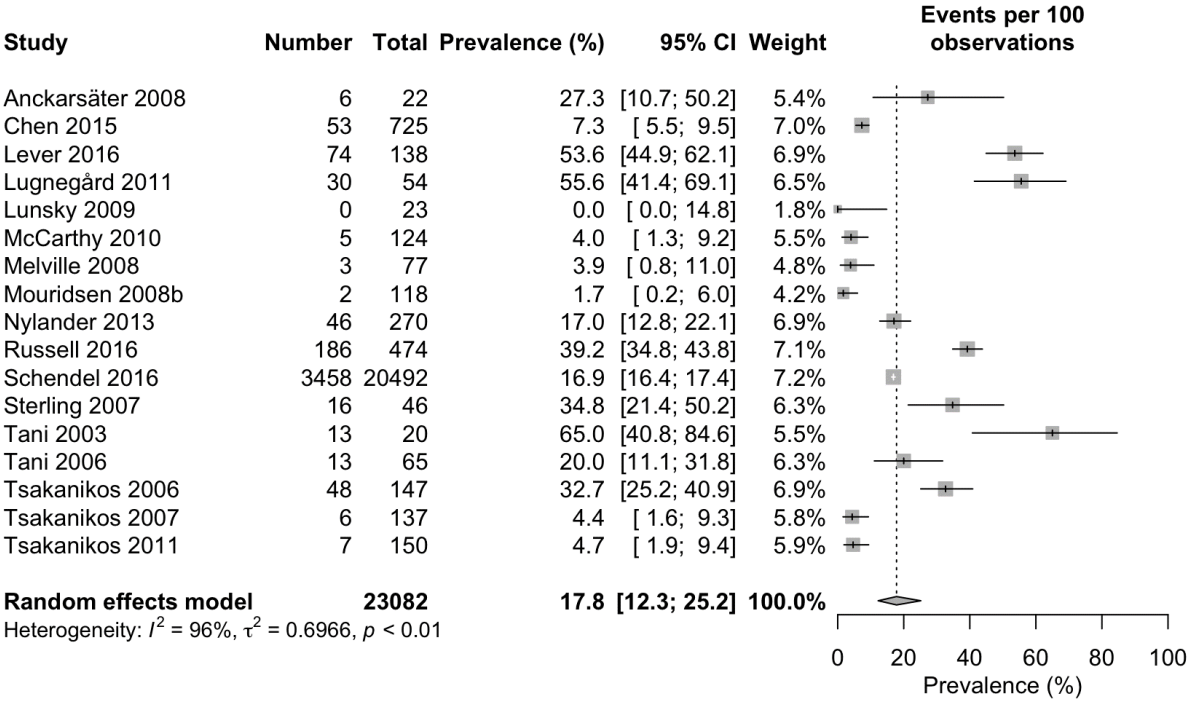


Figure 7. Forest plot of the pooled prevalence of ED in adults with ASD.

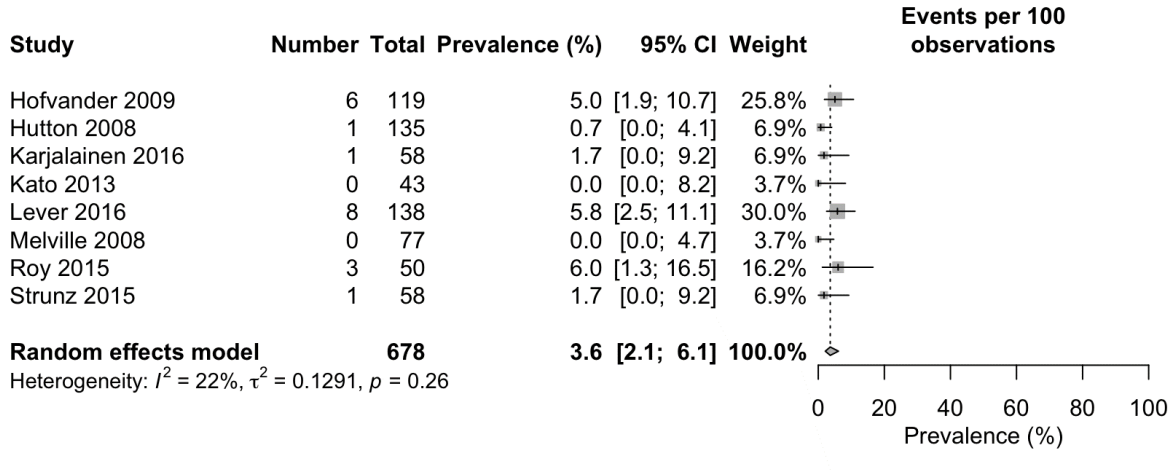


Figure 8. Forest plot of the pooled prevalence of PD in adults with ASD.

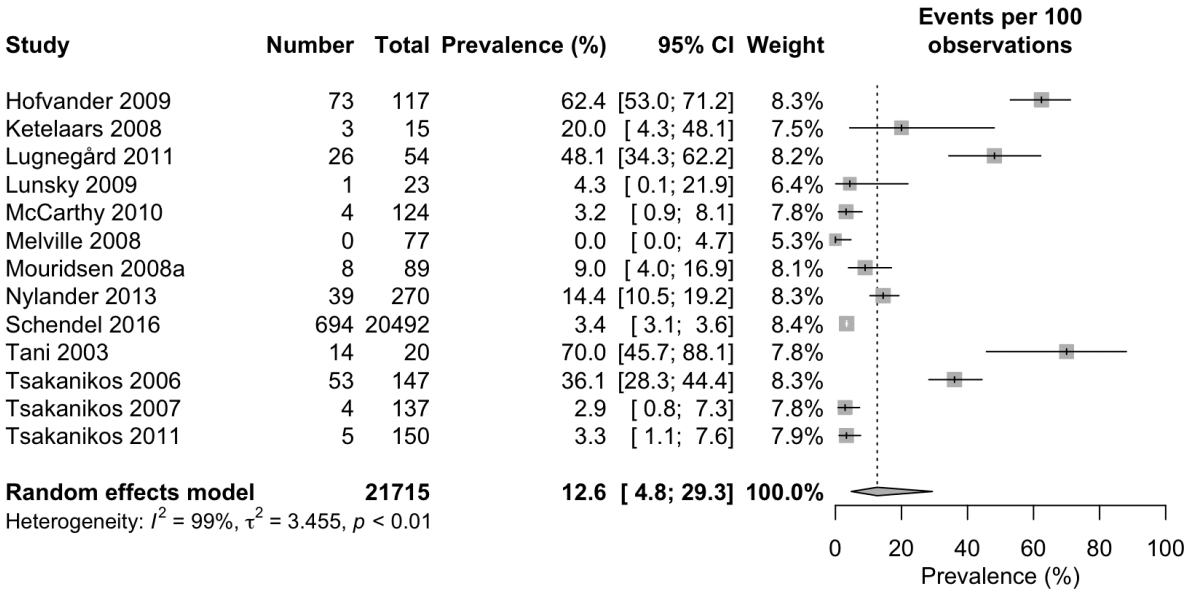


Figure 9. Forest plot of the pooled prevalence of ADHD in adults with ASD.

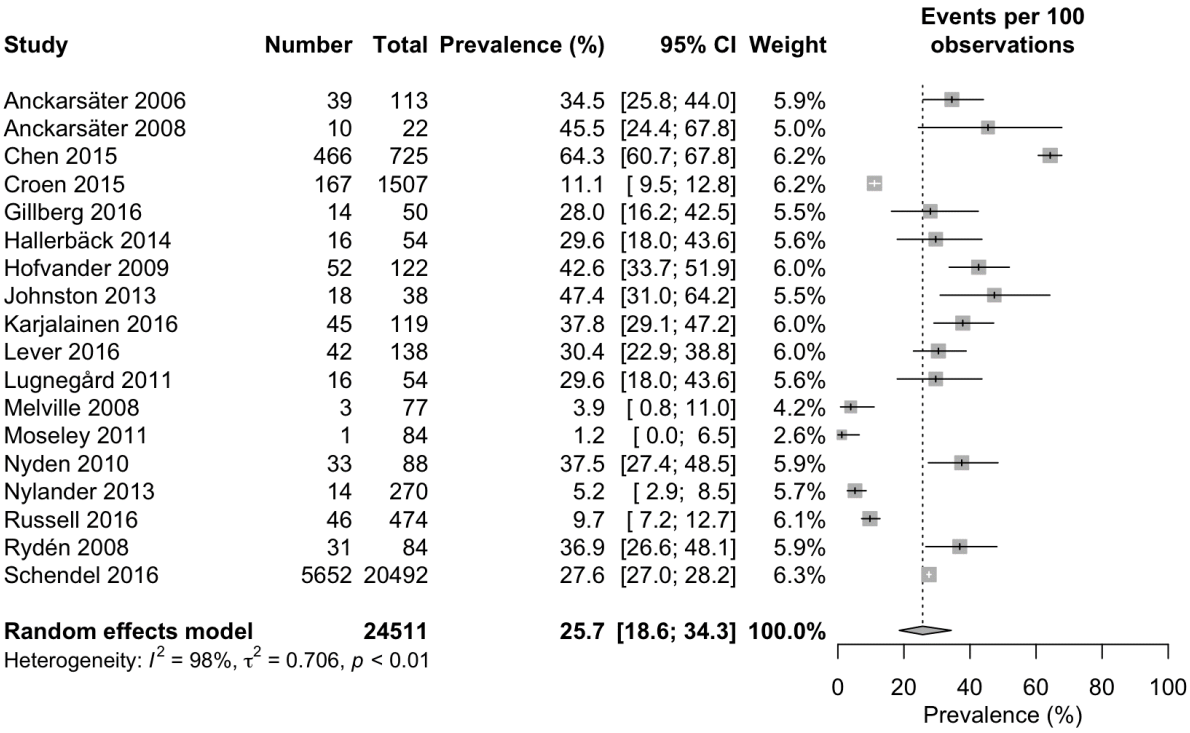
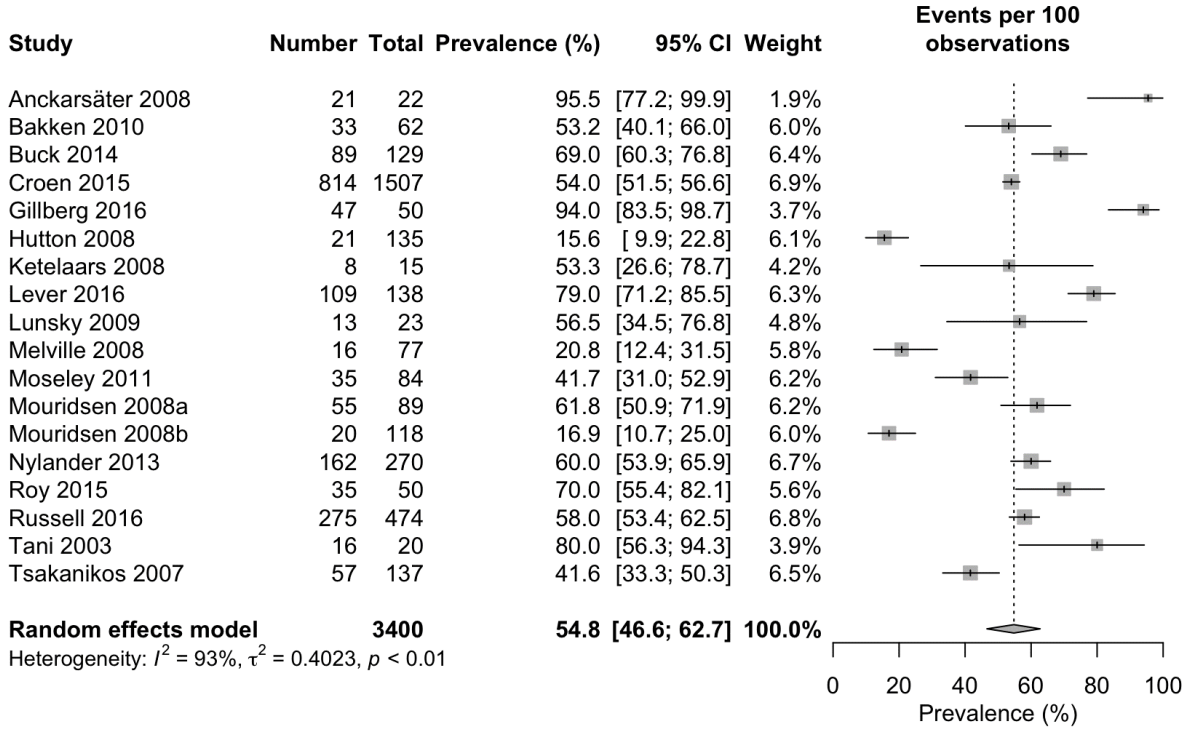


Figure 10. Forest plot of the pooled prevalence of APD in adults with ASD.



Appendix A. Table 1. Electronic search strategy

1. Autism OR "Autism Spectrum Disorder*" OR ASD OR "Autistic Disorder*" OR "Pervasive Developmental Disorder*" OR PDD OR "PDD-NOS" OR "High Functioning Autism" OR "Asperger*" OR "Asperger Syndrome"
2. Comorbidity OR "Co morbidity" OR Comorbidities OR "Secondary pathology" OR Coexistence OR Multimorbidity OR "Dual diagnosis"
3. Adult* OR "Young Adult" OR "Middle Aged" OR Aged OR Elderly
4. ((Descriptive OR Prevalence OR Cross-Sectional OR Cohort OR Longitudinal OR Follow-up OR Prospective OR Incidence OR "Case Control" OR Retrospective) Study) OR Epidemiology
5. "Minimal Brain Dysfunction" OR "Intellectual Disabilit*" OR (Mental (Retard* OR Deficienc*)) OR "Attention Deficit Hyperactivity Disorder*" OR "Hyperkinetic Syndrome" OR ADDH OR ADHD OR "Substance-Related Disorders" OR Paranoia* OR ((Schizophren* OR Psychotic OR Schizoaffective OR Schizophreniform OR Delusional OR Paranoid) Disorder*) OR (("Brief Reactive" OR Paranoid) Psychos*) OR "Paranoid Schizophrenia*" OR ((Mood OR Affective OR Cyclothym* OR Bipolar OR Manic OR Depressive OR "Mixed anxiety-depressive") Disorder* OR Neurosis OR Syndrome) OR Mania OR Depression OR ((Bipolar OR Unipolar) Depression) OR ((Anxiety OR Neurotic OR Panic OR Phobic) Disorder* OR Neuros*s OR Attack) OR Phobia* OR Claustrophobia* OR Social Phobia* OR "Anankastic Personalit*" OR "Obsessive Compulsive Disorder*" OR OCD OR Neuros*s OR (("Post-Traumatic Stress" OR Adaptive) Disorder*) OR PTSD OR (Dissociati* OR Conversion (Disorder* OR Reaction OR Hysteria)) OR Fugue OR Globus Hystericus OR Hypochondriacal Neuros*s OR ((Somatoform OR Somatization OR Pain) Disorder*) OR ((Bulimia OR Anorexia) Nervosa*) OR ((Eating OR Feeding OR Appetite OR "Binge Eating") Disorder*) OR ((Sleep Walking OR Hypersomnolence OR "Sleep Terror*") Disorder*) OR Insomnia OR Hypersomnia OR Nightmares OR Sleepwalking OR Nocturnal Wandering OR Frigidity OR (("Psychological Sexual" OR Psychosexual OR "Hypoactive Sexual Desire" "Sexual Aversion" OR Orgasmic OR "Sexual Arousal") Dysfunction* OR Disorder*) OR "Gender dysphoria" OR Transsexualisms OR Transgender OR Trichotillomanias OR (("Impulse Control" OR "Intermittent Explosive") Disorder*) OR Kleptomania OR "Firesetting Behaviors" OR Pyromania OR Arson OR Gambling* OR "Pathological Gambling" OR ((Avoidant OR Narcissistic OR Antisocial OR Sociopathic OR Psychopathic OR Dyssocial OR Borderline OR "Obsessive Compulsive" OR Dependent OR Hysterical OR Histrionic OR Paranoid OR Negativistic OR "Passive Agressive" OR Schizoid OR Schizotypal) Personality Disorder*) OR Voyeurisms OR Paraphili* Disorder* OR Sex Deviations OR Exhibitionisms OR Fetishisms OR "Sexual Masochisms" OR Pedophilias OR "Sexual Sadisms" OR Transvestisms
6. #1 AND #2 AND #3 AND #4 AND #5
7. Search range: 01/01/2000 – 05/31/2016
8. Lenguage: English
9. Academic Journals (Peer Reviewed)
10. Age range: adults (>18 years)
11. #6 AND #7 AND #8 AND #9 AND #10

Table 2. Summary of inclusion and exclusion criteria and rationale

Inclusion Criteria
Observational studies focusing on psychiatric comorbidity in ASD
Clinical diagnoses which had been established on the basis of diagnostic classifications in DSM (any version) and/or ICD-10[a]
English-written studies
Peer reviewed articles
Exclusion Criteria
Studies related to genetic / medical conditions[b]
Studies based on children and youth population samples (<18 years)[c]
Small samples (N <10)[d]

[a] Rationale is to include results from studies that use two of the most commonly used standards for stablishing clinical diagnoses

[b] Rationale is to remove the influence of specific confounding variables

[c] Rationale is that because ASD are conceptualized as developmental disorders, research regarding co-occurrent psychiatric disorders has been focused in the first years of life and there are a lack of knowledge about psychiatric problems in adulthood

[d] Rationale is that random effects model will be used to conduct meta-analysis and substantial heterogeneity is expected. In this situation, weights tend to become more equal and even even a small study may have almost the same weight as a large one. We assume that studies with small samples are of poorer quality and they are not likely to be a random sample of all the small studies population.

Table 1. Characteristics of included studies

				ASD GROUP						
Author (Year)	**Country**	**Context**	**Recruitment source**	**N (% Male)**	**Mean Age (SD) (Range)**	**Mean IQ (SD) (Range)**	**% ID**	**Diagnostic Criteria**	**Diagnostic Measures**	**Diagnostic Subtypes**
Anckarsäter (2006)	Sweden	Clinical	Child Neuropsychiatric Clinic	113 (NR)	NR (NR) (19-60)	NR	NR	DSM-IV	ASSQ, ASDI, DSM-IV Checklist	AD: 6 AS: 46 AA: 61
Anckarsäter (2008)	Sweden	Clinical	Forensic Psychiatric Hospital	22 (77.3)	NR (NR) (18-47)	NR	27.3	DSM-IV	ASSQ, ASDI	AD: 7 AS: 5 AA: 10
Bakken (2010)	Norway	Clinical	Autism Team	62 (27.4)	23.9 (NR) (14-57)	NR	100	ICD-10	Clinical examination	AD: 62
Billstedt (2005)	Sweden	Clinical	Child Neuropsychiatric Clinic	108 (NR)	NR (NR) (17-40)	NR	96.3	DSM-IV/ICD-10	DISCO-10	AD: 73 AS: 35
Buck (2014)	USA	Community	UCLA University of Utah	129 (75.2)	36.4 (5.9) (26.1-54.4)	NR	72.8	DSM-III/DSMIV-TR	NR	NR
Cederlund (2008)	Sweden	Clinical	Child Neuropsychiatric Clinic	AS 70 (100) AD 70 (100)	21.5 (4.4) (16-33.9) 24.5 (5.4) (16.1-36.1)	103 (14.8) (66-143) 59.6 (17.9) (NR)	1.4 93	DSM-IV/ICD-10	DISCO-10	AD: 70 AS: 70
Chen (2015)	Taiwan	Clinical	National Health Insurance Research Database	725 (77.2)	18.3 (13.4) (NR)	NR	NR	ICD9-CM	NR	NR
Croen (2015)	USA	Clinical	Kaiser Permanente in Northern California	1507 (73.1)	29 (12.2) (NR)	NR	19.2	ICD-9-CM	NR	NR
Esan (2015)	England	Clinical	Specialized Forensic Inpatient Service	42 (85.7)	30.1 (9.14) (NR)	NR	100	ICD-10	NR	NR
Gillberg (2016)	Sweden	Clinical	Child Neuropsychiatric Clinic	50 (100)	30.2 (5) (23-43)	107.6 (NR) (NR)	0	DSM-IV/ICD10	ASSQ, ASDI, DISCO-11	NR
Hallerbäck (2014)	Sweden	Clinical	Two Outpatient Clinics	54 (48.2)	27 (3.9) (NRNR)	NR	NR	DSM-IV	DISCO-11	AS: 54
Hofvander (2009)	France/Sweden	Clinical	Albert Chevalier Hospital Child Neuropsychiatric Clinic Psychiatric Outpatient Clinic	122 (67.2)	NR (NR) (16-60)	NR	0	DSM-IV	ASDI	AD: 5 AS: 67 PDD-NOS: 50
Hutton (2008)	England	Clinical	Maudsley Hospital Outpatient Clinic	135 (77)	34.9 (NR) (21-57)	>30	NR	DSM-IV	ADI-R, ADOS	NR
Johnston (2013)	England	Clinical	Tertiary level assessment Clinic	48 (85.4)	25.6 (12.09) (19-62)	NR	0	ICD-10	ADOS, ADI-R	AS: 1 HFA: 23 PDD-NOS: 7
Joshi (2013)	USA	Clinical	University Hospital	63 (65.1)	29.2 (11) (18-63)	104.4 (17.3) (55-136)	3	DSM-IV	NR	AD: 41 AS: 16 PDD-NOS: 6
Karjalainen (2016)	Sweden	Clinical	Child Neuropsychiatric Clinic	119 (NR)	>18	NR	NR	DSM-IV	ASDI, DSM-IV Checklist	NR
Kato (2013)	Japan	Clinical	Advanced Critical Care Center Tokai University Hospital	43 (81.4)	33.7 (12.6) (NR)	NR	NR	DSM-IV	AQ	NR
Ketelaars (2008)	Netherlands	Clinical	Outpatient Psychiatric Center Outpatient Psychiatric Clinic	15 (80)	22 (5) (18-24)	104 (10) (NR)	0	DSM-IV	AQ, ADOS-G, ADI-R, Self-developed Interview	AS: 4 HFA:1 PDD-NOS:10
Kronenberg (2015)	Netherlands	Clinical	The Dual Diagnosis Dept. of Dimence Victas Centre for addiction care	31 (94)	40 (NR) (NR)	>80	0	DSM-IV	NR	NR
Lever (2016)	Netherlands	Mixed	Mental Health Institutions, Websites	138 (30.4)	46.5 (NR) (NR)	113.8 (NR)	0	DSM-IV	ADOS	AD: 21 AS:69 PDD-NOS: 43
Lugnegård (2011)	Sweden	Clinical	Two Outpatient Clinics	54 (48.2)	27 (3.9) (NR)	102 (12) (NR)		DSM-IV	DISCO-11	AS: 54
Lugnegård (2012)	Sweden	Clinical	Two Outpatient Clinics (DAH, NCCA)	54 (48.2)	27 (3.9) (NR)	102 (12) (73-143)	0	DSM-IV	DISCO-11	AS: 54
Lunsky (2009)	Canada	Clinical	Three psychiatric hospitals	23 (74)	35.4 (9.12) (NR)	NR	100	ICD-9	CCAR	NR
Maddox (2015)	USA	Mixed	University Center for Autism University Autism Clinic ASD Support groups for adults	28 (53.6)	23.9 (6.9) (16.4)	106.7 (16.6) (80-141)	0	DSM-IV	AQ, ADOS-2, SRS-2-A	NR
McCarthy (2010)	England	Clinical	Specialist Mental Health Service	124 (69.3)	NR (NR) (18-65)	NR	100	ICD-10	NR	NR
McDermott (2005)	USA	Clinical	Family medicine physicians	51 (78.4)	26.7 (NR) (NR)	NR	100	ICD-9	NR	NR
Melville (2008)	Scotland	Mixed	Greater Glasgow Health Board	T1 77 (76.6) T2 50 (NR)	T1 37.8 (14.1) (NR) T2 NR	T1 NR T2 NR	100	DSM-IV/ICD-10	PAS-ADD Checklist, Clinical Interview	NR
Moseley (2011)	Australia	Community	Community Developmental Assessment Services	84 (82.1)	19.5 (4.6) (NR)	NR	79	DSM-IV/ICD-10	Clinical Interview and Observations	AD: 84
Mouridsen (2008a)	Denmark	Clinical	University Hospital	89 (65.2)	45.3 (7.2) (27-60)	NR	39	ICD-10	NR	AA: 89
Mouridsen (2008b)	Denmark	Clinical	University Hospital	118 (72)	40.6 (7.7) (25-55)	NR	70	ICD-10	NR	AD: 118
Munesue (2008)	Japan	Clinical	Outpatient Clinic	44 (63.6)	NR (NR) (13-39)	NR	0	DSM-IV	TABS, AQ, ASSQ	AD: 9 AS: 27 PDD-NOS: 8
Nydén (2010)	Sweden	Clinical	Child Neuropsychiatric Clinic	88 (65.9)	32 (10) (NR)	> 71	0	DSM-IV	ASSQ, ASDI, DSM-IV Checklist	AD: 3 AS: 44 PDD-NOS: 41
Nylander (2013)	Sweden	Clinical	University Hospital	270 (69)	30.7 (11.5) (16-63)	NR	0	ICD-9/ICD-10	NR	NR
Raja (2011)	Italy	Clinical	Psychiatric Intensive Care Unit of a General Hospital	26 (96.15)	30.2 (9.8) (16-56)	83.5 (18.2) (46-121)	15.4	DSM-IV-TR	Medical charts, Interview with relatives	AD: 5 AS: 16 PDD-NOS: 5
Roy (2015)	Germany	Clinical	Psychiatric Intensive Care Unit of a General Hospital	50 (68)	36.4 (NR) (20.62)	NR	NR	DSM-IV	AQ, EQ, Self-developed Interview	AS: 50
Russell (2016)	England	Clinical	National Specialist Clinic	474 (78.4)	30.6 (11.18) (NR)	NR	NR	ICD-10R	AQ, ADOS-G, ADI-R	AD: 115 AS: 212 AA: 100
Rydén (2008)	Sweden	Clinical	Tertiary Psychiatric Clinic	84 (53.6)	30 (10) (NR)	>70	0	DSM-IV	FTF, ASSQ, ASDI	AD: 5 AS: 51 PDD-NOS: 28
Schendel (2016)	Denmark	Clinical	Danish Psychiatric Central Research Register	20492 (77.6)	NR	NR	16	ICD-8/ICD-10	Medical records	NR
Sizoo (2009)	Netherlands	Clinical	Two specialized clinics	76 (81.6)	34.1 (11.9) (NR)	103 (13.6)	0	DSM-IV	ADI-R, DSM-IV Checklist	AD: 10 AS:32 PDD-NOS: 34
Stahlberg (2004)	Sweden	Clinical	Child Neuropsychiatric Clinic	129 (61.2)	30.6 (9.7)	NR	NR	DSM-IV	ASSQ, ASDI, DSM-IV Checklist	AD: 13 AS:49 AA:67
Sterling (2008)	USA	Community	University Of Washington Autism Center	46 (91.3)	23.7 (7.21) (18-44)	NR (NR) (57-139)	NR	DSM-IV	ADOS-WPS/ADOS-G, ADI-R	NR
Strunz (2015)	Germany	Clinical	Charité University Medicine Berlin	58 (45.8)	32.7 (10.9)	>70	0	DSM-IV	ADOS, ADI-R	AS: 49 HFA: 10
Tani (2003)	Finland	Community	Helsinki Asperger Centre	20 (70)	27.2 (7.3)	111.6 (11.9)	NR	DSM-IV	ASSQ	AS: 20
Tani (2006)	Finland	Community	Helsinki Asperger Center	20 (70)	27.2 (7.3) (NR)	111.6 (11.9) (NR)	NR	DSM-IV	ASSQ	AS: 20
Tsakanikos (2006)	England	Clinical	Specialist Mental Health Service	147 (67.3)	NR (NR) (16-84)	NR	100	ICD-10	NR	NR
Tsakanikos (2007)	England	Clinical	Specialist Mental Health Service	137 (67.2)	28.4 (NR) (NR)	NR	100	ICD-10	NR	NR
Tsakanikos (2011)	England	Clinical	Specialist Mental Health Service	150 (66.7)	28.5 (10.6) (16-84)	NR	100	ICD-10	NR	NR

ASD – Autism Spectrum Disorders; NR – Non-reported; SD – Standard deviation; IQ – Intelligence quotient; ID – Intellectual disability; ASSQ – Asperger Syndrome Screening Questionnaire; ASDI – Asperger Syndrome Diagnostic Interview; DISCO – Diagnostic Interview for Social and Communication Problems; ADI-R – Autism Diagnostic Interview Revised; ADOS – Autism Diagnostic Observational Schedule; AQ – Autism Quotient; CCAR – Colorado Client Assessment Record; SRS – Social Responsiveness Scale; PAS-ADD - Psychiatric Assessment Schedule for Adults with Developmental Disabilities; TABS – Tokyo Autistic Behavior Scale; EQ – Empathy Quotient; FTF-Q – Five-to-Fifteen Questionnaire; AD – Autistic Disorder; AS – Asperger Syndrome; AA – Atypical Autism; PDD-NOS – Pervasive Developmental Disorder Not Otherwise Specified; HFA – High-Functioning Autism.

Table 2. Disorders due to psychoactive substance use (SUD)

Author (Year)	N ASD	N CG	Psychiatric disorders measures	Outcome
Anckarsäter (2008)	22	-	Medical files Structured Interviews	2 (9.1%), 1 (4.5%) and 2 (9.1%) had a SUD, OH and Mixed SUD diagnose, respectively.
Croen (2015)	1507	15,070	Medical records	**ASD:** OH abuse 33 (2.2%) OH dependence 16 (1.1%) Drug abuse 39 (2.3%) Drug dependence 27 (1.8%) **Non-ASD:** OH abuse 591 (4%) OH dependence 296 (2%) Drug abuse 418 (2.8%) Drug dependence 325 (2.5%)
Esan (2015)	42	96	Medical records	5 (11.9%) and 34 (35.4%) individuals had a harmful use or dependence on substances in the ASD and ID groups, respectively.
Gillberg (2016)	50	-	ASRS	2 (4%) reported current alcohol dependency. None reported current drug dependency.
Hallerbäck (2014)	54	41	SCID-I	**ASD:** SUD 6 (11.1%) OH 4 (7.4%) CAN 2 (3.7%) STI 4 (7.4%) Other drugs 2 (3.7%) **SQZ:** SUD 13 (31.1%) OH 6 (14.6%) CAN 4 (9.8%) STI 7 (17.1%) Other drugs 0
Hofvander (2009)	122	-	SCID-I DSM-IV Checklist Interview	19 (16%) individuals had a lifetime SUD. The majority of diagnoses were related to alcohol (n = 15, 12%), 4 (3.3%) subjects met criteria for cannabis use disorder, 3 (2.5%) for amphetamine use disorder, 2 (1.6%) had a history of taking non-prescribed opiates or analgetics, and 1 (0.8) had used anabolic steroids. Another subject, a 27-year-old man with Autistic Disorder, had a history of inhaling solvents.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** Any SUD 21 (33%) 7 (11%) OH abuse 18 (29%) 4 (6%) OH dependence 8 (13%) 2 (3%) Drug abuse 9 (14%) 2 (3%) Drug dependence 3 (5%) 1 (2%) **Non-ASD:** Any SUD 28 (44%) 5 (8%) OH abuse 5 (8%) 3 (5%) OH dependence 17 (27%) 2 (3%) Drug abuse 12 (20%) 0 Drug dependence 11 (18%) 2 (3%)
Kato (2013)	43	544	MINI	1 (2.3%) and 42 (7.7%) participants fulfilled diagnostic criteria for a substance abuse disorder in the ASD and Non-ASD groups, respectively.
Ketelaars (2008)	15	21	SCAN-2.1	3 (20%) and 2 (10%) reported a current SUD in the ASD and Non-ASD groups, respectively.
Kronenberg (2015)	31	50	NR	**ASD**: OH 71 % CAN 13% HER 0% COC 7% STI 3% **SUD**: OH 66% CAN 18% HER 4% COC 8% STI 0% **SUD+ADHD**: OH 39% CAN 24% HER 2% COC 7% STI 15%
Lever (2016)	138	170	MINI	22 (15.9%) and 43 (25.3%) had a substance abuse disorder in the ASD and Non-ASD, respectively.
Lugnegard (2011)	54	-	SCID-I	6 participants (11%) had had a previous SUD (one woman and one man with a combination of alcohol and drug dependence, two men with alcohol dependence and two men with drug dependence).
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	0 (0%), 3 (13%) and 8 (34.8%) participants fulfilled diagnostic criteria for a substance abuse disorder in the ASD group, ID group and non-ID group, respectively.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	0 participants fulfilled Alcohol/substance disorder diagnostic criteria at T1
Mouridsen (2008a)	89	258	Medical records	9 (10.1%) and 2 (0.8) individuals had a SUD during the follow-up period in the ASD and Non-ASD groups, respectively.
Mouridsen (2008b)	118	336	Medical records	1 (0.8%) and 8 (2.4%) individuals had a SUD during the follow-up period in the ASD and Non-ASD groups, respectively.
Nylander (2013)	270	437	NR	13 (4.8%) and 93 (21.3%) had a SUD diagnosis in the ASD and ADHD groups, respectively.
Raja (2011)	26	-	Record charts	4 (15.4%) had a SUD diagnosis.
Roy (2015)	50	-	SCID-I	6 adults (12%) were cannabis abusers; and 5 (10%) and 4 adults (8%) were diagnosed with alcohol abuse or dependence, respectively
Russell (2016)	474	385	Neuropsychiatric Asesssment	**ASD:** OH dependence 3 (0.6%) Drug dependence 1 (0.2%) **Non-ASD:** OH dependence 10 (2.5%) Drug dependence 5 (1.2%)
Schendel (2016)	20,492	1,892,412	Medical records	422 (2.1%) and 15,835 (0.8%) had a SUD diagnosis in the ASD and Non-ASD groups, respectively.
Sizoo (2009)	76	53	NR	**ASD:** any SUD 21 (28%) OH 10 (47%) CAN 6 (29%) Other drugs or gambling 5 (24%) **ADHD:** any SUD 32 (60%) OH 8 (25%) CAN 9 (28%) Other drugs or gambling 15 (47%)
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	MINI SCID-I	**ASD**: OH dependence 0, OH abuse 0, Drug dependence 0, Drug abuse 0 **BOR**: OH dependence 14 (18.2), OH abuse 20 (26), Drug dependence 14 (18.2), Drug abuse 9 (11.7) **NAR**: OH dependence 7 (11.3), OH abuse 10 (16.1), Drug dependence 7 (11.3), Drug abuse 2 (3.2) **NCC**: OH dependence 0, OH abuse 0, Drug dependence 0, Drug abuse 0

ASD – Autism Spectrum Disorders; CG – Comparison group;; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; ADHD – Attention deficit and hyperactivity disorder; NCC – Non-clinical Controls; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; MINI – MINI International Neuropsychiatric Interview; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; CCAR – Colorado Client Assessment Record; SUD – Substance use disorders; OH – Alcohol; CAN – Cannabis; HER – Heroine; COC – Cocaine; STI – Stimulants; SQZ – Schizophrenia.

Table 3. Schizophrenia, schizotypal, or delusional disorders (SSD)

Author (Year)	N ASD	N CG	Psychiatric disorders measures	Outcome
Anckarsäter (2008)	22	-	Medical files Structured Interviews	2 (9.1%) had a SSD diagnose, one a psychotic disorder and the other SQAFF.
Bakken (2010)	62	132	PAC	15 (25.1%) and 12 (9.1) participants had a diagnosis of Psychosis in the ASD and ID groups, respectively.
Billstedt (2005)	108	-	Observation, a semi-structured interview and a brief psychiatric examination	7 individuals (5 males, 3 females) had been diagnosed as suffering from psychosis. Only in one individual (male) had the psychotic condition been labelled Schizophrenia.
Buck (2014)	129	-	Mini PAS-ADD Clinical Interview	Six participants (5 %) endorsed current and 13 (10 %) endorsed lifetime symptoms meeting psychosis criteria.
Cederlund (2008)	AD 70 AS 70	-	NR	3 (4.3%) and 4 (5.7%) participants have been diagnosed as suffering from psychosis in the AS and AD groups, respectively. No individuals have been diagnosed with schizophrenia in either both groups.
Chen (2015)	725	-	Medical charts	81 (11.2%) had a Schizophrenia diagnosis
Croen (2015)	1507	15,070	Medical records	118 (7.8%) and 56 (0.4%) individuals had Schizophrenic disorders (295.xx) in the ASD and Non-ASD group, respectively. 95 (6.3%) and 83 (0.6%) individuals had Other psychoses (297.1x; 297.3x; 298.8x; 298.9x; 301.22) in the ASD and Non-ASD group, respectively.
Esan (2015)	42	96	Medical records	6 (14.3%) and 21 (21.9%) individuals had a Psychosis diagnosis in the ASD and ID groups, respectively.
Gillberg (2016)	50	-	ASRS	1 (2%) had reported Schizophrenic psychosis ever.
Hofvander (2009)	122	-	SCID-I DSM-IV Checklist and Interview	15 (12%) individuals had a lifetime Psychotic disorder. 4 (3.3%) patients met criteria for a schizophreniform disorder, 3 (2.5%) for brief psychotic disorder, and 1 (0.8%) for a delusional disorder. No subject met criteria for schizoaffective disorder.
Hutton (2008)	135	41	SAPPA	There were no cases of schizophrenia
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** 8 (13%) and 5 (8%) had lifetime and current psychosis, respectively. **Non-ASD:** None individual had lifetime neither current psychosis.
Ketelaars (2008)	15	21	SCAN-2.1	4 (19%) reported a Psychotic disorder NOS in the Non-ASD group. None individual in either group had current Schizophrenia diagnosis.
Lugnegard (2011)	54	-	SCID-I	2 (3.7%) met criteria for psychosis (one brief psychotic episode, and one psychotic syndrome NOS). 7 participants (13%) had experienced recurrent (primarily auditory) hallucinations without other signs of psychosis. No participant met criteria for SQZ, SQZAFF or substance induced psychotic disorder.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	6 (26.1%), 18 (78.3%) and 19 (82.6%) participants fulfilled diagnostic criteria for a psychotic disorder in the ASD group, ID group and non-ID group, respectively.
McCarthy (2010)	124	562	Medical records Clinical interview	7 (5.6%) and 102 (18.1%) had a SSD in the ASD and ID groups, respectively.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	1 (1.3%) participants fulfilled psychotic disorder diagnostic criteria at T1 Incidence at two years follow-up was 0 for psychotic disorder.
Mouridsen (2008a)	89	258	Medical records	**ASD:** Any SSD 31 (34.8%) SQZ 25 (28.1%) DD 2 (2.3%) Acute Psychotic Disorder 1 (1.1%) SQZAFF 0 Psychotic disorder NOS 3 (3.4%) **Non-ASD:** Any SSD 8 (3.1%) SQZ 5 (1.9%) DD 0 Acute Psychotic Disorder 2 (0.8%) SQZAFF 1 (0.4%) Psychotic disorder NOS 0
Mouridsen (2008b)	118	336	Medical records	**ASD:** Any SSD 8 (6.8%) SQZ 4 (3.4%) DD 1 (0.8%) Acute Psychotic Disorder 1 (0.8%) Psychotic disorder NOS 2 (1.6%) **Non-ASD:** Any SSD 3 (0.9%) SQZ 3 (0.9%) DD 0 Acute Psychotic Disorder 0 Psychotic disorder NOS 0
Nylander (2013)	270	437	NR	57 (21.1%) and 30 (6.9%) had a psychotic disorder in the ASD and ADHD groups, respectively.
Raja (2011)	26	-	Record charts	16 (61.5%) were diagnosed with Schizophrenia.
Roy (2015)	50	-	SCID-I	1 (2%) individual were diagnosed with Paranoid Schizophrenia.
Russell (2016)	474	385	Neuropsychiatric Assessment	6 (1.2%) and 9 (3.2%) individuals had SQZ in the ASD and Non-ASD groups, respectively.
Rydén (2008)	53	37	Medical records	5 (9.4%) and 5 (15.5%) had a psychosis disorder in the ASD and Non-ASD groups, respectively.
Schendel (2016)	20,492	1,892,412	Medical records	1146 (5.6%) and 1263 (0.7%) had a SSD diagnosis in the ASD and Non-ASD groups, respectively.
Tsakanikos (2006)	147	605	Medical records	23 (16.4%) and 109 (18.5%) individuals had a SSD in the ASD and ID groups, respectively.
Tsakanikos (2007)	137	-	Medical records	22 (16.1%) individuals had a SSD.
Tsakanikos (2011)	150	-	Medical records	25 (17.2%) had a SSD.

ASD – Autism Spectrum Disorders; CG – Comparison group; AD – Autistic disorder; AS – Asperger Syndrome; ID – Intellectual Disability; ADHD – Attention Deficit and Hyperactivity Disorder; T1 – First-time measure; T2 – Second-time measure; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; CCAR – Colorado Client Assessment Record; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; SSD – Schizophrenia Spectrum disorders; SQZ – Schizophrenia; DD – Delusional Disorder; SQZAFF – Schizoaffective Disorder; NOS – Not otherwise specified.

Table 4. Mood disorders (MD)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2008)	22	-	Medical files, Structured Interviews	2 (9.1) and 7 (31.8%) had DEP and BPD, respectively.
Bakken (2010)	62	132	PAC	23 (37.1%) and 20 (15.2%) participants had a diagnosis of Depression in the ASD and ID groups, respectively.
Billstedt (2005)	108	-	Observation a semi-structured interview and a brief psychiatric examination	1 individual had been diagnosed with BPD. 1 individual had recurrent unipolar depressive episodes.
Buck (2014)	129	-	Mini PAS-ADD Clinical Interview	Depression rate from lifetime Mini PAS-ADD was 13 % (n = 17). Two (2 %) participants met current criteria for expansive mood (hypomania/mania) and 8 (6 %) met lifetime criteria.
Cederlund (2008)	AD 70 AS 70	-	NR	1 (1.4%) participant have been diagnosed with BPD in the AS.
Chen (2015)	725	-	Medical charts	29 (4%) and 56 (7.7%) had a BPD and Depressive disorder diagnosis
Croen (2015)	1507	15,070	Medical records	159 (10.6%) and 251 (1.7%) individuals had a BPD in the ASD and Non-ASD groups, respectively. 388 (25.8%) and 1490 (9.9%) individuals had a Depression in the ASD and Non-ASD groups, respectively.
Esan (2015)	42	96	Medical records	4 (9.5%) and 11 (11.5%) individuals had a BPD in the ASD and ID groups, respectively. 3 (7.1%) and 19 (19.8%) individuals had a Depressive disorder in the ASD and ID groups, respectively.
Gillberg (2016)	50	-	ASRS	29 (58%) and 14 (28%) had depressive disorders ever and current, respectively. From this groups, 16 (32%) and 2 (4%) had MDD ever and current, respectively. None individual had DYS ever. 2 (4%) had BPD, one of them with psychotic-manic episodes.
Hofvander (2009)	122	-	SCID-I DSM-IV Checklist and Interview	65 (53%) individuals had a MD. Criteria for a BPD were met by 10 (8.2%) subjects.
Hutton (2008)	135	41	SAPPA	8 (6%) participants developed an affective disorder with marked obsessional features; 3 (2.2%) complex affective disorders; 4 (3%) more straightforward affective disorders; 1 (0.7%) a bipolar disorder.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** 48 (77%) and 19 (31%) had lifetime and current MDD, respectively. 16 (25%) and 4 (6%) had lifetime and current BPD, respectively. **Non-ASD:** 29 (46%) and 14 (23%) had lifetime and current MDD, respectively. 8 (13%) and 3 (5%) had lifetime and current BPD, respectively.
Kato (2013)	43	544	MINI	8 (18.6%) and 186 (34.2%) participants fulfilled diagnostic criteria for a mood disorder in the ASD and Non-ASD groups, respectively.
Ketelaars (2008)	15	21	SCAN-2.1	4 (26.7%) had a MD in the ASD group, two of them with psychotic symptoms. 3 (14%) individuals had MD without psychotic symptoms in the Non-ASD group.
Lever (2016)	138	70	MINI	**ASD:** MD 79 (57.2), DEP 74 (53.6), and DYS 25 (18.1) **Non-ASD:** MD 31 (18.2), DEP 28 (16.5), and DYS 5 (2.9)
Lugnegard (2011)	54	-	SCID-I	38 participants (70%) had experienced at least one episode of major depression, and 27 (50% of the total group) had had recurrent major depressions. 5 participants (9% of the total group) met criteria for bipolar II disorder, whereas none met criteria for bipolar I disorder.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	6 (26.1%), 3 (13%) and 1 (4.3%) participants fulfilled diagnostic criteria for a mood disorder in the ASD group, ID group and non-ID group, respectively.
McCarthy (2010)	124	562	Medical records Clinical Interview	9 (7.3%) and 69 (12.3%) had a depressive disorder in the ASD and ID groups, respectively.
McDermott (2005)	51	-	Medical records Clinical Interview	3 (5.9) had Depression (ICD-9 300.4, 311, 296.2, 296.3 or 309.1)
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	4 (5.2%) participants fulfilled affective disorder diagnostic criteria at T1. Incidence at two years follow-up was 4 for affective disorder. Three of the affective disorders were depressive episodes, and one was a mixed affective disorder. Incidence at two years follow-up was 0 for mania.
Moseley (2011)	84	-	Clinical Assessment Protocol, Developmental Behavior Checklist	9 (11%), 1 (1%), 3 (4%) and 1 (1%) participants have developed MDD, Dysthymia and BPD and MDD not otherwise specified, respectively.
Mouridsen (2008a)	89	258	Medical records	10 (11.2%) and 10 (3.9%) individuals had any MD in the ASD and Non-ASD groups, respectively.
Mouridsen (2008b)	118	336	Medical records	4 (3.4%) and 4 (1.2%) individuals had any MD in the ASD and Non-ASD groups, respectively.
Munesue (2008)	44	-	Clinical interview	16 (36.4%) individuals had a MD: 4 (9.1%) MDD and 12 (27.3%) BPD
Nylander (2013)	270	437	NR	47 (17.4%) and 119 (27.3%) had a MD diagnosis in the ASD and ADHD groups, respectively.
Raja (2011)	26	-	Record charts	3 (11.5%) and 1 (3.8%) were diagnosed with Depression and Mania with psychotic signs, respectively. Other 3 (11.5%) participants were diagnosed with MD with psychotic signs.
Roy (2015)	50	-	SCID-I	24 (48%) and 12 (24%) had a MDD and DYS, respectively. In 7 participants (14%) a combination of MDD and DYS was observed (double depression). MAN and BPD were not noted in the adults with AS.
Russell (2016)	474	385	HADS	95 (20%) and 86 (22.3%) individuals had any MD in the ASD and Non-ASD groups, respectively. 75 (15.8%) and 49 (12.7%) individuals had a Depressive episode in the ASD and Non-ASD groups, respectively. 4 (0.8%) and 5 (1.2%) individuals had BPD in the ASD and Non-ASD groups, respectively.
Rydén (2008)	53	37	Medical records	26 (49%) and 23 (68%) had a MDD in the ASD and Non-ASD groups, respectively. 2 (3.7%) and 1 (2.9%) had a BPD in the ASD and Non-ASD groups, respectively.
Schendel (2016)	20,492	1,892,412	Medical records	1803 (8.8%) and 33063 (1.8%) had a MD diagnosis in the ASD and Non-ASD groups, respectively.
Sterling (2007)	46	-	FHI-RDC	20 (43.5%) were depressed.
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	MINI, SCID-I	**ASD:** MDD 9 (15.5) DYS 5 (8.6) **BOR:** MDD 24 (31.2) DYS 17 (22.1) **NAR:** MDD 23 (37.1) DYS 12 (19.4) **NCC:** MDD 0 DYS 0
Tani (2003)	20	-	SCID-I	5 (25%) AS subjects had mild to moderate depressive disorder and none of them had severe MDD.
Tsakanikos (2006)	147	605	Medical records	53 (9%) and 9 (6.4%) individuals had a Depressive disorder in the ASD and ID groups, respectively.
Tsakanikos (2007)	137	-	Medical records	9 (6.6%) individuals had a Depressive disorder
Tsakanikos (2011)	150	-	Medical records	9 (6.9%) had a depressive disorder.

ASD – Autism Spectrum Disorders; CG – Comparison group; AD – Autistic disorder; AS – Asperger Syndrome; ID – Intellectual Disability; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; NCC – Non-clinical Controls; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; MINI – MINI International Neuropsychiatric Interview; CCAR – Colorado Client Assessment Record; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; HADS – Hamilton Anxiety and Depression Scale; FHI-RDC – Family History Interview with Research Diagnostic Criteria; MD – Mood Disorders; DEP – Depressive episode; BPD – Bipolar Disorder; MDD – Major Depressive Disorder; DYS – Dysthymia.

Table 5. Neurotic, stress-related, somatoform disorders (ANX)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2008)	22	-	Medical files Structured interviews	6 (27.3%) had anxiety disorders. One of them had OCD, another had AGO and another one had DIS
Bakken (2010)	62	132	PAC	21 (33.9%) and 12 (9.1%) participants had a diagnosis of anxiety in the ASD and ID groups, respectively. 8 (12.9%) and 4 (3.3%) participants had a diagnosis of OCD in the ASD and ID groups, respectively.
Buck (2014)	129	-	Mini PAS-ADD Clinical Interview	The most common current and lifetime psychiatric disorder identified by the Mini PAS-ADD was anxiety [40 % (n = 51) and 53 % (n = 68), respectively], followed by OCD [33 % (n = 43) and 36 % (n = 47), respectively].
Chen (2015)	725	-	Medical charts	53 (7.3%) had an anxiety disorder diagnosis
Croen (2015)	1507	15,070	Medical records	439 (29.1%) and 1371 (9.1%) individuals had an ANX in the ASD and Non-ASD groups, respectively. 115 (7.6%) and 74 (0.5%) individuals had an OCD in the ASD and Non-ASD groups, respectively.
Gillberg (2016)	50	-	ASRS	5 (10%) met criteria for current GAD, 4 (8%) men had a diagnosis of current OCD, 3 (6%) reported current AGO, 2 (4%) individuals reported current SAD, and 1 (2%) individual had a current PAN. None reported PTSD.
Hofvander (2009)	122 (119)	-	SCID-I DSM-IV Checklist and Interview	29 (24%) out of 122 individuals had an OCD. 59 (50%) and 6 (5%) out of 119 individuals had a lifetime ANX and SMF, respectively. GAD was common (n = 18, 15%) as was SAD (n = 16, 13%). 13 subjects (11%) met criteria for PAN and/or AGO and 7 (6%) met criteria for a specific phobia. 2 (1.7%) patients suffered from PTSD, and one had an ANX-NOS.
Hutton (2008)	135	41	SAPPA	5 (3.7%) individuals developed an obsessive-compulsive disorder and/or catatonia. 1 individual experienced an acute anxiety state complicated by alcohol excess.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** >=2 ANX 37 (59%) and 24 (38%) AGO 22 (35%) 15 (24%) GAD 22 (35%) 18 (29%) SAD 35 (56%) 25 (40%) OCD 15 (24%) 10 (16) PAN 5 (15%) 2 (3%) PTSD 7 (11%) 3 (5%) **Non-ASD:** >=2 ANX 11 (17%) and 7 (11%) AGO 4 (6%) 2 (3%) GAD 11 (17%) 9 (16%) SAD 12 (19%) 10 (16%) OCD 0 0 PAN 6 (18%) 1 (2%) PTSD 1 (2%) 0
Kato (2013)	43	544	MINI	7 (16.3%) and 107 (19.7%) participants fulfilled diagnostic criteria for anxiety disorders in the ASD and Non-ASD groups, resp. 30 (70%) and 226 (41.5%) participants fulfilled diagnostic criteria for adjustment disorders in the ASD and Non-ASD groups, resp. 0 (0%) and 14 (2.6%) participants fulfilled diagnostic criteria for dissociative disorders in the ASD and Non-ASD groups, resp. 0 (0%) and 8 (1.5%) participants fulfilled diagnostic criteria for somatoform disorders in the ASD and Non-ASD groups, resp.
Ketelaars (2008)	15	21	SCAN-2.1	**ASD:** PAN/AGO 2 (13%) OCD 1 (7%) Other ANX 1 (7%) SAD 3 (20%) **Non-ASD:** PAN/AGO 1 (5%) OCD 1 (5%) Other ANX 0 SAD 4 (19%)
Lever (2016)	138	170	MINI	**ASD:** ANX 74 (53.6%), PAN 21 (15.2%), AGO 29 (21%), SAD 21 (15.2%), PTSD 4 (2.9%), OCD 30 (21.7%), GAD 22 (15.9%), and SMF 8 (5.8%) **Non-ASD:** ANX 25 (14.7%), PAN 6 (3.5%), AGO 6 (3.5%), SAD 8 (4.7%), PTSD 1 (0.6%), OCD 1 (0.6%), GAD 5 (2.9%), and SMF 3 (1.8%)
Lugnegard (2011)	54	-	SCID-I	Thirty individuals (56%) met criteria for at least one ANX, and 11 of these fulfilled diagnostic criteria for two or more ANX. 12 (22%) had SAD, 12 (22%) had generalized GAD, 7 (13%) had PAN, 8 (15%) had AGO and 4 participants (7%) had OCD.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	0 (0%), 2 (8.7%) and 0 (0%) participants fulfilled diagnostic criteria for a substance abuse disorder in the ASD group, ID group and non-ID group, respectively.
Maddox (2015)	28	-	ADIS-IV	14 (50%) individuals had SAD.
McCarthy (2010)	124	562	Medical recrods Clinical Interview	5 (4%) and 44 (7.8%) had an ANX in the ASD and ID groups, respectively. 3 (2.4%) and 26 (4.6%) had an Adjustment reaction in the ASD and ID groups, respectively.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	4 (5.2%) and 0 participants fulfilled anxiety disorder and OCD diagnostic criteria at T1, respectively. Incidence at two years follow-up was 1 for anxiety disorder and 0 for OCD.
Moseley (2011)	84	-	Clinical Assessment Protocol, Developmental Behavior Checklist	7 (8.3%), 3 (3.5%), 3 (3.5%), 2 (2.4%), 1 (1.2%) and 1 (1.2%) participants have developed GAD, specific phobia, separation anxiety disorder, PAN, and anxiety not otherwise specified, respectively.
Mouridsen (2008a)	89	258	Medical records	7 (7.9%) and 8 (3.1%) individuals had any ANX in the ASD and Non-ASD groups, respectively.
Mouridsen (2008b)	118	336	Medical records	2 (1.7%) and 6 (1.8%) individuals had any ANX in the ASD and Non-ASD groups, respectively.
Nylander (2013)	270	437	NR	46 (17%) and 80 (18.3%) had an ANX diagnosis in the ASD and ADHD groups, respectively.
Raja (2011)	26	-	Record charts	2 (7.7%) were diagnosed with OCD.
Roy (2015)	50	-	SCID-I	Anxiety disorders, such as panic disorder (7, 14%), agoraphobia (7, 14%), and social phobia (6, 12%), as well as OCD (7, 14%) with obsessive thoughts (4, 8%) and behavior (4, 6%), were also frequent comorbidities. 3 (6%) individuals had SMF.
Russell (2016)	474	385	Neuropsychiatric Assessment, OCD Inventory Revised	**ASD:** Any ANX 186 (39.2%) PAN 1 (0.2%) AGO 19 (4%) OCD 85 (17.9%) SAD 59 (12.4%) GAD 56 (11.8%) PTSD 2 (0.4%) **Non-ASD:** Any ANX 127 (32.9%) PAN 0 AGO 7 (1.8%) OCD 51 (13.2%) SAD 47 (12.2%) GAD 46 (11.9%) PTSD 0
Rydén (2008)	53	37	Medical records	**ASD:** SAD 9 (17%) OCD 12 (23%) PAN 5 (9.4%) GAD 3 (5.7) PTSD 1 (1.9%) **Non-ASD:** SAD 3 (9%) OCD 5 (16%) PAN 3 (9.1%) GAD 1 (3%) PTSD 0
Schendel (2016)	20,492	1,892,412	Medical records	3458 (16.9%) and 64362 (3.4%) had an ANX diagnosis in the ASD and Non-ASD groups, respectively.
Sterling (2007)	46	-	FHI-RDC	16 (80%) and 11 (55%) had ANX and OCD, respectively.
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	MINI SCID-I	**ASD:** PAN 0 AGO+PAN 0 AGO-PAN 0 SAD 8 (13.8) ADJ 0 OCD 1 (1.7) PTSD 4 (6.9) **BOR:** PAN 3 (3.9) AGO+PAN 5 (6.5) AGO-PAN 3 (3.9) SAD 4 (5.2) AD 3 (3.9) OCD 3 (3.9) PTSD 21 (5.2) **NAR:** PAN 5 (8.1) AGO+PAN 2 (3.2) AGO-PAN 3 (4.8) SAD 5 (8.1) AD 4 (6.5) OCD 1 (1.6) PTSD 4 (6.5) **NCC:** PAN 0 AGO+PAN 0 AGO-PAN 0 SAD 0 ADJ 0 OCD 0 PTSD 0
Tani (2003)	20	-	SCID-I	13 (65%) AS subjects met the diagnostic criteria of one or more anxiety disorders, the most prevalent being social phobia (n = 8).
Tani (2006)	20	-	SCID-I	13 (65%) had an ANX and 7 (35%) had showed some clinical anxiety symptoms, though not reaching the threshold of a specific anxiety disorder.
Tsakanikos (2006)	147	605	Medical records	48 (8.1%) and 6 (4.3%) individuals had an ANX in the ASD and ID groups, respectively. 38 (6.5) and 7 (5%) individuals had an Adjustment reaction in the ASD and ID groups, respectively.
Tsakanikos (2007)	137	-	Medical records	6 (4.4%) and 7 (5.1%) individuals had an ANX and an Adjustment reaction, respectively.
Tsakanikos (2011)	150	-	Medical records	7 (4.8%) had an ANX. 7 (4.8%) had an adjustment reaction

ASD – Autism Spectrum Disorders; CG – Comparison group; ID – Intellectual Disability; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; NCC – Non-clinical Controls; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; MINI – MINI International Neuropsychiatric Interview; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; CCAR – Colorado Client Assessment Record; ADIS-IV – Anxiety Disorders Interview Schedule for DSM-IV; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; FHI-RDC – Family History Interview with Research Diagnostic Criteria; ANX – Anxiety disorders; AGO – Agoraphobia; SAD – Social Anxiety Disorder; PAN – Panic Disorder; GAD – Generalized Anxiety Disorder; OCD – Obsessive-Compulsive Disorder; PTSD – Post-Traumatic Stress Disorder; ADJ – Adjustment Disorder; DIS – Dissociative Disorder; SMF – Somatoform Disorder.

Table 6. Behavioral syndromes associated with physiological disturbances and physical factors (BEH)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Hofvander (2009)	119	-	SCID-I DSM-IV Checklist and Interview	6 (5%) out of 119 individuals had an ED.
Hutton (2008)	135	-	SAPPA	1 (0.7) woman also had a severe eating disorder.
Karjalainen (2016)	119	109	SCID	**ASD:** ED 9 (7.6%) AN 6 (5%) BN 2 (1.7%) Binge eating disorder 1 (0.8%) **ADHD:** ED 9 (8.3%) AN 2 (1.8%) BN 0 Binge eating disorder 7 (6.4%)
Kato (2013)	43	544	MINI	0 (0%) and 14 (2.6%) participants fulfilled diagnostic criteria for eating disorders in the ASD and Non-ASD groups, respectively.
Ketelaars (2008)	15	21	SCAN-2.1	4 (27%) and 6 (29%) had a current SLE in the ASD and Non-ASD groups, respectively.
Lever (2016)	138	170	MINI	8 (5.8) and 1 (0.6) had an Eating disorder diagnosis in ASD and Non-ASD groups, resp.
Lugnegard (2011)	54	-	SCID-I	Two participants (4%) had bulimia nervosa, and none had anorexia nervosa.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	0 participants fulfilled ED diagnostic criteria at T1. Incidence at two years follow-up was 0 for ED.
Nylander (2013)	270	437	NR	1 (0.4%) woman had anorexia nervosa in the ASD group and 7 (1.6%) participants had an ED in the **ADHD** group.
Roy (2015)	50	-	SCID-I	2 (4%) and 1 (2%) had Binge-eating disorder and BN, respectively. No adult had AN.
Russell (2016)	474	385	Neuropsychiatric Assessment	1 (0.2%) and 0 individuals had an ED in the ASD and Non-ASD groups, respectively.
Rydén (2008)	53	37	Medical records	**ASD:** AN 7 (13.2) BN 0 **Non-ASD:** AN 0 BN 1 (3.3)
Schendel (2016)	20,492	1,892,412	Medical records	511 (2.5%) and 12795 (0.7%) had a BEH diagnosis in the ASD and Non-ASD groups, resp.
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	MINI SCID-I	**ASD:** AN 0 BN 0 **BOR:** AN 2 (2.6) BN 15 (19.5) **NAR:** AN 4 (6.5) BN 2 (3.2) **NCC:** AN 0 BN 0

ASD – Autism Spectrum Disorders; CG – Comparison group; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; ADHD – Attention Deficit and Hyperactivity Disorder; NCC – Non-clinical Controls; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; MINI – MINI International Neuropsychiatric Interview; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; CCAR – Colorado Client Assessment Record; ADIS-IV – Anxiety Disorders Interview Schedule for DSM-IV; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; FHI-RDC – Family History Interview with Research Diagnostic Criteria; BEH – Behavioral syndromes associated with physiological disturbances and physical factors; ED – Eating Disorders; AN – Anorexia Nervosa; BN – Bulimia Nervosa; SLE – Sleep Disorders.

Table 7. Disorders of adult personality and behavior (PD)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2006)	74	81	SCID-II	**ASD:** PAR (19, 25.7%) SCHZT (14, 19%) SCHZ (21, 28.4%) HIS (0) NAR (4, 5.4%) BOR (9, 12.2%) ANT (5, 6.8%) AVO (19, 25.7%) DEP (10, 13.5%) OBS (28, 37.8%). **ADHD:** PAR (18, 22.2%) SCHZT (4, 4.9%) SCHZ (10, 12.3%) HIS (0) NAR (3, 3.7%) BOR (30, 37%) ANT (25, 30.9%) AVO (18, 22.2%) DEP (21, 25.9%) OBS (11, 13.6%).
Anckarsäter (2008)	22	-	Medical files Structured Interviews	3 (13.6%) had IMP. One of them had Kleptomania, another had Pyromania and another one had gambling 2 (9.1%) had SEX diagnosis (Paedophilia).
Esan (2015)	42	96	Medical records	**ASD:** Cluster A PD 15 (35.7%) ANT 14 (33.3%) BOR 6 (14.3) **ID:** Cluster A PD 62 (64.6%) ANT 54 (56.3%) BOR 32 (33.3)
Gillberg (2016)	50	-	ASRS	6 (12%) men showed clear signs of antisocial personality disorder.
Hofvander (2009)	122 (117)	-	SCID-I SCID-II DSM-IV Checklist and Interview	73 (62%) out of 117 individuals had at least one PD. PAR (22, 19%) SCHZT (15, 13%) SCHZ (25, 2%) HIS (0) NAR (3, 3%) BOR (10, 9%) ANT (4, 3%) AVO (29, 3%) DEP (6, 5%) OBS (37, 3%). 11 (9%) out of 122 individuals had an IMP. Among patients affected with IMP, intermittent explosive disorder was the most common diagnosis (n = 7, 6%), followed by kleptomania, pyromania, pathological gambling, trichotillomania, and impulse control disorder NOS, all affecting one patient each.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	6 (10%) and 3 (5%) had lifetime and current ANT in the ASD group, respectively. 5 (8%) and 1 (2%) had lifetime and current ANT in the Non-ASD group, respectively.
Ketelaars (2008)	15	21	IPDE	**ASD:** Any PD 3 (20%) PAR 0 SCHZ 1 (7%) SCHZT 0 ANT 0 BOR 1 (7%) AVO 1 (7%) OBS 0 **Non-ASD:** Any PD 3 (20%) PAR 0 SCHZ 1 (5%) SCHZT 0 ANT 0 BOR 0 AVO 2 (10%) OBS 3 (14%)
Lugnegård (2012)	54	-	SCID-II Medical records	Twenty-six participants (48%; 9 women and 17 men) did meet criteria for at least 1 Axis II disorder. Fourteen participants (26% of the whole AS group; 5 women and 9 men) met criteria for schizoid PD, 7 (13%; 3 women and 4 men) met criteria for avoidant PD, and 10 (19%; 3 women and 7 men) met criteria for obsessive-compulsive PD. One individual (a woman) met criteria for schizotypal PD. None met criteria for paranoid PD, antisocial PD, histrionic PD, borderline PD, narcissistic PD, or dependent PD.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	1 (4.3%), 6 (26.1%) and 7 (30.4%) participants fulfilled diagnostic criteria for a personality disorder in the ASD group, ID group and non-ID group, respectively.
McCarthy (2010)	124	562	Medical records Clinical Interview	4 (3.2%) and 27 (4.8%) had a PD in the ASD and ID groups, respectively.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	0 participants fulfilled any PD diagnostic criteria at T1.
Mouridsen (2008a)	89	258	Medical records	8 (9%) and 7 (2.9%) individuals had any PD in the ASD and Non-ASD groups, respectively.
Nylander (2013)	270	437	NR	39 (14.5%) and 71 (16.2%) had a PD diagnosis in the ASD and ADHD groups, respectively. 3 (1.1%) and 0 were diagnosed with schizotypy (F21.0) in the ASD and ADHD groups, respectively. None participant in either both groups were diagnosed with a disorder of impulse control.
Russell (2016)	474	385	Neuropsychiatric Assessment	4 (0.8%) and 8 (2%) individuals had a PD in the ASD and Non-ASD groups, respectively. 4 (0.8%) and 7 (1.8%) had a SCHZT in the ASD and Non-ASD groups, respectively.
Rydén (2008)	53	37	Medical records	7 (13.5%) and 3 (9.1%) had a BOR diagnosis in the ASD and Non-ASD groups, respectively.
Schendel (2016)	20,492	1,892,412	Medical records	694 (3.4%) and 23524 (1.2%) had a PD diagnosis in the ASD and Non-ASD groups, respectively.
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	SCID-II	**ASD**: AVO 1 (1.7) OBS 10 (17.2) PAR 1 (1.7) SCHZT 0 SCHZD 21 (36.2) HIS 0 ANT 0 **BOR**: AVO 28 (38.4) OBS 1 (1.4) PAR 9 (12.3) SCHZT 0 SCHZD 0 HIS 5 (6.8) ANT 12 (16.4) **NAR:** AVO 7 (12.3) OBS 5 (8.7) PAR 14 (24.6) SCHZT 0 SCHZD 3 (5.3) HIS 7 (12.3) ANT 10 (17.5) **NCC**: AVO 0 OBS 0 PAR 0 SCHZT 0 SCHZD 0 HIS 0 ANT 0
Tani (2003)	20	-	SCID-II	14 (70%) subjects met the full diagnostic criteria of any axis-II disorders. 5 AS subjects had Cluster A (paranoid, schizoid, schizotypal) personality disorder, and 3 subjects had cluster B (antisocial, borderline, histrionic, narcissistic) disorder. 13 subjects presented Cluster C (avoidant, dependent, obsessive-compulsive, passive-aggressive) personality disorder. 5 subjects had both cluster A and cluster C personality disorder. Obsessive-compulsive personality disorder (12 subjects) or traits of it (7 subjects) were the most common axis-II disorders.
Tsakanikos (2006)	147	605	Medical records	53 (9%) and 4 (2.9%) individuals had a PD in the ASD and ID groups, respectively.
Tsakanikos (2007)	137	-	Medical records	4 (2.9%) individuals had a PD.
Tsakanikos (2011)	150	-	Medical records	5 (3.4%) had a PD diagnosis.

ASD – Autism Spectrum Disorders; CG – Comparison group; ID – Intellectual Disability; ADHD – Attention deficit and hyperactivity disorder; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; NCC – Non-clinical Controls; SCID-II – Structured Clinical Interview for DSM – Axis II disorders; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; IPDE – International Personality Disorder Examination; CCAR – Colorado Client Assessment Record; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; PD – Personality Disorders; PAR – Paranoid Personality Disorder; SCHZ – Schizoid Personality Disorder; SCHZT – Schizotypal Personality Disorder; ANT – Antisocial Personality Disorder; BOR – Borderline Personality Disorder; HIS – Histrionic Personality Disorder; OBS – Obsessive-Compulsive Personality Disorder; AVO – Avoidant Personality Disorder; DEP – Dependent Personality Disorder; NAR – Narcissistic Personality Disorder; IMP – Impulse control Disorders; SEX – Sexual disorders.

Table 8. Behavioral and emotional disorders with juvenile onset (INF)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2006)	113	-	DSM-IV Checklist for ADHD	39 (34.5%) individuals had an ADHD.
Anckarsäter (2008)	22	-	Medical files Structured Interviews	10 (45.5%) had ADHD, 2 (9.1%) had TOU and 11 (50%) had TICS.
Billstedt (2005)	108	-	Observation, a semi-structured interview and a brief psychiatric examination	1 woman had a severe case of Tourette Syndrome. 25 individuals were reported to have periods of substantial tics without fulfilling the criteria of Tourette Syndrome.
Chen (2015)	725	-	Medical charts	26 (3.6%) had a tics disorder diagnosis. Out of the whole ASD group (n=1,191), 466 (39.1%) had ADHD.
Croen (2015)	1507	15,070	Medical records	167 (11.1%) and 294 (2%) individuals had an ADHD in the ASD and Non-ASD groups, respectively.
Gillberg (2016)	50	-	ASRS DISCO-11	22 (50%) out of 44 individuals reported tic disorder in childhood/adolescence (6 individuals met criteria for TOU and 16 had either vocal or motor tics). 14 men (28 %) had clear signs of a current diagnosis of ADHD.
Hallerbäck (2014)	54	41	WRAADS SNAP	Eight men and eight women in the AS group (16/54, 30%) had an ADHD diagnosis. Two men and two women in the SP group (4/41, 10%) had an ADHD diagnosis.
Hofvander (2009)	122	-	SCID-I DSM Checklist and Interview A-TAC Semi-structured collateral interview based on the ASDI, ADHD-RS, FTF-Q and WURS	52 (43%) and 25 (20%) individuals had an ADHD and TICS diagnosis, respectively.
Johnston (2013)	38	-	BAARS	18 (47.4%) of 38 participants that fulfilled the BAARS had any type of ADHD.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** ADHD 42 (68%) 26 (42%) OPD 33 (53%) 17 (27%) TICS 7 (11%) 4 (6%) TOU 3 (5%) 3 (5%) **Non-ASD:** ADHD 44 (70%) 36 (57%) OPD 9 (20%) 5 (11%) TICS 7 (11%) 3 (5%) TOU 0 0
Karjalainen (2016)	119	-	DSM-IV Checklist for ADHD	45 (%) individuals had ADHD diagnosis.
Lever (2016)	138	170	ADHD Rating Scale	42 (30.4%) and 9 (5.3%) had an ADHD diagnosis in ASD and Non-ASD groups, respectively.
Lugnegard (2011)	54	-	Medical records	Sixteen participants (30%) had been given a diagnosis of AD/HD before the study. One individual (2%) had been diagnosed with Tourette syndrome.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	3 (3.9%) and 4 (5.2%) participants fulfilled ADHD and Pica diagnostic criteria at T1.
Moseley (2011)	84	-	Clinical Assessment Protocol, Developmental Behavior Checklist	1 (1.2%) participant have developed ADHD.
Nyden (2010)	88	-	DSM-IV Checklist	33 ASD participants fulfilled ADHD diagnostic criteria
Nylander (2013)	270	437	NR	14 (5.2%) had an ADHD diagnosis in the ASD group. 4 (1.5%) and 7 (1.6%) had a diagnosis of Tourette Syndrome in the ASD and ADHD groups, respectively.
Russell (2016)	474	385	Neuropsychiatric Assessment	46 (9.7%) and 39 (10.1%) individuals had an ADHD in the ASD and Non-ASD groups, respectively. 7 (1.4%) and 1 (0.3%) had a TICS in the ASD and Non-ASD groups, respectively.
Rydén (2008)	84	-	WRAADS Adult ADHD Self-report Scale	31 (37%) had an ADHD diagnosis in the ASD group.
Schendel (2016)	20,492	1,892,412	Medical records	8074 (39.4%) and 45761 (2.4%) had an INF diagnosis in the ASD and Non-ASD groups, respectively. 5652 (27.6%) and 28191 (1.5%) had an ADHD diagnosis in the ASD and Non-ASD groups, respectively.

ASD – Autism Spectrum Disorders; CG – Comparison Group; T1 – First-time measure; T2 – Second-time measure; ASRS – Autism Spectrum Rating Scale; DISCO-11 – Diagnostic Interview for Social and Communication Disorders; WRAADS – The Wender-Reimherr Adult Attention Deficit Rating Scale; SNAP – The Swanson, Nolan and Pelham Questionnaire; SCID-I – Structured Clinical Interview for DSM – Axis 1 disorders; ASDI – Asperger Syndrome Diagnostic Interview; ADHD-RS – Attention Deficit and Hyperactivity Disorder Rating Scale; FTF-Q – Five-to-Fifteen Questionnaire; WURS – Wender-Utah Rating Scale; A-TAC – Autism-Tics, ADHD and other Comorbidities; BAARS – The Barley Adult ADHD Rating Scale; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; INF – Behavioral and Emotional Disorders with juvenile onset; ADHD – Attention Deficit and Hyperactivity Disorder; TOU – Tourette Syndrome; TICS – Tics Disorders; OPD – Oppositional Defiant Disorder.

Table 9. Any psychiatric disorder

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2008)	22	-	Medical files Structured Interviews	21 (95.5%) had at least one psychiatric disorder.
Bakken (2010)	62	132	PAC	33 (53.2%) and 23 (17.4%) had at least one psychiatric disorder in the ASD and Non-ASD groups, respectively.
Buck (2014)	129	-	Mini PAS-ADD Clinical Interview	57 % (n = 73) of the participants met Mini PAS-ADD criteria for at least one current psychiatric disorder and an additional 12.4 % (n = 16) met criteria for experiencing at least one lifetime psychiatric disorder. Thus, a total of 89 (69 %) participants met Mini PAS-ADD criteria for a psychiatric disorder at any point during their lifetime.
Croen (2015)	1507	15,070	Medical records	More than half (54%) of adults with ASD were diagnosed with a psychiatric condition
Gillberg (2016)	50	-	ASRS	47 (94%) and 27 (54%) reported any psychiatric disorder ever and currently, respectively.
Hutton (2008)	135	41	SAPPA	21 (16%) participants had a definite new-onset psychiatric Disorder. There were also another 8 individuals (6%) with a dubious or uncertain new psychiatric disorder.
Ketelaars (2008)	15	21	SCAN-2.1 IPDE	8 (53%) and 14 (67%) had at least one psychiatric disorder currently in the ASD and Non-ASD groups, resp.
Lever (2016)	138	170	MINI ADHD-RS	109 (79%) and 83 (48.8%) had at least one psychiatric disorder in the ASD and Non-ASD, resp.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	13 (56.5%) participants fulfilled diagnostic criteria for at least one psychiatric disorder in the ASD group.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	16 (20.8%) 36 (23.4%) participants had mental-ill health of any type, excluding problem behaviors, in the ASD and ID groups, resp. Incidence at two years follow-up for mental-ill health of any type, excluding problem behaviors, was 6 and 14 in the ASD and ID groups, resp.
Moseley (2011)	84	-	Clinical Assessment Protocol, Developmental Behavior Checklist	35 (41.7%) participants have developed at least one psychiatric disorder.
Mouridsen (2008a)	89	258	Medical records	Fifty-five persons (61.8%) from the case group were given a psychiatric diagnosis other than PDD during the observation period.
Mouridsen (2008b)	118	336	Medical records	During the observation period, 20 subjects (17%) in the case group were given a psychiatric diagnosis other than PDD or mental retardation compared with 9 individuals (2.7%) in the CG.
Nylander (2013)	270	437	NR	162 (60%) and 268 (38.7%) had at least one psychiatric disorder in the ASD and ADHD groups, respectively.
Roy (2015)	50	-	SCID-I	35 (70%) had at least one comorbid psychiatric disorder in their lifetime.
Russell (2016)	474	385	Neuropsychiatric Assessment HADS OCD-Inventory-R	275 (58%) received one or more co-morbid psychiatric diagnoses.
Tani (2003)	20	-	SCID-I SCID-II	16 (80%) individuals had at least one psychiatric disorder.
Tsakanikos (2007)	137	-	Medical records	57 participants (41.6%) had at least one psychiatric disorder.

ASD – Autism Spectrum Disorders; CG – Comparison Group; ID – Intellectual Disability; ADHD – Attention Deficit and Hyperactivity Disorder; PDD – Pervasive Developmental Disorder; T1 – First-Time measure; T2 – Second-Time measure; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; MINI – MINI International Neuropsychiatric Interview; IPDE – International Personality Disorder Examination; ADHD-RS – Attention Deficit and Hyperactivity Disorder Rating Scale; CCAR – Colorado Client Assessment Record; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; HADS – Hamilton Anxiety and Depression Scale; SCID-II - Structured Clinical Interview for DSM – Axis II disorders.

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Appendix C. Quality assessment of the selected studies performed with Berra et al. (2008)

Study reference	Research question and objective	Participants	Groups comparison	Variables definition and measurement	Statistical analysis and bias risk	Internal validity	Results	Conclusions, external validity and aplicability	Conflict of interests	Global quality
Anckarsäter (2006)	Medium	Low	NA	Good	Good	Medium	Medium	Medium	Medium	Medium
Anckarsäter (2008)	Very good	NA	NA	Medium	Low	Low	Good	Good	Medium	Medium
Bakken (2010)	Very good	Medium	Good	Good	Low	Low	Medium	Medium	Good	Medium
Billstedt (2005)	Very good	Medium	NA	Good	Medium	Medium	Medium	Medium	NA	Medium
Buck (2014)	Very good	Good	NA	Good	Good	Good	Good	Good	Medium	High
Cederlund (2008)	Very good	Very good	NA	Good	Good	Good	Good	Good	Good	High
Chen (2015)	Very good	Good	Good	Very good	Good	Good	Very good	Good	Very good	High
Croen (2015)	Good	Medium	Good	Medium	Very good	Medium	Very good	Good	Very good	High
Esan (2015)	Good	Medium	NA	Medium	Medium	Medium	Good	Medium	NA	Medium
Gillberg (2016)	Very good	Good	NA	Good	Good	Good	Good	Good	Very good	High
Hallerbäck (2014)	Good	Low	NA	Good	Low	Low	Good	Good	NA	Medium
Hofvander (2009)	Very good	Medium	NA	Good	Very good	Good	Good	Good	Very good	High
Hutton (2008)	Very good	Good	NA	Good	NA	Medium	Good	Good	NA	Medium
Johnston (2013)	Very good	Medium	Medium	Good	Good	Medium	Medium	Medium	NA	Medium
Joshi (2013)	Very good	Good	Good	Good	Good	Good	Good	Good	Medium	High
Karjalainen (2016)	Very good	Medium	NA	Medium	Good	Medium	Medium	Medium	Good	Medium
Kato (2013)	Very good	Medium	NA	Medium	Medium	Medium	Medium	Medium	Good	Medium
Ketelaars (2008)	Very good	Medium	Medium	Medium	Medium	Medium	Medium	Medium	NA	Medium
Kronenberg (2015)	Very good	Medium	Very good	Good	Good	Good	Good	Good	Very good	High
Lever (2016)	Good	Very good	Very good	Very good	Very good	Very good	Very good	Very good	Very good	High
Lugnegård (2011)	Very good	Good	NA	Good	Medium	Medium	Medium	Good	Very good	High
Lugnegård (2012)	Good	Good	Good	Very good	Medium	Good	Good	Good	NA	Medium
Lunsky (2009)	Very good	Good	NA	Medium	Good	Medium	Good	Good	NA	Medium
Maddox (2015)	Very good	Good	Very good	Very good	Good	Good	Good	Very good	Very good	High
McCarthy (2010)	Very good	Low	Medium	Good	Good	Medium	Good	Good	NA	Medium
McDermott (2005)	Very good	Medium	Medium	Medium	Good	Medium	Very good	Good	Good	Medium
Melville (2008)	Very good	Good	Good	Good	Good	Good	Good	Very good	Very good	High
Moseley (2011)	Good	Good	NA	Good	Good	Medium	Good	Good	Good	Medium
Mouridsen (2008a)	Good	Medium	Medium	Medium	Good	Medium	Good	Medium	Medium	Medium
Mouridsen (2008b)	Very good	Medium	Medium	Good	Medium	Medium	Good	Good	Medium	Medium
Munesue (2008)	Medium	Low	NA	Low	Medium	Low	Medium	Medium	Very good	Medium
Nydén (2010)	Very good	Good	NA	Good	Medium	Medium	Good	Good	Good	High
Nylander (2013)	Good	Medium	NA	Good	Medium	Medium	Medium	Good	Medium	Medium
Raja (2011)	Very good	Medium	NA	Medium	Good	Medium	Good	Good	NA	Medium
Roy (2015)	Very good	Low	NA	Good	NA	Medium	Very good	Good	Very good	Medium
Russell (2016)	Very good	Medium	NA	Good	Low	Medium	Good	Good	Very good	Medium
Rydén (2008)	Very good	Medium	Very good	Good	Good	Good	Medium	Good	NA	High
Schendel (2016)	Good	Medium	Good	Good	Very good	Good	Very good	Good	Medium	High
Sizoo (2009)	Good	Very good	Good	Very good	Good	Good	Very good	Good	Good	High
Stahlberg (2004)	Very good	Good	NA	Good	Medium	Medium	Good	Good	NA	High
Sterling (2008)	Very good	Low	NA	Good	Medium	Medium	Medium	Good	Good	Medium
Strunz (2015)	Very good	Medium	Good	Very good	Good	Medium	Good	Good	NA	Medium
Tani (2003)	Very good	Medium	Good	Good	Good	Medium	Good	Good	Very good	High
Tani (2006)	Medium	Low	Good	Good	Very good	Medium	Medium	Medium	NA	Medium
Tsakanikos (2006)	Good	Medium	Medium	Good	Good	Medium	Good	Medium	NA	Medium
Tsakanikos (2007)	Good	Medium	NA	Medium	Good	Medium	Medium	Medium	NA	Medium
Tsakanikos (2011)	Good	Medium	Medium	Medium	Good	Medium	Medium	Medium	NA	Medium

NA *Not applicable*

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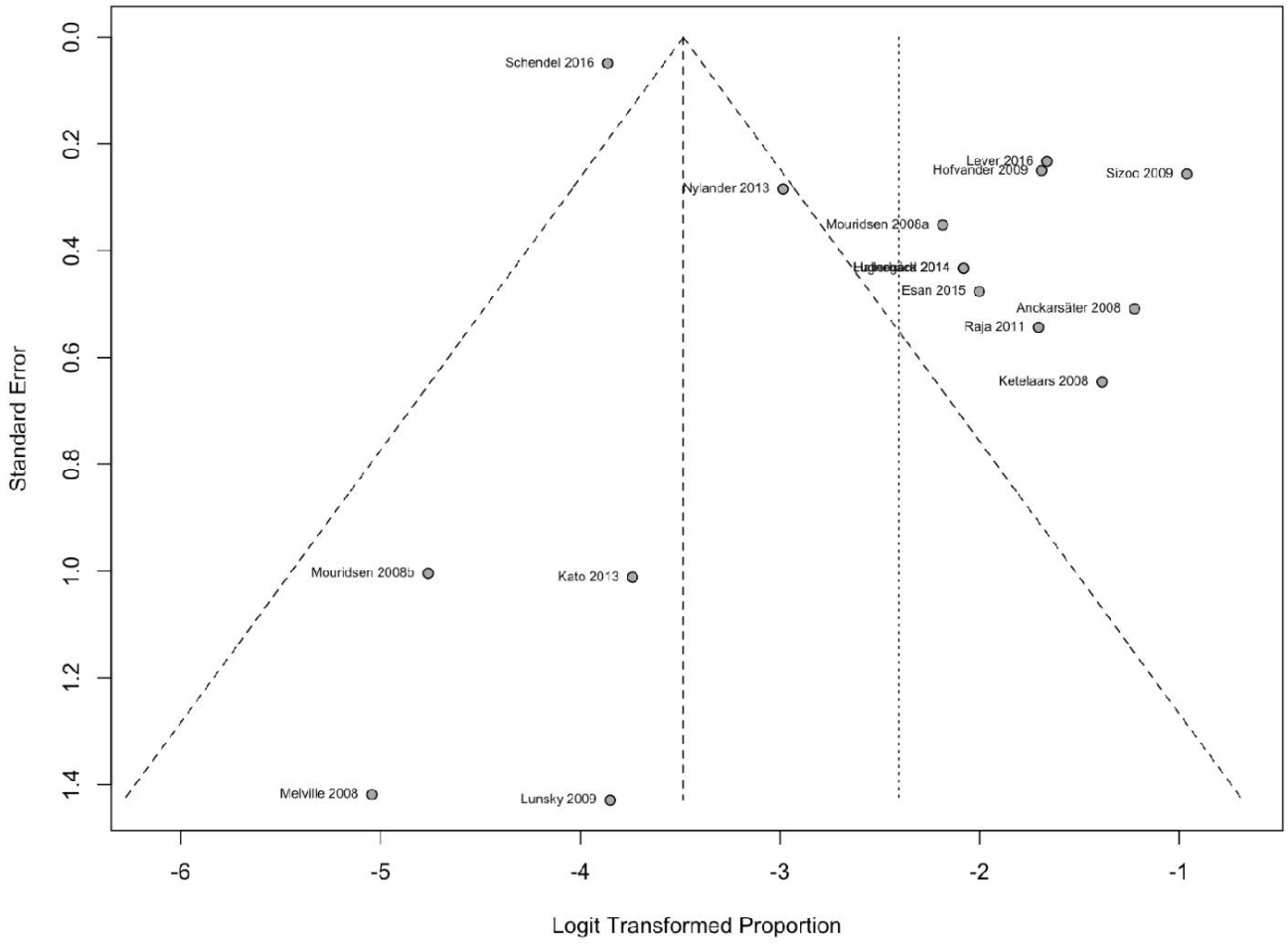
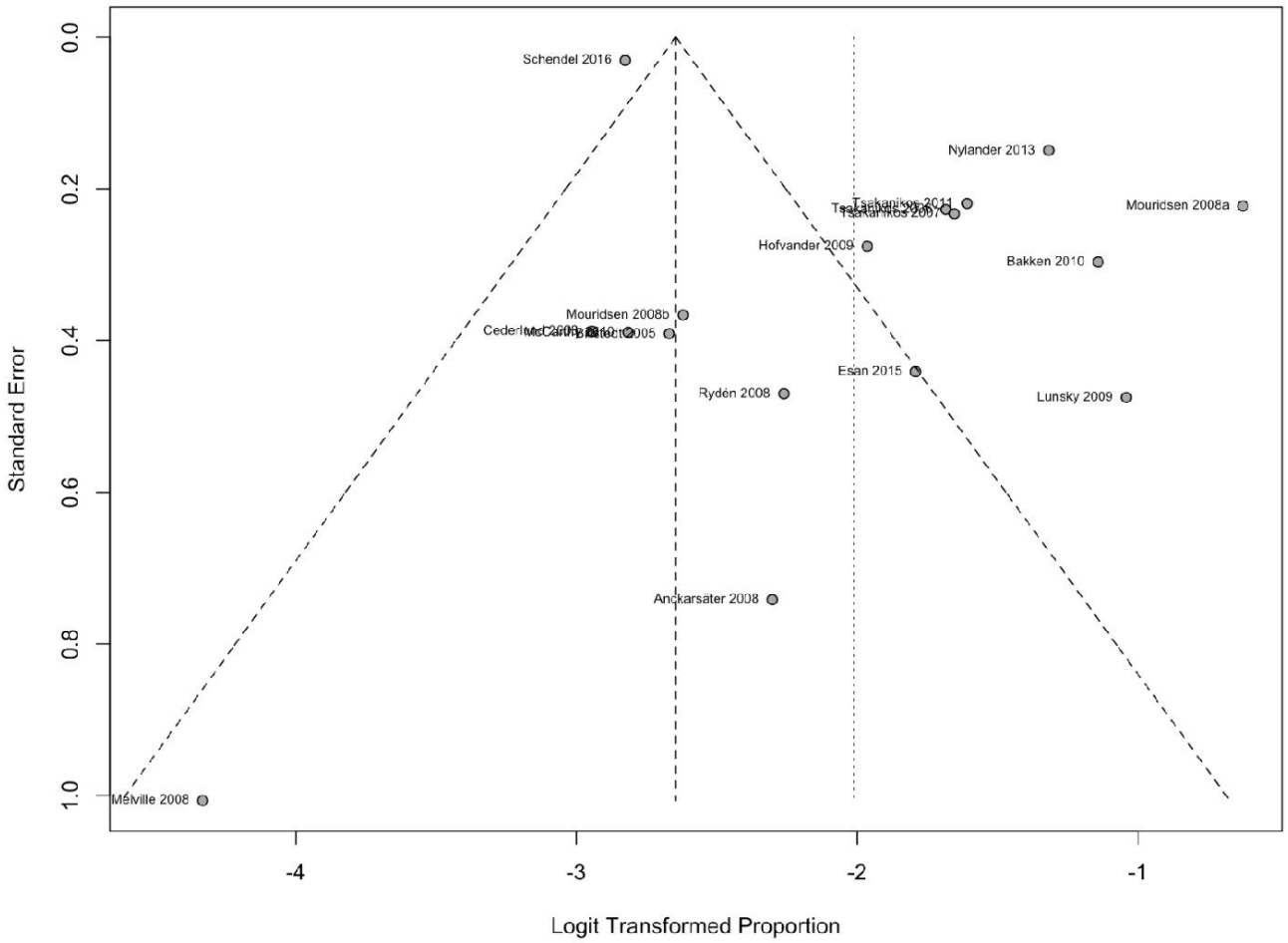
Appendix D. Publication risk of bias

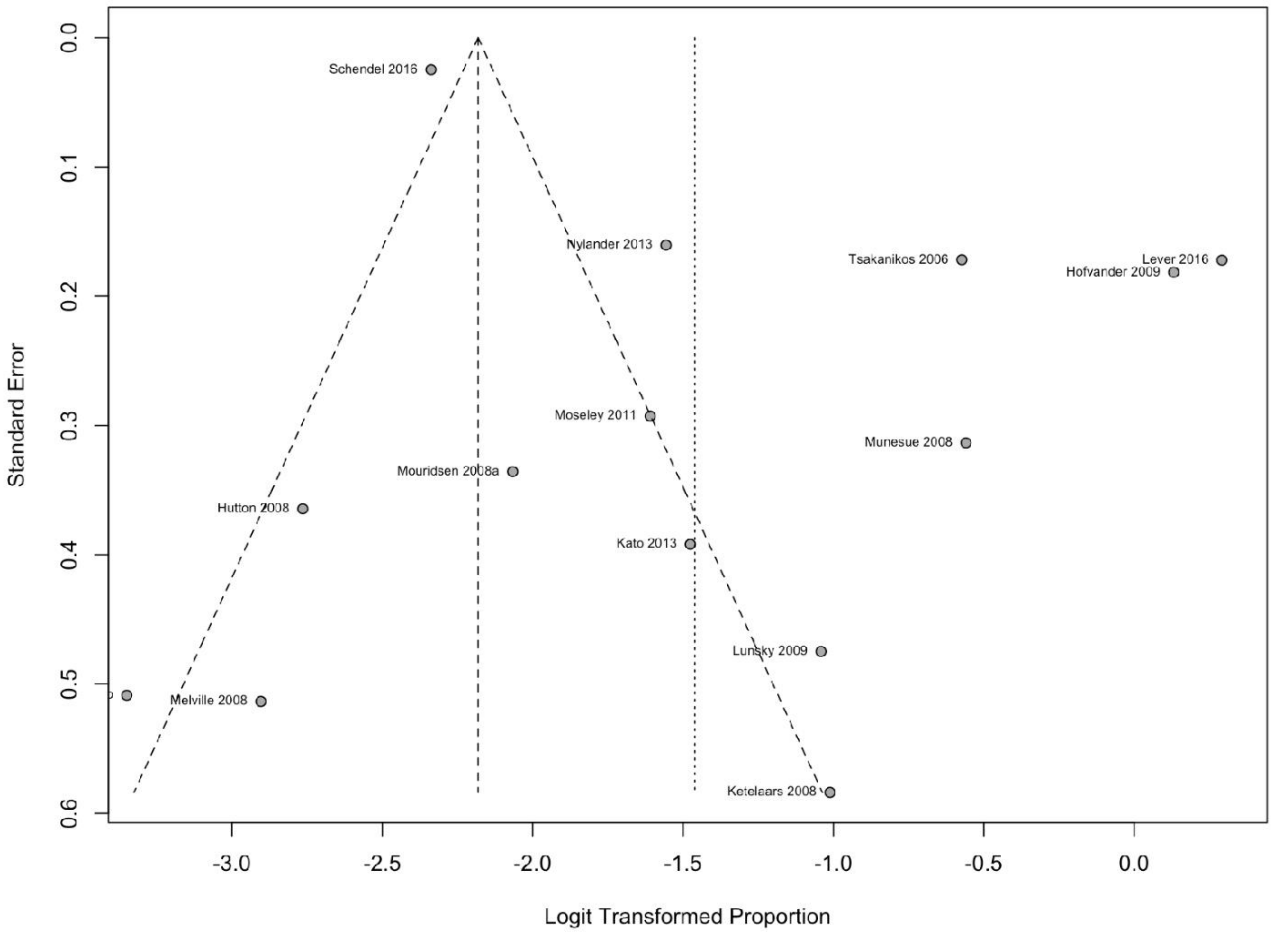
Substance Use Disorders



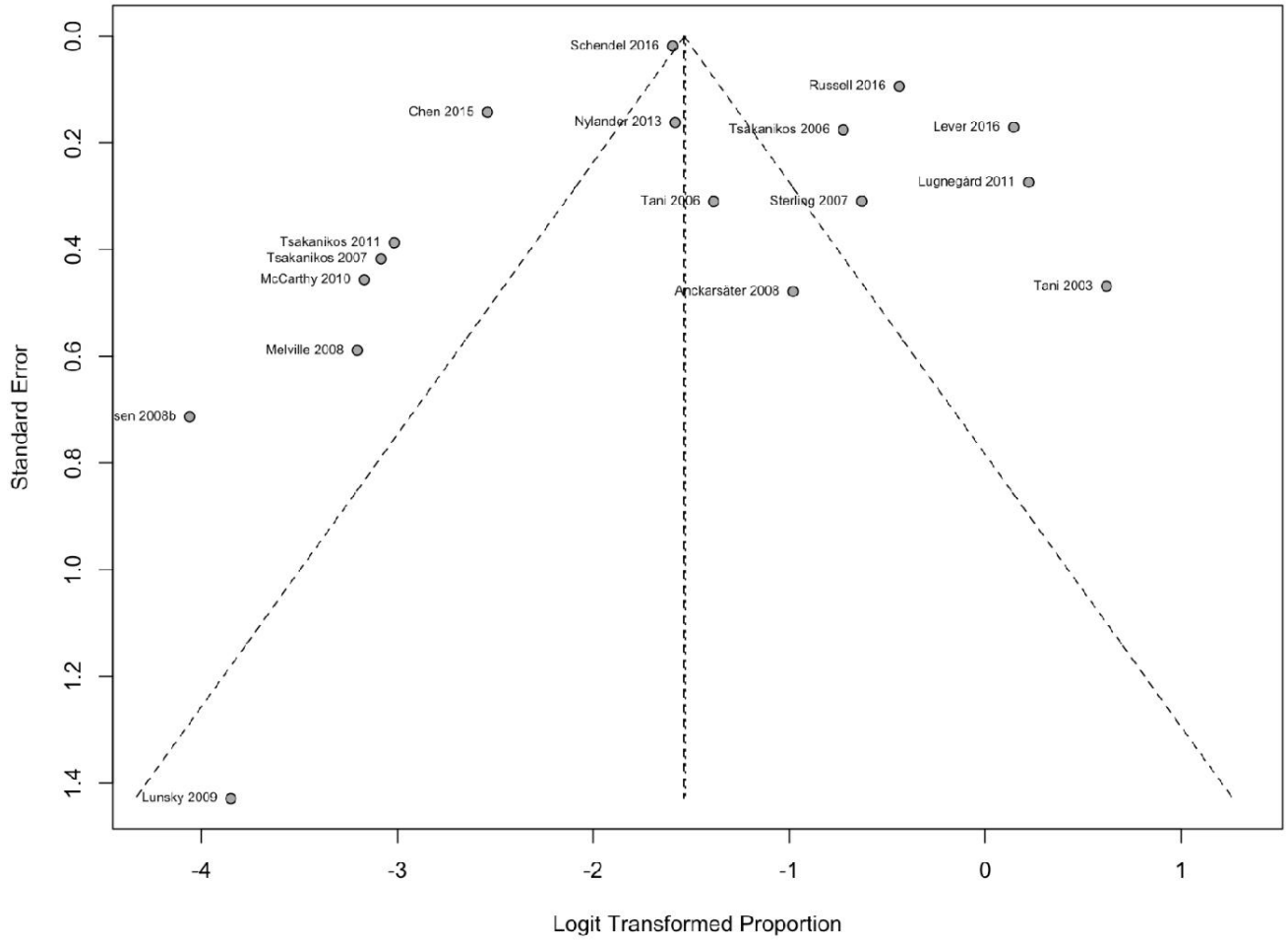
Schizophrenia Spectrum Disorders



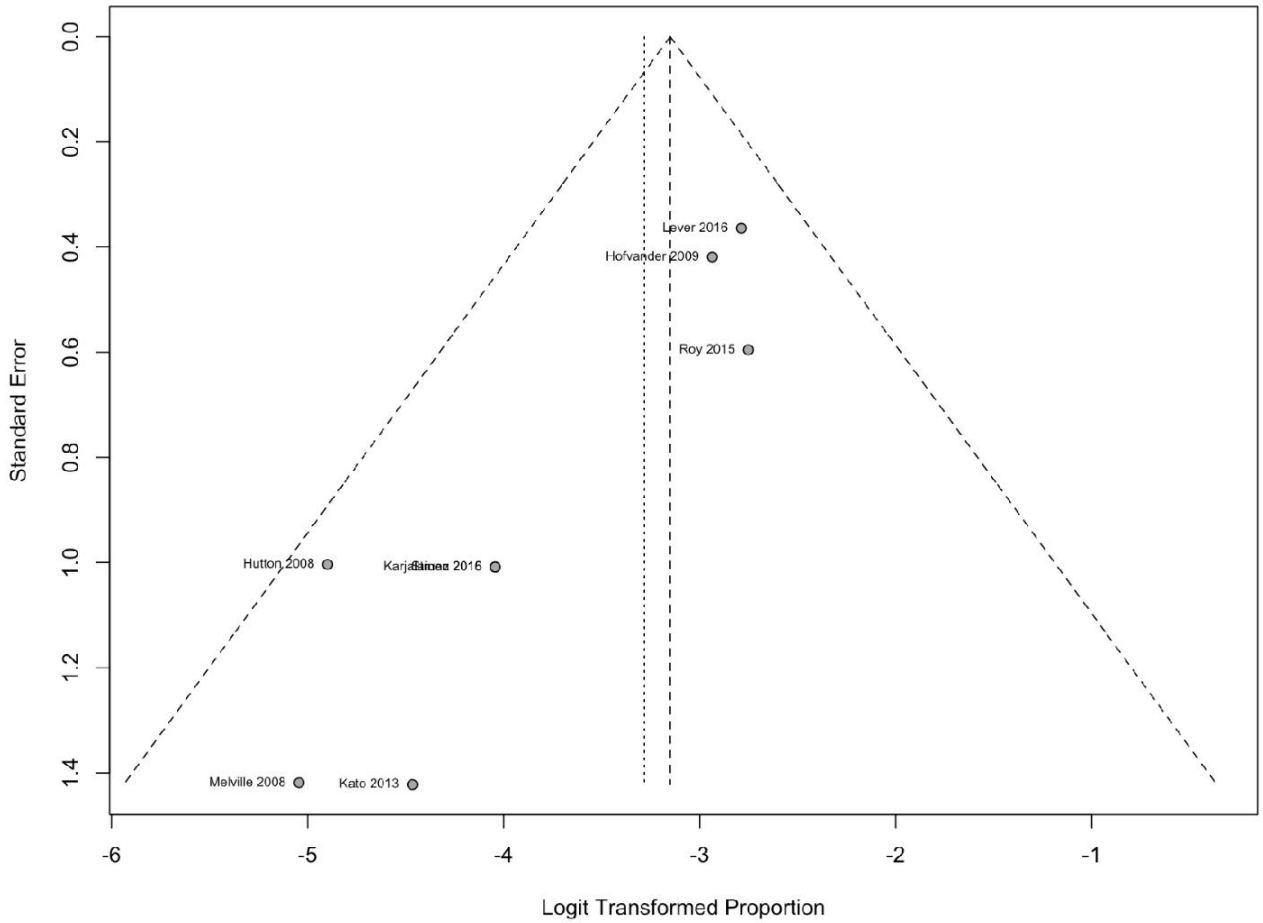
Mood Disorders



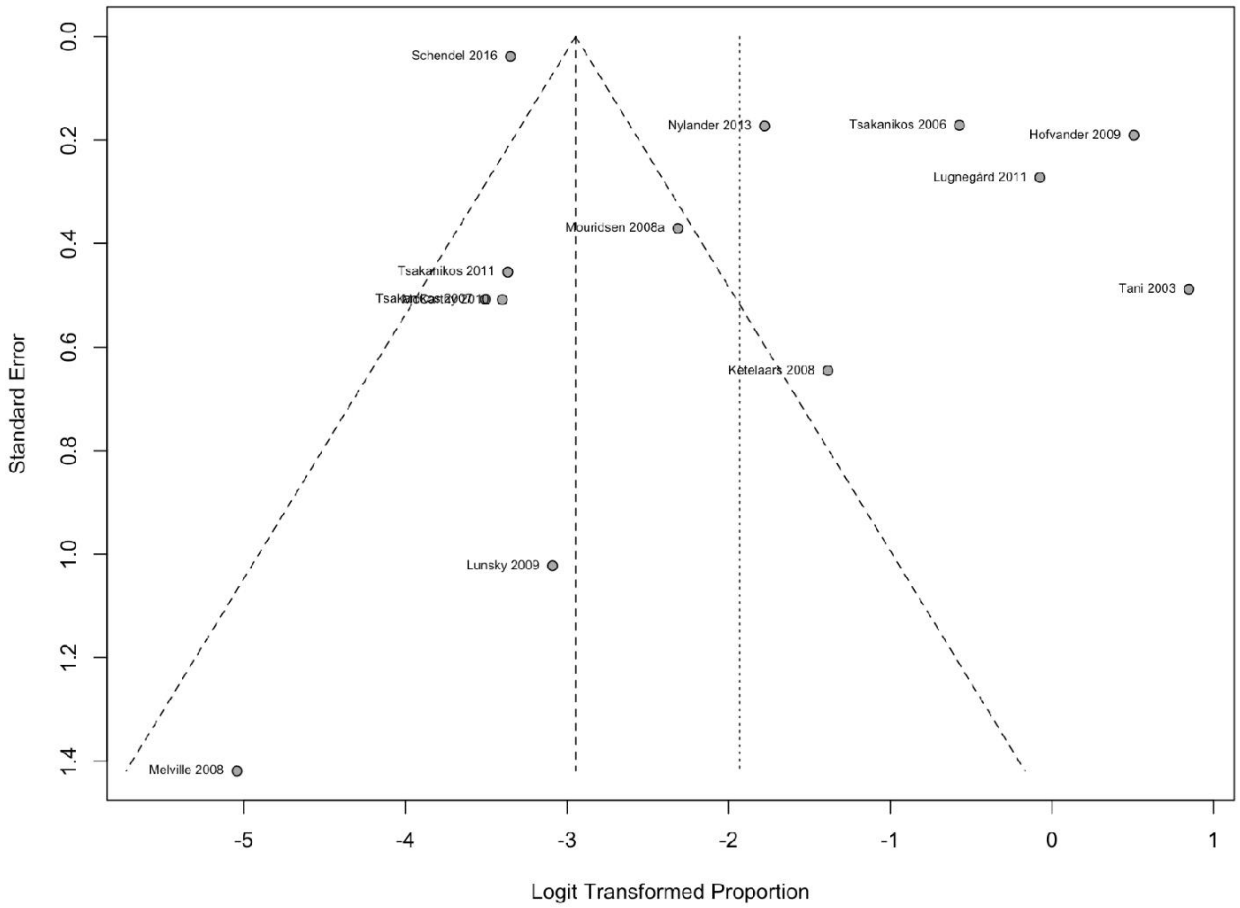
Anxiety Disorders



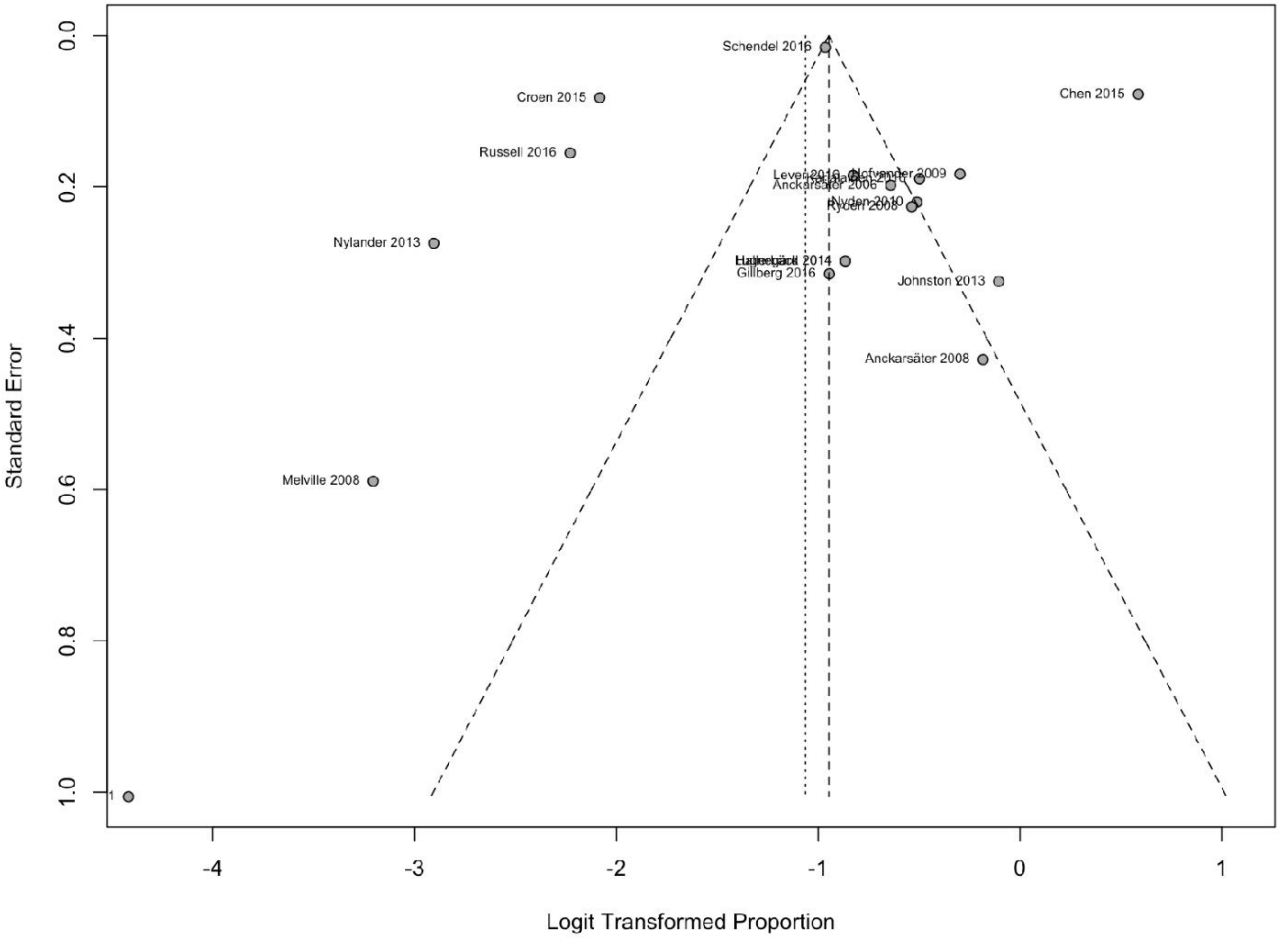
Eating Disorders



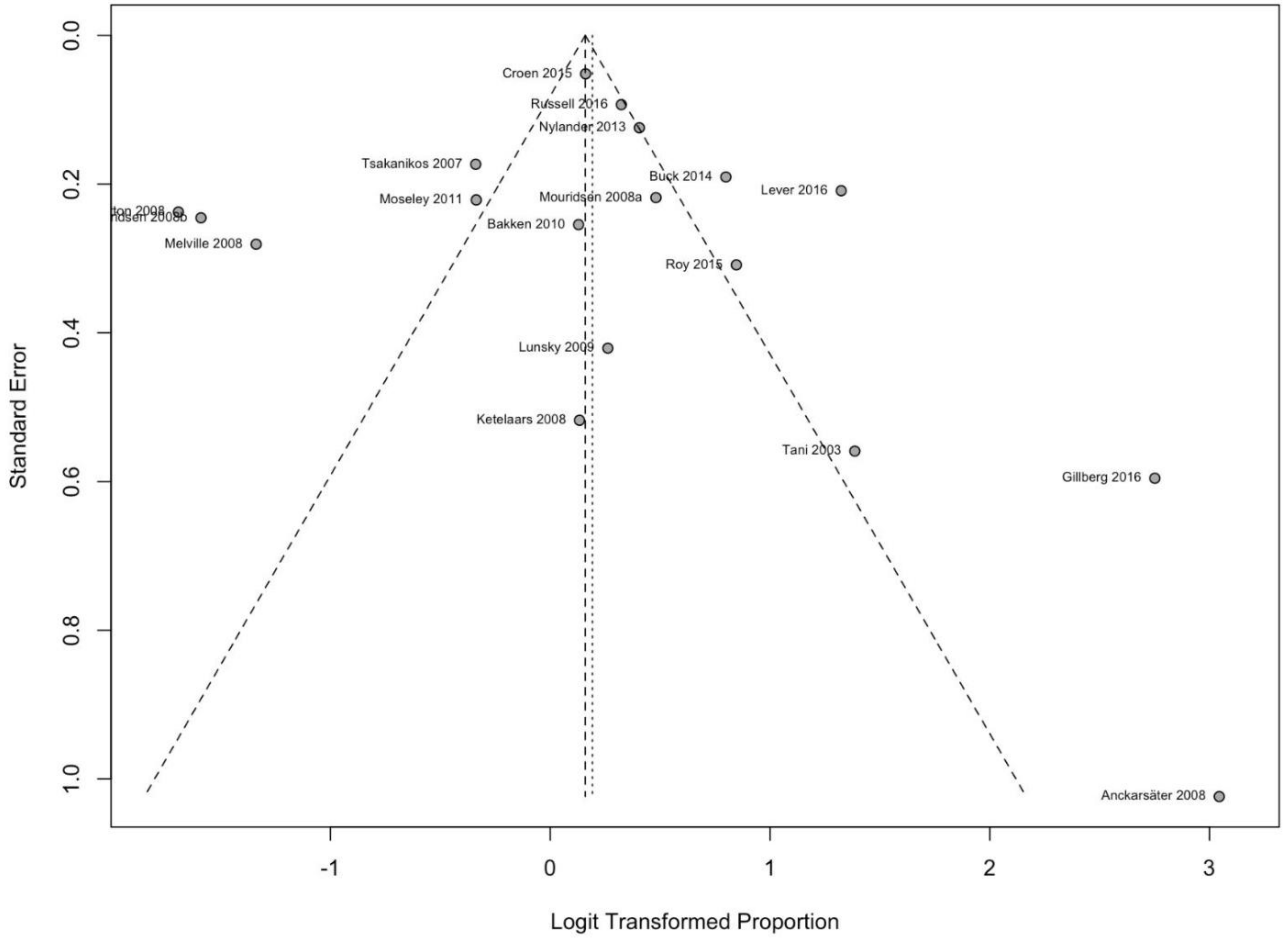
Personality Disorders



Attention Deficit and Hyperactivity Disorder



Any Psychiatric Disorder



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

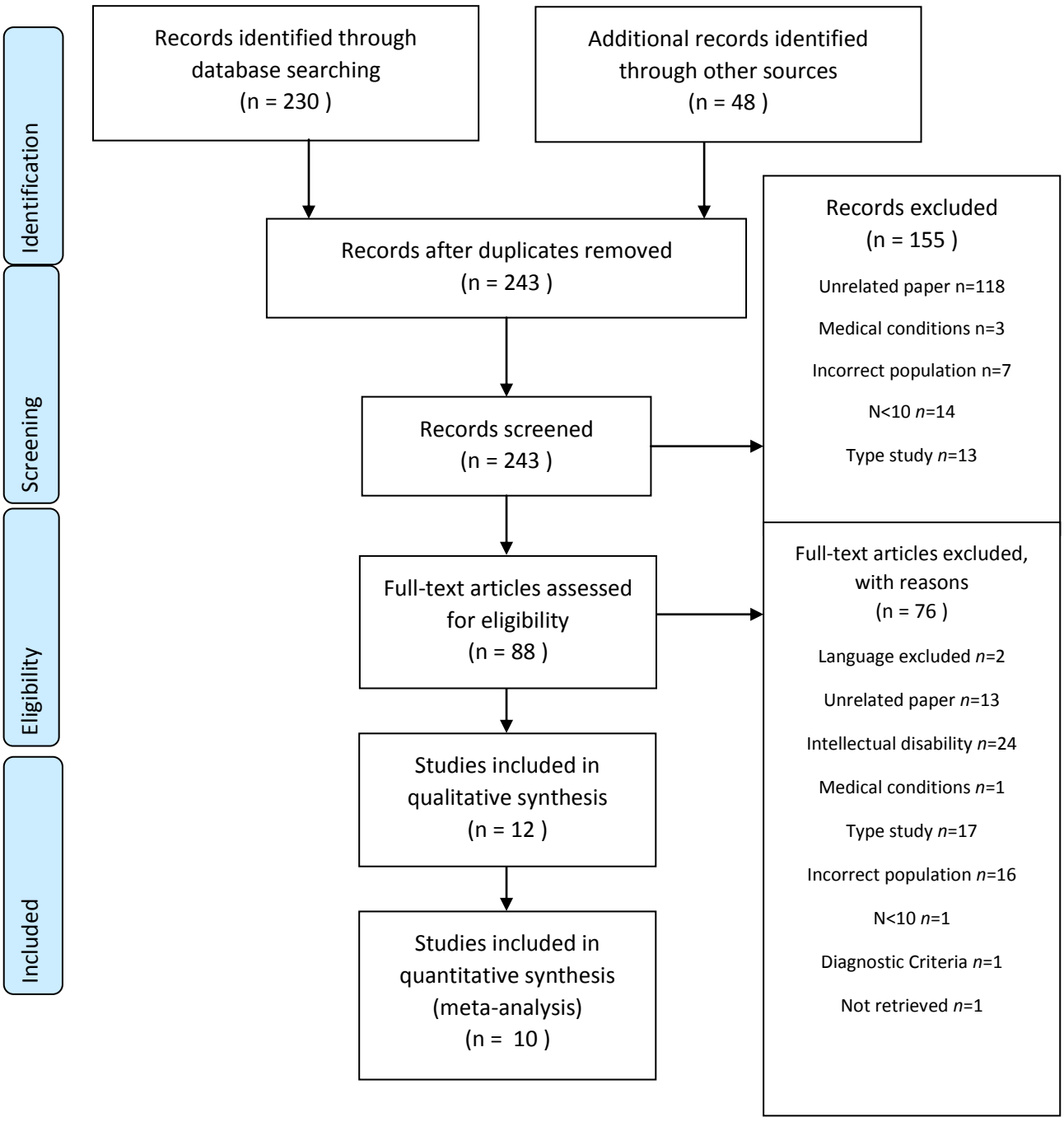

Figure 2. Forest plot of the pooled prevalence of SSD in average-IQ adults with ASD.

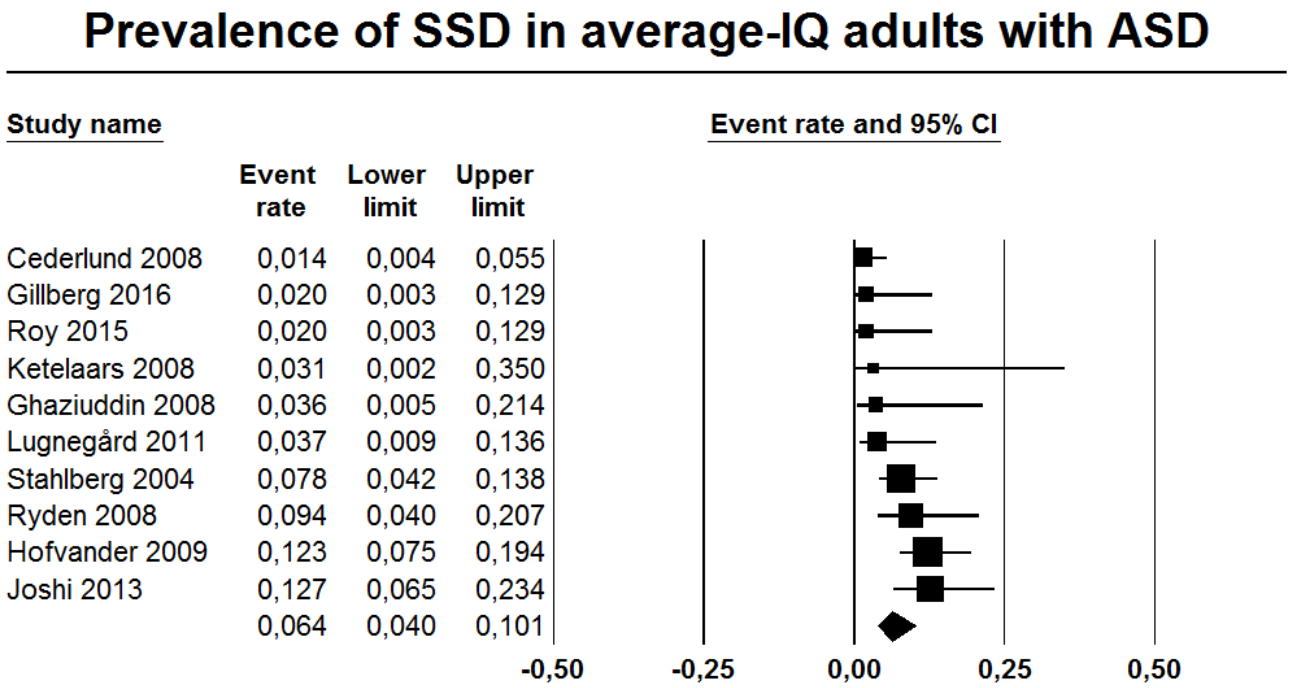

Figure 3. Funnel plot of Standard Error by Logit event rate. Large standard errors are indicative of a small sample size. A logit event rate that is negative in sign corresponds to an actual event rate that is smaller than 0.5 (50%), and vice versa.

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.

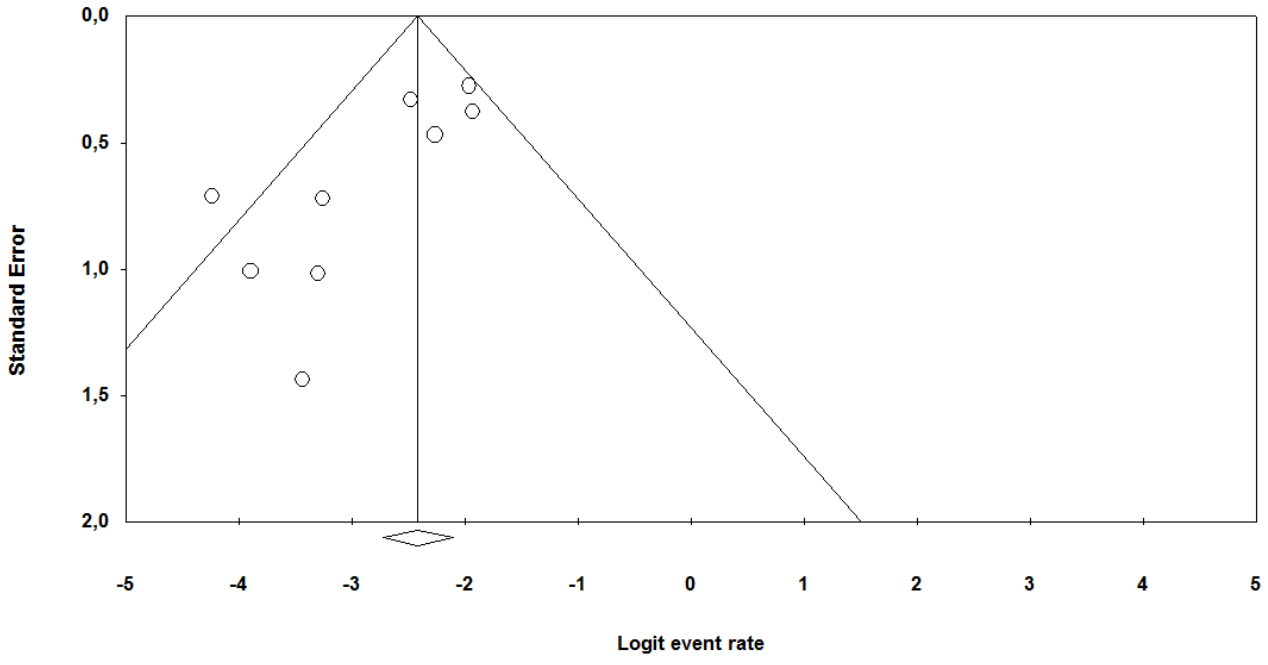

Table 2. Quality assessment of included studies

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

Artículo III

Referencia: Lugo-Marín, J., Díez-Villoria, E. Magán-Maganto, M., Pérez-Méndez, L.; Alviani, M.; de la Fuente-Portero, J.A.; & Canal-Bedia, R. (2019). Spanish validation of the Autism Quotient Short Form Questionnaire for adults with Autism Spectrum Disorder. *Journal of autism and developmental disorders,* accepted for publication.

Título: Validación española de la forma abreviada del cuestionario 'Cociente Autista' en población adulta con Trastorno del Espectro Autista

Resumen

Introducción: Debido a la inclusión aun reciente de las formas más leves de Trastorno del Espectro Autista (TEA) en las clasificaciones diagnósticas, muchas personas adultas que presentan características relacionadas con el TEA pueden no haber sido identificadas en los primeros estadios del desarrollo. Si sabemos que esta población presenta una alta frecuencia de trastornos psiquiátricos co-ocurrentes, es probable que hayan establecido contacto con servicios de psiquiatría en la edad adulta, en los que la exploración diagnóstica se centra únicamente en la patología concomitante. Más aún, el solapamiento de las características relacionadas con el TEA con otras entidades diagnósticas de aparición en el principio de la edad adulta, especialmente los trastornos del espectro de la esquizofrenia (TEE), han podido sobreestimar la prevalencia de estos, desviando el foco de la intervención hacia los síntomas derivados en lugar de intervenir en las dificultades relacionadas con el TEA.

Objetivo: el objetivo del presente estudio fue adaptar y validar la versión abreviada del cuestionario Cociente Autista en una muestra de adultos de habla española.

Método: Un total de 46 adultos con TEA, 41 familiares de personas con TEA, 17 pacientes con TEE, y 190 adultos sin historia reportada de patología psiquiátrica completaron el cuestionario

Cociente Autista abreviado. Se estudió la fiabilidad a través del análisis de la consistencia interna y la fiabilidad test-retest. Un análisis factorial confirmatorio se llevó a cabo para poner a prueba el modelo factorial previamente propuesto por los autores del cuestionario. Las diferencias intergrupo en las puntuaciones del cuestionario, así como la correlación con una medida gold-standard de evaluación de TEA (ADOS-2) también fueron objeto de análisis. Por último, el análisis de las habilidades discriminatorias del test fue realizado mediante el estudio de curvas ROC.

Resultados: los resultados del análisis factorial confirmatorio fueron aceptables, pero no excelentes, con valores RMSEA cercanos a .07, y valores CFI y TLI entre.90 y .95, y valores WRMR > .90. El análisis de la consistencia interna mostró que el Cociente Autista abreviado presenta una muy buena estructura interna en los cuatro grupos, con valores entre $C\alpha$ =.79 y $C\alpha$ =.88, y una fiabilidad test-retest buena con valores entre *r* = .812 y *r* = .942. El cuestionario mostró una elevada validez convergente con la medida gold-standard de evaluación en TEA (ADOS-2) (*r* = .734, *p* = <.01) y un buen poder discriminante entre los distintos grupos (71.77%). Las diferencias entre grupos en las puntuaciones del cuestionario resultaron significativas, con el grupo TEA mostrando una puntuación significativamente mayor al resto de grupos. El punto de corte de >63 mostró buenas propiedades psicométricas en la detección de adultos con TEA versus no clínicos (sensibilidad de .98 y especificidad de .84) y TEA versus TEE (punto de corte >65, sensibilidad de .94 y especificidad de .77)

Conclusiones: el cuestionario Cociente Autista abreviado presenta propiedades psicométricas aceptables para la detección de adultos con TEA en población de habla española. Las puntuaciones en el cuestionario apoyan el argumento de un continuo dimensional en la manifestación de las características relacionadas con el TEA. El cuestionario puede ser útil en el proceso de evaluación diagnóstica de adultos con sospecha de TEA, así como en el diagnóstico diferencial con los TEE.

De: "Fred Robert Volkmar" <em@editorialmanager.com>
Asunto: Your Submission JADD-D-19-00182R2
Fecha: 20 de junio de 2019, 13:10:25 CEST
Para: "Ricardo Canal-Bedia" <rcanal@usal.es>
Responder a: "Fred Robert Volkmar" <jaddassist@yale.edu>

Dear Dr. Canal-Bedia,

We have completed our review of your revised manuscript: "Spanish validation of the Autism Quotient Short Form Questionnaire for adults with autism spectrum disorder". 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-19-00182R2, 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,
Fred Robert Volkmar, MD
Editor in Chief
Journal of Autism and Developmental Disorders

Spanish validation of the Autism Quotient Short Form for adults with autism spectrum disorder

Abstract

The objective of this study was to adapt and validate the abbreviated version of the "Autism-Spectrum Quotient" (AQ-Short) in a sample of Spanish native adults. A total of 46 individuals with ASD, 41 ASD-relatives, 17 patients with schizophrenia spectrum disorders (SSD) and 190 non-clinical adults were administered the Spanish version of the AQ-Short. The results of the confirmatory factorial analysis found two high-order factors (Social Behaviour and Numbers/Patterns) and four subscales (Social Skills, Routines, Switching and Imagination). The reliability analysis showed very good internal structure and test-retest reliability. The AQ-Short also showed moderate convergent validity with ADOS-2. Differences by group were found in the ASD group when compared to other groups. Gender differences were only found in the non-clinical group.

Keywords: Autism Spectrum Quotient; ASD; Validity; Reliability; Factor Analysis; Schizophrenia Spectrum Disorders; Diagnosis

Spanish validation of the Autism Quotient Short Form for adults with autism spectrum disorder

The dimensional approach to autism spectrum disorder (ASD) assumes that the defining characteristics of ASD, that is, the difficulties in social communication and the repetitive behaviours and restricted interests, are the extreme expression of common features present in the general population (American Psychiatry Association, 2013). A disorder of the autistic spectrum would thus be considered as a diagnosis when the intensity of characteristics is severe enough that it would not allow the individual to adapt to their environment.

This dimensional approach has acquired great relevance in the last two decades due to its usefulness for both clinical practice and in the identification of endophenotypes that can be analysed in genetic research (Chakrabarti et al., 2009; Grzadzinski, Huerta, & Lord, 2013). That is why various studies have been conducted to determine the presence of autism-like traits in specific populations, such as in first-degree relatives of people with ASD, where a milder phenotype is often observed but with a profile similar to the defining traits of ASD, which is called the broader autism phenotype (BAP) (Bishop et al., 2004; Eyuboglu, Baykara, & Eyuboglu, 2018; Klusek, Losh, & Martin, 2014; Losh, Childress, Lam, & Piven, 2008; Micali, Chakrabarti, & Fombonne, 2004; Piven et al., 1990; Piven & Palmer, 1999; Ruta, Mazzone, Mazzone, Wheelwright, & Baron-Cohen, 2012; Ruzich et al., 2015).

But this broad phenotype is not restricted to family members of individuals with ASD, and numerous studies have provided evidence suggesting that autistic traits are continuously distributed in the general population (Constantino & Todd, 2003; Ruzich et al., 2015). This fact has led to the idea that individuals in the general population who score high on BAP measures should also express some degree of deficit in the same characteristic areas of autism. Following this approach, a wide variety of studies have attempted to identify subclinical characteristics of autism in the general population. For example, some studies have analyzed the difficulties in social functioning related to BAP (Jobe & White, 2007) or whether autistic traits affect

relationship satisfaction (Pollmann, Finkenauer, & Begeer, 2010), as well as social characteristics such as lower tendency to correspond to direct gaze (Chen & Yoon, 2011), and the reciprocal relation between face recognition and autistic traits (Halliday, MacDonald, Sherf, & Tanaka, 2014). Other studies have examined the relationship between measures of the BAP and cognitive characteristics associated with autism, such difficulties in perceptual speech processing (Stewart & Austin, 2009), or whether the capacity to engage in detailed visuospatial analysis, a frequent feature in autism, extend into the general population (Grinter, Van Beek, Maybery, & Badcock, 2009).

BAP is also a topic of special interest because it can help clinicians identify autism traits in patients with disorders other than ASD. For example Sizoo et al. (2009), investigated the presence of autism traits in patients with ADHD and substance use. BAP has also been studied in patients with social anxiety disorder (Hoekstra, Bartels, Cath, & Boomsma, 2008), in patients with obsessive-compulsive disorder (Hoekstra et al., 2008; Mito et al., 2014; Wikramanayake et al., 2018), patients with anorexia nervosa (Rhind et al., 2014), depressed patients (Takara & Kondo, 2014) and patients with schizophrenia spectrum disorders (Gillespie, Mitchell, & Abu-Akel, 2017; Naito, Matsui, Maeda, & Tanaka, 2010; Solomon et al., 2011).

The case of schizophrenia spectrum disorders (SSD) needs to be considered when approaching concurrent psychiatric disorders in ASD. This group has been repeatedly identified as having a higher presence of autistic-like traits than the general population (Hallerbäck, Lugnegård, & Gillberg, 2012; Lugnegård, Hallerbäck, & Gillberg, 2015; Naito et al., 2010; Wouters & Spek, 2011). This is not surprising, because autism was first conceptualised as a core feature of the schizophrenic disorder (Bleuler, 1911). Both disorders share a set of common characteristics that make differential diagnosis challenging. Difficulties in social communication (Couture et al., 2010), emotion recognition (Bölte & Poustka, 2003), mentalizing skills (Martinez et al., 2017; Pilowsky, Yirmiya, Arbelle, & Mozes, 2000), a high prevalence of formal thought disorders (Gaag, Caplan, Engeland, Loman, & Buitelaar, 2005; Solomon, Ozonoff, Carter, & Caplan, 2008), and findings at a neuropsychological level (Eack et al., 2013; Marinopoulou,

Lugnegård, Hallerbäck, Gillberg, & Billstedt, 2016) suggest the need for diagnostic instruments that allow clinicians to better differentiate between both disorders. Regarding the study of clinical overlap, numerous studies have shown interest in empirically explore this issue. When measuring the presence of autistic-like traits in adults with SSD, studies have reported a high prevalence of these, suggesting a direct relationship between both disorders (Barlati, Deste, Gregorelli, & Vita, 2018; Lugnegård et al., 2015; Spek & Wouters, 2010). In the same way, many people with ASD often develop psychotic-like symptoms (Blackshaw, Kinderman, Hare, & Hatton, 2001; Craig, Hatton, Craig, & Bentall, 2004; Jänsch & Hare, 2014), considering autistic characteristics a risk factor for receiving a diagnosis that falls into the schizophrenia spectrum (Lugo et al., 2018). Due to the late inclusion of mildest-forms of ASD (with an average intellectual quotient and preserved verbal language) in the diagnostic classifications, adults with a possible ASD, who currently have obvious adaptive difficulties, are entering the clinical setting in recent years. It is possible that in these people, now adults, no ASD symptoms were identified during their childhood (Lai & Baron-Cohen, 2015). Thus, when considering the overlap between the diagnostic criteria for SSD and those for ASD, it is not difficult to realize that many of them may have been misdiagnosed, overestimating the prevalence of SSD in people with ASD.

Several instruments have been developed to assess the BAP (Landry & Chouinard, 2016). One of the most widely used is the Autism Quotient (AQ) (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). The AQ is a self-reported screening instrument with 50 items, in which the person must choose whether to agree or disagree with questions related to ASD characteristics (e.g., I prefer to do things the same way over and over again; I tend to have very strong interests). Factor analysis showed a theoretical model composed of five domains: social skills, attention to detail, attention switching, communication and imagination. According to the original validation, a score above 32 would suggest that the individual may have clinically significant levels of autistic traits, which does not mean that the individual actually has ASD, since in order to reach that conclusion, a more comprehensive evaluation would be needed to

identify the presence and clinical significance of core autism traits in that individual (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). In 2011, Hoekstra et al. developed an abbreviated 28 item version of the instrument (AQ-Short), in order to increase the efficiency of the test. Five subscales were identified in the AQ-Short: social skills, routines, switching, imagination, and numbers/patterns. These subscales were combined into two higher-order factors: social behavioural difficulties and a fascination with numbers/patterns. AQ-Short can also be valuable as a rapid assessment of autistic traits for screening purposes (Hoekstra et al., 2011). The study of these authors indicates that a score above 65 would merit a referral to a specialized service to confirm (or rule out) a diagnosis of autism.

Although the AQ has been adapted and validated in several languages, showing appropriate psychometric properties (do Egito, Ferreira, Gonçalves, & Osório, 2017; Hoekstra et al., 2008; Lau et al., 2013; Lepage, Lortie, Taschereau-Dumouchel, & Théoret, 2009; Wakabayashi, Baron-Cohen, Wheelwright, & Tojo, 2006), a validation for the Spanish-speaking population has not yet been conducted. The language validation is an essential process in ensuring the conservation of the psychometric properties of the tests. The process of translating and adapting a scale requires more than translation into the target language. It is necessary to ensure that the scores obtained with the translated version are equivalent to those obtained with the original test. It is therefore necessary for the Spanish-speaking population to provide answers on the psychometric characteristics and the clinical value of the AQ-Short questionnaire. It was, therefore, the aim of the present study to validate the AQ- Short for use with the Spanish adult general population. The characteristics of the Spanish AQ- Short, including test–retest reliability, internal consistency, convergent validity, and confirmatory factor analysis were studied. Also, group differences between individuals with ASD and other three groups of participants (ASD first-degree relatives, SSD patients and Non-Clinical comparison subjects) were analysed in order to explore the discriminative power of the AQ with the SSD and Non-Clinical groups and to explore the presence of the BAP, meaning subclinical autistic traits, in the ASD relatives and the SSD patients, thus supporting the dimensional approach of ASD.

METHODS

Participants

All participants were born in Spanish territory, had Spanish as their mother tongue, and were 18 years old or above. Four groups of participants were evaluated in order to establish between-group comparisons with the AQ-Short and other studied variables. The groups were as follows.

ASD group. Participants from this group (n = 46) were recruited from ASD community assistance centres and via online announcements in ASD associations webpages. All participants reported that they had received prior to evaluation a diagnosis of ASD regarding DSM-5 criteria (American Psychiatric Association, 2013), and provided the diagnosis signed by a qualified clinician. Below average IQ was set as an exclusion criterion, as it could affect the appropriate understanding of the test.

ASD-relatives group. The participants in this group (n = 41) were recruited via public and online announcements on ASD associations webpages.

SSD group. Participants from this group (17 patients with SSD) were recruited from the care units of the psychiatric service of the Hospital Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife, Spain) and all of them fulfilled DSM-5 criteria for any SSD at the time of the study (American Psychiatric Association, 2013). They were asked to complete the AQ-Short. Excluding criteria were acute psychotic symptoms at the time of the evaluation, intellectual difficulties and an above-threshold score in an ASD gold-standard measure (Autism Diagnostic Observation Schedule-2) (Lord et al., 2012).

Non-clinical group. Data was collected from 190 non-clinical participants recruited via internet advertisements and by word of mouth through acquaintances of the authors. This group were explicitly defined as not having received an ASD diagnosis, nor any other psychiatric disorder diagnosis prior to the evaluation. Participants were directly asked whether they believed they

had an undiagnosed ASD, ruling out their scores for the data analysis, thus decreasing the risk of overestimating their scores in the AQ-Short.

For all participants, when not able to directly measure IQ, this was considered into the average range when reporting a higher qualification and/or the absence of a prior diagnosis of intellectual disability.

Instruments

Demographic Questionnaire: the following data was collected regarding the socio-demographic and clinical characteristics of all participants: age, gender, higher education level, work/academic status, psychopharmacological treatment, and psychiatric history.

The Spanish Autism-Spectrum Quotient (AQ-Short): The AQ-Short was translated into Spanish after obtaining permission from the original author, Professor Simon Baron-Cohen. . The translation was done by a native Spanish speaker, a professor of English philology who remained blind to the construct that was intended to be measured by the questionnaire. The instruction given to this translator was that, instead of being literal, the translation should seek semantic, linguistic and cultural equivalence. This first translation was revised by the first author of this article to verify that the items of this first Spanish version corresponded to the items of the original version. Subsequently, a bilingual psychologist specialized in ASD translated the Spanish version back into English. Afterwards, a panel of 4 bilingual professionals, experts in ASD, compared the original version of the AQ-Short and the translated version, discussed the points of discrepancy and reached agreements to introduce the necessary corrections in the Spanish version to reflect as accurately as possible the content of each item. The final version of the Spanish AQ is similar to the original English, maintaining the same format of 28 forced choice items. The Spanish version of the AQ-Short is composed of 28 items. The total AQ-Short score and the subscales were based on the original Likert responses (1 = "definitely agree", 2 = "slightly agree", 3 = "slightly disagree", and 4 = "definitely

disagree"). Items 2, 4, 5, 7, 10, 13, 14, 15, 16, 22, 23, 25 and 26 were reverse scored. In the original study by Hoekstra et al. (2011), the minimum score was 28 points and the maximum 112, with 65 points an acceptable cut-off point for distinguishing autistic-like traits, with sensitivity and specificity values of .97 and .82, respectively.

Reynolds Intelligence Screening Test (RIST) (Reynolds & Kamphaus, 2003b)**:** This is a screening test that estimates a general measure of the IQ in an age-range from 3 to 94 years. The RIST has its origin in the Reynolds Intelligence Assessment Scales (RIAS) (Reynolds & Kamphaus, 2003a) and is composed of two of its subtests: 'Guess what' (verbal subtest) and 'Odd-item out' (non-verbal subtest). The verbal subtest is a classic measure of crystallised intelligence, and the non-verbal subtest is closely related to the assessment of fluid intelligence. Both subtests have shown good psychometric properties. The Spanish RIST was used for this study, which was validated with more than 2,000 Spanish individuals and showed good psychometric properties (Santamarıa & Fernández Pinto, 2009).

Autism Diagnostic Observation Schedule (ADOS-2) (Lord et al., 2012)**:** The Autism Diagnostic Observation Schedule (ADOS-2) is a standardised and semi-structured assessment of communication, social interaction and play/imagination skills for people with suspected ASD. The scale is structured in five modules (T, 1, 2, 3 and 4), each created to be used as a function of the chronological age and language level of each individual. Each module is composed of a set of activities that provide standardised contexts, where an evaluator can observe (or not) the presence of certain social and communicative behaviours relevant to the diagnosis of ASD. After conducting the Module 4 (adults) protocol and obtaining the algorithm scores, there are three possible outcomes: autism, autism spectrum and non-ASD.

Positive and Negative Symptoms Scale (PANSS) (Kay, Fiszbein, & Opler, 1987)**:** This is a semi-structured clinical interview consisting of 30 items and four scales: Positive Symptoms (PANSS-P); Negative Symptoms (PANSS-N); Composite Scale (PANSS-C); and General Psychopathology (PANSS-GP). Each item is scored according to a Likert scale of seven degrees

of severity. The Spanish PANSS was used for this study, which has showed good psychometric properties in the diagnosis of SSD (Peralta & Cuesta, 1994).

Procedure

Participants were asked to complete the socio-demographic and AQ-Short questionnaires individually through a web survey application or in paper-and-pencil format. In order to evaluate the ASD diagnosis and the IQ, a single subgroup was extracted from ASD (n = 24) and non-clinical (n = 18) groups. These two subgroups, plus the whole SSD group (n = 17), were assessed individually with the ADOS-2 and the RIST by a clinical psychologist trained and accredited in the use of these instruments. The SSD group was also assessed with the PANSS in order to confirm the absence of acute psychotic symptomatology at the time of evaluation. Only the socio-demographic and AQ-Short questionnaires were administered to the ASD-relatives group. In order to explore test-retest reliability, randomly selected participants from the ASD (n = 26), SSD (n = 9) and non-clinical (n = 61) groups were asked to complete the AQ-Short a second time. The windows between the first and second evaluations were from 2 to 16 weeks.

Statistical analysis

Reliability was studied through the analysis of internal consistency (Cronbach's alpha), and the test-retest analysis with Spearman rho correlations and intraclass correlation coefficients (ICC3) (Shrout & Fleiss, 1979). Cronbach's α internal consistency measures were considered minimally acceptable when α= .65, acceptable when α= .70, and optimal when α= .80 (Nunnally & Bernstein, 1994).

Confirmatory factor analysis was conducted to test the factor model structure most commonly proposed for the AQ-Short. This factor structure had been tested previously in a control sample (Hoekstra et al., 2011) and in a sample of adults with clinically diagnosed ASD (Kuenssberg, Murray, Booth, & McKenzie, 2014). Due to the limited sample size of the ASD and SSD

groups the factor structure was tested with all the sample responses (and also replicated with the non-clinical sample excluding ASD and SSD). The model was estimated using Lavaan version 0.5-23.1097 (Rosseel, 2012), via robust diagonally least squares estimation (WLSMV) (Beauducel & Herzberg, 2006). WLSMV is recommended when there are four (or less) ordered response categories, as is the case for the AQ-Short response Likert-scale. Model fit was evaluated using the usual χ^2, as well as the comparative fit index (CFI) and Tucker Lewis index (TLI) as incremental fit indices, and the weighted root mean square residual (WRMR) and root mean squared error of approximation (RMSEA) as baseline fit indices.

Group differences in AQ scales and subscales by group were analysed using Kruskall Wallis, and the Dwass-Steel-Critchlow-Fligner (Douglas & Michael, 1991; Dwass, 1960; Steel, 1960) procedure was used for multiple pairwise comparisons. Group differences in AQ scales and subscales by gender were analysed using Welch's *t*-tests. Gender DIF (Differential Item Functioning) was analysed with the iterative hybrid ordinal logistic regression/item response theory (Choi, Gibbons, & Crane, 2011) because it can effectively handle the polytomous property of AQ items (4-point Likert scale).

The convergent validity of the AQ-Short was explored with a correlational analysis with the ADOS-2. We considered correlation coefficients small when $r = .10$, moderate when $r = .30$ and large when $r = .50$ (Cohen, 1988). Linear discriminant analysis was used to evaluate discriminant validity (i.e. the ability of AQ global and subscales to discriminate between groups with known differences).

A receiver operating characteristic (ROC) curve analysis was carried out to evaluate the AQ-Short cut points suggestive of an ASD diagnosis. As the primary interest was to quantify how accurately AQ-Short can discriminate between ASD and non-clinical subjects only those groups were included in the analysis. The area under the curve (AUC), accuracy, sensitivity and specificity for the Youden index-based cut-off scores were calculated, and ROC curve plots were used to draw the specificity versus the sensibility for the candidate threshold values between 0.0 and 1.0.

Unless otherwise specified, an alpha level of .05 was used to test for significance. All statistical analyses were performed using the computing environment R (R Core Team, 2013)

Ethics approval

Approval for this study was obtained from the Hospital Universitario Nuestra Señora de Candelaria Research Ethics Committee (PI-32/17). All participants gave written or web-based consent in accordance with the Declaration of Helsinki.

RESULTS

The socio-demographic and clinical characteristics of the four groups are shown in Table 1. A non-parametric one-way ANOVA Kruskal-Wallis found a significant difference regarding age between groups, with ASD-relatives being older than other participants (x^2 (3) = 45.1, $p < .001$). Differences regarding IQ reached significance for the IQ-Total ($w = 3.27$, $p < .002$) and non-verbal-IQ scores ($w = 4.03$, $p < .004$), with the ASD group having lower scores than the non-clinical participants. Global gender proportion differences were found as a function of Group ($\chi^2(3) = 47.5$; $p < .001$). A set of two tailed binominal tests showed proportion differences ($p < .05$) in the SSD group (more males than females) , and the ASD-relatives ($p < .01$) and non-clinical groups ($p < .001$) which were mostly female. No proportion differences were found in the ASD group ($p = .01$).

[Insert Table 1 about here]

Internal Consistency and Test-Retest Reliability

Internal consistency was assessed for the four groups of participants (Table 2). All AQ-Short scales showed satisfactory internal consistency for the four groups, ranging from $C\alpha$ =.79 to $C\alpha$ =.88. In the ASD group, items 14 (*When reading a story, I find it difficult to work out the character's intentions*) and 16 (*I notice patterns in things all the time*) correlated negatively with the total scale. In the SSD group, items 3 (*Trying to imagine something, I find it easy to create a picture in my mind*), 11 (*I find making up stories easy*) and 20 (*I find it easy to work out what someone is thinking or feeling*) also correlated negatively with the total scale.

[Insert Table 2 about here]

Table 3 shows the very good test-retest reliability of the AQ-Short version and all the subscales (ICC ranging from .90 to .97). No significant differences were found between the two measurement times across subscales, implying sufficient constancy.

[Insert Table 3 about here]

Factor analysis

As shown in Table 4, the model fit can be considered acceptable but not excellent, with good fit to the data according to RMSEA values close to .07 and CFI or TLI values between .90 and .95 (Hu & Bentler, 1998), but worse fit according to WRMR (values > 1.0); (Yu, 2002) and the null of perfect fit rejected (but see DiStefano, Liu, Jiang, and Shi (2018) for evidence of the unexpected behaviour of WRMR in some situations; and Brown (2014), for the relative value of chi-square to test the quality of the model).

Figure 1 shows the parameter estimates for the structural analysis of the AQ-Short.

[Insert Table 4 about here]

[Insert Figure 1 about here]

Intergroup differences in AQ-Short

A set of non-parametric Kruskall-Wallis H tests showed significant differences by group for the global score ($\chi^2(3) = 101$, $p < .001$) and also for the two high-order factors, Social Behaviour ($\chi^2(3) = 95$, $p < .001$) and Numbers/Patterns ($\chi^2(3) = 55.2$, $p < .001$), and the four subscales included in the Social Behaviour higher order factor: Social Skills ($\chi^2(3) = 60.4$, $p < .001$), Routines ($\chi^2(3) = 64.7$, $p < .001$), Switching ($\chi^2(3) = 85.6$, $p < .001$) and Imagination ($\chi^2(3) = 80.5$, $p < .001$) (see Table 5). Multiple comparisons between groups controlling for the error rate simultaneously for all contrasts (Dwass-Steel-Critchlow-Fligner procedure) showed significant differences in all scores for the ASD group when compared to others. The SSD and ASD-relatives groups did not differ on any AQ scale. Compared to the non-clinical sample, the SSD group scored higher in the AQ total score ($w = -4.92$, $p < .001$), Social Behaviour high-order factor ($w = -4.72$, $p < .001$) and the Switching ($w = -4.91$, $p < .001$) and Imagination ($w = -5.57$, $p < .001$) subscales. The ASD-relatives group scored significantly higher than the Non-Clinical group in the AQ total score ($w = -3.92$, $p < .006$) Social Behaviour high-order factor ($w = -4.08$, $p < .004$) and the Social Skills ($w = -3.35$, $p < .018$), Switching ($w = -3.78$, $p < .008$) and Imagination ($w = -4.40$, $p < .002$) subscales. Figure 2 shows the violin plots for the AQ total scale and intergroup differences (see Appendix A for other AQ scales).

[Insert Table 5 about here]

[Insert Figure 2 about here]

Convergent and Discriminant Validity

A correlation analysis was conducted to determine the relationship between AQ-Short and ADOS-2. The analysis showed a significant correlation between two instruments (r = .734, p = <.001), meaning moderate convergent validity. A subgroup analysis showed only a significant positive correlation in the Non-Clinical group (r = .7, p = <.001) (Figure 3)

[Insert Figure 3 about here]

Discriminant validity was explored by way of a linear discriminant analysis to find if a linear combination of the AQ-Short subscales can be used to correctly classify participants in the four groups. As can be seen in the prediction-accuracy figure (Figure 4), model's correct prediction was higher in the non-clinical group (178 out of 190 = 93.68%) than in the ASD group (32 out of 46 = 69.57%). This result indicates that AQ-Short has a better negative predictive than positive predictive value. In the case of ASD relatives and SSD groups, prediction-accuracy was quite low (2.44% and 0% respectively), as those cases were classified as Non-clinical according to AQ-Short subscales scores. Overall accuracy was 71.77%.

[Insert Figure 4 about here]

Cut-Off Scores of AQ Total

Table 6 shows predictive values for a range of potential cut-offs. In our study the total AQ-Short score of >63 gives a sensitivity of .98 and a specificity of .84. The area under the curve was .95, indicating excellent test accuracy. Consistently with previous discriminant analysis results, positive and negative predictive values were 0.6 and 0.994, respectively. Figure 5 shows the ROC curve for AQ total and subscales comparing ASD and Non-Clinical groups. Similar predictive properties were found when comparing participants reaching ASD threshold in the ADOS-2 (ASD n=24) to those who did not (SSD (n=17) and Non-Clinical (n=18), with a cut-off of >65 giving a sensitivity of 1 and specificity of .82. When comparing both clinical groups (ASD vs SSD) a cut-off point of >65were found, with a sensitivity of .94 and specificity of .77.

[Insert Table 6 about here]

[Insert Figure 5 about here]

DISCUSSION

To the extent of our knowledge, this study is the first Spanish validation of any version of the AQ questionnaire and the first replication in a non-English language of the abridged version of the AQ. Moreover, this study is the first validation of the AQ questionnaire which includes ASD diagnostic gold-standard measures not only in an ASD adult sample, but also other clinical/non-clinical groups.

The results of the reliability analysis suggest the good internal structure of the AQ-Short, supporting the results previously found in the original validation (Hoekstra et al., 2011). When comparing four groups in the AQ total scores, it seems that clinical groups (ASD, SSD) are less coherent in their responses, suggesting the need to identify the possible difficulties of these groups when understanding the items. An extension of the sample size could resolve this issue. Even so, both groups showed great reliability in the AQ-Short total score ($C\alpha$ = 0.8). When considering AQ-Short domains, the ASD and SSD groups showed lower than acceptable correlations (<.65) in the Routines, Switching and Imagination subscales. Three items weighing in the Imagination factor scale was found to negatively correlate with the total AQ-Short scale in the SSD group. It is plausible that some items from the Imagination factor correlate negatively with the total scale score in the SSD group, since people with SSD do not have a problem imagining *per se*, although the content and structure of what they imagine is different (Rasmussen & Parnas, 2015). The literature has provided abundant evidence that the ability to imagine clearly differentiates people with ASD from people with SSD (Crespi, Leach, Dinsdale, Mokkonen, & Hurd, 2016). The inverse relationship between imagination domain scores and total AQ-Short scores in the SSD group may be in accordance with the characteristic trend/imagery trait of people with SSD, which clinically differentiates them from people with ASD. This finding, however, should be confirmed with a larger sample of people with SSD, which, if so, would increase confidence in this instrument as a clinical resource with which to discriminate between the two disorders. It also raises the need to further study the abilities to imagine and to use imagination in a social context as relevant characteristics that should be different in both disorders.

Factor analysis showed good to very good model fitting to the two-factor model proposed by the original validation of the AQ-Short (Hoekstra et al., 2008; 2011). Two previous studies have suggested the existence of three underlying factors: social skills, details/patterns, and communication/mindreading (Austin, 2005; Hurst, Mitchell, Kimbrel, Kwapil, & Nelson-Gray, 2007). Another recent study (Murray, McKenzie, Kuenssberg, & Booth, 2017) tried to adjust a

bifactorial model confirming the AQ and the AQ-Short, assessing the extent to which the specific symptom areas measured by this questionnaire reflect the specific factors desired compared to a general factor of ASD. Their results indicate that for the AQ-Short, the covariance of the items mainly reflects the existence of a general factor rather than specific factors, with the exception of the items corresponding to the Numbers/Patterns scale. The finding of these authors is consistent with that obtained by Hoekstra et al. (2011) and by our study. Our study found a greater correlation between Social Behaviour and Numbers/Patterns (.62) which would question the hypothesis that Numbers/Patterns is a relatively different construct from that of Social Behaviour, as suggested in the study by Hoekstra et al. (2011).

The ASD group showed a significantly higher AQ-Short total score compared to other groups. This difference also reached statistical significance when comparing AQ subscales. The Routines and Numbers/Patterns subscales were clearly the best with which to discriminate ASD from other groups. Interestingly, the SSD and ASD-relatives groups did not differ in any AQ scale, thus suggesting a similar prevalence of BAP in both populations. The results found here support the dimensional approach to BAP in general population, with ASD participants reaching the highest scores, followed by SSD and ASD-relatives, and the non-clinical participants having the lowest BAP of all.

One of the main strengths of the present study was the use of gold-standard measures for ASD in a subsample of participants in order to study the association with AQ-Short scores. Correlation analysis indicated a moderate association between both measures when comparing all groups, but correlation analysis by group showed a positive significant correlation only in the non-clinical group, with both ASD and SSD showing non-significant correlations. This may be due to the small sample size and lower variability of ADOS-2 scores in both clinical samples, with the non-clinical group having a higher number of participants.

The original cut-off score reported by Hoekstra et al. (2011) was 65 points, with a sensitivity and specificity of .97 and .82, respectively. These results are similar to those found in the present study (cut-off point of >63, sensitivity of .98 and specificity of .84), supporting the

value of the AQ-Short as a screening test when the 50-item original AQ may be too demanding in terms of cognitive and time resources.

Limitations

Our study has some limitations which need to be considered. First, the small sample sizes may have biased the results found here, especially those regarding cut-off points for screening ASD. Also, the AQ-Short is a self-report measure. It has been suggested that people with ASD might have poor insight when asked about their own behaviours (Johnson, Filliter, & Murphy, 2009). As the AQ-Short items point to preferences rather than behaviours, dependence on a reliable self-knowledge on individual difficulties is overcome (Baron-Cohen et al., 2001).

ASD diagnosis must be based in both standardised measures and clinical judgment, and this is imperative when it comes to research. Only a few participants of the ASD group in this study were assessed by a clinician who specialised in ASD using the current gold-standard measure to support diagnosis. The self-description of the rest of the participants on having received an ASD diagnosis in the past was enough to fulfill this inclusion criteria. As can be easily inferred, some participants may not really have fulfilled a clinical ASD diagnosis, thus confounding the validity of the group scores. The opposite effect can also be found, where non-diagnosed participants who think they may have an unidentified ASD diagnosis try to fulfill their prophecy by overestimating their chance of falling into the autism spectrum when answering the AQ-Short. This issue was addressed in our study by asking participants directly whether they believed they had an undiagnosed ASD, ruling out their scores for the data analysis, thus decreasing the risk of overestimating their scores in the AQ-Short.

Finally, it is important to consider the differences found in gender-ratios between clinical vs. non-clinical groups in our study. The SSD group was mostly male, while the ASD-relatives and non-clinical groups were predominantly female. This may have affected the results of the AQ-

Short scores found in our study, which pointed to a higher prevalence of BAP in male participants, but only in the Non-Clinical group.

In order to explore these differences, a robust ANOVA (10% trimmed means) showed a significant effect of Group factor (Q = 198; p < .001) but not for Gender nor the interaction Group x Gender. In any case, a series of Welchs t tests were conducted to test for gender differences in each group, finding a significant effect of gender only in the non-clinical group (t (84) = 3.29, p < .01, d = 0.51, 95% CI [0.22, 0.92]*)*, indicating a higher proportion of ASD characteristics for males (M = 51.4; SE=1.03) than for females (M = 57.5; SE=1.52). An additional analysis of item differential functioning by gender was conducted in all participants, showing that the AQ-Short did not exhibit overall item response differences between males and females (see Appendix B). Further research is needed into gender differences in the scores obtained in the AQ, being this aim out of the scope of the present study.

Clinical implications

The results of the present study suggest the AQ-Short is a reliable instrument for the screening of ASD in Spanish native-speaker adults. It shows very good internal structure and a good convergence with diagnostic ASD gold-standard measures. Further, the AQ-Short seems to clearly differentiate ASD from other specific populations (SSD, ASD-relatives), and is thus a useful instrument in the screening stage. As this is the only reported validation of the AQ-Short in a non-English language, more evidence on the accuracy of this instrument in other languages is needed.

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Figure 1. Factor structure of the AQ-Short, including factor correlation and factor loadings (N=294; all subjects)

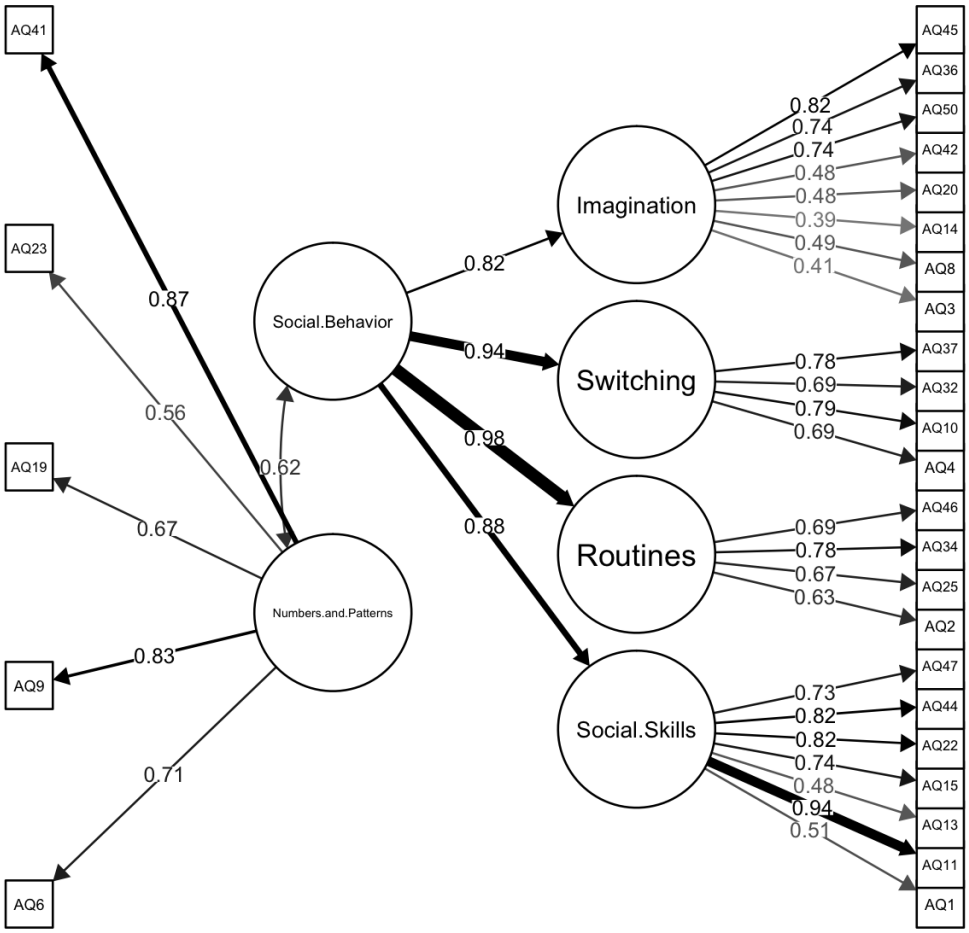
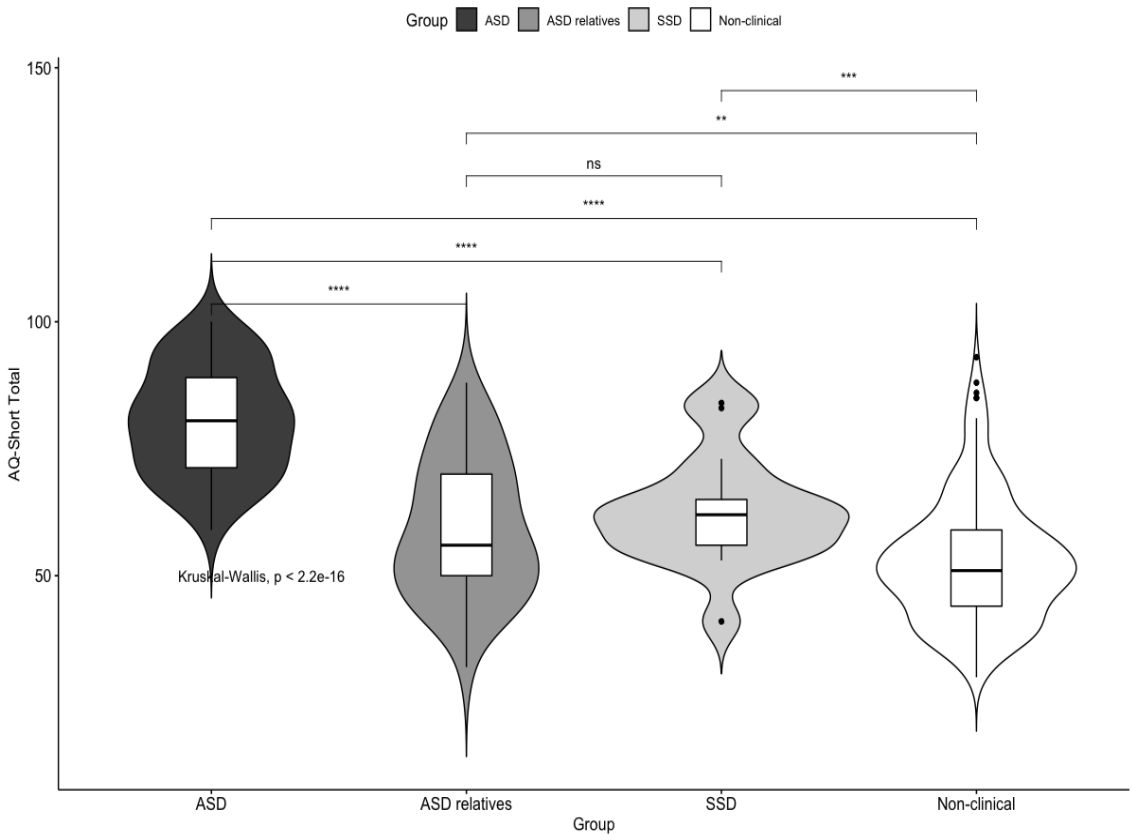


Figure 2. AQ total inter-group differences (non-parametric one-way ANOVA Kruskal-Wallis)



* $p < .05$ ** $p < .01$ *** $p < .001$

Figure 3. Scatter plot with line of best fit (95% confidence interval) correlation analysis of AQ-Short and ADOS-2 score by group.

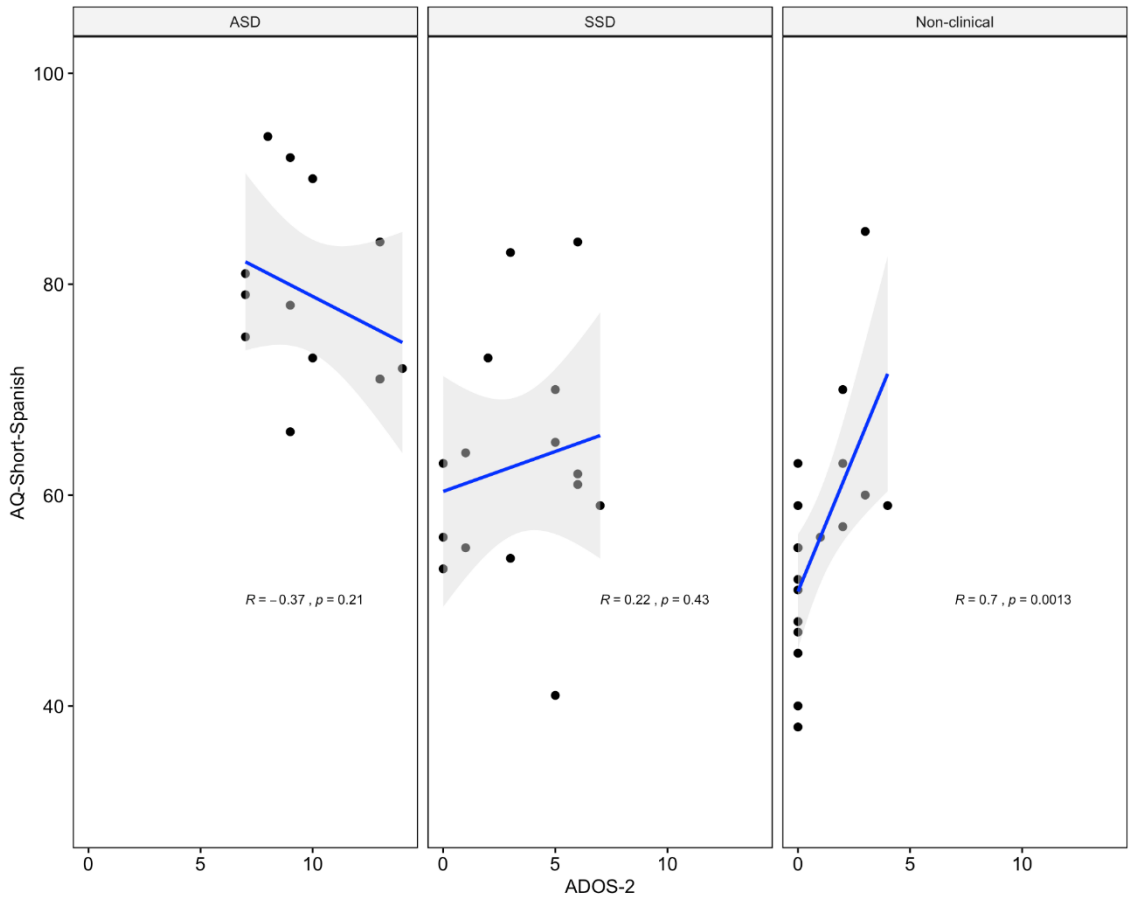


Figure 4. Group prediction-accuracy derived from the linear discriminant analysis (all AQ-Short subscales as predictors). Diagonal shows the number of observed cases correctly predicted by the model as belonging to the corresponding group.

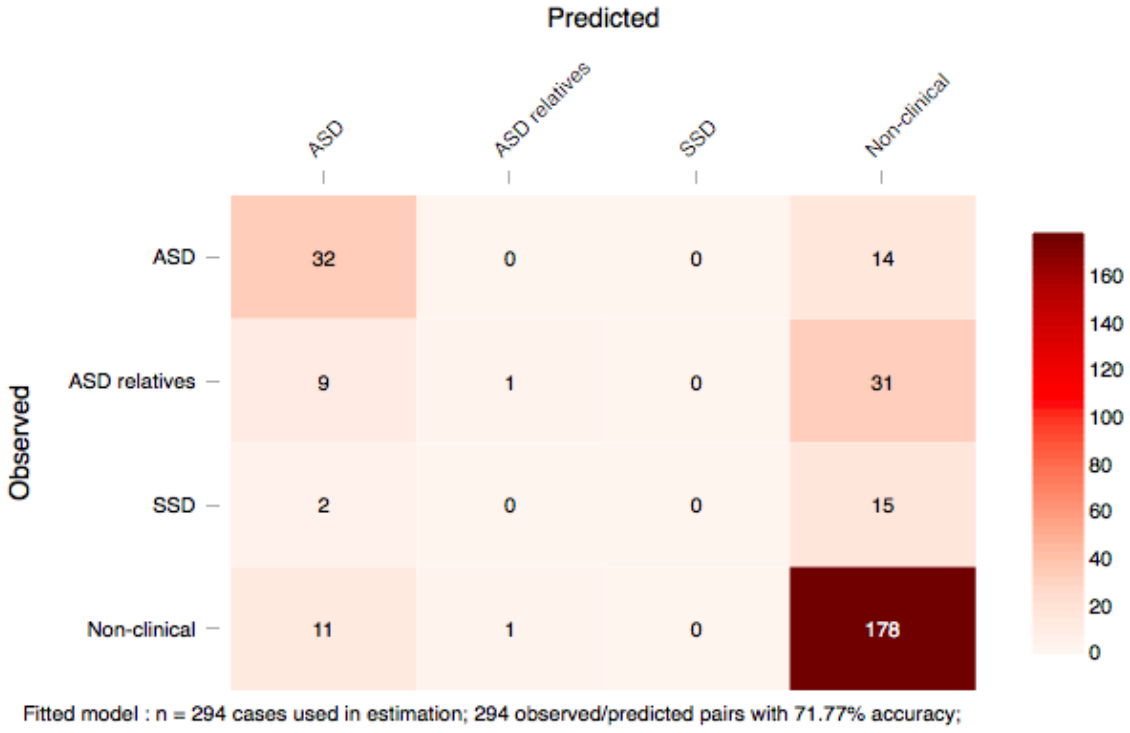
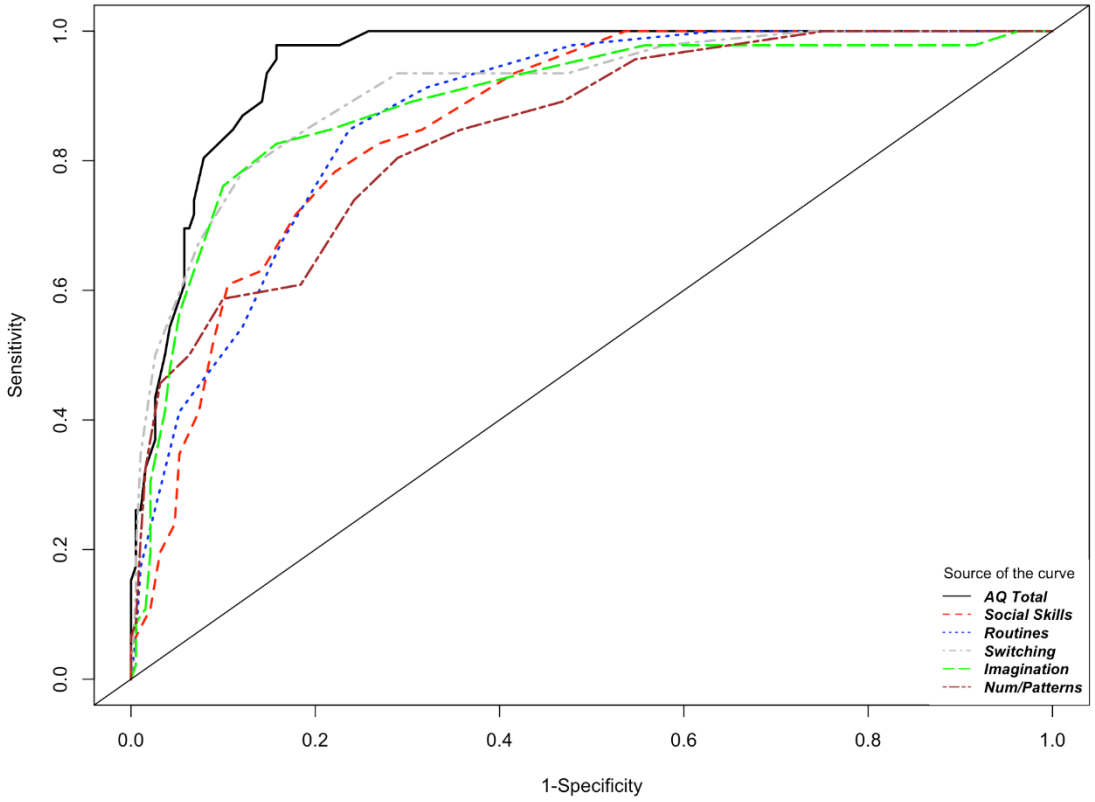


Figure 5. Receiver operating characteristic (ROC) curves illustrating the ability of the full AQ scale and AQ domains to identify any ASD cases at alternative cut-off points.



N = 236 (ASD versus Non-Clinical groups)

Table 1. Characteristics of the participants in the study and differences

	Group[1]				Differences[2]
	ASD (n = 46)	ASDR (n = 41)	SSD (n = 17)	NC (n = 190)	
Age [mean (sd)]	31.81 (9.11)	46.64 (9.73)	34.36 (9.28)	34.28 (10.11)	ASDR > (ASD, SSD, NC) **
IQ mean T scores (sd)					
N of IQ calculation	24	0	17	18	
Verbal	47.08 (13.8)	-	50.47 (10.5)	52.06 (10.8)	
Non-verbal	46.33 (12.1)	-	51.29 (9.2)	56.17 (7.5)	ASD< NC **
Full-IQ	93.75 (16)	-	101.53 (13.5)	105.56 (13.6)	ASD < NC *
Gender					
Male	63,0%	26,8%	82,4%	22,6%	
Female	37,0%	73,2%	17,6%	77,4%	
Education level					
Primary	2,2%	2,4%	11,8%	,5%	
Secondary	10,9%	2,4%	11,8%	3,2%	
Bachelor	23,9%	14,6%	35,3%	18,4%	
Professional Training	26,1%	29,3%	29,4%	9,5%	
University	28,3%	51,2%	11,8%	68,4%	
Work/Academic status					
Student	28,3%	0,0%	41,2%	22,1%	
Worker	19,6%	68,3%	11,8%	57,9%	
Student+Worker	8,7%	2,4%	0,0%	7,9%	
Unemployed	30,4%	12,2%	17,6%	6,8%	
Home worker	2,2%	7,3%	0,0%	4,2%	
Pensioner	2,2%	2,4%	29,4%	,5%	
Retired	0,0%	4,9%	0,0%	,5%	
Psychofarmacological treatment					
Any psychofarmacological treatment	28,3%	9,8%	88,2%	0,0%	
Antipsychotic	10,9%	0,0%	82,4%	0,0%	
Antidepressant	13,0%	4,9%	29,4%	0,0%	
Anxiolytic	13,0%	4,9%	35,3%	0,0%	
Hypnotics	2,2%	0,0%	29,4%	0,0%	
Mood stabilizer	0,0%	2,4%	17,6%	0,0%	
Metiylphenidate	2,2%	0,0%	0,0%	0,0%	
Psychiatric disorders					
Any psychiatric disorder (other than ASD)	58,7%	39,0%	100,0%	0,0%	
Substance Use Disorders	2,2%	0,0%	0,0%	0,0%	
Schizophrenia Spectrum Disorders	4,3%	0,0%	100,0%	0,0%	
Mood Disorders	17,4%	22,0%	17,6%	0,0%	
Anxiety Disorders	19,6%	34,1%	17,6%	0,0%	
Eating Disorders	6,5%	0,0%	0,0%	0,0%	
Personality Disorders	4,3%	0,0%	5,9%	0,0%	
Attention Deficit/Hyperactivity Disorder	17,4%	0,0%	0,0%	0,0%	

1: ASD: Autism Spectrum Disorder; ASDR: ASD relatives; SSD: schizophrenia spectrum disorders NC: Non-Clinical

2: Based on Dwass-Steel-Critchlow-Fligner pairwise comparisons: * $p < .05$; ** $p < .01$

Table 2. Internal consistencies (Cronbach's Alpha) for all five subscales of the AQ-short.

AQ scales	ASD (n = 46)	ASD relatives (n = 41)	SSD (n = 17)	Non-clinical (n = 190)
Social Behavior (23 items)	.78	.88	.78	.88
Social Skills (7 items)	.76	.79	.82	.83
Routines (4 items)	.42	.66	.45	.70
Switching (4 items)	.56	.61	.41	.68
Imagination (8 items)	.63	.71	.33	.64
Numbers/Patterns (5 items)	.72	.74	.64	.75
AQ-Short Total (28 items)	.79	.88	.80	.88

Table 3. Independent samples t-tests, means, standard deviations, Spearman rho correlation and intraclass correlation coefficients for the test-retest reliability of the AQ and its subscales for ASD (n = 26), SSD (n = 9) and Non-clinical (n = 61) participants.

AQ scales	Mean T1 (sd)	Mean T2 (sd)	*t*	*p*	r_s	ICC
Social Behavior	50.33 (13.8)	50.32 (15.1)	0.02	.99	.94***	.97***
Social Skills	15.34 (5.4)	15.28 (5.5)	0.28	.78	.91***	.96***
Routines	9.55 (3.1)	9.66 (3.2)	-0.53	.60	.82***	.90***
Switching	9.19 (3.2)	9.13 (3.2)	0.33	.74	.81***	.91***
Imagination	16.25 (4.5)	16.26 (5.2)	-0.04	.97	.81***	.91***
Numbers/Patterns	10.48 (4.1)	10.50 (4.1)	-0.09	.92	.83***	.93***
AQ-Short Total	60.81 (16.3)	60.82 (18.1)	-0.02	.99	.94***	.97***

T1 = time one, T2 = time two

*** $p < .001$

Table 4. Fit values based on WLSMV extractions for second-order Social Skills + Numbers/Patterns AQ-S model

Sample	**WLSMV χ^2**	**df**	**RMSEA (90% CI)**	**CFI**	**TLI**	**WRMR**
All subjects (N = 294)	828.94**	345	0.069 (.063 - .075)	.942	.937	1.293
Non-clinical (N = 231)	671.99**	345	0.064 (.057 - .071)	.913	.905	1.211

** p < .001; WLSMV = robust weighted least squares; RMSEA=root mean square error of approximation; CFI = comparative fit index; TLI = Tucker-Lewis Index; WRMR = weighted root mean square residual.

Table 5. Independent samples t-tests means and standard deviations of the AQ total score and its subscales for all groups.

	Group[1]				
AQ scales	**ASD (n = 46)**	**ASDR (n = 41)**	**SSD (n = 17)**	**NC (n = 190)**	**Differences[2]**
Social Behavior	66.37 (9.2)	49.80 (11.9)	52.29 (9.4)	43.84 (10.8)	ASD > (ASDR, SSD,NC)** SSD > NC ** ASDR > NC **
Social Skills	20.28 (4.3)	15.22 (4.5)	15.12 (4.9)	13.59 (4.5)	ASD > (ASDR, SSD,NC)** ASDR > NC **
Routines	12.61 (2)	9.41 (2.8)	9.76 (2.4)	8.62 (2.7)	ASD > (ASDR, SSD,NC)**
Switching	12.33 (2.5)	8.54 (2.6)	9.65 (2.4)	7.38 (2.5)	ASD > (ASDR, SSD,NC)** SSD > NC ** ASDR > NC **
Imagination	21.15 (4.3)	16.63 (4.7)	17.76 (3.2)	14.25 (3.7)	ASD > (ASDR, SSD,NC)** SSD > NC ** ASDR > NC **
Numbers/Patterns	14.09 (3.8)	9.44 (3.5)	10.29 (3.2)	8.95 (3.2)	ASD > (ASDR, SSD,NC)**
AQ Total	80.46 (10.6)	59.24 (13.7)	62.59 (10.7)	52.79 (12.2)	ASD > (ASDR, SSD,NC)** SSD > NC ** ASDR > NC **

1: ASD: Autism Spectrum Disorder; ASDR: ASD relatives; SSD: schizophrenia spectrum disorders NC: Non-Clinical

2: Based on Dwass-Steel-Critchlow-Fligner pairwise comparisons: * $p < .05$; ** $p < .01$

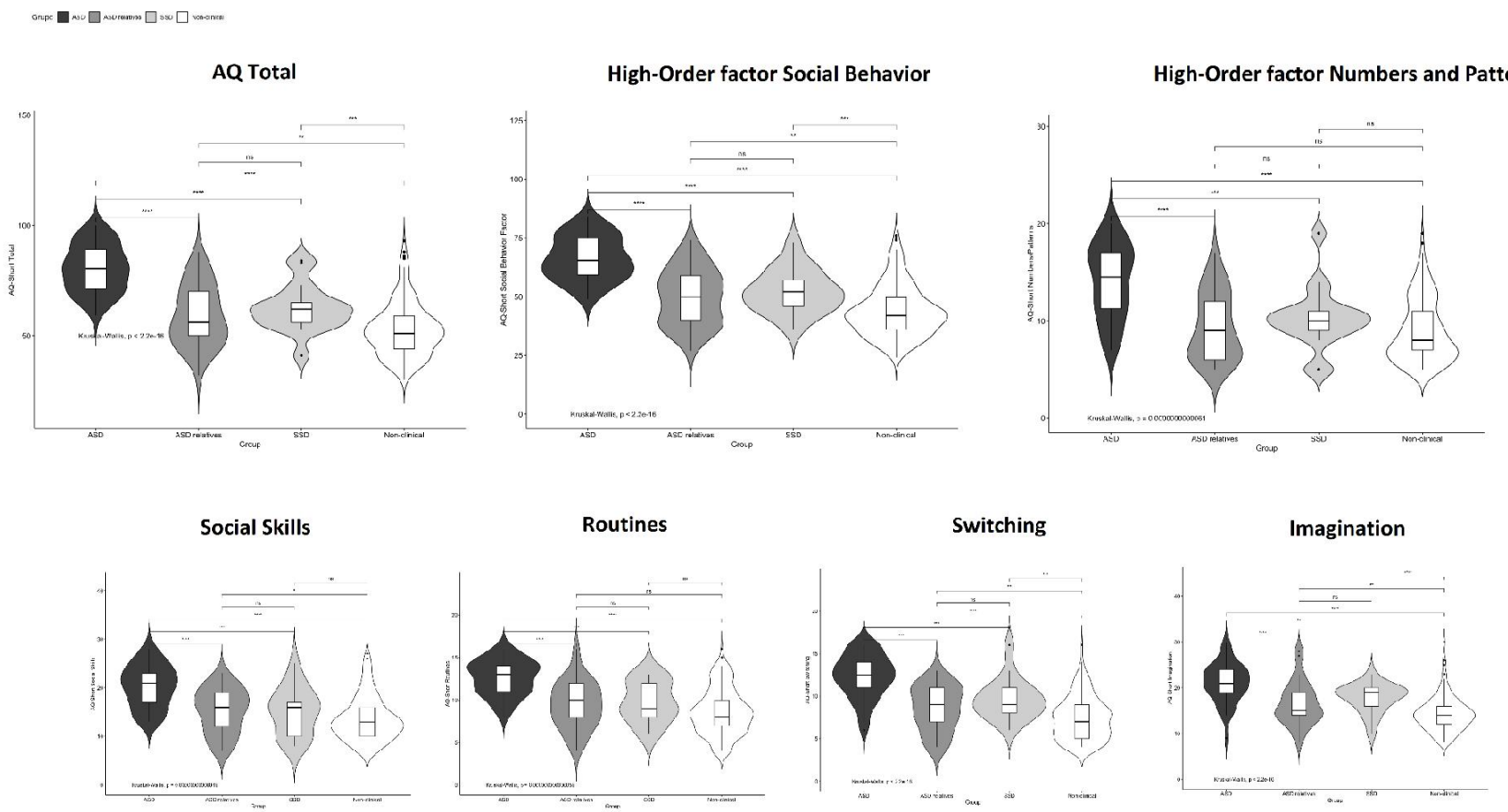
Table 6. Area under the curve (AUC), accuracy, sensitivity and specificity, positive (PPV) and negative (NPV) predictive values for the Youden index-based cut-off scores for full scale and five domains

AQ Scale	Cut-off	AUC (95% CI)	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
AQ Total	63.5	0.948 (0.948-0.974)	0.869 (0.868-0.87)	0.978 (0.936-1.02)	0.842 (0.79-0.894)	0.6 (0.489-0.711)	0.994 (0.982-1.006)
Social Skills	16.5	0.859 (0.859-0.91)	0.78 (0.778-0.781)	0.783 (0.663-0.902)	0.779 (0.72-0.838)	0.462 (0.351-0.572)	0.937 (0.899-0.975)
Routines	10.5	0.87 (0.87-0.918)	0.78 (0.778-0.781)	0.848 (0.744-0.952)	0.763 (0.703-0.824)	0.464 (0.358-0.571)	0.954 (0.921-0.987)
Switching	10.5	0.908 (0.908-0.955)	0.86 (0.859-0.861)	0.783 (0.663-0.902)	0.879 (0.833-0.925)	0.61 (0.486-0.735)	0.944 (0.909-0.978)
Imagination	17.5	0.889 (0.889-0.945)	0.839 (0.838-0.84)	0.826 (0.717-0.936)	0.842 (0.79-0.894)	0.559 (0.441-0.677)	0.952 (0.92-0.985)
Numbers/Patterns	10.5	0.844 (0.844-0.904)	0.729 (0.727-0.73)	0.804 (0.69-0.919)	0.711 (0.646-0.775)	0.402 (0.302-0.502)	0.938 (0.898-0.977)

N = 236 (ASD versus Non-Clinical groups)

Appendix A

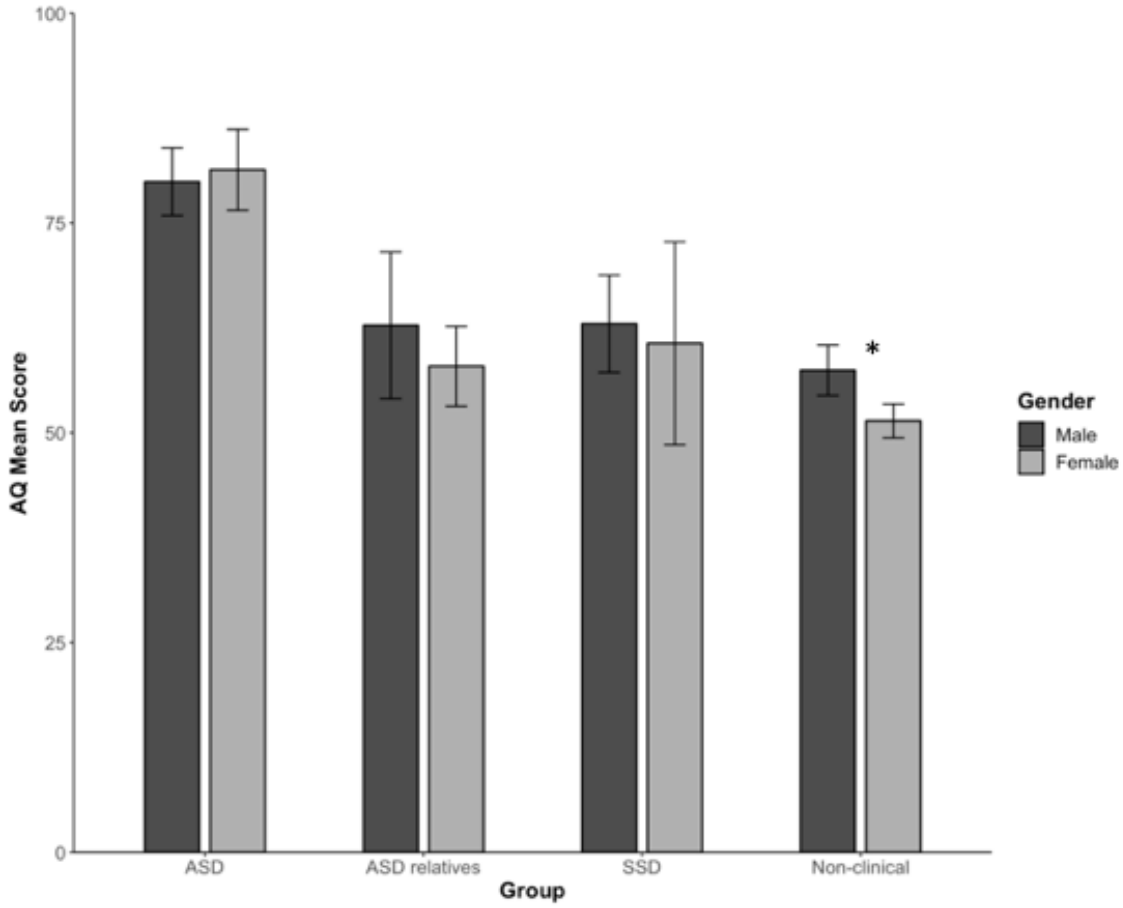
Figure 1. Violin plots for AQ inter-group differences (non-parametric one-way ANOVA Kruskal-Wallis)



* $p < .05$ ** $p < .01$ *** $p < .001$

Appendix B

Figure 3 shows the mean AQ-Short total scores for the four groups sorted by gender.

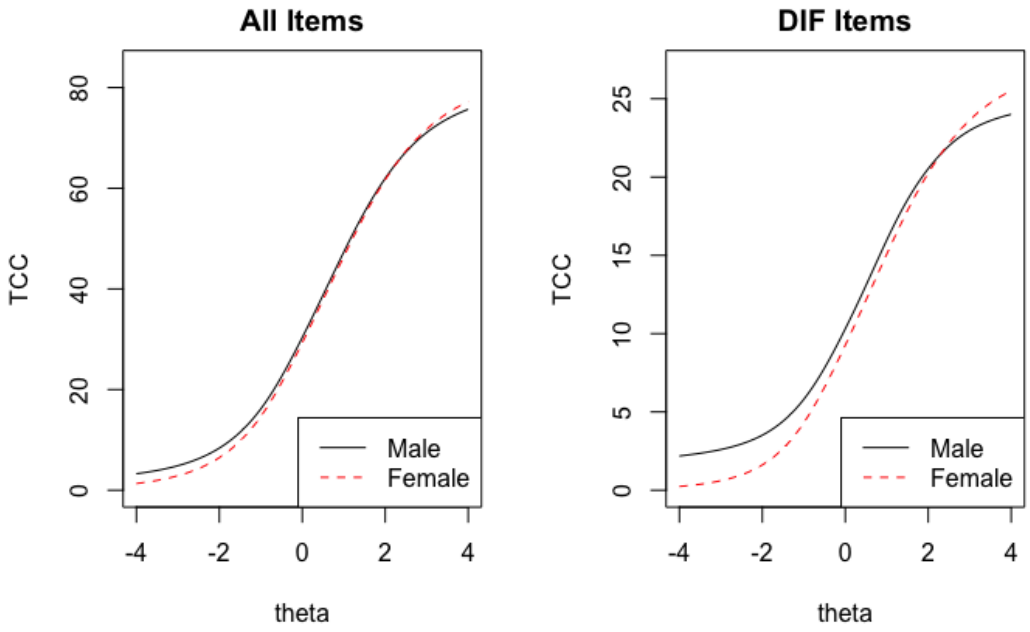


* $p < .05$

Differential item functioning (DIF) was used to examine whether an item performed differently for the male group than for the female group. Hybrid ordinal logistic regression has shown good power for detecting DIF, but inflated type I error rates (i.e., items with very small DIF valued as DIF items.) have also been reported with large samples. For this reason, DIF was considered present considering the likelihood ratio χ^2 tests (statistical significance) in conjunction with effect size measures (pseudo R^2 statistic >.20) and proportional β_1 change >10%.

Nine items were flagged for DIF (χ^2 significance as criteria), but none of those items also met the other two stablished criteria. As shown in Figure 1, a difference in test characteristic curves (TCC) between males and females can be seen for DIF items, however, as can be seen in the right figure of the panel, the absolute magnitude of the difference is very small and mainly due to a decrease in the probability of response for females at the lower level of the lower extreme ability level and an increase in the probability of females at the upper extreme ability level.

Figure 1. Impact of gender DIF on test characteristics curves (TCC)



Conclusiones

El objetivo del presente trabajo fue determinar la concurrencia de patología psiquiátrica en personas adultas con TEA. De igual modo, tras detectar un riesgo de solapamiento diagnóstico con los TEE, se decidió llevar a cabo la validación de un instrumento de cribaje diagnóstico que permitiese discriminar entre ambas categorías diagnósticas. Por último, se puso a prueba la estructura dimensional de las características TEA, según la cual se establece un continuo dimensional en la manifestación de dichas características en población sin diagnóstico de TEA.

A continuación, se enumeran las principales conclusiones alcanzadas durante la realización de este trabajo:

1. Las personas adultas con TEA presentan una prevalencia de trastornos psiquiátricos superior a la encontrada en población general.
2. El TEA podría ser un factor de vulnerabilidad para el desarrollo de patología psiquiátrica en la edad adulta.
3. Los trastornos más prevalentes en personas adultas con TEA son el Trastorno por Déficit de Atención e Hiperactividad, los trastornos afectivos y los trastornos del espectro de la ansiedad.
4. Existe un riesgo de solapamiento diagnóstico entre las características relacionadas con el TEA y otras entidades diagnósticas.
5. Las personas adultas con TEA y capacidad intelectual en rango normativo presentan una prevalencia de TEE superior a la reportada en población general.
6. El instrumento Cociente Autista abreviado presenta buenas propiedades psicométricas para su uso en el proceso de evaluación diagnóstica de personas adultas con TEA de habla española.

7. El instrumento Cociente Autista abreviado presenta una buena convergencia con una medida gold-standard de evaluación de TEA en adultos.
8. Las personas con diagnóstico de TEE presentan características TEA en mayor proporción a poblaciones no clínicas.
9. Los familiares de primer grado de personas con TEA presentan características TEA en mayor proporción a población sin historia de patología psiquiátrica.
10. Las características TEA se manifiestan a lo largo de un continuo de intensidad, confirmando la estructura dimensional del TEA propuesta en las clasificaciones diagnósticas actuales.

Entre las limitaciones del presente trabajo, cabe señalar el reducido tamaño muestral empleado para la validación de la prueba de cribaje diagnóstico Cociente Autista abreviado. También, las diferencias en la proporción de hombres y mujeres en las distintas muestras estudiadas harían pensar en un posible sesgo del género en las puntuaciones obtenidas en el instrumento. Por último, no todos los participantes del grupo TEA fueron evaluados directamente por el autor de este trabajo, siendo incluidos en la muestra aquellos que reportasen un diagnóstico de TEA emitido por un facultativo especialista en psiquiatría o psicología.

Los resultados reportados en el presente trabajo permitirán establecer líneas de actuación a nivel clínico y de investigación. En el primer caso, estableciendo perfiles psicopatológicos específicos en población adulta con TEA, poniendo especial atención al riesgo de solapamiento con otras entidades diagnósticas. En el segundo caso, aportando un instrumento diagnóstico para detectar características TEA en población adulta con riesgo de presentar un TEA. Futuras investigaciones deberán establecer relaciones causales entre la presencia de características

TEA y el desarrollo de trastornos psiquiátricos, así como la detección de factores protectores que eviten su aparición.

Conclusions

The objective of the present work was to determine the concurrence of psychiatric pathology in adults with ASD. Similarly, after detecting a risk of diagnostic overlap with SSD, it was decided to carry out the validation of a diagnostic screening instrument that would allow to discriminate between both diagnostic categories. Finally, the dimensional structure of the ASD characteristics was tested, according to which a dimensional continuum of such characteristics can be found in non-ASD populations.

The following are the main conclusions reached during the development of this work:

1. Adults with ASD show a higher prevalence of psychiatric disorders when compared with the general population.

2. ASD could be a factor of vulnerability for the development of psychiatric pathology in adulthood.

3. The most prevalent disorders in adults with ASD are Attention Deficit and Hyperactivity Disorder, Affective Disorders and Anxiety Spectrum Disorders.

4. There is a risk of diagnostic overlap between the ASD characteristics and other diagnostic entities.

5. Adults with ASD without intellectual disability have a higher prevalence of SSD when compared with the general population.

6. The Autism Quotient Short Form has good psychometric properties for use in the diagnostic evaluation of Spanish-native adults with ASD.

7. The Autism Quotient Short Form shows a good convergence with a gold-standard measure of ASD in adults.

8. People diagnosed with SSD show ASD characteristics in greater proportion to non-clinical populations.

9. First-degree relatives of people with ASD show ASD characteristics in greater proportion when compared with non-clinical adults.

10. ASD characteristics are manifested along a continuum of intensity, confirming the dimensional structure of the ASD proposed in the diagnostic classifications.

Among the limitations, we should point out the small sample size used for the validation of the AQ-Short. Also, the differences in the proportion of men and women in the different samples studied would suggest a possible gender bias in the scores obtained in the instrument. Finally, not all the participants of the ASD group were directly evaluated by the author of this work, being included in the sample those who reported a diagnosis of ASD made by a specialist in psychiatry or psychology.

The results reported in the present work will allow to develop lines of action at clinical and research level. In the first case, establishing specific psychopathological profiles in the adult population with ASD, paying special attention to the risk of overlap with other diagnostic entities. In the second case, providing a diagnostic tool to detect ASD characteristics in the adult population at risk of presenting an ASD. Future investigations should establish causal relationships between the presence of ASD characteristics and the development of psychiatric disorders, as well as the detection of protective factors that prevent their appearance.

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Anexo 1: Cuestionario Cociente Autista abreviado

ID: Género: ☐ Masculino ☐ Femenino

Fecha de nacimiento: / / Fecha de hoy: / /

		Totalmente de acuerdo	**Un poco de acuerdo**	**Un poco en desacuerdo**	**Totalmente en desacuerdo**
1.	Prefiero hacer las cosas con otras personas más que solo.				
2.	Prefiero hacer las cosas de la misma manera una y otra vez.				
3.	Cuando me imagino algo, tengo facilidad para crear mentalmente una imagen.				
4.	Con frecuencia me quedo en gran medida abstraído en una cosa.				
5.	Normalmente presto atención a las matrículas de los coches o similares secuencias de información.				
6.	Al leer una historia tengo facilidad para imaginarme la apariencia de los personajes.				
7.	Siento fascinación por las fechas.				
8.	En un grupo social puedo llevar con facilidad el hilo de las diferentes conversaciones de la gente.				
9.	Las situaciones sociales me resultan fáciles.				
10.	Preferiría ir a una biblioteca más que a una fiesta.				
11.	Me resulta fácil inventar historias.				
12.	Me siento mucho más identificado/a con la gente que con las cosas.				
13.	Siento fascinación por los números.				
14.	Al leer una historia, me es difícil averiguar las intenciones del personaje.				
15.	Tengo dificultades para hacer nuevos amigos.				
16.	Continuamente me doy cuenta de patrones en las cosas				
17.	No me incomoda que se me interrumpa en mi rutina diaria.				
18.	Tengo facilidad para hacer más de una cosa a la vez.				
19.	Disfruto haciendo cosas de forma espontánea.				
20.	Tengo facilidad para averiguar lo que alguien está pensando o sintiendo.				
21.	En caso de ser interrumpido puedo volver a lo que estaba haciendo de forma muy rápida				
22.	Me gusta coleccionar información sobre categorías de cosas (por ejemplo, tipos de coches, tipos de pájaros, tipos de trenes, tipos de plantas, etc.).				
23.	Me es difícil imaginar cómo sería, de ser otra persona.				
24.	Me encantan las celebraciones sociales.				
25.	Tengo dificultad para averiguar las intenciones de la gente.				
26.	Las situaciones nuevas me crean ansiedad.				
27.	Me encanta conocer gente nueva.				
28.	Encuentro muy fácil jugar con niños a juegos que implican fingir o simular.				

Anexo 2: Artículos del autor relacionados con el tema de la tesis

Referencia: Lugo, J., & Alviani, M. (2017). El diagnóstico de la psicosis en adultos con trastornos del espectro autista. *Revista de la Asociación Española de Neuropsiquiatría*, *37*(131), 113-126.

Título: El diagnóstico de la psicosis en adultos con trastornos del espectro autista

Resumen

Existe cierta controversia en el diagnóstico diferencial de dos entidades aparentemente bien delimitadas como son la psicosis y el autismo, especialmente cuando se trata de población adulta. Se presentan tres casos de pacientes en edad adulta que fueron atendidos en una unidad de internamiento breve y en los que se evidenció la presencia de un posible trastorno del espectro autista de base. En la evaluación de la presencia de un trastorno psicótico en el autismo se debe atender a las características particulares de cada diagnóstico. El pensamiento rígido y el discurso idiosincrásico del paciente con autismo pueden confundirse respectivamente con la convicción delirante y la desorganización típicas de la esquizofrenia. Un análisis exhaustivo de la historia evolutiva del paciente es imprescindible para el diagnóstico diferencial. Se hace necesaria una mayor investigación sobre la comorbilidad entre ambos trastornos.

Palabras clave: trastorno autístico, síndrome de Asperger, psicosis, diagnóstico diferencial.

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El diagnóstico de la psicosis en adultos con trastornos del espectro autista

Diagnosing psychosis in adults with autism spectrum disorders

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Resumen: Existe cierta controversia en el diagnóstico diferencial de dos entidades aparentemente bien delimitadas como son la psicosis y el autismo, especialmente cuando se trata de población adulta. Se presentan tres casos de pacientes en edad adulta que fueron atendidos en una unidad de internamiento breve y en los que se evidenció la presencia de un posible trastorno del espectro autista de base. En la evaluación de la presencia de un trastorno psicótico en el autismo se debe atender a las características particulares de cada diagnóstico. El pensamiento rígido y el discurso idiosincrásico del paciente con autismo pueden confundirse respectivamente con la convicción delirante y la desorganización típicas de la esquizofrenia. Un análisis exhaustivo de la historia evolutiva del paciente es imprescindible para el diagnóstico diferencial. Se hace necesaria una mayor investigación sobre la comorbilidad entre ambos trastornos.

Palabras clave: trastorno autístico, síndrome de Asperger, psicosis, diagnóstico diferencial.

Abstract: There is some controversy in the differential diagnosis of two apparently distinct entities such as psychosis and autism, especially when it comes to adult population. We present three cases of adult patients who were seen in a brief hospitalization unit and

where the presence of a possible autism spectrum disorder was evident. In assessing the presence of a psychotic disorder in autism must be addressed the particular characteristics of each diagnosis. Rigid thinking and idiosyncratic speech in the autistic patient may respectively be confused with the typical delusional conviction and disorganization of schizophrenia. An exhaustive analysis of the developmental history of the patient is essential for differential diagnosis. More research on the comorbidity between the two disorders is necessary.

Key words: autistic disorder, Asperger syndrome, psychosis, differential diagnosis.

El concepto de esquizofrenia

La esquizofrenia puede considerarse un grupo heterogéneo de síndromes de etiología desconocida, que difieren en sintomatología, curso y resultado final, y cuyo diagnóstico descansa básicamente en criterios clínicos (1). Las áreas más frecuentemente afectadas son la percepción, la cognición, el lenguaje, la memoria, la emoción, la volición y los comportamientos adaptativos (2). En la clasificación actual del DSM-5 (3) se incluye dentro del apartado "Espectro de la esquizofrenia y otros trastornos psicóticos", estableciendo como criterios diagnósticos la presencia de anomalías en uno de los siguientes dominios: delirios, alucinaciones, pensamiento/discurso desorganizado, comportamiento motor alterado (con inclusión de la catatonía) y sintomatología negativa. Al contrario que en las ediciones previas del manual, se ha suprimido la clasificación de los subtipos que existía hasta el DSM-IV-TR (4).

En 1911, el psiquiatra suizo Eugen Bleuler acuñó el término *esquizofrenia* para denominar el cuadro clínico descrito unos años antes por Emil Kraepelin como *demencia precoz* (5). En la descripción que realizó Bleuler de los síntomas cardinales o *fundamentales* de la esquizofrenia se encontraba el cuarteto conocido como las *cuatro A*es, que incluía: trastornos de las asociaciones, alteraciones en la afectividad, ambivalencia y autismo. Al contrario que Kraepelin, que veía como síntomas primarios el delirio, las alucinaciones, los trastornos formales del pensamiento y la negatividad, para Bleuler estos síntomas eran secundarios o *accesorios*. Otra aportación importante de este autor fue destacar las características propias de la esquizofrenia –que aparecen tanto en su forma leve como más grave–, diferenciándola de otros trastornos mentales (6, 7).

Posteriormente, Kurt Schneider invirtió la jerarquía entre los síntomas cardinales y secundarios de Bleuler, delimitando un grupo de síntomas psicóticos e introduciendo el concepto de "síntomas de primer rango" que incluían la sonorización del pensamiento, la audición de voces, las experiencias corporales de influencia, el

robo y difusión del pensamiento, la percepción delirante y la convicción de ser influenciado en los sentimientos, tendencias y voliciones.

Desde la aparición de la primera edición del *Manual Diagnóstico y Estadístico de los Trastornos Mentales* (DSM) en 1952, han prevalecido los criterios diagnósticos para la esquizofrenia desarrollados por Kraepelin: "El término es sinónimo del antiguo de demencia precoz. Representa un grupo de reacciones psicóticas caracterizadas por anomalías básicas en la relación con la realidad y la formación de conceptos, a las que se añaden alteraciones afectivas, conductuales e intelectuales en grados y combinaciones diversas. El trastorno está marcado por una fuerte tendencia al distanciamiento de la realidad, incongruencia emocional, anomalías imprevisibles en el flujo del pensamiento, conductas regresivas, y, en algunos casos, tendencia al 'deterioro'" (8).

El término *autismo* se reservó para el cuadro que Leo Kanner definió en 1943 y que se relacionó preferentemente con la infancia (9). En la actualidad forma parte del síndrome que se denomina en el DSM-5 "Trastornos del Espectro Autista" (TEA) dentro de los "Trastornos del Neurodesarrollo", e incluye trastornos previamente clasificados como "autismo de la primera infancia", "autismo infantil", "autismo de Kanner", "autismo de alto funcionamiento", "autismo atípico", "trastorno generalizado del desarrollo no especificado", "trastorno desintegrativo de la infancia" y "síndrome de Asperger". Dos son los criterios principales que permiten realizar el diagnóstico de los TEA: el deterioro persistente de la comunicación y la interacción social, así como las alteraciones en los patrones de conducta. Estos patrones de funcionamiento están presentes desde la primera infancia, limitando el funcionamiento cotidiano del individuo y generando problemas de inadaptación social y la aparición de comorbilidades psiquiátricas como, por ejemplo, trastornos psicóticos (10-12).

El concepto de autismo

Como se ha descrito anteriormente, fue Bleuler (13) quien introdujo el término *autista* para referirse al ensimismamiento que presentaban las personas afectadas de esquizofrenia. Estas personas presentaban comportamientos que hoy serían reconocidos como típicamente autistas. Tres décadas más tarde, Kanner (14) presentó un trabajo en el que describía varios casos de niños y niñas con características peculiares en cuanto al comportamiento social, el desarrollo del lenguaje y los procesos cognitivos. Determinó que padecían una forma severa de *autismo*, estableciendo la diferenciación con los diagnósticos que habían recibido hasta entonces, en su mayoría, retraso mental y esquizofrenia.

Simultáneamente, Hans Asperger (15), psiquiatra austríaco, informaba de varios casos de niños similares a los descritos por Kanner y a los que denominó como *psicópatas*

autistas, haciendo especial énfasis en las peculiaridades de la comunicación verbal y no verbal y la maestría en temas en los que mostraban un fuerte interés. Sin embargo, tuvieron que pasar cuatro décadas para que los hallazgos presentados por Asperger fuesen presentados a la comunidad científica angloparlante. Esto fue posible gracias al trabajo de Lorna Wing (16), psiquiatra inglesa y madre de una niña con autismo que realizó un estudio de seguimiento de varios niños y niñas con autismo que habían sido diagnosticados erróneamente con trastornos del espectro de la psicosis, entre otros. Desarrolló la que se conoce como la triada de Wing: deterioro de la comunicación verbal y no verbal, deterioro de la interacción social, y patrones de conducta, intereses y actividades restringidos. Introdujo el término *síndrome de Asperger*, en relación a los casos que mostraban las mismas características que había descrito Hans Asperger casi medio siglo atrás.

Una década más tarde, el diagnóstico de síndrome de Asperger fue incluido en el DSM (17). No es de extrañar semejante retraso, pues hasta la tercera edición del manual el autismo se había venido considerando como una forma infantil de esquizofrenia (18). En la tercera edición revisada se amplió el espectro de síndromes, estableciendo tres grupos de criterios para el diagnóstico que coincidían con los propuestos por Wing (19). En la cuarta edición, así como en su posterior revisión, apenas se produjeron cambios, más allá del establecimiento de cinco grandes grupos dentro del espectro autista: "trastorno autista", "trastorno de Rett", "trastorno desintegrativo infantil", "síndrome de Asperger", y "trastorno generalizado del desarrollo no especificado". Dicha clasificación ha sido eliminada en la última revisión del manual (3), estableciendo un constructo dimensional bajo el concepto general de "Trastornos del Espectro Autista", en el que se diferencian distintos niveles de gravedad en base, principalmente, al nivel intelectual y el desarrollo del lenguaje del individuo. Asimismo, dos de los criterios de la triada de Wing (déficits en la comunicación y la interacción social) se unifican en uno solo, manteniéndose intacto el criterio referente a los intereses restringidos.

¿Dos entidades separadas?

La diferenciación entre los diagnósticos de psicosis y autismo parece estar claramente establecida en el plano teórico. La presencia de síntomas psicóticos, esto es, de alteraciones del contenido del pensamiento o de la sensopercepción, guiarían el diagnóstico hacia el primero. Ahora bien, es conocido que muchos de los síntomas que presentan las personas con autismo pueden confundirse con síntomas del espectro de la psicosis (alteraciones sensoriales, rigidez en el pensamiento, retraimiento social, etc.) (20). Teniendo en cuenta que muchas de las personas con un trastorno del espectro autista, especialmente aquellas con un alto funcionamiento, no fueron diagnosticadas durante los primeros años de vida (21), y debido a la dificultad en el diagnóstico fiable

en la edad adulta (22), cabe pensar en una posible confusión en la práctica clínica entre ambos diagnósticos.

Una forma habitual de evolución de los pacientes con TEA en la edad adulta es la aparición de episodios con síntomas parecidos a la psicosis (*psychosis-like symptoms*) (11). Estos episodios se caracterizan por ser relativamente diferentes a los presentes en un trastorno del espectro de la psicosis. Su discurso idiosincrásico suele confundirse habitualmente con el habla desorganizada típica de la esquizofrenia. Otra fuente de posible confusión diagnóstica es la presencia de ideas o creencias que la persona con autismo mantiene con fuerte convicción y que son resistentes a la evidencia. Esto podría provocar la confusión con una idea de tipo delirante. La diferencia radica en que en el delirio el razonamiento que se ha seguido hasta llegar a la conclusión carece de una base lógica, mientras que en el autismo la idea se ajusta a los parámetros de realidad e incluso puede ser compartida por más personas. De igual modo, la ausencia de una percepción de perjuicio individual también nos aleja de un diagnóstico de trastorno delirante (22).

Existe escasa investigación en cuanto a la posible comorbilidad de ambos diagnósticos. Varios estudios de seguimiento de niños con diagnóstico de TEA han encontrado resultados que apuntarían a una posible evolución del trastorno autista hacia la esquizofrenia (24-26). Igualmente, estudios retrospectivos han encontrado alteraciones significativas en el desarrollo, evaluadas mediante entrevista familiar, en pacientes con diagnóstico de esquizofrenia que se acercarían a un diagnóstico de autismo (27). En la actualidad, el DSM-5 admite la comorbilidad entre ambos diagnósticos, si bien se establece como requisito que la aparición del trastorno autista sea anterior al primer episodio psicótico. Esto resulta especialmente complicado cuando los pacientes no han sido diagnosticados en la infancia. Si bien existen instrumentos diagnósticos que han mostrado una alta validez en la detección del autismo (28, 29), el carácter retrospectivo de la evaluación en la etapa adulta podría sesgar los resultados, ya que la información dependería de factores extrínsecos tales como la capacidad de los familiares para recordar e identificar signos atípicos en el desarrollo del paciente, así como la percepción subjetiva de una "mala praxis" por parte de estos, la cual les podría llevar a experimentar sentimientos de culpabilidad que afectarían al contenido de la información referida.

A continuación, se presentan tres casos clínicos tratados en una unidad de hospitalización breve en los que se observan varias características que desafían el establecimiento de una diferenciación empírica entre ambas entidades nosológicas.

Caso 1

Varón de 24 años que es trasladado al servicio de urgencias por presentar alteraciones conductuales. La familia refirió que el paciente presentaba desde hacía

cuatro años aislamiento, abandono de sus actividades habituales, alteraciones en el contenido del pensamiento y en la sensopercepción que se han ido agravando en los últimos meses.

Al comienzo del ingreso el paciente presentó una elevada desorganización en el discurso, en el cual primaban las asociaciones laxas. Se identificaba con un personaje de animación ("Gru" de la película *Gru, mi villano favorito*) y reconocía a algunos miembros del personal como personajes de la misma película. Interpretaba de manera delirante los gestos casuales que se realizaban en su presencia y refería voces que le transmitían mensajes con un contenido místico-religioso o persecutorio.

La entrevista familiar, que se realizó con los padres y una tía materna, ayudó a clarificar el cuadro. No hubo dificultades en el embarazo ni en el parto y, en relación a su psicodesarrollo, los padres destacaron las dificultades del paciente en la adquisición del lenguaje y la socialización desde la primera infancia. Lo describieron como un niño muy tranquilo, ordenado, con patrones de comportamiento restrictivos y con una marcada dificultad en el área social que se agravó en la adolescencia, manteniendo un grupo restringido de amigos y escasas salidas sociales. Dentro de sus antecedentes personales destacaba una evaluación en Salud Mental a la edad de 22 años debido a la presencia de sintomatología ansiosa. Como antecedentes familiares, un cuadro de psicosis tóxica en un primo materno que también requirió ingreso en la unidad de internamiento breve.

Sus dificultades en la interacción social se agravaron al comienzo de la enseñanza secundaria, al encontrarse en un entorno nuevo sin sus amigos del colegio. Comentó que tenía dificultades para entenderse con sus compañeros al no comprender los dobles sentidos o las bromas, que interpretaba de manera literal. A los 19 años presentó un cuadro de "alergia generalizada" que le llevó a aislarse en su domicilio durante dos años con escaso contacto exterior, dedicado la mayor parte del tiempo a visionar películas de animación de contenido infantil y a los juegos de rol online. Debido a la insistencia de sus padres, realizó con éxito un ciclo formativo de soldadura, consiguiendo un empleo en la empresa en la que había realizado la formación práctica. Su rendimiento disminuyó cuando tuvo que afrontar el cambio en su ciclo vital, de estudiante a trabajador. A los seis meses abandonó este empleo y comenzó otra formación profesional en carpintería, que también se planteó abandonar por la ansiedad que le producía la relación con sus compañeros.

Durante el ingreso se mostró colaborador en las entrevistas, aunque evitaba participar en las terapias grupales, mostrando preferencia por actividades solitarias. Se definía como una persona antisocial que no necesitaba estar con los otros, ya que refería no saber qué decir en las situaciones sociales o no entender lo que los demás le decían.

En el seguimiento posterior al alta hospitalaria se completó la evaluación. En la Escala de Inteligencia de Wechsler para Adultos (WAIS) (30) todas las subescalas

se encontraban dentro del rango de normalidad excepto la subescala "comprensión", la cual evalúa la capacidad para entender las situaciones sociales. Obtuvo una puntuación elevada en el Cociente de Espectro Autista (AQ) (31) debido a sus dificultades en el área social. En las entrevistas de seguimiento comentó que en algunas ocasiones participaba de actividades grupales lúdicas con sus compañeros de clase, si bien tras varias horas sentía la necesidad de retirarse con una elevada sensación de angustia. Su explicación se repetía: "No sé qué decir. No entiendo lo que me dicen". Esta situación se agravaba cuando sus compañeros hacían uso de dobles sentidos o ironías que él entendía de manera literal.

Al reincorporarse a sus actividades académicas, el paciente presentó sintomatología ansiosa dentro del contexto de la interacción con sus compañeros de clases. Por esta razón, prefiería las salidas bien con su familia o bien en solitario. Más aún, una de sus actividades habituales consistía en dar paseos de varios kilómetros en completa soledad.

Su rigidez mental y su dificultad para comprender los mensajes sociales le llevan a realizar interpretaciones erróneas que pueden terminar siendo autorreferenciales, favoreciendo su tendencia a evadirse en actividades solitarias como defensa ante la ansiedad que le provoca la interacción con otras personas.

Caso 2

Se trata de un varón de 30 años remitido al servicio de urgencias por su psiquiatra habitual debido a alteraciones conductuales en el entorno familiar. Ha venido desarrollando en los últimos meses unos hábitos alimentarios que han puesto en peligro su salud, rechazando algunos alimentos por considerar que estaban "contaminados". Cuando se ha tratado de modificar estas conductas, se ha mostrado irritado y con agresividad hacia su madre y su hermano menor. En la entrevista se mostró colaborador, con aspecto descuidado debido a la falta de higiene. El contacto era peculiar, mostrando sonrisas inapropiadas y una alta latencia de respuesta en el discurso. Negaba alteraciones de la sensopercepción y del pensamiento. Refirió tratamiento por crisis epilépticas con buena evolución en la infancia. A los 18 años acudió a una consulta de psiquiatría por problemas de conducta; allí recibió el diagnóstico de síndrome de Asperger. A pesar de que no refirió sintomatología psicótica en aquella ocasión, se le pautó tratamiento neuroléptico que abandonó por reacción adversa. En el momento de la valoración no se encontraba bajo tratamiento psiquiátrico.

En el ingreso, el paciente se mostraba tranquilo y colaborador. En la primera consulta, solicitó un tiempo previo a la entrevista para poder realizar un paseo por los pasillos de la planta, ya que esto le ayudaba a calmarse. Cuando se exploró el

motivo del ingreso, mostró escasa conciencia de enfermedad, refiriendo encontrarse en desacuerdo con la necesidad del mismo. Sin embargo, no mostraba signos de desconfianza, presentando buena disposición a recibir tratamiento. Su madre refirió que desde la primera infancia había notado que algo era diferente en el paciente, si bien reconocía que no recibió información sobre el diagnóstico de síndrome de Asperger hasta que fue mayor de edad. El paciente comentaba que sus compañeros de colegio se reían de él porque utilizaba un vocabulario muy formal. El rendimiento académico fue excelente hasta el bachillerato, momento en el que comenzó a suspender asignaturas a pesar de contar con una capacidad intelectual superior a la media. Hasta el momento del ingreso pasaba la mayor parte del tiempo en su casa, donde convivía con su madre y su hermano menor. Comentaba que a menudo solía dar largos paseos o se desplazaba en autobús, actividades que realizaba siempre en solitario. Refería un fuerte interés por las ciencias naturales.

Al avanzar el ingreso, se le observaba más distendido, con menor rigidez postural y menor latencia de respuesta en el discurso. También se redujeron las sonrisas inmotivadas, las cuales reaparecían en el contexto de la interacción con personas desconocidas. El tratamiento antipsicótico se mostró eficaz en la reducción de la irritabilidad del paciente. La rigidez en relación a las ideas sobre la alimentación y los hábitos de higiene y sueño continuaron al alta.

Caso 3

Se trata de un varón de 23 años que fue remitido al servicio de urgencias de nuestro hospital por alteraciones de la conducta en la vía pública. Sus padres referían que desde hacía un mes el paciente había ido disminuyendo de forma progresiva las horas de sueño, así como verbalizado ideas de carácter mesiánico. Parecía llevar una vida desorganizada con descuido de las tareas básicas, dedicación excesiva a los videojuegos y deficiente alimentación. En la entrevista se mostró hostil, suspicaz, e interpretativo con el entorno, especialmente con los colores, llegando a referir que se "sentía" azul. Negó alteraciones en la esfera sensoperceptiva. Desde hacía tres años se encontraba en seguimiento por psiquiatría debido a varios episodios psicóticos y afectivos, con buena respuesta al tratamiento psicofarmacológico, que había abandonado en los últimos meses.

Ya en la unidad, el paciente se mostró tranquilo, pero muy desconfiado. Explicó lo sucedido como resultado de la percepción de "pistas falsas" que le llevaron a alertar a determinadas personas de que estaban en peligro. Su madre refirió llevar varios años en tratamiento psiquiátrico por distimia, mientras que el padre había recibido un diagnóstico de trastorno obsesivo compulsivo en el pasado. Los familiares no refirieron ninguna alteración en el desarrollo del paciente, si bien él mismo reconoció

que siempre se había sentido un "bicho raro". Recordaba la etapa escolar como un "infierno", presentando un mal manejo de las relaciones interpersonales, hasta el punto de reconocer que le daba "fobia" la cara de las personas. Es por esta razón por la que desde la adolescencia mantenía contacto interpersonal casi de manera exclusiva a través de juegos de ordenador en línea.

A medida que avanzó el ingreso se le observaba más distendido, si bien refería sentirse incómodo rodeado de gente. También comentó que le molestaba el sonido del tubo del televisor situado en una de las salas comunes de la unidad, el cual percibía de forma nítida. Como estrategia de afrontamiento en los momentos de estrés, deambulaba por el pasillo siguiendo una secuencia rutinaria que podía durar varias horas y que, según decía, le ayudaba a relajarse. Mencionó tener habitualmente "paranoias" que asociaba con su comportamiento anterior al ingreso. Relacionó el episodio conductual con un sentimiento profundo de soledad y frustración por su incapacidad para mantener relaciones interpersonales estables. Al ser preguntado por la relación entre percepción y color manifestada en el servicio de urgencias, respondió que se trataba de la letra traducida de una canción (en inglés la palabra "blue" presenta dos significados: azul y triste. Al decir sentirse azul el paciente realmente expresaba un sentimiento de tristeza).

El paciente presentó buena respuesta al tratamiento antipsicótico, si bien tanto los síntomas afectivos como la rigidez en el pensamiento nunca desaparecieron.

La tabla 1 muestra la comparación de los resultados en la Escala de Inteligencia Wechsler para Adultos (WAIS) (30), la Escala de Síndromes Positivos y Negativos (PANSS) (32) y el Cociente de Espectro Autista (AQ) (31) en los tres pacientes. La tabla 2 muestra una comparación entre los criterios de esquizofrenia y autismo compartidos en los tres casos descritos.

Tabla 1

Comparación de resultados en la evaluación psiquiátrica de los tres pacientes

		Caso 1	**Caso 2**	**Caso 3**
WAIS	CI Verbal	88	126	122
	CI Manipulativo	112	100	131
	CI Total	98	116	129
PANSS	Síndrome positivo	15	8	33
	Síndrome negativo	18	26	31
	Psicopatología general	40	31	41
AQ		36	28	26

Tabla 11

Comparación de los criterios de esquizofrenia y autismo en los tres casos

Criterios DSM-5		*Caso 1*	*Caso 2*	*Caso 3*
Espectro de la esquizofrenia y otros trastornos psicóticos	Delirios	X	¿?	X
	Alucinaciones	X		
	Discurso desorganizado	X		X
	Comportamiento muy desorganizado o catatónico	X		X
	Síntomas negativos	X	X	X
Trastornos del Espectro Autista	Déficit comunicación social	X	X	X
	Comportamientos restringidos y repetitivos	X	X	X

Discusión

Se observa una elevada presencia de síntomas propios de un trastorno del espectro autista en la base de los tres casos comentados. Se pueden observar dificultades en el área social y de la comunicación presentes desde una edad temprana del desarrollo, si bien no es hasta la adolescencia cuando comienzan a manifestarse estas dificultades debido a las imposiciones propias de esta etapa del ciclo vital, cuando se comienza a hacer frente a los desafíos de la vida independiente lejos de la protección que proporciona la familia (33). Los videojuegos online y las plataformas digitales suelen servir de gran ayuda para mantener el contacto con el mundo exterior. Estos entornos virtuales salvan las dificultades en el área de la comunicación verbal, permitiendo desarrollar fuertes vínculos sociales a través de los mismos (34). Por otro lado, se observa la presencia de unos intereses restringidos y conductas repetitivas prototípicas de este tipo de trastornos en los tres casos. Estas personas suelen desarrollar intereses en campos de la ciencia y la tecnología, convirtiéndose en expertos de la materia objeto de su interés. Asimismo, son frecuentes las rutinas de deambulación, que presentan un componente relajante que pudo observarse en los tres casos presentados. En cuanto a la presencia de delirios, estos parecen evidentes en el primero y el tercero de los casos, si bien en el segundo la cuestión es más difícil de resolver. El paciente refería no querer ingerir alimentos por miedo a que estos estuviesen contaminados. A la exploración de estas ideas se evidenciaron componentes culturales que sostenían dicha creencia. Más aún, el paciente se

mostró colaborador en este sentido, llegando a afirmar que no le importaría que el contenido de la entrevista fuese registrado mediante algún dispositivo de grabación. Esta apertura no suele ser frecuente en pacientes con psicosis en los que la ocultación del contenido delirante suele marcar la entrevista. A pesar de esto, parece difícil establecer una diferenciación entre los contenidos delirantes de la psicosis con la rigidez mental de los trastornos autistas.

La evaluación psicométrica arrojó resultados llamativos. En primer lugar, se observaron semejanzas en las puntuaciones de las subescalas negativa y psicopatología general, aunque es la subescala de síntomas positivos la que mejor discrimina entre ambos trastornos. Esto es lógico, teniendo en cuenta la frecuencia de los síntomas positivos (delirios y alucinaciones) en los trastornos psicóticos. La Escala Wechsler de Inteligencia suele presentar un patrón típico en las personas con trastornos del espectro autista. Estas suelen presentar una marcada discrepancia entre las dos áreas evaluadas, verbal y manipulativa, mostrando un mejor rendimiento en las pruebas del área manipulativa (35). Tan sólo en uno de los casos presentados (Caso 2), el paciente rindió mejor en el área verbal, presentando una diferencia elevada con respecto al área motora. En el Caso 1, llama la atención la puntuación verbal que obtuvo el paciente (CI 88). En un análisis de los distintos subtests se observó que en la subescala "Comprensión" había obtenido una puntuación típica de 6, por debajo del rango de normalidad, debido a su elevada dificultad para entender qué *debía* hacer en determinadas situaciones sociales y cómo debía comprender el significado simbólico de un refrán. Por último, las puntuaciones en el cociente de espectro autista resultaron significativas en los tres pacientes. La puntuación de corte que haría pensar en la presencia de un probable trastorno autista se ha estimado en 26, siendo 32 la media obtenida por personas con síndrome de Asperger (36). Los casos expuestos alcanzan puntuaciones que igualan o superan la puntuación de corte en una alta proporción. Sin embargo, este instrumento es insuficiente para poder descartar un cuadro psicótico, ya que los constructos evaluados podrían presentar un cierto solapamiento con la sintomatología negativa presente en los trastornos del espectro psicótico.

Conclusiones

La presencia de sintomatología psicótica en los trastornos del espectro autista hace pensar en un posible origen común de ambos cuadros. Los casos aquí presentados pueden servir de apoyo a las teorías que defienden la existencia de una entidad única con diferentes manifestaciones (37-40). En las clasificaciones de los trastornos mentales previas al DSM-5 se planteaba la incompatibilidad en la comorbilidad de ambos trastornos. Esto llevó a infradiagnosticar la presencia simultánea de ambos

síndromes, lo que generó un inadecuado abordaje en la práctica clínica. Se hace pues necesaria una mayor investigación en la diferenciación de ambos trastornos, así como una detección precoz que salve la confusión diagnóstica observada en la edad adulta. Esto redundará en una mejora en la intervención de las personas con trastornos del espectro autista, ya que un diagnóstico erróneo podría centrar la intervención en el manejo de los síntomas psicóticos, dejando de lado el abordaje de las dificultades propias de las personas con TEA.

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