A systematic review of two outcomes in autism spectrum disorder – epilepsy and mortality

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ABBREVIATIONS

ASD	Autism spectrum disorder
SMR	Standardized mortality ratio
AD	Autistic Disorder

AIM It has been reported that rates of epilepsy and mortality are higher among the population with autism spectrum disorder (ASD) than in the general population. The aim of this systematic review is to provide comprehensive evidence for clinicians, carers, and people with ASD regarding these outcomes.

METHOD Studies were eligible for inclusion if the main focus of the study involved observation over a period of 12 months or more of an initially defined population (with appropriate diagnostic label). Studies were also required to have at least 30 participants in order to differentiate case series from cohort studies. The Cochrane Database of Systematic Reviews, the Database of Reviews of Effectiveness, MEDLINE, PsycINFO, EMBASE, and CINAHL were searched. The date of the last search was September 2010. The risk of bias of included studies was assessed and a meta-analysis was undertaken.

RESULTS Twenty-one studies were identified, 16 measuring the percentage of participants with epilepsy and five measuring mortality using a standardized mortality ratio. The pooled estimate for the percentage of participants with epilepsy was 1.8% (95% CI 0.4–9.4%) in studies in which the majority did not have an intellectual disability and the mean age was <12 years at follow-up, and 23.7% (95% CI 17.5–30.5%) in studies in which the majority did have an intellectual disability and the mean age at follow-up was more than 12 years. The pooled estimate for the standardized mortality ratio was 2.8 (95% CI 1.8–4.2).

INTERPRETATION The prevalence of epilepsy is higher among the population with ASD than in the general population. People with ASD have a higher risk of mortality than the general population. This has important health promotion implications.

Autism spectrum disorder (ASD) affects between 60 and 70 children per 10 000.[1] The core features of ASD are severe and pervasive deficits in social communication and interactions and restricted, repetitive patterns of behaviour, interests, and activities.[2] Males are affected about four times more frequently than females. Although there is currently no known cause, evidence suggests that the cause is highly genetic with multifactorial risk factors that interact, leading to changes in brain development.[2]

The International League Against Epilepsy defines epilepsy as 'a chronic neurologic condition characterized by recurrent spontaneous epileptic seizures'.[3] The lifetime prevalence of epilepsy in the general population has been reported to range from 14 to 92 per 10 000 people and the incidence from 32 to 66 per 100 000 person-years.[4] The prevalence of epilepsy has been reported to be higher among individuals with ASD, with the highest prevalence evident in adolescence and young adulthood.[5] The incidence and prevalence of epilepsy reported in studies vary and are dependent on factors such as coexistent intellectual disability, family history, severe language delay, underlying genetic conditions/syndromes, the age and sex of the participants in the study, and the severity of autistic features.[5] A recent meta-analysis of 23 studies found a pooled prevalence of epilepsy of 21.5% (2150/10 000) among participants with autism and intellectual disability compared with 8% (800/10 000) among participants with autism but without intellectual disability.[6] Being female also increased the risk of having epilepsy. This meta-analysis predominantly consisted of cross-sectional studies and included only studies that reported epilepsy as a function of IQ or sex.

Increased mortality among people with ASD has been reported in follow-up studies of clinic and population cohorts. Those with comorbid epilepsy or intellectual disability have been described as being at increased risk. The majority of studies have reported mortality as an outcome in follow-up of a clinic sample, which limits the generalizability of these findings.[7,8]

Clinicians need robust evidence to support the advice that they provide to families and children with autism about the

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future risks caused by their condition. Epilepsy and mortality are important outcomes for children affected by ASD and their families. The purpose of this systematic review is to identify studies that investigate these outcomes, evaluate their methodological quality, and describe the occurrence of epilepsy and mortality of people with ASD.

METHOD

Types of participants

Studies were included if participants were children who had received a diagnosis of pervasive developmental disorder, pervasive developmental disorder not otherwise specified, atypical autism, unspecified pervasive developmental disorder, Asperger disorder/syndrome, autism, autistic disorder, or childhood autism. The diagnosis must have been made using a standardized diagnostic instrument or by using established diagnostic criteria, using an accepted classification system at the time of DSM III-IV-IV TR[9,10] or ICD 9–10.[11,12] A dual diagnosis (e.g. Asperger disorder and attention-deficit–hyperactivity disorder, or autism and fragile X) did not prevent inclusion.

Types of studies

Studies were eligible for inclusion if the main focus of the study involved observation over a period of 12 months or more of an initially defined population (with appropriate diagnostic label). To differentiate case series from cohort studies, we required included studies to have at least 30 participants.

Types of outcome measures

There were two types of outcome measures: epilepsy and mortality. Epilepsy required a clear history of non-febrile clinical seizures or 'epilepsy' to have been reported in the study during the period of follow-up. Electroencephalographic changes alone without clinical seizures were not sufficient.

Mortality as a standardized mortality ratio (SMR) was measured from a population-based register. The SMR is used to compare the mortality risk of a study population with that of a standard population. It is the ratio of the observed to expected mortality.

Search strategy for identification of studies

The Cochrane Database of Systematic Reviews, the Database of Reviews of Effectiveness, MEDLINE, PsycInNFO, EMBASE, and CINAHL were searched. The last search date was September 2010. The methodological search filter 'prognosis, sensitive' for the MEDLINE database, devised by Wilczynski and Haynes,[13] was adapted for the databases that did not include this search filter at the time of the searches. Content search terms that limited the search to autism and ASD were also used.[1] Conference proceedings and dissertation abstracts were also searched, reference lists of articles identified through the search strategy were reviewed, and known experts in the field were contacted. The search strategy was examined by the search coordinator of the Cochrane Developmental, Psychosocial and Learning Problems.

What this paper adds

- In this systematic review, the percentage of study participants with ASD who had epilepsy at follow-up ranged from 1.8% to 23.7% depending on the mean age of the participants and whether the majority of the study group had an intellectual disability.
- The expected number of deaths is two to three times higher in populations with autism spectrum disorder than in the general population.
- This systematic review illustrates the need for ongoing health promotion and surveillance for people with ASD.

Review of studies

The titles and abstracts of all references identified were screened and non-relevant studies were excluded. The initial screening of titles and abstracts was performed by two of the reviewers. A second 'strict' screening of titles and abstracts was performed by three reviewers, with two reviewers assessing every title and abstract. Potentially relevant articles were then retrieved for a final screening based on full text assessment by at least two of three reviewers. Disagreement in all cases was resolved by consensus, and articles that did not fulfil inclusion criteria were discarded.

Quality assessment

Clinical information that would influence the applicability and interpretation of findings and is necessary to allow the assessment of the homogeneity of the studies included in this review, such as autism diagnostic groups, presence or absence of intellectual disability in the majority of participants, age of inception cohort, and duration of follow-up, was extracted.

The risk of bias was assessed by examining the sample selected, recruitment method, completeness of follow-up, timing of diagnosis, and blinding. This was modified from current literature that addresses the assessment of quality in prognostic systematic reviews.[14] Studies were assigned as being low risk if the sample came from a population base, the follow-up period was prospective, the follow-up was more than 80% of the sample, the cohort was diagnosed with ASD as stated in the inclusion criteria at baseline or before recruitment to study, and blinding of outcomes was adequate.[2] Studies could receive a tick, cross, or question mark for each of these criteria. A study that recruited from a clinic that served a designated population was given a 'population' rating, otherwise a 'clinic-based' rating was applied. Analysis for confounders was not assessed as we were not investigating predictors of outcomes and in only one study was there analysis of IQ in relation to the outcome of epilepsy. The variability in these predictor measures and data presented meant that the authors did not feel that a meaningful comparison was possible.

If the information required to make an assessment was not available in studies published after 2000, the authors were emailed to ask for further information.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data extraction was done by at least two reviewers independently. We have presented the information in a way in which

[1]For full search strategy please email corresponding author.

[2]For full quality criteria please email corresponding author.

variations in similar outcomes can be examined, taking into account length of follow-up, age at ascertainment, and other clinically important differences, such as diagnostic group or presence/absence of intellectual disability in the majority of participants (defined as more than 70% of participants having an IQ or equivalent measure more than 2SD below the norm) when that information was available.

To determine pooled estimates of the percentage of participants with epilepsy at the end of the follow-up period, the variances of the raw percentages were stabilized using a Freeman–Tukey arcsine square root transformation.[15] Back-transformation used the harmonic mean of the denominators.[16] The I^2 statistic was calculated as a measure of the percentage of the overall variation in the pooled estimates of outcome that was attributable to between-study heterogeneity.[17] We anticipated large heterogeneity between studies considering the potential variations in baseline characteristics such as differences in diagnostic groups, intellectual disability, and the average age of participants at the end of the follow-up period. The DerSimonian–Laird random effects model was used to pool the transformed percentages.[18] This method regards the studies that were included in the model as a sample from theoretical potential studies. It implicitly incorporates uncertainty due to heterogeneity into the confidence intervals (i.e. produces wider confidence intervals than those produced with fixed-effects methods). Pooled estimates of SMR were also obtained from random effects models (after first stabilizing the variances with log transformation).

RESULTS

The literature search for this review was completed at two time points, with the final search completed at the end of September 2010. The combined search yielded 13 293 titles. Full-text reviews were conducted on 117 promising papers and 21 studies met the inclusion criteria.

Epilepsy

Characteristics of included studies

Sixteen studies measured the percentage of participants with epilepsy at the end of follow-up as an outcome.[8,19–33] Seven studies were of participants classified as having autistic disorder (AD) only and the remainder of the studies included participants from the broader autism spectrum (i.e. autistic disorder, and/or pervasive developmental disorder not otherwise specified and/or Asperger syndrome). In 11 studies, the majority of participants had an intellectual disability. Mean age at baseline ranged from 2 years 7 month to 16 years 11 months. Study duration ranged from 2 to 24 years. In three studies, the mean age at follow-up was under 12 years. In terms of risk of bias, two studies had a low risk of bias for all measures, three studies had one measure that was at high risk of bias (a retrospective study design or lack of blinding), and the remainder[11] had two or more measures that were at a high risk of bias and/or were unclear (Table I).

Pooled estimate of percentage of participants with epilepsy at follow-up

Figure S1 (supporting information published online) shows the pooled estimates of the percentage of participants with epilepsy for the duration of follow-up and the presence or absence of intellectual disability in the majority of the cohort. In the one study in which the majority of participants did not have an intellectual disability and the age at follow-up was under 12 years,[21] 1.8% (95% confidence interval [CI] 0.4–9.4%) had epilepsy at follow-up. For the four studies in which the majority of participants did not have an intellectual disability and the age at follow-up was 12 years or more,[19,24,25,28] the pooled estimate of the percentage of participants having epilepsy at follow-up was 8.9% (95% CI 3.7–15.7%). Of these papers, two gave separate data for sex,[21,25] with 2% to 5.2% of females in the sample having epilepsy, in contrast to 0% to 3.9% of males.

Table I: Characteristics of the included studies on the outcome of epilepsy in ASD

First author	Year	Diagnosis	Risk of bias number: low risk/total	IQ <70 in 70%	Mean age at baseline (y) (SD or range)	Mean follow-up (y)	*n*	% Epilepsy (*n*)
Takeda[21]	2005	ASD	2/5	No	2.6 (0.3)	3	57	2 (1)
Lounds[28]	2007	ASD	3/5	No	16.9	4.5	220	11 (23)
Venter[24]	1992	AD	3/5	No	8 (7–16)	8	58	10 (6)
Shavelle[25]	2001	AD	5/5	No	8.5 (2–15)	14	13 111	4 (551)
Howlin[19]	2004	AD	4/5	No	7.24 (3.1)	22	68	15 (10)
Jonsdottir[30]	2007	ASD	4/5	Yes	3.4 (0.8)	2	41	7 (3)
Baghdadli[31]	2007	ASD	3/5	Yes	5.4 (0.6)	3	280	6 (16)
Garca-Peas[23]	2009	ASD	2/5	Yes	4 (2–18)	8	690	29 (200)
Burd[33]	2002	ASD	3/5	Yes	7.7	12	59	9 (5)
Eaves[24]	2008	ASD	2/5	Yes	6.8 (3–12)	17	76	12 (9)
Hara[22]	2007	ASD	2/5	Yes	7.5 (1–14)	17	130	25 (33)
Billstedt[32]	2005	ASD	5/5	Yes	11 (4–18)	18	120	36 (43)
Kawasaki[27]	1997	AD	2/5	Yes	11.5 (2.6–29)	7	158	39 (62)
Kobayashi[8]	1992	AD	3/5	Yes	6.4 (2.8)	15	231	16 (36)
Wolf[26]	1986	AD	2/5	Yes	8 (1–15)	17	80	20 (16)
Mouridsen[20]	1999	AD	4/5	Yes	4.3 (1.9)	24	39	33 (13)

ASD, autism spectrum disorder; AD, autistic disorder.

Table II: Pooled estimates of epilepsy percentage and heterogeneity statistics for subgroup analyses

Subgroup	Nr. of studies	Pooled estimate of epilepsy, % (95% CI)	I^2 (%)	Q^a (df)	*p*-value
<70% with IQ <70; mean age <12y	1	1.8 (0.4–9.4)	NA	NA	NA
<70% with IQ <70; mean age +12y	4	8.9 (3.7–15.7)	89.1	27.6 (3)	<0.001
>70% with IQ <70; mean age <12y	2	6.1 (3.8–9.0)	0.0	0.3 (1)	0.568
>70% with IQ <70; mean age <12y	9	23.7 (17.5–30.5)	86.9	61.1 (8)	<0.001

[a]Cochran's *Q* statistic; df, degrees of freedom; NA, not applicable.

For the two studies in which the majority of participants did have an intellectual disability and the age at follow-up was under 12 years,[30,31] the pooled estimate of the percentage of participants having epilepsy at follow-up was 6.1% (95% CI 3.8–9.0%). For the nine studies in which the majority of participants did have an intellectual disability and the age at follow-up was 12 years or more,[8,20,22,23,26,27,29,32,33] the pooled estimate of the percentage of participants having epilepsy at follow-up was 23.7% (95% CI 17.5–30.5%) with high heterogeneity. Of these papers, three gave separate data for sex,[8,22,27] with 3% to 10% of females in the sample having epilepsy, in contrast to 13% to 29% of males (Fig. S1; Table II).

Mortality

Characteristics of included studies

Five population-based studies measured the SMR. Two of these studies were from the same population-based register in the USA, the California Developmental Disability System, at different time periods, the first being 1983 to 1997[25] and the second being 1998 to 2002,[34] so there would have been some overlap of participants between these two studies. The other three studies were from population-based registers in Sweden (2) or Denmark (1).[35–37] The two Swedish studies measured mortality as an outcome for the same group of 341 participants from the same population-based register but at different time periods.[36,37] The mean age of participants at baseline ranged from 8 years 6 months to 11 years. The mean duration of follow-up ranged from 14 to 36 years. All of these studies had a low risk of bias for all measures. They had between 120 and 13 111 participants. There appeared to be no trend in SMR over time (Table III).

Risk factors identified for increased risk of mortality in the participant studies were moderate to profound intellectual disability, having epilepsy, and female sex. In the study by Shavelle et al.,[25] the SMR for participants with no or mild intellectual disability was 1.4, compared with 3.1 for those with moderate, severe, or profound intellectual disability. Gillberg et al.[35] found a significant increase in the proportion of deaths among the group of children with severe intellectual disability and any medical disorder (with or without epilepsy). However, no difference in mortality risk between those with or without an intellectual disability was noted by Mouridsen et al.[36] Shavelle et al.[25] also reported that seizures were associated with an SMR of 36.9, and other medical conditions were also associated with an increased SMR. Mouridsen et al.[36] reported an SMR of 35.0 associated with epilepsy. All studies found an increased risk of death associated with female sex. As in other chronic conditions, the relative disparity (as measured by the SMR) was highest in the youngest age groups.[34,36] However, as for other chronic diseases, and for the population generally, the absolute risk of death for people with autism will increase as they age into middle adulthood and beyond.

Causes of death (Table IV) were categorized as physical, accidental, and suicide. Epilepsy accounted for only 7% to 30% of the deaths; a wide range of other conditions were also found to cause death, including circulatory, malignancy, and respiratory conditions, and external causes including drowning, motor vehicle accidents, and suffocation played a role. It

Table III: Characteristics of the studies on the outcome of mortality in ASD

First author	Country	Year	Mean age at diagnosis (range)	Diagnosis	Risk of bias number: low risk/total	IQ in 70% <70	Mean follow-up (y)	Years of follow-up	Observed deaths	Expected deaths	SMR (95% CI)
Gillberg[35]	Sweden	2010	11 (4–18)	ASD	5/5	Yes	22.5	1962–2008	9	1.6	5.6 (2.5–10.5)
Isager[37]	Denmark	1999	9.5 (2–17)	ASD	5/5	Yes	23.7	1960–1993	12	6.2	1.9 (1.0–3.4)
Intermediate period (calculated)	Denmark	–	–	–	–	–	–	1994–2006	14	7.3	1.9 (1.0–3.2)
Mouridsen[36] (total)	Denmark	2008	9.5 (2–17)	ASD	5/5	Yes	35.5	1960–2006	26	13.5	1.9 (1.3–2.8)
Shavelle[25]	USA	2001	8.5 (2–15)	ASD	5/5	No	14	1983–1997	202	84.2	2.4 (2.1–2.8)
Pickett[34] (intermediate period)	USA	2006	–	–	–	–	5	1998–2002	78	30	2.6 (2.1–3.2)
Pickett (total)	USA	–	8.5 (2–15)	ASD	5/5	n	19	1983–2002	280	114.2	2.5 (2.2–2.8)

SMR, standardized mortality ratio; CI, confidence interval; ASD, autism spectrum disorder.

Table IV: Findings of the three most recent studies on causes of death in the population with ASD

Author	Year	Total number of deaths	Cause of death					
			Circulatory (%)	Epilepsy or neurological (%)	Respiratory (%)	External (accidental or deliberate) (%)	Malignancy (%)	Other (%)
Gillberg	2010	9	Cardiac insufficiency 1/9 (11)	SUDEP 3/9 (30) Cerebral infection 1/9 (11)	Pneumonia/SUDEP 1/9 (11)	Accident 1/9 (11)	Cerebral malignancy 1/9 (11)	Unknown 1/9 (11)
Mouridsen	2008	26	Cardiac 6/26 (23)	Epileptic attack 4/26 (15) Meningitis 1/26 (4)	Pneumonia 4/26 (15) Accidental suffocation 2/26 (8)	Accidental overdose 1/26 (4) Drowning 1/26 (4) Jump 1/26 (4) Deliberate overdose 1/26 (4)	Malignancy 2/26 (8)	Acute appendicitis 1/26 (4) Urethral bleed 1/26 (4) Unknown 1/26 (4)
Shavelle	2001	202	Circulatory 22/202 (11)	Seizures 15/202 (7) Diseases of the nervous and sense organs 10/202 (5)	Respiratory 13/202 (6) Suffocation 8 (4)	Drowning 11/202 (5) Other external causes 30/202, mostly motor vehicle accidents (15)	Cancer 21/202 (10)	Digestive 13/202 (6) Congenital anomalies 16/202 (8) All other causes not previously listed 43/202 (22)

SUDEP, sudden unexpected death in epilepsy.

is unclear if accidental suffocation was synonymous with sudden unexplained death in epilepsy.

Pooled estimate of standardized mortality ratio

It was not sensible to statistically pool all five of the mortality studies because of overlapping populations (Table III). We therefore combined the three most recent studies with mutually exclusive populations: those by Pickett et al.,[34] Gillberg et al.,[35] and Mouridsen et al.[36] The resultant pooled SMR was 2.8 (95% CI 1.8–4.2) (Fig. S2, supporting information published online). Among males, the overall SMR was 2.1 (95% CI 1.7–2.7) with minimal heterogeneity (I^2=0.0%), and among females the overall SMR was 7.2 (95% CI 3.0–17.2) with high heterogeneity (I^2=77.3%). For females, the Gillberg et al.[35] study reported an extremely large SMR of 20.7 (95% CI 7.6–45.0), but the SMRs obtained by Mouridsen et al.[36] (4.0; 95% CI 1.7–7.9) and Pickett et al.[34] (5.2; 95% CI 3.0–8.4)[36] were also higher than the SMR for males.

Combining the three studies of Pickettet al.[34] Gillberg et al.,[35] and Mouridsen et al.[36] produced an overall SMR of 2.8 (95% CI 1.8–4.2) with high heterogeneity (Fig. S2).

DISCUSSION

When a child is diagnosed with an ASD, his or her parents want and need clear and accurate information regarding possible long-term outcomes associated with this complex neurodevelopmental condition. This systematic review of the literature examined the outcomes of epilepsy and mortality to provide the best currently available evidence on these serious outcomes. It has also provided future directions for research in terms of what is needed in future studies to help fill our 'evidence gaps'.

To provide high-quality evidence regarding the outcomes of ASD, we applied well-described methodological approaches that have been used in other systematic reviews of prognosis and outcome studies.[14] First, information should be collected prospectively on a sample of children who are diagnosed according to best practice at the start of the study. Of the studies that met the inclusion criteria for this review, less than one-third were retrospective in follow-up design, with all children meeting DSM or ICD diagnostic criteria at the beginning of the study. In addition, in 80% of the studies there was adequate follow-up, with over 80% of the original sample traced. All the identified mortality studies used population-based samples; however, the majority of the epilepsy studies used a clinic-based sample, which has a potential impact on the applicability of the study results for practitioners if they are working in different clinical environments. In over half of the studies there was either no blinding or it was unclear from the paper whether there was blinding of outcome assessors, although one can argue that this a less important source of bias when objective outcomes such as epilepsy or mortality are being measured.

This systematic review found that the overall percentage of participants with epilepsy at follow-up ranged between 1.8% in participants aged under 12 years, the majority of whom did not have an intellectual disability, and 23.7% of participants

aged over 12 years, of whom the majority did have an intellectual disability. These are significantly greater percentages than those reported in the literature for the general population, but are similar to those found for intellectual disability.[38,39] Our findings were also consistent with a previous systematic review that showed that the pooled prevalence of epilepsy was 21.5% among participants with autism and an intellectual disability compared with 8% among participants with autism without intellectual disability.[6] Of interest, our systematic review included only one study[20] that overlapped with the review by Amiet et al.[6] and identified an additional 15 studies. One could conjecture that the increased rates of epilepsy seen in people with ASD is a function of their comorbid intellectual disability; however, it is interesting to note that both systematic reviews found a higher prevalence among those without intellectual disability as well as in comparison with the general population. Amiet et al.[6] in their systematic review argue that this may be attributable to the heterogeneous nature of ASD and that differing neurobiological and genetic processes in the pathogenesis of ASD result in subgroups with a greater or lesser risk of epilepsy, independent of comorbid intellectual disability. As our systematic review did not investigate predictors, we were unable to investigate these possible relationships further.

This systematic review found that people with ASD have SMRs ranging from 1.9 to 5.6. Overall, the SMR when all studies were combined was 2.8 (95% CI 1.8–4.2). This means that the expected number of deaths among the population with ASD is approximately two to three times higher than that among peers of the same age and sex in the general population. In our systematic review, we found that the SMR to be higher for females than for males. Our findings are similar to the all-cause mortality rates among the population with intellectual disability alone, which is reported to be up to three times higher than among the general population, with mortality being particularly high among young adults, women, and people with Down syndrome.[40] Epilepsy as a condition in its own right has also been found to increase mortality rates, particularly when there is comorbid intellectual disability and/or recurrent seizures.[41,42] However, the causes of death usually reflect patterns of morbidity in the general population.[42] This was the case in our systematic review, in which, although epilepsy was responsible for 7% to 30% of deaths, it is worth noting that the causes of death were heterogeneous and reflected the wide range of causes found in the general community, which emphasizes the importance of general health promotion strategies for people with ASD around maintaining health and well-being.

This systematic review was limited by the available studies, which measured only the patterns of prevalence of the outcomes in clinical subgroups categorized by, for example, sex, age, and intellectual disability (in which case primary studies could be grouped) rather than predictors of outcomes. Any differences between these subgroups cannot be analysed in any further depth in terms of the relationship between possible predictors and the outcomes studied. This was in part because the relationship between potential predictors and outcome was not adequately reported or available in the primary studies and partly because there was great variability in how potential predictors were measured in the studies included. Analysis of confounders was not assessed as we did not investigate predictors of outcomes.

The challenge for clinicians, parents/carers, and individuals with ASD is how to sensibly use this evidence that people with ASD are at an increased risk of having epilepsy or dying relative to comparison individuals without ASD. We would argue that this information alerts us to the need for health promotion and regular health surveillance of individuals with ASD, especially as children and adolescents with ASD transition into adulthood. In particular, we would advocate that clinicians be alert for any new signs or symptoms that could indicate the emergence of a physical or mental health problem, and support those with autism and their carers to attend regular review of their well-being. Increased vigilance with injury prevention and encouragement of other health-promoting activities such as smoking cessation and an active lifestyle is also required. This information is important to parents, clinicians, and those developing services to cater for the needs of children with ASD across their lifespan. However, risk of bias among the studies published to date and the relative lack of information about outcomes in clinically important subgroups of children mean that we are a long way from offering families high-quality information about the risk of adverse or favourable outcomes for their child.

For researchers, we recommend that both epilepsy onset and resolution be reported. In addition, epilepsy occurrence should be reported in association with duration of follow-up for each child, and survival curves could be used for this. This would provide more accurate information about the peak age of diagnosis of epilepsy and likelihood of resolution.

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SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

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