Prevalence and Risk Factors for Autism Spectrum Disorder Within Epilepsy: A Systematic Review and Meta-Analysis

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Abstract

Aim: The current review assessed the prevalence and risk factors for Autism Spectrum Disorder (ASD) within epilepsy, in order to better understand the relationship and comorbidity between these disorders.

Methods: PsychINFO and PubMed were searched for articles published in the past 15 years that examined prevalence of ASD within individuals with epilepsy.

Results: A total of 19 studies were found with a pooled ASD prevalence of 6.3% within epilepsy. When divided by type, general epilepsy, infantile spasms, focal seizures, and Dravet syndrome showed a 4.7%, 19.9%, 41.9%, and 47.4% risk of ASD, respectively. Studies with populations under 18 years showed a 13.2x greater ASD risk than study populations over 18 years, and samples with a majority (>50%) of individuals with intellectual disability (ID) showed a 4.9x greater risk than studies with a minority of individuals with ID. The main risk factors for ASD reported in the present studies included presence of ID, gender, age, and symptomatic aetiology of epilepsy.

Interpretation: Current research supports a high prevalence of ASD within epilepsy. This study helps define the clinical profile of patients with epilepsy at-risk for ASD, which may help clinicians in early screening and diagnosis of ASD within this population.

Keywords: autism, epilepsy, intellectual disability, prevalence, risk factors

What this paper adds:

- Critically evaluates prior studies which examine the prevalence of Autism Spectrum Disorder within individuals with epilepsy
- A meta-analysis of 19 studies showed a pooled ASD prevalence of 6.3% within individuals with epilepsy
- Studies which included majority of individuals with intellectual disability or younger population age had higher prevalence rates of Autism
- Risk factors reported in studies included presence of intellectual disability, gender, age, and symptomatic epilepsy origin

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Epilepsy is an enduring predisposition to generate seizures which is active in approximately 0.4% to 0.8% of the population[1,2]. Autism spectrum disorder (ASD) is characterized by impairments in communication and social interactions along with presence of repetitive and perseverant behaviours, and is prevalent in 0.75% to 1.1% of the population[3-5]. Notably, the presence of either disorder greatly augments the probability of developing the other. The coexistence between these disorders has been reported for over 50 years, however, many questions about their relation remain unanswered[6]. For instance, what is the prevalence of ASD within epilepsy? What factors increase the risk for co-occurrence? Is there a causal relationship between epilepsy and ASD, or do both disorders result from the same underlying risk factors?

The first question that arises concerns the exact prevalence and risk factors for the ASD-epilepsy comorbidity. For individuals with ASD, estimates of the prevalence of developing epilepsy within a lifetime range from 2.7% to 44.4%[7-15], with a recent review reporting a sevenfold increased risk of epilepsy within individuals with ASD relative to the general population[16]. A key risk factor reported is the presence of intellectual disability (ID), which increases epilepsy risk in ASD by 3 to 5 times[7,17]. Other risk factors for epilepsy in ASD include female gender[7], older age[14], lower socioeconomic status[16] and a family history of ASD[8].

Another question relates to understanding the mechanisms underlying the high comorbidity between these disorders. One theory is that epilepsy may contribute to— or even cause —certain developmental impairments, thus predisposing an individual towards ASD[18]. Accordingly, early seizures have numerous disruptive effects on neural development, including lasting physiological and functional deficits in the hippocampus, abnormal synaptic reorganization, and cortical interneuron dysfunction[19,20]. These seizures may cause maladaptive synaptic plasticity leading to imbalances of the excitation/inhibition neurotransmitter systems which impairs learning and behavioural development[18]. This in turn disrupts the construction of cortical networks necessary for acquiring certain skills during development, and may pre-

dispose an individual towards developing ASD[21]. Alternatively, epilepsy and ASD may both be side effects of a common underlying neural pathology[22-24]. This is supported by findings that ASD and epilepsy have common biological pathways, such as abnormalities in gene transcription regulation, cellular growth, synaptic channel function and/or dysregulation of the excitation/inhibition system[22,23]. Further, risk for both epilepsy and ASD is elevated in numerous genetic disorders, such as Rett Syndrome, Fragile X Syndrome, and Tuberous Sclerosis Complex[22]. Current research postulates that these theories are not mutually exclusive and that they both contribute to the comorbidity seen between these disorders[18].

Where prior reviews have examined the risk of epilepsy within the individuals with ASD[17], no review to date has examined ASD prevalence and risk factors within epilepsy. Thus, the main goal of this review is to identify and analyze prevalence and risk factors for ASD within different epilepsy populations. In doing so, this review hopes to augment our understanding of the developmental outcomes and prognosis for individuals with epilepsy. Additionally, this review aims to propose novel insights on the role of epilepsy within ASD, and on the complex relationship underlying these co-occurring disorders.

Methods

Search Strategy and Inclusion Criteria

Articles were retrieved from PubMed and PsychINFO (November, 2016) using the keywords "epilepsy" and "autism". Articles were required to be presented in English, based on human research, and published within 15 years of the search date (2001-2016). Each study also had to be conducted in an epilepsy population where the entire population did not have an alternative medical condition (e.g., Downs Syndrome, Cerebral Palsy, Tuberous Sclerosis Complex). Article abstracts needed to provide a prevalence statistic, odds ratio or numerical report of the comorbidity of ASD within an epilepsy population. Full articles must have contained a reported or calculable prevalence statistic for ASD within text (if not provided in abstract).

Quality Appraisal

Risk of bias within each study was assessed using a modified QUIPS tool[25], adapted to suit the specific testing materials and methods used in the studies reviewed (Appendix A). This appraisal method was chosen to examine the level of bias within each study and to determine the reliability of the individually reported prevalences. Of note, the quality appraisal was conducted specifically on the population with epilepsy within each study who partook in the ASD assessment and may not have referred to the entire population or other methodology within the paper.

Statistical Analysis

As large heterogeneity between studies was anticipated due to variations in baseline characteristics (e.g., epilepsy type, age, gender, presence of ID) within each sample, the pooled prevalence was calculated using a DerSimonian-Laird random effects model on the raw percentages [26]. The Cochran's Q statistic was used to detect the presence of heterogeneity between studies[27]. The I^2 statistic was used to quantify the percentage of variation in the pooled prevalence that was due to heterogeneity between studies [28]. All analyses were conducted using metan[29] on Stata 14 [30].

Results

Article Selection

The initial search criteria yielded 1738 results. Of screened titles, 57 articles contained a prevalence or odds ratio for co-morbid epilepsy and ASD, with 36 based in a population with ASD and 21 based in a population with epilepsy. Only one study was excluded from final analysis as it did not contain a calculable ASD prevalence within text (see Figure 1 and Table 1)[31-50].

Critical Appraisal

Based on the QUIPS tool, the most commonly found risk factors for bias within the studies reviewed included for participation, ASD measure used, and study confounds (see Table 2). Key issues with

participation in studies were: a) using a non-representative sample, b) high proportion or unspecified exclusion of eligible persons, or c) not providing baseline sample descriptives. Key issues with ASD measure used involved: a) not adequately describing ASD measures, or b) using non-diagnostic or self-reported ASD measure. For study confounds, key issues were: a) not reporting ID or other confounds, b) not providing definitions of ID measures, or c) not accounting for ID/other confounds within study design and analysis. Trends of risk for bias did not seem to be related to the type of epilepsy, sample size, or age of sample, with relatively even levels of risk found within all study types. However, a general trend was found for studies with the highest number of risk factors for bias reporting higher epilepsy prevalence.

Pooled estimates

Reilly et al. (2015)[33] was removed from statistical analysis as the population and testing was the same as Reilly et al. (2014)[32]. An ASD pooled prevalence of 6.3% was found for overall epilepsy (see Figure 2 and Table 3). Once divided by type of epilepsy, general epilepsy (i.e., all epilepsy types included), infantile spasms (IS), complex partial seizures (CPS), and Dravet Syndrome (DS), had ASD prevalences of 4.7%, 19.9%, 41.9%, and 47.4%, respectively. Studies with mean population ages under 18 years had a 13.2x greater risk of ASD relative to older samples. Studies with a majority (>50%) of participants with ID also showed a 4.9x greater risk over studies with a minority (<50%) of participants with ID. Further, studies with the highest number of risk factors (3/4) had 2.6x greater risk for ASD then studies with the lowest number of risk factors (1/4). Estimated 95% predictive interval for data was between 3.9 and 8.6.

Risk Factors

Within studies reviewed, risk factors consistently reported (≥4 studies) include presence of ID, male gender, earlier age of epilepsy onset, and symptomatic origin of epilepsy. Other risk factors less frequently reported (≤3 studies) include seizure recurrence, duration of epilepsy, neural abnormalities, and parental epilepsy. Risk factors inconsistently reported were type of epilepsy, seizure frequency, and number of anti-epileptic drugs (AEDs), with conflicting results found between studies (see Table 4).

Discussion

This review analyzed all studies that examined the prevalence of ASD within an epilepsy population over the past 15 years, which matched the current search criteria. A pooled prevalence of 6.3% for ASD was found within individuals with epilepsy, which is substantially higher than the reported prevalence of 0.75% to 1.1% in the general population[4,5]. This rate is similar to two recent large-scale, population-based studies examining epilepsy in ASD, which found a 6.3% and 6.6% likelihood of epilepsy within ASD[51,52]. Higher prevalence were found for studies with younger age groups, higher rates of reported ID, and specific epilepsy syndromes (IS/CPS/DS).

Epidemiology

The wide variance in prevalences found in the current review likely arises as a result of baseline and methodological differences between studies. Differences in baseline sample characteristics include epilepsy type, presence/definition of ID, age of testing, and gender ratio. As this study found gender, presence of ID and epilepsy type to impact ASD comorbidity, variance in these factors may have a substantial impact on the different prevalences reported.

Methodological differences between studies, such as in study design, sample size and characteristics, inclusion/exclusion criteria, definitions of epilepsy and ASD, and method of ASD assessment, may also impact the prevalence statistics reported. For instance, where epilepsy is typically defined as the presence of two unprovoked seizures more than 24 hours apart[35], one study only required one seizure[50], and in studies that used self-reported surveys, exact epilepsy definition could be subjective according to each participant. Where ASD is typically diagnosed using a clinical assessment between ages 3 and 5[54], at least 4 studies began testing as early as 1 year, a developmental stage where ASD symptoms may not yet be present or reliably tested. Another key methodological difference may be the variability in testing measures used to diagnose ASD. Specifically, numerous studies used early screening questionnaires over formal diagnostic measures, which increase the risk of false positives for ASD in individuals with epilepsy[53]. For example, Eom and colleagues reported a 54% risk of ASD using an early ASD screening measures, however only 6% proceeded to receive a formal ASD diagnosis using later diagnostic

measures[34]. It is possible that early ASD screening measures are confounded by ID or developmental delay, which are common among individuals with epilepsy[22]. Thus, studies using early ASD questionnaires and screening measures may not assess ASD risk directly, but rather more general risks for a broader developmental delay or ID. Further, sample size may contribute to prevalence inconsistencies, with the two population-based nationwide studies reporting the lowest prevalences of 1.3% and 1.6%[40,42]. However, within these studies rates of ASD were still elevated relative to the general population (e.g., in Sundelin et al., controls showed an atypically low ASD rate of only 0.2%)[40]. Further, Sundelin et al. reported a hazard ratio of 10.5 (95% CI 9.6 -11.5) and Selassie et al. reported an odds ratio of 22.2 (95% CI 16.8 – 29.3) for developing ASD in individuals with epilepsy relative to controls[40,42]. Thus, larger, population-based studies showed lower rates of ASD relative to smaller studies, but still reported high prevalence risk relative to the general population.

When studies were assessed for methodological risk factors for bias in the current critical appraisal, the highest number of risks for bias (3/4) found a 2.6x increase in pooled prevalence then studies with the lowest number of risks for bias (1/4). This demonstrates that certain methodological considerations, including sample characteristics, ASD definition/measurement, and/or consideration of ID and other confounds, may augment prevalence scores reported.

Clinical Characteristics

Intellectual Disability. ID is defined by an IQ score ≤70 accompanied by impairments in conceptual, social and practical adaptive functioning[3]. This review found that when the majority of a study's sample had an ID, there was over a sevenfold risk of developing ASD than samples with a minority with ID. This finding is similar to previous studies of epilepsy within the ASD population, where intelligence levels were found to be inversely correlated with epilepsy risk[14]. Interestingly, the pooled prevalences for ASD in individuals with and without ID within the epilepsy population (38.9% vs. 5.2%) were higher than those reported for epilepsy with and without ID in the ASD population (23.7% vs. 1.8%)[17]. Overall, these results support the strong connection between ID, epilepsy, and ASD[55].

Gender. The majority of studies that examined sex difference in people with ASD found an increased risk in males, which is consistent with higher male prevalence for ASD within the general population[56]. However, the male:female sex ratios for ASD in these studies were between 1.58:1[39] and 2.4:1[38], which is substantially below the general population ASD sex ratio of 4:1[56]. Therefore, the risk may actually be higher in females when base rate sex differences for ASD within the general population are considered. This is consistent with Sundelin et al.[40] and Su, Chi, Lin and Yang[31], who reported a higher number of males to develop epilepsy, but a higher hazard ratio for females once ASD base rates in controls were considered. This is also consistent with previous studies within ASD populations, which report higher epilepsy risk in females[7,51]. One potential reason for this may be that a higher proportion of females with ASD have severe ID than males, which predisposes them to epilepsy risk[56].

Age. Samples with a mean age under 18 years had a 13.2x risk of ASD relative to samples over 18 years. The earlier a sample is tested, the younger the individuals may have onset with epilepsy, and earlier seizure onset is a known risk factor for poorer neurodevelopment outcomes[57, 58]. Clarke and colleagues found that the greatest risk for developing ASD is in patients with seizure onset before 2 years[39]. One further study found that, of children with both ASD and epilepsy, 80% had their seizure onset in the first year of life[59]. This may be due to the contributing role of disruptive seizures in ASD during early development. These findings support the theory that early seizure activity may play a role in the atypical development seen in ASD.

Seizure Type. Within ASD research, there is no predominant epilepsy type or syndrome reported[60]. However, some of the larger studies have found focal seizures (FS) with a dyscognitive component (i.e., CPS) more commonly reported than primary generalised seizures[51]. In the current review, numerous studies found focal epilepsy reported in a majority of individuals who developed ASD [33,34,38]. Although only one study examined FS explicitly, it found an 8.9x risk of ASD development relative to generalised epilepsy. One potential reason for this is that focal seizures are the most common seizure type seen in individuals with epilepsy onset ≤10 years, whereas generalised convulsive seizures are seen in the

majority of individuals with later onset [38]. This suggests that FS may be a risk for ASD-epilepsy comorbidity, with age of epilepsy onset serving as a potential mediator.

Contrary to findings in ASD research, the current review did find that different epilepsy syndromes (i.e., IS and DS) demonstrated increased ASD risk relative to general epilepsy. One reason for this is that both DS and IS tend to onset within the 1st year of life, which has been previously mentioned as an increase risk factor for ASD [49,61]. DS, which showed the highest risk, is a genetic form of epilepsy with mutations in the SCN1A gene[62]. Findings on DS may demonstrate that underlying genetic aetiologies lead to more severe risk for ID and ASD, as further discussed below.

Underlying Aetiology. Previous studies within the ASD population have found that syndromic ASD (i.e., associated with underlying neural/genetic abnormalities) had a higher epilepsy risk than idiopathic ASD (i.e., no known cause)[60]. For instance, Pavone and colleagues found that epilepsy was seen in in 55% of patients with syndromic ASD, compared to only 7.4% of individuals with idiopathic ASD[63]. Similarly, most studies reviewed demonstrate that individuals with secondary epilepsy (i.e., due to underlying neural/genetic condition) have a higher risk for ASD than individuals with idiopathic epilepsy (i.e., no known cause). These findings are aligned with theories that one abnormal neural dysfunction may make the brain more susceptible to other neurological disorders [21]. This supports the hypothesis that epilepsy, ID and ASD may all be the result of a mutual underlying neurological condition. Further research is needed to understand which underlying biological mechanisms or abnormalities can simultaneously raise risk for these disorders and how these processes occur.

Family History. Family history of ASD has been consistently reported as a risk factor for ASD development in the general population [64], but was not reported in any study as a risk factor in the current review. This implies that the underlying cause or development of ASD within the epilepsy population may differ from that in the general population, potentially due to the presence of detrimental seizures or underlying genetic or neural abnormalities. Further, some studies have found that a family history of ASD or epilepsy has been linked to a greater risk for the other disorder [65]. In a study of ASD, multiplex families (i.e., more than one family member with ASD) had a 12.8% epilepsy prevalence relative to 2.4% seen

in simplex families (i.e., only one family member with ASD)[8]. In addition, unaffected siblings from multiplex families had a 2.3% epilepsy prevalence, a rate nearly double that in the general population [65]. Similarly, Sundelin and colleagues found that siblings and offspring of individuals with epilepsy were also at substantially elevated risk for ASD[40]. This supports the theory that there may be a common underlying genetic cause, and brings forth an interesting question of whether there is some heritable underpinning that predisposes individuals to either condition, and accounts for the high comorbidity seen between conditions. Further research is needed to explore this idea in order to provide novel insight into the inheritance patterns, and potential overlap, of these disorders.

Directionality. Only a few studies reviewed explicitly addressed the matter of directionality. Matsuo et al. and Berg et al. found epilepsy to precede ASD in 36.7% (vs. 25.3% with ASD first) and 85.7% (vs. 14.3% with ASD first) of cases, respectively [36,38]. In both these studies, epilepsy diagnosis more often preceded ASD diagnosis then vice versa. ASD was more often Matsuo and colleagues compared the populations and found less impaired ID, younger age of epilepsy onset, and older age of ASD diagnosis in individuals initially diagnosed with epilepsy over those initially diagnosed with ASD. This implies that the presentation of the epilepsy-ASD comorbidity may be different depending on which condition develops first. A recent nationwide study by Su et al. (2016) [31] found that epilepsy was present in 13.7% of individuals with primary ASD (i.e. diagnosed with ASD prior to epilepsy) and ASD was present in 3.4% of individuals with primary epilepsy (i.e. diagnosed with epilepsy prior to ASD). This implies that different co-occurrence rates occur depending on which diagnosis presents first. However, it is important to note that ASD symptoms may be present within these populations before they can be formally diagnosed at around 3 to 5 years old[54] or epilepsy may have been present earlier but have gone unrecognized. Therefore, exact directionality is difficult to determine based on presenting symptoms and formal diagnosis. This study does, however, demonstrate that the presence of either condition significantly increases risk for the other disorder, an effect which was augmented with the presence of ID. Further research is required explicitly addressing the directionality of this relationship in order to determine the possible role of epilepsy in the development of ASD, or vice versa.

Limitations

One main limitation within the current review is that the vast heterogeneity in the sample size, population characteristics, and methodology of all the studies made these samples difficult to compare. For example, individual studies varied in their definitions of ASD and epilepsy, classification of seizure types and epilepsy syndromes, and the reliability of ASD assessment tools used. Further, this review found risk factors for bias to greatly vary between studies, thus implying that each study may vary in how it represents the population as a whole. Overall, it is suggested that future research use standardized definitions and classifications of disorders and validated ASD diagnostic tools in order to provide more reliable information which can be easily compared across studies.

Clinical Implications

By providing information on the prevalence and risk factors for ASD within epilepsy, this review intended to better define the clinical characteristics of a patient at-risk for ASD development. These steps are necessary to allow clinicians to predict future co-occurrence and possibly lead to earlier screening and diagnosis, which is a fundamental step in producing positive developmental outcomes within ASD [66]. Further, presence of ID and ASD within this population may help to decide the level of care and support provided to individuals and families. Previous research has found that children with epilepsy and comorbid ID have over double the average number of care needs relative to children with epilepsy without ID. These children with epilepsy and ID had increased presence of medical conditions (e.g., acquired brain injury, visual impairments, congenital brain, heart and other anomalies, constipation, disordered sleep, microcephaly, gastro-oesophageal reflux, recurrent chest infection), language, behavioural and emotional disorders, as well as increased rates of family, school, housing and child protection issues, relative to those without ID.[67] Thus, health care professionals working with individuals with epilepsy must be well trained and capable of identifying ID and ASD within this population, in order to provide early intervention and appropriate care.

A better understanding of the presentation and underlying factors of co-morbid epilepsy-ASD may also help clinicians and families to develop targeted therapies for individuals with these co-morbid

conditions. At present, the specific role of epilepsy in ASD is unclear, however, due to the high comorbidity between these disorders, the potential contributing role of epilepsy should not be overlooked. Numerous studies have indeed reported regression within ASD to be associated with an increase in epileptic activity [68,69]. Thus, care and interventions within this population need to actively integrate identification and treatment of epilepsy and ASD, and monitor potential bidirectional impacts.

Conclusion

This review found an overall pooled prevalence of 6.3% for ASD within epilepsy. Higher prevalence was found for studies with younger age, greater inclusion of ID, and specific epilepsy syndromes (IS and DS). The reviewed studies also highlighted gender, symptomatic epilepsy, age at epilepsy onset, and underlying brain abnormalities as risk factors for ASD development. This information may be used to form a clinical profile of an epilepsy patient at-risk for ASD, which may allow for earlier diagnosis and intervention. Much further research is needed to define the relationship and directionality between epilepsy and ASD in order to determine whether underlying commonalities, causative impacts of seizures, or both factors contribute to the increased prevalence of ASD seen in individuals with epilepsy.

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Study	Prevalence		Article Information		Demographics					
	Percentage	Odds/Hazard Ratio	Direction	Study Type	Population	Sample Size w/ epilepsy	Male	Age at testing mean (range/SD)	Inclusion of ID/DD (>50%)	Method of ASD Diagnosis
Su, Chi, Lin & Yang (2016)	2.4%	8.4	Epilepsy	Cohort (medical records)	Childhood epilepsy	3755	57%	8.2 (± 5.5)	N (4.2% ID)	Medical Records
Reilly et al., (2015)	21%		Unknown	Cross-sectional (psychological assessment)	Childhood epilepsy	85	51.8%	10.7 (5.1-15.8)	N (40% ID)	Medical records & Screening (ASSQ)
Eom, Fisher, Dezort & Berg (2014)	Early measures: 54% Formal Diagnosis: 6.4%		Unknown	Cross-sectional (parent questionnaires)	Childhood epilepsy	236	57.6%	6.7(±4.6)	Y (82% DD)	Screening (ASQ, mCHAT, SCQ, SDQ)
Fisher, Dezort, Nordli, & Berg (2012)	37%		Unknown	Cross-sectional (parent questionnaires)	Childhood epilepsy	65	58%	2.5 (2m -5y)	Y (72% DD)	Screening (ASQ, mCHAT, SCQ, SDQ)
Berg, Plioplys & Tuchman (2011)	5%		Both (ASD first = 14.3%, Epilepsy first = 85.7%)	Cohort - 5&9 years (parent questionnaires, school reports, and medical records)	Childhood epilepsy	555	51.7%	19.9 (6-33)	N (25% ID)	Parent Report and Medical Records
Russ, Larson & Halfon (2011)	16%		Unknown	Cross-sectional (telephone survey)	Childhood epilepsy	977	52.0%	X (0-17)	Y (51% DD)	Parent report
Matsuo, Maeda, Sasaki, Ishii, & Hamasaki (2010)	15.2%		Both (ASD first = 25.3%, epilepsy first =36.7%, unknown = 38.0%)	Cross-sectional (psychological assessment)	Childhood epilepsy	519	74.7%	X (1-18)	Y (67.7% ID)	Screening (PARS)
Clarke et al. (2005)	32%		Unknown	Cross-sectional (parent questionnaires)	Childhood epilepsy	97	53%	12.7 (±4.1)		Screening (ASQ)
Sundelin et al. (2016)	1.6%	10.5	Epilepsy	Cross sectional (nationwide medical records)	Lifetime epilepsy	85,201	53%	X (0-60+)		Medical Records
Selassie et al. (2014)	Full sample =1.3% Under 18 = 4.3%	22.2	Unknown	Cross-sectional (hospital records)	Lifetime epilepsy	64,188	48.7%	41.6 (±22.5)	N (7.3% ID)	Hospital Records
Rai et al. (2012)	8.1%	6.2	Unknown	Cross-sectional (mail survey)	Lifetime epilepsy	94	47.9%	X (16+)		1) Self-report/screening 2) Diagnostic (ADOS)
Matsuo et al. (2011)	42%		Unknown	Cross-sectional (psychological assessment)	Complex Partial Seizures	86		X (1-9)	N (39.5% ID)	Screening (PARS)
Berkvens et al. (2015)	61.5%		Epilepsy	Cross-sectional (medical records)	Dravet Syndrome	13	69.2%	34.7 (18-60)	Y (100% ID)	Screening (AVZ-R, SGZ and TVZ)
Li et al. (2011)	24.3%		Epilepsy	Cohort- 2-6years (clinical records)	Dravet Syndrome	37	73%	9.3 (±3.6)	Y (94.6% ID)	1) Screening (ABC) 2) Diagnostic (CARS)
Rosander & Hallbrook (2015)	60%		Epilepsy	Cross-sectional (parent questionnaires)	Dravet Syndrome	30		7.0 (1-17)	Y (67% ID)	Play observation and parent interviews
Bitton et al. (2015)	22.7%		Epilepsy	Cohort- 2.5 - 5 years (clinical Assessment)	Infantile Spasms	44	68.2%	(approx. 30-60 months)		1)Screening (CHAT) 2) Diagnostic (ADOS -G)
Dilber et al. (2013)	23.3%		Epilepsy	Cross-sectional (neuroimaging study)	Infantile Spasms	90	57.8%	7.8 (3 - 16)		1)Screening (ABC) 2) Diagnostic (CARS)
Saemundsen, Ludvigsson & Rafnsson (2007a)	35.3%		Epilepsy	Cross-sectional(hospital records and psychological assessment)	Infantile Spasms	17	58.8%	11.6 (±4.5)	Y (65% ID)	1) Screening (SCQ) 2) Diagnostic (ADI-R/ADOS/ CARS)
Saemundsen, Ludvigsson, Hilmarsdottir, & Rafnsson (2007b)	7.1%		Epilepsy	Cross-sectional (hospital records and psychological assessment)	Unprovoked seizures (not infantile spasms) in first year of life	84	33.3%	11.1 (±6.1)	N (14.3% ID)	1) Screening (SCQ) 2) Diagnostic (ADI-R/ADOS/ CARS)

ASD = Autism Spectrum Disorder, DD = developmental disability, ID = Intellectual Disability, SD = Standard Deviation, Y= Yes, N= No

ABC = Autism Behavioral Checklist, ADI-R= Autism Diagnostic Interview-Revised , ADOS (G) = Autism Diagnostic Observational Schedule (generic), ASQ = Ages and Stages Questionnaire, ASSQ = autism spectrum screening questionnaire, AVZ-R = Pervasive Developmental Disorder in Mental Retardation scale - Revised, CARS = Childhood Autism Rating Scale, (m)CHAT = (modified) Checklist for Autism in Toddlers, PARS = Pervasive Developmental Disorder - Autism Society Japan Rating Scale, SCQ = Social Communication Questionnaire, SDQ = Strengths and Difficulties Questionnaire, SGZ = Maladaptive Behaviour Scale for individuals with ID, TVZ = Temperament scale for individuals with ID

Table 2. Critical Appraisal

Study	Risk Factors for Bias				
	Participation	**Study Attrition**	**ASD measure**	**Study Confound**	**Overall**
Su, Chi, Lin & Yang (2016)	Low	Low	Moderate	Low	1/4
Reilly et al. (2015)	Low	Moderate	Moderate	Low	2/4
Reilly et al. (2014)	Low	Moderate	Moderate	Low	2/4
Eom, Fisher, Dezort & Berg (2014)	Low	Moderate	High	Moderate	3/4
Fisher, Dezort, Nordli, & Berg (2012)	Moderate	Low	High	Moderate	3/4
Berg, Plioplys & Tuchman (2011)	Low	Moderate	Moderate	Low	2/4
Russ, Larson & Halfon (2011)	Low	Low	High	High	2/4
Matsuo, Maeda, Sasaki, Ishii, & Hamasaki (2010)	Moderate	Low	High	Low	2/4
Clarke et al. (2005)	Low	High	High	Moderate	3/4
Sundelin et al. (2016)	Low	Low	Moderate	Moderate	2/4
Selassie et al. (2014)	Low	Low	Moderate	High	2/4
Rai et al. (2012)	Low	Moderate	Low	Moderate	2/4
Matsuo et al. (2011)	Moderate	Low	High	Low	2/4
Berkvens et al. (2015)	Moderate	Low	High	Moderate	3/4
Li et al. (2011)	Low	Moderate	Low	Low	1/4
Rosander & Hallbrook (2015)	Low	Moderate	High	High	3/4
Bitton et al. (2015)	Low	Moderate	Low	Low	1/4
Dilber et al. (2013)	High	Low	Low	High	2/4
Saemundsen, Ludvigsson & Rafnsson (2007a)	Low	Moderate	Low	Low	1/4
Saemundsen, Ludvigsson, Hilmarsdottir, & Rafnsson (2007b)	Low	Moderate	Low	Low	1/4

ASD = Autism Spectrum Disorder
Overall = number of moderate and high risk factors/total risk factors

Table 3. Pooled prevalence Statistics for ASD based on age, epilepsy type, inclusion of Intellectual Disability, and number of risk factors

	Number of studies	Pooled estimates of ASD (CI)	I^2	Q (df)	p-value
Overall	19	6.3 (5.4-7.1)	96.9%	572.8 (18)	p < .001
Age					
Age < 18	14	22.4 (16.3- 28.5)	96.8%	411.9(13)	p < .001
Age > 18	5	1.7 (1.3- 2.2)	94.0%	66.9(4)	p < .001
Epilepsy Type					
General	11	4.7(4.0 – 5.6)	97.5%	394.49(10)	p < .001
IS	4	19.9 (8.0-31.7)	80.8%	15.6(3)	p < .01
Complex Partial Seizures	1	41.9 (31.4-52.3)	N/A	N/A	N/A
Dravet Syndrome	3	47.4 (20.7-74.3)	83.9%	12.4(2)	p < .01
Inclusion of ID					
Under 50%	6	5.2(3.2-7.1)	95.7%	117.0(5)	p < .001
Over 50%	8	25.4 (18.1 – 32.9)	91.8%	85.3(7)	p < .001
Unspecified	5	16.9 (5.3 – 28.4)	95.1%	81.2(4)	p < .001
Risk Factors for Bias*					
1/4	5	14.5 (5.4-23.6)	87.0%	30.7(4)	p < .001
2/4	9	5.4 (4.5-6.3)	97.9%	377.3(8)	p < .001
3/4	5	37.7 (16.2-59.2)	95.6%	89.9(4)	p < .001
4/4	0	N/A	N/A	N/A	N/A

ASD = Autism Spectrum Disorder, ID = Intellectual Disability, IS = Infantile Spasms, df = degrees of freedom, CI = confidence interval

Inclusion of ID = studies which report under/over 50%

*Risk of bias as determined by modified QUIPS tool (see Table 2)

Table 4. Risk Factors for ASD within studies

Study	Gender	Age at Onset	Aetiology	Cognitive/ Intellectual Impairment/Developmental Delay (% with ASD)	Type of Epilepsy	Neural Abnormalities	Family History of ASD	Seizure Frequency	Number of AEDs	Other Risk Factors/Comorbidities
Su, Chi, Lin & Yang (2016)	Y (F>M)	N		Y						
Eom, Fisher, Dezort & Berg (2014)				Y						
(Reilly et al., 2015)				Y (61.1%)						
(Reilly et al., 2014)			Y (idiopathic)	Y (61.1%)	Y (generalized seizures)					Duration of epilepsy (>8 years)
Fisher, Dezort, Nordli, & Berg (2012)				Y (65%)						
Berg, Plioplys & Tuchman (2011)	Y (M>F)*	Y	Y (symptomatic)	Y (13.8%)	Y (West Syndrome)					
Russ, Larson & Halfon (2011)										
Matsuo, Maeda, Sasaki, Ishii, & Hamasaki (2010)	Y(M>F)*				Y (CPS)					
Clarke et al. (2005)	Y (M>F) *	Y			N			N	Higher number of AEDs	
Sundelin et al. (2016)	Y(F>M)	Y								Parental Epilepsy
Rai et al. (2012)										
Selassie et al. (2014)										
Matsuo et al. (2011)	Y (M>F)	Y*	N/A (symptomatic epilepsy excluded from study)	Y	N/A	Epileptiform discharges localized in frontal area		Y	Multiple AEDs*	Seizure recurrence (within 2 years)
Berkvens et al. (2015)					N/A					
Li et al. (2011)	N	N		Y	N/A	N	N		Lower number of AEDs (≥3)	
Rosander & Hallbrook (2015)					N/A					
Bitton et al. (2015)	Y (M>F) *		Y (symptomatic)	Y	N/A	Epileptic discharges in frontal and temporal lobes				Non-white origin, persistent epileptiform abnormalities
Dilber et al. (2013)	N		Y (symptomatic)	Y	N/A	Decreased temporal, parietal and frontal lobe metabolic activity on PET	-			
Saemundsen, Ludvigsson & Rafnsson (2007a)			Y (symptomatic)*	Y	N/A					
Saemundsen, Ludvigsson, Hilmarsdottir, & Rafnsson (2007b)				Y	N/A					Abnormal EEG findings*

*= trend which did not reach significance, Y = Yes, N= No, N/A = Not Applicable (due to only studying one type of epilepsy), M = male, F = female, ASD = Autism Spectrum Disorder, ID = Intellectual Disability, CPS = complex partial seizures, AEDs = Anti-Epileptic Drugs, PET =positron emission tomography, EEG= electroencephalogram

Figure 1. Flowchart illustrating the article selection process

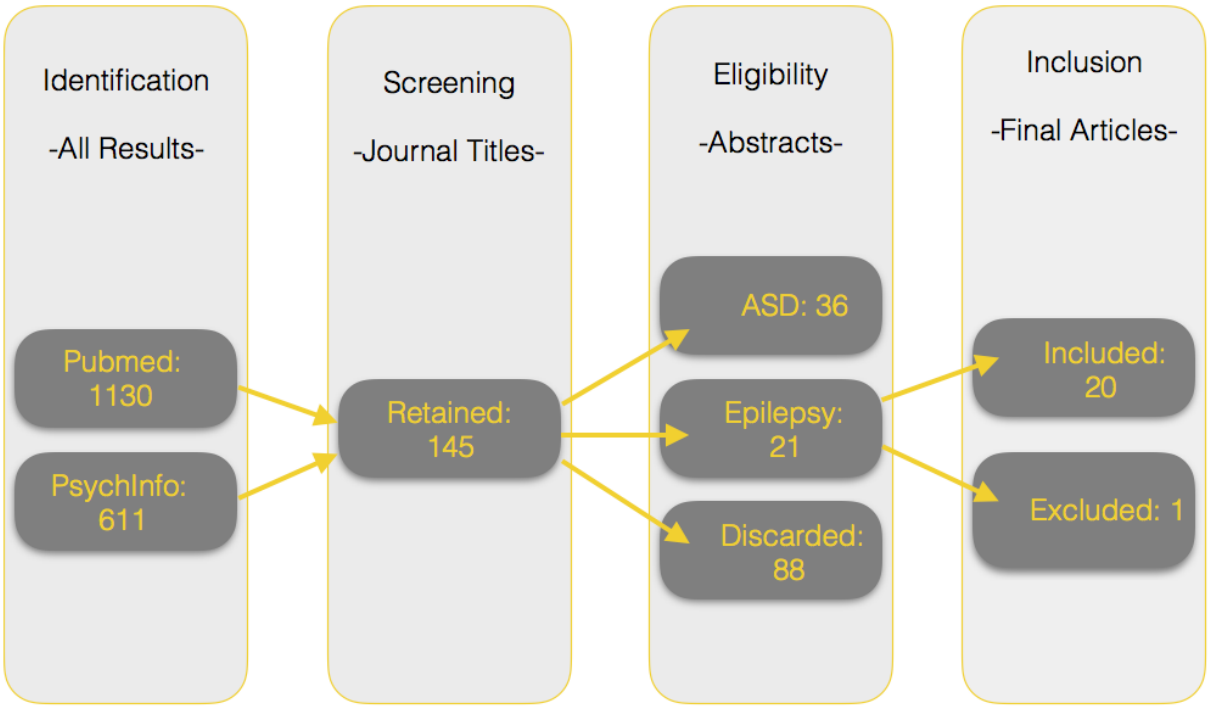
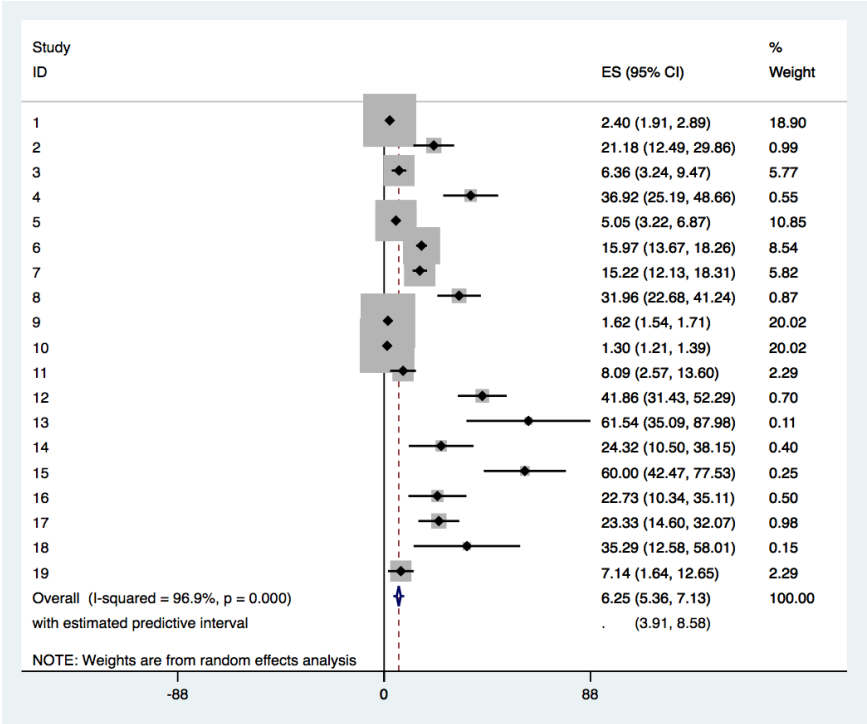


Figure 2. Random Effect Meta-Analysis of ASD Prevalence Data



*Study ID = study number, ES = reported ASD prevalence in given study
Weights are assigned to studies based on the relative sample sizes of each study relative to the total population of all studies