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Review

The co-occurrence of epilepsy and autism: A systematic review

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ABSTRACT

Objective: We aimed to review the literature to determine the incidence and prevalence of autism in epilepsy and epilepsy in autism, conditions that are often comorbid.
Methods: We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards, and the protocol was registered with PROSPERO. MEDLINE, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews were searched from inception until July 4, 2016. Studies were included if they reported an incidence or prevalence of autism in epilepsy or epilepsy in autism. These estimates were described using mean, standard deviation, median, and interquartile range.
Results: Seventy-four studies reporting on 283,549 patients were included. The median overall period prevalence of epilepsy in people with autism was 12.1% while the median overall period prevalence of autism in people with epilepsy was 9.0% when including all population types. When excluding studies that investigated patients with syndromic epilepsy or developmental delay, the median overall period prevalence of epilepsy in people with autism was 11.2% while the median overall period prevalence of autism in people with epilepsy was 8.1%. We observed trends for sex as the prevalence of autism in epilepsy was higher in males while the prevalence of epilepsy in autism was higher in females. It is important to interpret these estimates with caution, as there was significant heterogeneity between studies. Meta-regression found no association between study quality and prevalence or incidence estimates (all p-values > 0.05).
Conclusions: The period prevalence of epilepsy in people with autism, and vice versa, was consistently higher than previously reported estimates of the occurrence of these disorders in the general population. These findings highlight the importance of screening for autism in people who have epilepsy and epilepsy in people who have autism and may help shed light on shared pathogenesis between these conditions.

1. Introduction

Epilepsy and autism often co-occur. This co-occurrence is likely due to underlying components that influence both disease processes. In autism spectrum disorder (ASD), a great amount of etiological heterogeneity has been identified, many of which are also associated with epilepsy [1]. Factors such as genetic and chromosomal abnormalities [2], metabolic conditions [3], environmental factors, e.g., maternal rubella during pregnancy [4], and brain damage via neonatal jaundice [5], are examples that have been recognized as predisposing to both epilepsy and autism.

In 2010, the prevalence of ASD in the general population was estimated at 0.76% and responsible for 7.7 million disability adjusted life years (DALYs) across the globe [6]. Similarly, the active prevalence of epilepsy in the general population is 0.6% [7], and it was the fourth most burdensome (DALY) neurological disorder worldwide in 2015 [8].

Determining the bidirectional prevalence of autism and epilepsy is important to inform interventions and allocation of resources. Further, understanding these comorbidities will have a profound effect on the management of these challenging patient populations. For example, it has been found that autistic symptoms can be minimized when epilepsy is treated in patients with both conditions [9]. While there are two systematic reviews that have examined the prevalence of epilepsy in persons with autism [10,11], neither examined the epidemiology of autism in epilepsy. In addition, one of the systematic reviews only looked at the relationship between autism and epilepsy in terms of intellectual disability and sex [10]. Therefore, we aimed to systematically

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Table 1
Population-based studies reporting on the prevalence and incidence of epilepsy and autism.

1a. Prevalence and/or incidence of epilepsy in patients with autism

Author, date (country)	Population studied (autism type)	Sample size	Age range studied (years)	Diagnostic criteria or admin codes epilepsy	Diagnostic criteria or admin codes autism	Years of data collection	Groups studied and prevalence/incidence estimate (per 100)	Overall quality score
Danielsson, 2005 (Sweden)	Autistic disorder	92	17–40	NR	DSM-III-R	1980–2001	Pr overall: 43.0	5/8
Kielinen, 2004 (Finland)	Autistic disorder	187	NR	ILAE	DSM-IV	1996–1997	Pr overall: 14.4	6/7
Takano, 2014 (Japan)	Autistic disorder	247	1–17	ILAE	DSM-IV	2002–2012	Pr overall: 14.6	3/6
Croen, 2015 (USA)	ASD	1507	18–29	ICD-9	ICD-9-CM	2008–2012	Pr overall: 11.9	5/7
Jokiranta, 2014 (Finland)	ASD	4705	Children (age NR)	ICD-9; ICD-10	ICD-9; ICD-10	NR	Pr overall: 6.63	6/7
Kantzer, 2013 (Sweden)	ASD	125	1.6–4.1	NR	DSM-IV-TR	NR	Pr overall: 6.4	4/8
Levy, 2010 (USA)	ASD	2568	8	NR	DSM-IV-TR; ICD (version NR)	2002–2002	Pr overall: 2.4	4/7
Su, 2016 (Taiwan)	ASD	4221	0–18	ICD-9	ICD-9-CM	1997–2008	IR overall: 1.4	6/7
Suren, 2008 (Norway)	ASD	2352	0–11	ICD-10	DSM-IV; ICD-10	2008–2010	Pr overall: 11.2	6/7
Saemundsen, 2013 (Iceland)	ASD	267	NR	NR	DSM-IV; ICD-10		Pr overall: 7.1	6/7
Schendel, 2016 (Denmark)	ASD	20,492		ICD-10	ICD-8; ICD-10	1980–2010	Pr overall: 6.3	6/7
Viscidi, 2013 (USA)	ASD	NSCH: 918 Genetic collaborative sample: 4509	2–17	NR	NR	NR	Based on NSCH: Pr overall: 9.6 Genetic collaborative sample: Pr overall: 4.5	6/7
Barak, 1999 (Israel)	Autism	290	10–34	NR	DSM-III	1960–1989	Pr overall: 41.0	4/7
Chen, 2009 (Taiwan)	Autism	3440	NR	ICD-9-CM	ICD-9-CM	1997–2009	Pr overall: 13.6	6/7
Cederlund, 2004 (Sweden)	Asperger's syndrome	100	NR	NR	ICD-10; DSM-IV	1985–1999	Pr overall: 4.0	6/8
Mourisden, 2013 (Denmark)	Asperger's syndrome	4180	4–31	ICD-10	ICD-10	1994–2011	Pr overall: 3.9	6/7
Mouridsen, 2011 (Denmark)	Infantile autism	118	2–15	ICD-8; ICD-10	ICD-8; ICD-10	1960–1984	Pr overall: 24.6	6/7
Mouridsen, 2011 (Denmark)	Syndromic atypical autism	89	3–17	ICD-8; ICD-10	ICD-8; ICD-10	1960–1984	Pr overall: 22.5	6/7
Delobel, 2013 (France)	Atypical autism Infantile autism Asperger's syndrome	Haute-Garonne: 192 Isère: 167	8	NR	ICD-10	1995–2002	Pr overall Haute-Garonne: 10.4 Pr overall Isère: 8.38	4/6
Nordin, 1996 (Sweden)	Autistic disorder ASD-not otherwise specified	24	5–19	NR	DSM-III-R	1991–1993	Pr overall: 33.3	6/7
Jacobson, 1983 (USA)	Autism in people with developmental disabilities	1268	0–45 +	NR	NR	1978–1982	Pr overall: 12.2	4/8
Saemundsen, 2010 (Iceland)	Autism in people with intellectual disabilities	25	19–63	NR	ICD-10	NR	Pr lifetime epilepsy overall: 60.0	4/8

1b. Prevalence and/or incidence of autism in patients with epilepsy

Author, date (country, region)	Population studied (autism type in patients with epilepsy)	Sample size	Age range studied (years)	Diagnostic criteria or admin codes epilepsy	Diagnostic criteria or admin codes autism	Years of data collection	Groups studied and prevalence/incidence estimate (per 100)	Overall quality score
Andell, 2015 (Sweden)	ASD	766	0–18	ILAE	ICD-10	2001–2006	Pr overall: 6.1	5/7
Berg, 2011 (USA)	ASD	555	6–33	ILAE	DSM-IV	1993–1997	Pr overall: 5.0	8/8
Rai, 2012 (UK)	ASD	94	≥16	NR	DSM-IV	NR	Pr (weighted) overall: 8.1	4/8
Reilly, 2014 (UK)	ASD	85	Children (age NR)	ILAE	DSM-IV-TR	2011–2012	Pr overall (active epilepsy): 21	5/8
Selassie, 2014 (USA)	ASD	64,188	41.6 ± 22.5 (mean, SD)	ICD-9-CM	ICD-9-CM	2000–2011	Pr overall: 1.3	7/7
Sundelin, 2016 (Sweden)	ASD	85,201	NR	ICD-7; ICD-8; ICD-9; ICD-10	ICD-9; ICD-10	1987–2009	IP during study follow-up period: IP overall: 1.6	6/7
Su, 2016 (Taiwan)	ASD	26,713	0–18	ICD-9	ICD-9-CM	1997–2008	IR overall: 0.34	6/7
Suren, 2008	ASD	4298	0–11	ICD-10	DSM-IV; ICD-10	2008–2010	Pr overall: 6.1	6/7

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Table 1 (*continued*)

1b. Prevalence and/or incidence of autism in patients with epilepsy

Author, date (country, region)	Population studied (autism type in patients with epilepsy)	Sample size	Age range studied (years)	Diagnostic criteria or admin codes epilepsy	Diagnostic criteria or admin codes autism	Years of data collection	Groups studied and prevalence/incidence estimate (per 100)	Overall quality score
(Norway)								
Russ, 2012 (USA)	Autism/ASD	Current epilepsy/seizure disorder: 526 Former epilepsy/seizure disorder: 451	0–17	NR	NR	(2007 NSCH)	Pr in current epilepsy/seizure disorder: 12.4 Pr in former epilepsy/seizure disorder: 5.5	6/8
Rosander, 2015 (Sweden)	Patients with Dravet syndrome ASD	30	0–17	ICD-10	NR	2007–2011	Pt overall: 60	5/7
Day, 2005 (USA)	Patients with developmental delay Autism	10,030	5–69	NR	NR	1988–2002	Pr overall (lifetime epilepsy): 4.5	4/7
Steffenburg, 1995 (Sweden)	Patients with mental retardation Autism	98	6–16.5	ILAE	DSM-III-R	NR	Pt overall (active epilepsy): 24.5	6/7
Forsgren, 1990 (Sweden)	Individuals with developmental delay Infantile autism	299	0–16	WHO, ICES	NR	NR	Pt overall (active epilepsy): 4.01	5/7
Jacobson, 1983 (USA)	Patients with developmental disabilities Autism	9099	0–45 +	NR	NR	1978–1982	Pr overall: 1.7	4/8

Estimate abbreviations: Pr: period prevalence, Pt: point prevalence, IR: incidence rate (per 100 person years), IP: incidence proportion.
Other abbreviations: ILAE: International League Against Epilepsy, ICD: International Classification of Diseases, DSM: Diagnostic and Statistical Manual of Mental Disorders, WHO: World Health Organization, ICES: International Classification of Epileptic Seizures, ASD: autism spectrum disorder, NSCH: National Survey of Children's Health, NR: not reported.

review the literature to determine the incidence and prevalence of autism in epilepsy and epilepsy in autism.

2. Methods

This study was registered with PROSPERO (ID: CRD42016039614). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were adhered to for this study [12].

2.1. Search strategy

PsycINFO, MEDLINE, Embase, and the Cochrane Database of Systematic Reviews were searched from inception until July 4, 2016. The search strategy included terms relating to epilepsy, autism, and epidemiology (Appendix e-1). We also hand searched included studies and relevant systematic reviews to identify any additional references that may have not been identified in our search.

2.2. Eligibility

Studies were included if they reported the incidence or prevalence of autism in epilepsy or epilepsy in autism. We did not place any restriction on age, type of epilepsy, or autism. We included all study designs except case series and studies with overall population size of less than 100 people. We excluded abstracts and review articles. No limits were placed on publication language, but we excluded non-English studies if they were not population-based and a native speaker was unavailable for translation (n = 1 study from Czechoslovakia; n = 2 studies from Japan).

2.3. Study selection

Title/abstract and full-text screening were independently conducted in duplicate by two reviewers. Reviewer disagreements were resolved through discussion with the principal investigator.

2.4. Data abstraction

Data were abstracted by one reviewer and confirmed by a second reviewer. The following variables were abstracted: study characteristics (e.g., country, years, study design), sample size, age, ascertainment (e.g., survey or registry), diagnostic methods (e.g., administrative codes or self-report), epilepsy and autism type, subgroups (e.g., if study stratified by sex, age), and prevalence/incidence data including confidence intervals (CI).

2.5. Quality assessment

Study quality was determined using a standard assessment tool developed for the evaluation of prevalence and incidence studies that has been used extensively to evaluate the quality of epidemiological (including incidence and/or prevalence) studies [13]. This eight-question tool appraises studies based on the following three domains: sampling, measurement, and analysis. Each question is worth one point, and if a question is not applicable, it is subtracted from the denominator. A higher score indicates a better study quality, but there is no established cutoff score recommended for designating high or low quality. The quality assessment was completed in duplicate, and any disagreement was resolved through discussion with the principal investigator.

2.6. Data synthesis and analysis

Prevalence estimates were categorized as follows: (1) period prevalence (defined as the number of cases during a period of time over the total population during the same time period, e.g., any existing cases during November 2016 to November 2017);, (2) point prevalence (defined as the number of cases at a specific point in time, e.g., January 12, 2017);, (3) incidence proportion (defined as the number of new cases during a specified time period over the total population at the start of the time period, e.g., new cases during November 2016 to November 2017);, and (4) incidence rate (defined as the number of new cases during a specified time period per person at risk in the population during the same time period, e.g., 6.0 per 100,000 person-years). Studies

Table 2
Nonpopulation-based studies reporting on the prevalence and incidence of epilepsy and autism.

2a. Prevalence and/or incidence of epilepsy in patients with autism

Author, date (country, region)	Population studied (autism type)	Sample size	Age range studied (years)	Diagnostic criteria or admin codes epilepsy	Diagnostic criteria or admin codes autism	Years of data collection	Groups studied and prevalence/incidence estimate (per 100)	Overall quality score
Giannotti, 2008 (Italy)	Autistic disorder	104	NR	ILAE	DSM-IV-TR	NR	Pr overall: 19.4	3/8
Kawasaki, 1989 (Japan)	Autistic disorder	158	2.6–28.8	NR	DSM-III-R	NR	IP overall during the study follow-up period: 39.24	2/6
Kobayashi, 1992 (Japan)	Autistic disorder	188	18–33	NR	DSM-III-R	NR	Pr overall: 19.1	3/8
Sharda, 2012 (India)	Autistic disorder	74	4–37	NR	DSM-IV	NR	Pr overall: 25.7	1/8
Zhang, 2011 (China)	Autistic disorder	170	NR	NR	DSM-IV-TR	?-2011	Pr overall: 3.5	3/8
Aldinger, 2015	ASD	3351	NR	NR	NR	NR	Pr overall: 6.5	2/6
Amiet, 2013	ASD	478	8.1 ± 4.7 (mean and SD)	NR	NR	2011-?	Pr overall: 12.8	2/7
Icasiano, 2004 (Australia)	ASD	177	2–17	NR	DSM-IV	NR	Pr overall: 6.2	3/8
Ko, 2016 (South Korea)	ASD	182	NR	ILAE	NR	2013–2015	Pr overall: 11.0	1/6
Kohane, 2012 (USA)	ASD	14,381	0–34	ICD-9	ICD-9	2001–2010	Pr overall: 19.4	5/6
Liu, 2006 (USA)	ASD	167	2.4–18.2	NR	NR	2004–2004	Pr overall: 11.0	3/8
Mahajnah, 2015 (Israel)	ASD	200	2.58–4.46	NR	DSM-IV	2008–2013	Pr overall: 7.5	2/6
Nomura, 2010 (Japan)	ASD	485	5–42	NR	NR	2008–2009	Pr overall: 50.3	2/6
Oslejskova, 2007 (Czech Republic)	ASD	205	5–15	NR	ICD-10	NR	Pr overall: 31.2	2/6
Viscidi, 2014 (USA)	ASD	2645	4–18	NR	DSM-IV-TR	NR	Pr overall: 2.2	4/6
Wong, 1993 (China)	ASD	246	4–15	ILAE	DSM-III	1987–1991	Pr overall: 5.7	2/6
Xue, 2008 (USA)	ASD	160	2–18	2 or more unprovoked seizures	DSM-IV	1999–2003	Pr overall: 13.8	4/8
van Eeghan, 2013 (USA)	Childhood onset epilepsy of unknown cause ASD	210	4–49	ILAE	DSM-IV	NR	Pr overall: 7.1	3/8
Cuccaro, 2011 (USA)	Autism/ASD	577	4–21	NR	DSM-IV	NR	Pr overall: 11.1	3/6
Fombonne, 1992 (France)	Autism	154	NR	ICD-9	French classification of child and adolescent psychiatric disorders	1975-?	Pr overall: 22.0	1/8
McDermott, 2005 (USA)	Autism	55		ICD-9	ICD-9	1990–2003	Pr of moderate epilepsy: 23.6 Pr of severe epilepsy: 1.8	4/6
Saltik, 2012 (Turkey)	Autism	121	3–18	NR	DSM-IV-TR	2010–2011	Pr overall: 19.8	5/8
Tuchman, 1991 (USA)	Autism	302	NR	The International Classification of Seizures	NR	1959–1988	Pr overall: 13.9	2/6
Yasuhara, 2010 (Japan)	Autism	1014	3–20	NR	DSM-IV	NR	IP overall over 3 years: 37.0	2/8
Hara, 2007 (Japan)	Autistic disorder Atypical autism	130	18–35	ILAE	DSM-IV	NR	IP overall over 3 years: 25.4	3/6
Baghdadli, 2003	Infantile autism	222	2–7	NR	ICD-10	1997–1999	Pr overall: 7.2	2/6

(continued on next page)

Table 2 (*continued*)

2a. Prevalence and/or incidence of epilepsy in patients with autism

Author, date (country, region)	Population studied (autism type)	Sample size	Age range studied (years)	Diagnostic criteria or admin codes epilepsy	Diagnostic criteria or admin codes autism	Years of data collection	Groups studied and prevalence/incidence estimate (per 100)	Overall quality score
(France)								
Tsai, 1981 (USA)	Infantile autism	102	3–20	NR	Kanner (1943) Rutter (1971, 1977)	1974–1979	Pr overall: 22.5	1/8
Volkmar, 1990 (USA)	Infantile autism	192	2–33	NR	DSM-III	NR	Pr overall: 21.4	2/6
Bolton, 2011 (UK)	Autism Asperger's syndrome	150	26–56	ILAE	ICD-10	1950–1985	Pr overall: 22.0	4/8
Williams, 2008 (England)	Childhood autism Atypical autism Asperger syndrome	86	NR	NR	ICD-10	NR	Pr overall: 10.3	4/6
Baghdadli, 2011 (France)	ASD in children with developmental disorders	152		ICD-10	ICD-10	1997–2009	Pr in 2000–2002: 6.6 Pr in 2007–2009: 17.1	3/8
Parmeggiani, 2002	Autistic disorder and macrocrania	21	3–28	NR	DSM-IV	NR	Pr overall: 47.6	1/8

2b. Prevalence and incidence of autism in patients with epilepsy

Author, date (country, region)	Population studied (autism type in patients with epilepsy)	Sample size	Age range studied (years)	Diagnostic criteria or admin codes epilepsy	Diagnostic criteria or admin codes autism	Years of data collection	Groups studied and prevalence/incidence estimate (per 100)	Overall quality score
Hancerli, 2011 (Turkey)	West syndrome Autistic disorder	90	0.42–15	ILAE	NR	1995–2007	Pr overall: 18.9	2/6
Hussin, 2011 (Egypt)	ASD	143	2–15	NR	NR	NR	Pr overall: 16.1	1/8
Matsuo, 2010 (Japan)	ASD	519	NR	NR	DSM-IV	2000–2008	Pr overall: 15.2	1/8
Ochoa-Gomez, 2016 (Spain)	ASD	605	1-NR	ILAE	NR	2008–2010	Pr overall: 9.9	4/6
van Eeghan, 2013 (USA)	Childhood onset epilepsy of unknown cause ASD	66	4–49	ILAE	DSM-IV	NR	Pr overall: 15.2	3/8
Matsuo, 2011 (Japan)	Focal impaired awareness seizures ASD	86	Infant and children (age NR)	NR	DSM-IV	2000–2008	Pr overall: 42	2/6
Li, 2011 (China)	Dravet syndrome ASD	37	Children (age NR)	ILAE	DSM-IV; ICD-10	1997–2008	Pr overall: 24.3	4/8
Henning, 2010 (Norway)	Autism	167	20–82	NR	NR	2006–2007	Pr overall: 0.6	3/8
Gelisse, 2001 (France)	Juvenile myoclonic epilepsy Autism	170	11.7–70	ILAE	DSM-IV	1981–1998	Pr overall: 0.6	3/8
Bandino, 2014 (USA)	Children, adolescent, and adults with developmentally disabilities ASD	264	5–21	NR	NR	2008–2010	Pr overall: 28.8	3/6

Estimate abbreviations: Pr: period prevalence, Pt: point prevalence, IR: incidence rate (per 100 person years), IP: incidence proportion.
Other abbreviations: ILAE: International League Against Epilepsy, ICD: International Classification of Diseases, DSM: Diagnostic and Statistical Manual of Mental Disorders, WHO: World Health Organization, ICES: International Classification of Epileptic Seizures, ASD: autism spectrum disorder.

were classified as population-based if representative of the general population (e.g., entire population surveyed or probability sampling used) and nonpopulation-based if not representative of the general population (e.g., hospital- or clinic-based studies). We stratified studies by age, sex, and epilepsy and autism types when feasible. Descriptive statistics [e.g., mean, standard deviation (SD), median, interquartile range (IQR)] were used to summarize prevalence and incidence estimates. Outliers were assessed using boxplots. Median overall period prevalence and incidence values were presented but pooled estimates were not presented because of between-study heterogeneity, inconsistent reporting of demographics- and disease-related characteristics, and variability in diagnostic criteria used. Pooled meta-analysis estimates were not presented since each group had too few papers.

Begg's and Egger's tests were used to assess publication bias [14]. These tests were conducted separately for study design (population-based and nonpopulation-based) as well as estimate type (autism in epilepsy and epilepsy in autism) for all estimates of overall period prevalence. Analyses were conducted using Excel and STATA/SE 14.1.

3. Results

3.1. Study selection and characteristics

The search identified 3857 unique abstracts, of which 193 were selected for full-text review and 60 were included (Fig. e-1). Fourteen additional studies were identified through hand searching and expert consultation, resulting in 74 included studies (Appendix e-2). The Kappa statistic between reviewers for study inclusion at the full-text stage was 0.82.

Characteristics of included population-based and nonpopulation-based studies are listed in Tables 1 and 2, respectively. Detailed versions of these tables with stratified estimates are also included (Supplemental Tables e-1 and e-2). Overall, 50 studies reported on

prevalence or incidence of epilepsy in autism; 20 reported on prevalence or incidence of autism in epilepsy; and four reported on both prevalence or incidence of epilepsy in autism and autism in epilepsy (Fig. e-1, Tables 1 and 2). The included studies were from United States of America (n = 19), Sweden (n = 9), Japan (n = 8), France (n = 5), Denmark (n = 4), United Kingdom (n = 4), China (n = 3), Finland (n = 2), Iceland (n = 2), Israel (n = 2), Norway (n = 2), Taiwan (n = 2), Turkey (n = 2), Egypt (n = 1), India (n = 1), Spain (n = 1), Italy (n = 1), Czech Republic (n = 1), South Korea (n = 1), Australia (n = 1), and unknown (n = 3) (Tables 1 and 2). The data collection period ranged from 1950 to 2016. There were 32 population-based (Table 1) and 42 nonpopulation-based studies (Table 2). Studies reported on various types of epilepsy (e.g., West syndrome, Dravet syndrome, juvenile myoclonic epilepsy, and focal impaired awareness seizures) and used various terms for autism (e.g., ASD, Asperger's syndrome, autistic disorder, infantile autism, and autism) (Tables 1 & 2). Although we planned a priori to stratify estimates by age, sex, study design, and epilepsy and autism type, we were only able to stratify estimates by study design and sex because of inconsistent reporting of the aforementioned variables between studies.

3.2. Epilepsy in autism

3.2.1. Prevalence

The median overall period prevalence of epilepsy in people with autism (n = 50 studies) was 12.1% (IQR: 15.4%) [range: 1.8–60%; mean (SD): 16.2% (13.0%)] (Table 3). Three estimates were identified as outliers. One study examined adults with autism and intellectual disability (60.0%) [15]; one was conducted in a tertiary care center (50.0%) [16]; and one examined adults with autistic disorder and macrocrania (47.6%) [17]. No studies reported point prevalence. Excluding studies that investigated patients with syndromic epilepsy or developmental delay such as West syndrome and Dravet syndrome, the median overall period prevalence of epilepsy in people with autism was 11.2% (IQR: 6.6%–21.7%) [range: 1.8%–50.3%; mean (SD): 15.4% (11.9%)].

3.2.2. Prevalence by population-based studies

The median period prevalence of epilepsy in autism (n = 20 studies) was 10.8% (IQR: 16.6%) [range: 2.5–60.0%; mean (SD): 16.3% (15.3%)] (Table 3).

3.2.3. Prevalence by nonpopulation-based studies

The median period prevalence of epilepsy in autism (n = 30 studies) was 13.8% (IQR: 14.7%) [range: 1.8–50.3%; mean (SD): 16.1% (11.4%)] (Table 3).

3.2.4. Prevalence by sex

The median period prevalence of epilepsy in females with any type of autism (n = 14 studies) was 19.0% (IQR: 21.2%) [range: 0–60.0%; mean (SD): 20.6% (15.0%)] (Table 3). The median period prevalence of epilepsy in males with any type of autism (n = 15 studies) was 11.4% (IQR: 13.6%) [range: 3.6–30.0%; mean (SD): 13.0% (8.5%)] (Table 3). There was generally a higher period prevalence of epilepsy in females with autism than in males with autism (Fig. 1, graph A). No studies reported sex-stratified point prevalence estimates.

3.2.5. Incidence

The median incidence proportion of epilepsy in people with autism (n = 3 studies) was 37.0% (IQR: 13.8%) [range: 25.4–39.2%; mean (SD): 33.9% (7.4%)] (Table 3) [18–20]. However, the follow-up period between studies varied or was not reported. The incidence rate of epilepsy in people with autism (n = 1 study in patients age 0–18 years old) was 14 per 1000 person-years (Table 3) [21].

3.2.6. Incidence by sex

The incidence rate of epilepsy in females and males with autism (n = 1 study) was 16 per 1000 person-years and 13 per 1000 person-years, respectively (Table 3) [21]. No studies reported sex-stratified incidence proportion estimates.

3.2.7. Trends by year

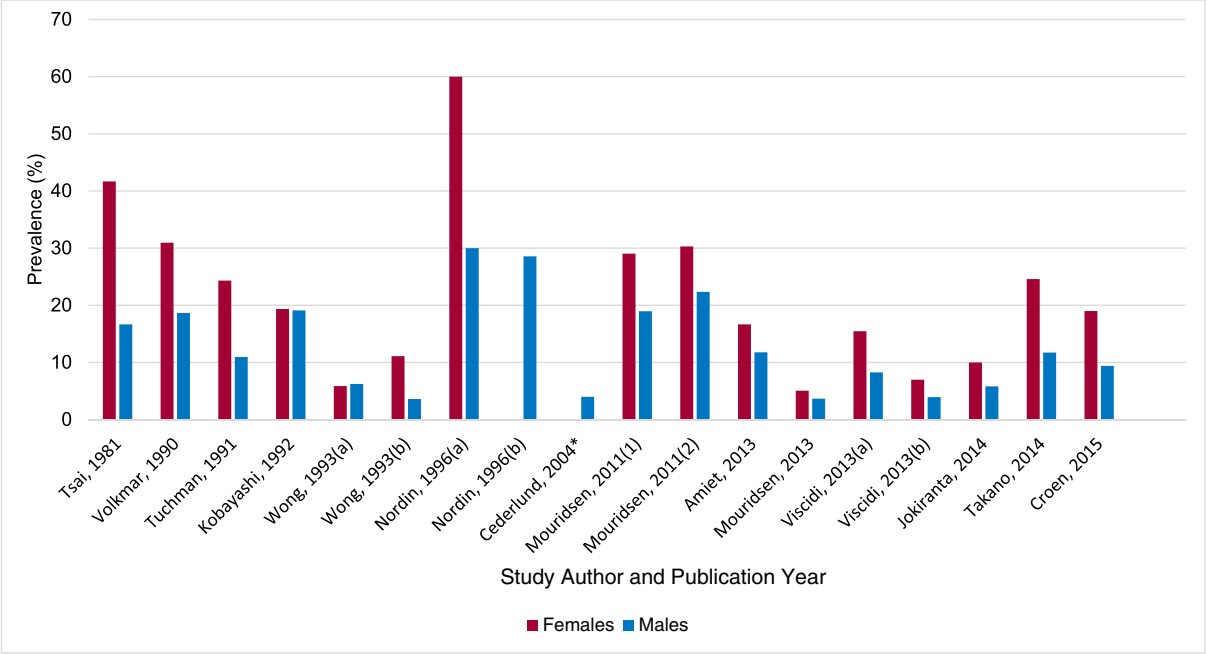
There were no trends observed for prevalence estimates by year of study publication (Fig. 2, graph A).

Table 3
Summary estimates of prevalence and incidence of epilepsy in people with autism.

Category	Study design (n)	Range (%) or estimate (%)	Median (IQR) (%)	Mean (SD) (%)
Prevalence				
Period prevalence	Overall (50)	1.8–60.0	12.1 (15.4)	16.2 (13.0)
	Pop (20)	2.5–60.0	10.8 (16.6)	16.3 (15.3)
	Nonpop (30)	1.8–50.3	13.8 (14.7)	16.1 (11.4)
Point prevalence	No studies	N/A	N/A	N/A
Period prevalence in females	Overall (14)	0.0–60.0	19.0 (21.2)	20.6 (15.0)
	Pop (7)	0.0–60.0	15.5 (23.6)	19.5 (18.4)
	Nonpop (7)	5.9–41.7	21.8 (22.5)	21.8 (11.3)
Period prevalence in males	Overall (15)	3.6–30.0	11.0 (14.1)	13.1 (8.7)
	Pop (8)	3.7–30.0	8.8 (19.9)	13.5 (10.5)
	Nonpop (7)	3.6–19.1	11.8 (12.4)	12.3 (5.6)
Incidence				
Incidence proportion	Overall (3)	25.4–39.2	37.0 (13.8)	33.9 (7.4)
	Pop (0)	N/A	N/A	N/A
	Nonpop (3)	25.4–39.2	37.0 (13.8)	33.9 (7.4)
Incidence rate	Overall (1)	14 per 1000 P-Y	N/A	N/A
	Pop (1)	14 per 1000 P-Y	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A
Incidence proportion in females	No studies	N/A	N/A	N/A
Incidence proportion in males	No studies	N/A	N/A	N/A
Incidence rate in females	Overall (1)	16 per 1000 P-Y	N/A	N/A
	Pop (1)	16 per 1000 P-Y	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A
Incidence rate in males	Overall (1)	13 per 1000 P-Y	N/A	N/A
	Pop (1)	13 per 1000 P-Y	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A

Abbreviations: pop: population-based studies, nonpop: nonpopulation-based studies, P-Y: person years.

Graph A: Prevalence of Epilepsy in People with Autism by Sex



(1) and (2) indicates two different studies published by the same author in the same year
(a) and (b) indicates multiple estimates reported in the same article
*Only reported on male participants

Graph B: Prevalence of Autism in People with Epilepsy by Sex

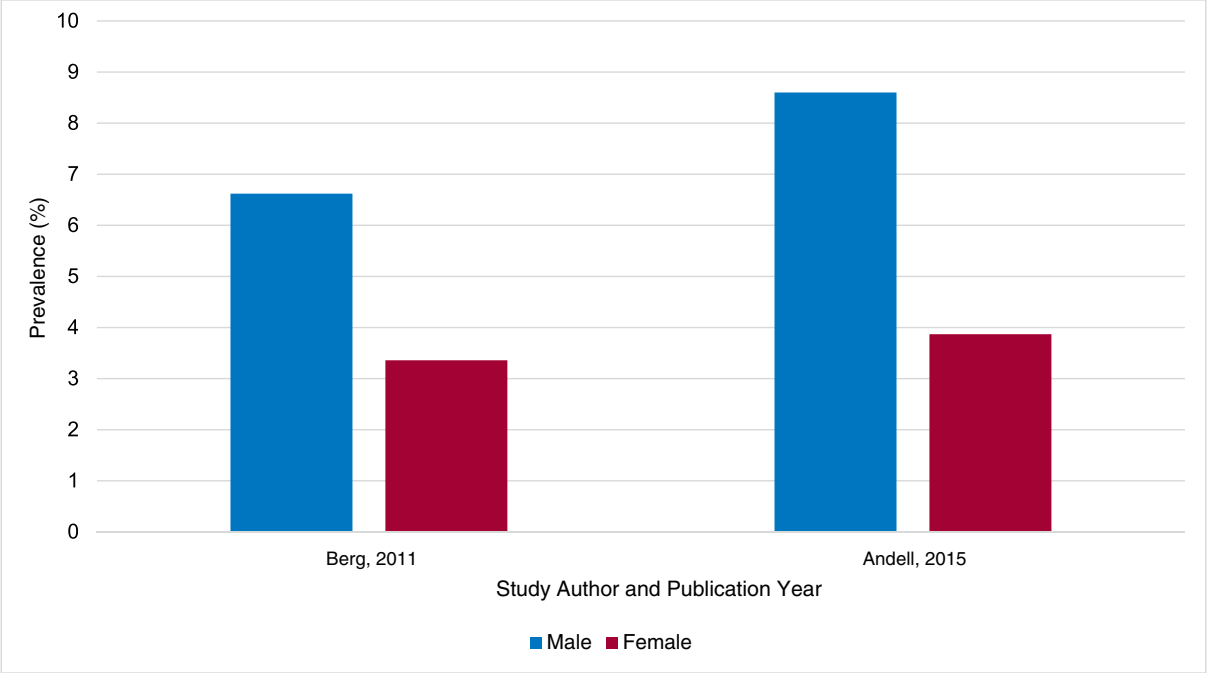


Fig. 1. Graph of trends by sex and by year of publication.

3.3. Autism in epilepsy

3.3.1. Prevalence

The median overall period prevalence of autism in people with epilepsy (n = 19 studies) was 9.0% (IQR: 12.7%) [range: 0.60–41.9%; mean (SD): 12.2% (10.8%)] (Table 4). One estimate from a study based on people with focal impaired awareness seizures was considered an outlier (41.9) [22]. However, approximately 45% of this sample had intellectual disability [22]. The median point prevalence (n = 3 studies) was 24.5% (IQR: 56.0%) [range: 4.0–60.0%; mean (SD): 29.5% (28.3%)] (Table 4) [23–25]. Since all studies reporting on point prevalence were population-based, these

estimates are not stratified further by study design. Excluding studies that investigated patients with syndromic epilepsy or developmental delay, the median overall period prevalence of autism in people with epilepsy was 8.1% (IQR: 5.0%–15.2%) [range: 0.6%–41.9%; mean (SD): 11.0% (10.5%)].

3.3.2. Prevalence by population-based studies

The median period prevalence of autism in epilepsy (n = 9 studies) was 5.8% (IQR: 3.6%) [range: 1.3–21.0%; mean (SD): 7.2% (5.8%)] (Table 4).

3.3.3. Prevalence by nonpopulation-based studies

The median period prevalence of autism in epilepsy (n = 10 studies) was 15.7% (IQR: 14.4%) [range: 0.6–41.9%; mean (SD): 17.1% (12.5%)] (Table 4).

3.3.4. Prevalence by sex

The mean period prevalence of autism in females with epilepsy (includes all types of autism) (n = 2 studies) was 3.6% (SD: 0.4%) [range: 3.4–3.9%] (Table 4) [26,27]. The mean period prevalence of autism in males with epilepsy (includes all types of autism) (n = 2 studies) was 7.6% (SD: 1.4%) [range: 6.6–8.6%] (Table 4) [26,27]. Males with epilepsy had higher period prevalence of autism compared to females with epilepsy (n = 2; Fig. 1, graph B) [26,27]. No studies reported on sex-stratified point prevalence (Tables 1, 2, and 4).

3.3.5. Incidence

The incidence proportion of autism in people with epilepsy (n = 1) was 1.6% (Table 4) [28]. The incidence rate of autism in people with epilepsy (n = 1) was 3.4 per 1000 person-years (Table 4) [21].

3.3.6. Incidence by sex

The incidence proportion of autism in females and males with epilepsy (n = 1 study) was 1.4% and 1.8%, respectively (Table 4) [28]. The incidence rate of autism in females and males with epilepsy (n = 1 study) was 2.9 per 1000 person-years and 3.8 per 1000 person-years, respectively (Table 4) [21].

3.3.7. Trends by year

There were no trends observed for prevalence estimates by year of study publication (Fig. 2, graph B).

3.4. Publication bias

There was statistical evidence of publication bias based on Begg's and Egger's test (all p-values < 0.05).

3.5. Study quality

The median study quality scores broken down by denominator were 2/6 (range: 1–5), 6/7 (range: 2–7), and 3/8 (range: 1–8) (Table e-3), with higher scores indicating higher quality. Meta-regression found no association between study quality and prevalence or incidence estimates (all p-values > 0.05).

4. Discussion

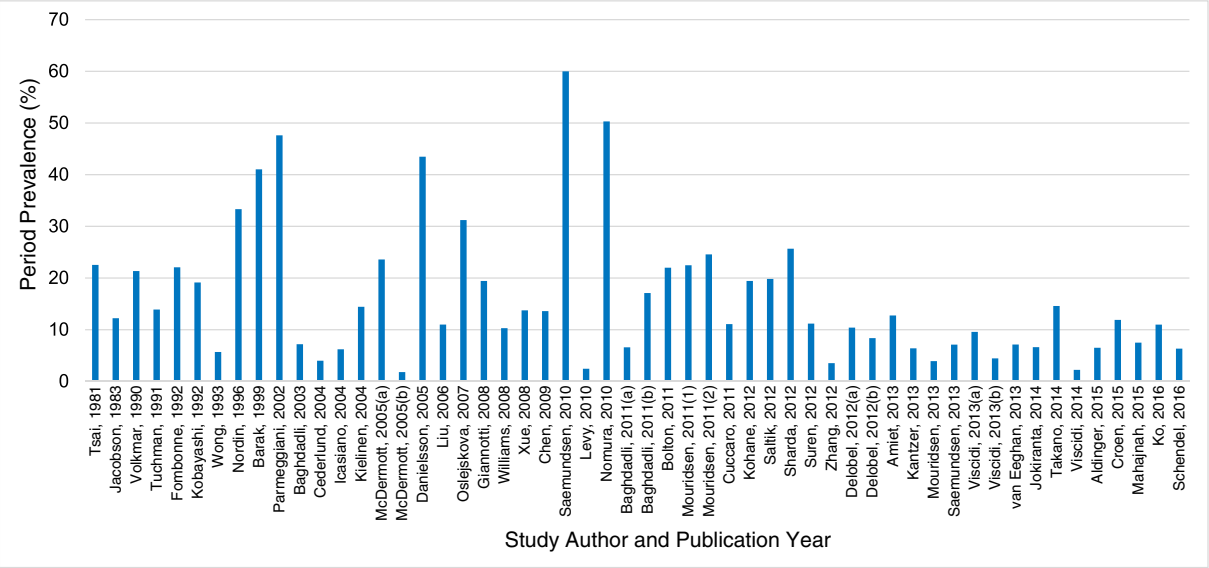
Out of the 74 eligible studies reporting on 283,549 patients identified in our study, the median period prevalence of epilepsy in autism was 12.1% while the prevalence of autism in epilepsy was 9%. The median period prevalence of epilepsy in people with autism and autism in people with epilepsy was found in this systematic review to be markedly higher than previously reported period prevalence of epilepsy or autism in the general population [6,7]. The first studies looking at the prevalence of autism conducted in the 1960s in Europe quoted an autism prevalence of around 4 cases per 10,000 children leading many to believe that autism was a rare childhood disorder [29]. Following an expansion of diagnostic criteria for autism occurring in the late 1980s, autism prevalence has increased globally. Recent studies from the Centers for Disease Control and Prevention (CDC) and Autism and Developmental Disabilities Monitoring (ADDM) Network quote the prevalence of autism to be 1.5–1.7% [30]. Previously quoted figures of epilepsy in autism using former constricted criteria will be much lower than the prevalence using current DSM 5 (Diagnostic and Statistical Manual of Mental Disorders) definitions. If children with intellectual disabilities (intelligence quotient (IQ) < 70) are omitted, the prevalence is still expected to be greater than the general population because of the fact that those with autism will be skewed towards a lower-than-average IQ. This increased prevalence of epilepsy in those with autism and IQ > 70 can be due to the positively skewed distribution towards a lower IQ in those with autism overall, rather than due to an explicit relationship with autism. In contrast, a broader definition of ASD infers that the prevalence of autism in children with epilepsy may be greater using the modern definition. More studies in this systematic review reported prevalence rather than incidence, and there were more nonpopulation-based studies than population-based studies. The quality of the included studies varied, and some studies provided insufficient information on sampling and data collection procedures; however, meta-regression showed no association between the prevalence and incidence estimates and study quality scores (p > 0.05).

Females with autism had a higher prevalence of epilepsy compared to males with autism. These findings are consistent with a previous systematic review, which reported that the prevalence of epilepsy was 34.5% in autistic females versus 18.5% in autistic males [10]. Only two studies in our systematic review reported a higher prevalence of epilepsy in males with autism [31,32]. One study found that males with infantile autism had a higher prevalence of epilepsy than females [31], and the other found a higher prevalence of epilepsy in males with ASD-not otherwise specified and intellectual disability (ID) (only two females were included in this subsample). ID may be a mediating factor in terms of this trend, since epilepsy is more frequent in autistic patients with ID than those without ID [10,33–35]. One systematic review also found that the prevalence of epilepsy in people with autism increased with increasing ID severity [10]. Since females with autism tend to have more severe ID compared to males [10,36], it is possible that the higher prevalence of epilepsy in autistic females is due to their greater ID severity. Because of significant between-study heterogeneity, we did not stratify our results by ID status. Conversely, we found that the prevalence of autism was higher in males with epilepsy than females with epilepsy. This finding may be because the prevalence of autism is higher in males than females in the general population [37].

We were unable to explore the relationship between age and prevalence/incidence estimates because of insufficient and inconsistent data. However, studies have found that age is associated with both prevalence and incidence of epilepsy in autism [33,35,38,39]. Three studies included in this systematic review reported on this trend. One study reported that epilepsy is more prevalent among children with autism aged 10 years or older compared to children younger than 10 years (OR [odds ratio]: 2.40; 95%CI: 1.51–3.82) [35]. Similarly, another study (ages 0–18 years old) found a higher prevalence of autism in older age groups [26]. Finally, one study found that the risk of epilepsy in children with autism was higher in early childhood and adolescence than in people with autism above the age of 19, but they only included patients ages 2 to 33 years old [38].

The aforementioned data restrictions prevented us from exploring trends in prevalence or incidence of autism based on ID or seizure type, syndrome, or etiology (e.g., the prevalence of autism in people with generalized seizures versus focal seizures). However, the literature suggests that the highest risk groups for comorbid autism are children with early onset, drug-resistant epilepsy, especially West syndrome [40].

Graph A: Period Prevalence of Epilepsy in People with Autism by Publication Year



(1) and (2) indicates two different studies published by the same author in the same year
(a) and (b) indicates multiple estimates reported in the same article

Graph B: Period Prevalence of Autism in People with Epilepsy by Publication Year

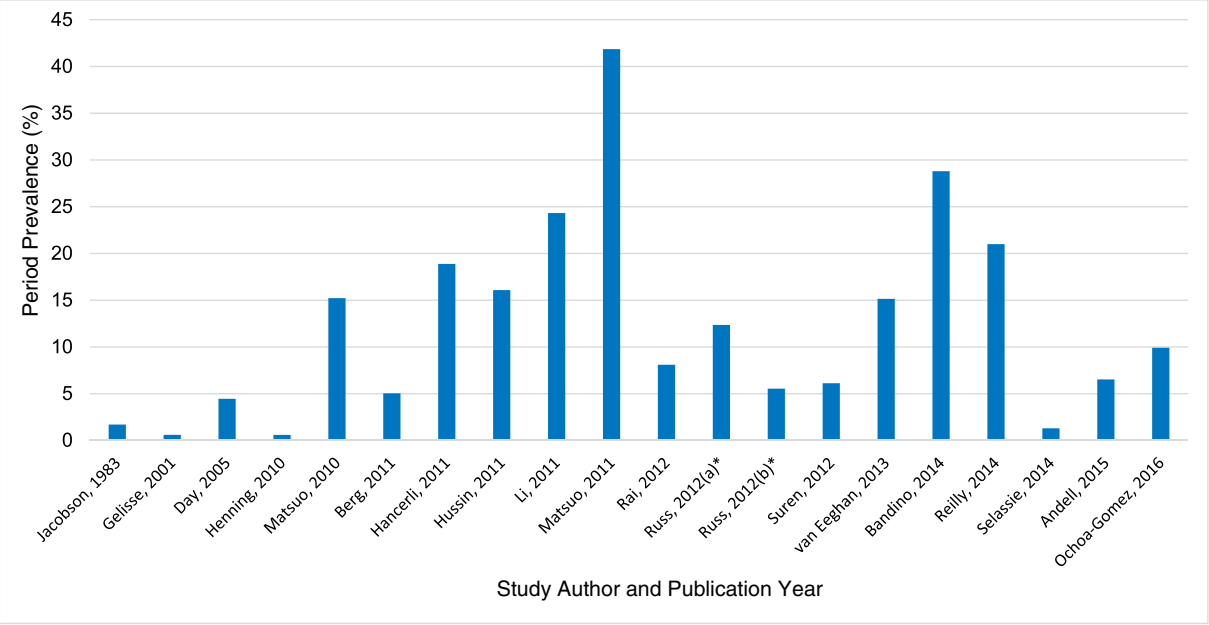


Fig. 2. Graph of trends by publication year.

Investigating epidemiological trends relating to autism over time is challenging because of changing diagnostic criteria as outlined in the DSM [41]. The most recent version, DSM-5, was published in 2013 [41]. Although the prevalence of ASD has been increasing in developing countries since the mid-90s [42], there are conflicting views on future trends relating to the incidence and prevalence of autism based on the new DSM criteria. There is evidence that the DSM-5 will reduce estimates of ASD compared to the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-IV- Text Revision), as some argue that DSM-5 criteria outline a higher symptom threshold for diagnosis [43]. Conversely, a recent study highlights an increase in the prevalence of autism in the United States from 1994 to 2014, citing broader diagnostic criteria as partially responsible for this increase [44]. However, since the DSM-5 was published in 2013, it is possible that this study is not capturing its full effects. In addition, the prevalence of autism according to this study is only slightly higher in 2014 compared to 2012, while the prevalence rose at higher rates in earlier years. Therefore, it is possible that the findings from these two studies are not in fact conflicting. The findings of our systematic review did not demonstrate any clear trends in the prevalence of autism in epilepsy over time.

Similar diagnostic issues also extend to epilepsy because diagnosing epilepsy is complex and epilepsy is often misdiagnosed. The presence of psychiatric or associated disorders may further affect the likelihood of misdiagnosis of epilepsy. People with ID are at an increased risk of epilepsy misdiagnosis because of their disability symptoms, such as stereotypic movements that may mimic seizures [45]. Patients with autism

Table 4
Summary estimates of prevalence and incidence of autism in people with epilepsy.

Category	Study design (n)	Range (%) or estimate (%)	Median (IQR) (%)	Mean (SD) (%)
Prevalence				
Period prevalence	Overall (19)	0.60–41.9	9.0 (12.7)	12.2 (10.8)
	Pop (9)	1.3–21.0	5.8 (3.6)	7.2 (5.8)
	Nonpop (10)	0.60–41.9	15.7 (14.4)	17.1 (12.5)
Point prevalence	Overall (3)	4.0–60.0	24.5 (56.0)	29.5 (28.3)
	Pop (3)	4.0–60.0	24.5 (56.0)	29.5 (28.3)
	Nonpop (0)	N/A	N/A	N/A
Period prevalence in females	Overall (2)	3.4–3.9	N/A	3.6 (0.4)
	Pop (2)	3.4–3.9	N/A	3.6 (0.4)
	Nonpop (0)	N/A	N/A	N/A
Period prevalence in males	Overall (2)	6.6–8.6	N/A	7.6 (1.4)
	Pop (2)	6.6–8.6	N/A	7.6 (1.4)
	Nonpop (0)	N/A	N/A	N/A
Incidence				
Incidence proportion	Overall (1)	1.6	N/A	N/A
	Pop (1)	1.6	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A
Incidence rate	Overall (1)	3.4 per 1000 P-Y	N/A	N/A
	Pop (1)	3.4 per 1000 P-Y	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A
Incidence proportion in females	Overall (1)	1.4	N/A	N/A
	Pop (1)	1.4	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A
Incidence proportion in males	Overall (1)	1.8	N/A	N/A
	Pop (1)	1.8	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A
Incidence rate in females	Overall (1)	2.9 per 1000 P-Y	N/A	N/A
	Pop (1)	2.9 per 1000 P-Y	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A
Incidence rate in males	Overall (1)	3.8 per 1000 P-Y	N/A	N/A
	Pop (1)	3.8 per 1000 P-Y	N/A	N/A
	Nonpop (0)	N/A	N/A	N/A

Abbreviations: pop: population-based studies, nonpop: nonpopulation-based studies, P-Y: person years.

can also be challenging to diagnose as many patients with autism have abnormal EEG (electroencephalogram) findings, even in the absence of epilepsy. Patients with autism also often have staring spells due to their autism, which can be mislabeled as epilepsy.

This systematic review has many strengths: we interrogated several large databases using a comprehensive search strategy; we did not exclude studies based on the type of epilepsy, autism, diagnostic criteria, time period, or study design; and we followed the PRISMA standards (Appendix e-3) to optimize reporting and ensure methodological rigor [46]. One possible limitation of our study is that we found statistical evidence of publication bias. However, this should be interpreted carefully since, unlike measures of association, we do not expect there to be bias towards studies that report lower prevalence estimates compared to studies that report higher prevalence estimates.

The literature regarding the epidemiology of autism in epilepsy and vice versa is very heterogeneous. We were unable to perform meta-analyses or report pooled estimates of all the included studies because of heterogeneity and the inconsistent reporting of study populations in terms of demographic characteristics (e.g., age ranges), as well as type of epilepsy and autism. The diagnostic criteria that used to establish a diagnosis of epilepsy and autism were also highly variable between studies, and sometimes no criteria were used. Prevalence and incidence studies are valuable in estimating disease burden, planning public health strategies, and making policy decisions around resource allocation [47]. Studies that adhere to high quality reporting standards can facilitate synthesis of available evidence. We recommend the use of the Standard of Reporting of Neurological Disorders checklist for future epidemiological studies of epilepsy and autism to reduce heterogeneity between studies, improve the rigor of such studies, and assist international comparisons [47]. Standard reporting across studies will facilitate the investigation of potential sources of heterogeneity in future studies of epilepsy and autism, some of which are highlighted in this review.

Finally, understanding the epidemiology of comorbid autism and epilepsy is important to guide future therapies aimed at preventing these comorbidities. Identifying genetic mutations as a cause for early onset epileptic encephalopathies is increasing. Many of these children have comorbid ID and/or autism. Understanding the specific effects of the genes/metabolic pathways affected may give us better insight into the pathogenesis of the developmental problems that are so devastating in these children. There is also interesting work on preventing autism and mitigating its severity in children with tuberous sclerosis by treating them at the time of first epileptiform EEG abnormality prior to onset of spasms, which may have a small effect on overall estimates of prevalence and incidence, although it is too early to say what the broader implications are [48]. Although the connection between epilepsy and autism often occurs from a common underlying element, it is essential that autistic features are not secondary to inadequately managed epilepsy. Well-managed epilepsy, autism, and associated comorbidities can significantly improve the quality of life in both patient and caregiver.

5. Conclusion

The occurrence of autism in persons with epilepsy and epilepsy in persons with autism is higher than the previously reported independent occurrence of each of these conditions in the general population. This trend demonstrates the importance of screening for autism in persons with epilepsy, and vice versa, to appropriately tailor treatment decisions and improve patient outcomes.

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We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of Competing Interest

Sara Lukmanji, Sofiya A. Manji, Sandra Kadhim, Khara M. Sauro, and Churl-Su Kwon report no disclosures.

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References

[1] Betancur C. Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting. Brain Res 2011;1380:42–77.
[2] Lee BH, Smith T, Paciorkowski AR. Autism spectrum disorder and epilepsy: disorders with a shared biology. Epilepsy Behav 2015;47:191–201.
[3] Baieli S, Pavone L, Meli C, Fiumara A, Coleman M. Autism and phenylketonuria. J Autism Dev Disord 2003;33:201–4.
[4] Chess S. Follow-up report on autism in congenital rubella. J Autism Child Schizophr 1977;7:69–81.
[5] Kuban KC, Joseph RM, O'Shea TM, Allred EN, Heeren T, Douglass L, et al. Extremely low gestational age newborn study I. Girls and boys born before 28 weeks gestation: risks of cognitive, behavioral, and neurologic outcomes at age 10 years. J Pediatr 2016;173:69–75 [e1].
[6] Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychol Med 2015;45:601–13.
[7] Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 2017;88:296–303.
[8] Vos T, Allen C, Arora M, Barber R, Bhutta Z, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1545–602.
[9] Matsuo M, Maeda T, Sasaki K, Ishii K, Hamasaki Y. Frequent association of autism spectrum disorder in patients with childhood onset epilepsy. Brain Dev 2010;32:759–63.
[10] Amiet C, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychol 2008;64:577–82.
[11] Woolfenden S, Sarkozy V, Ridley G, Coory M, Williams K. A systematic review of two outcomes in autism spectrum disorder - epilepsy and mortality. Dev Med Child Neurol 2012;54:306–12.
[12] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
[13] Loney PL, Chambers LW, Bennett KJ, Roberts JG, Stratford PW. Critical appraisal of the health research literature prevalence or incidence of a health problem. Chronic Dis Inj Can 1998;19:170.
[14] Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. BMJ 2001;323:101–5.
[15] Saemundsen E, Juliusson H, Hjaltested S, Gunnarsdottir T, Halldorsdottir T, Hreidarsson S, et al. Prevalence of autism in an urban population of adults with severe intellectual disabilities–a preliminary study. J Intellect Disabil Res 2010;54:727–35.
[16] Nomura Y, Nagao Y, Kimura K, Hachimori K, Segawa M. Epilepsy in autism: a pathophysiological consideration. Brain Dev 2010;32:799–804.
[17] Parmeggiani A, Posar A, Giovanardi-Rossi P, Andermann F, Zifkin B. Autism, macrocrania and epilepsy: how are they linked? Brain Dev 2002;24:296–9.
[18] Hara H. Autism and epilepsy: a retrospective follow-up study. Brain Dev 2007;29:486–90.
[19] Kawasaki Y. Developmental disorders and epilepsy. J Ment Health 1989;35:15–23.
[20] Yasuhara A. Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). Brain Dev 2010;32:791–8.
[21] Su C-C, Chi MH, Lin S-H, Yang YK. Bidirectional association between autism spectrum disorder and epilepsy in child and adolescent patients: a population-based cohort study. Eur Child Adolesc Psychiatry 2016;25:979–87.
[22] Matsuo M, Maeda T, Ishii K, Tajima D, Koga M, Hamasaki Y. Characterization of childhood-onset complex partial seizures associated with autism spectrum disorder. Epilepsy Behav 2011;20:524–7.
[23] Steffenburg U, Hagberg G, Viggedal G, Kyllerman M. Active epilepsy in mentally retarded children. I. Prevalence and additional neuroimpairments. Acta Paediatr 1995;84:1147–52.
[24] Rosander C, Hallbook T. Dravet syndrome in Sweden: a population-based study. Dev Med Child Neurol 2015;57:628–33.
[25] Forsgren L, Edvinsson SO, Blomquist HK, Heijbel J, Sidenvall R. Epilepsy in a population of mentally retarded children and adults. Epilepsy Res 1990;6:234–48.
[26] Andell E, Tomson T, Carlsson S, Hellebro E, Andersson T, Adelow C, et al. The incidence of unprovoked seizures and occurrence of neurodevelopmental comorbidities in children at the time of their first epileptic seizure and during the subsequent six months. Epilepsy Res 2015;113:140–50.
[27] Berg AT, Plioplys S, Tuchman R. Risk and correlates of autism spectrum disorder in children with epilepsy: a community-based study. J Child Neurol 2011;26:540–7.
[28] Sundelin HE, Larsson H, Lichtenstein P, Almqvist C, Hultman CM, Tomson T, et al. Autism and epilepsy: a population-based nationwide cohort study. Neurology 2016;15:15.
[29] Lotter V. Epidemiology of autistic conditions in young children. Soc Psychiatry 1966;1:124–35.
[30] Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveill Summ 2018;67:1–23.
[31] Wong V. Epilepsy in children with autistic spectrum disorder. J Child Neurol 1993;8:316–22.
[32] Nordin V, Gillberg C. Autism spectrum disorders in children with physical or mental disability or both. I: clinical and epidemiological aspects. Dev Med Child Neurol 1996;38:297–313.
[33] Jacobson JW, Janicki MP. Observed prevalence of multiple developmental disabilities. Ment Retard 1983;21:87–94.
[34] Kielinen M, Rantala H, Timonen E, Linna SL, Moilanen I. Associated medical disorders and disabilities in children with autistic disorder: a population-based study. Autism 2004;8:49–60.
[35] Viscidi EW, Triche EW, Pescosolido MF, McLean RL, Joseph RM, Spence SJ, et al. Clinical characteristics of children with autism spectrum disorder and co-occurring epilepsy. PLoS One 2013;8:e67797.
[36] Tsai L, Stewart MA, August G. Implication of sex differences in the familial transmission of infantile autism. J Autism Dev Disord 1981;11:165–73.
[37] Loomes R, Hull L, Mandy WPL. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. Adolescent Psychiatry;J Am Acad Child Adolesc Psychiatry 2017;56:466–74.
[38] Volkmar FR, Nelson DS. Seizure disorders in autism. J Am Acad Child Adolesc Psychiatry 1990;29:127–9.
[39] Xue M, Brimacombe M, Chaaban J, Zimmerman-Bier B, Wagner GC. Autism spectrum disorders: concurrent clinical disorders. J Child Neurol 2008;23:6–13.
[40] Bitton JY, Demos M, Elkouby K, Connolly M, Weiss SK, Donner EJ, et al. Does treatment have an impact on incidence and risk factors for autism spectrum disorders in children with infantile spasms? Epilepsia 2015;56:856–63.
[41] Diagnostic and statistical manual of mental disorders. 5th ed.; 2013.
[42] Van Naarden Braun K, Christensen D, Doernberg N, Schieve L, Rice C, Wiggins L, et al. Trends in the prevalence of autism spectrum disorder, cerebral palsy, hearing loss, intellectual disability, and vision impairment, Metropolitan Atlanta, 1991–2010. PLoS One 2015;10:e0124120.
[43] Maenner MJ, Rice CE, Arneson CL, et al. Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. JAMA Psychiat 2014;71:292–300.
[44] Graf WD, Miller G, Epstein LG, Rapin I. The autism "epidemic": ethical, legal, and social issues in a developmental spectrum disorder. Neurology 2017;88:1371–80.
[45] Bowley C, Kerr M. Epilepsy and intellectual disability. J Intellect Disabil Res 2000;44:529–43.
[46] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[47] Bennett DA, Brayne C, Feigin VL, Barker-Collo S, Brainin M, Davis D, et al. Development of the Standards of Reporting of Neurological Disorders (STROND) checklist: a guideline for the reporting of incidence and prevalence studies in neuroepidemiology. Neurology 2015;85:821–8.
[48] Jozwiak S, Kotulska K, Domanska-Pakiela D, Lojszczyk B, Syczewska M, Chmielewski D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Paediatr Neurol 2011;15:424–31.