

Autism and Epilepsy: Laying out the evidence

Full Report



Introduction

We aim to drastically reduce the unacceptable inequalities that autistic people with epilepsy face - within a generation.

People who are autistic and have epilepsy face some of the starkest inequalities in the world. We know that worldwide approximately 8.4 million people have both conditions. On average, they have poorer quality of life, poor health and can die early. We've known this for years, but a lack of evidence-based strategic action has blocked progress.

This document aims to provide the much-needed evidence for further research investment and will assist health, care and educational services in providing better support. It will also enable people affected by epilepsy and autism to further understand their conditions. The project was undertaken between September 2020 and February 2021 and explored three key themes:

Rates of co-occurring epilepsy in autistic people are much higher than in the general population. Knowledge of factors contributing to the co-occurrence of both conditions can enable health, educational, mental health and neurodisability services to more effectively identify and support autistic people with epilepsy as well as their families.

- 1. Risk factors of co-occurring epilepsy in autistic people**
- 2. Living with co-occurring autism and epilepsy**
- 3. Economic analysis of the costs of co-occurring autism and epilepsy**

Despite sharing some common mechanisms, autism and epilepsy remain virtually unstudied in combination.

Autistica has led a partnership with Epilepsy Research UK and Young Epilepsy to fund research to summarise the evidence focusing on co-occurring autism and epilepsy, outlining the scientific evidence and scale of the issue in human, social and economic terms.



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Understanding autism

Autism is a neurodevelopmental condition that affects the way people perceive and interact with the world around them. Autism is a lifelong developmental condition associated with sensory sensitivities and social communication differences.

Autism presents differently across individuals. Some people are able to learn, live and work independently, while many have learning differences or co-occurring health conditions that require specialist support. It is linked to higher mortality rates, and a higher rate of co-occurring health conditions than the general population (Jokiranta-Olkonieni et al, 2020).

It is estimated that 1 in 100 people in the UK are autistic. (Fombonne, 2020), 1 in 3 of whom has a learning difficulty or disability.

Diagnosis of autism

A diagnosis of autism is usually made based on a description of someone's development plus careful observations of their behaviour. While there is no one test used to diagnose autism, professionals may use autism-specific interviews or rating scales in addition to evaluations of the individual's cognitive (learning) ability, language, level of independence and social skills.

Somebody can be diagnosed as autistic based on professional opinions of:

Social Communication

Autistic people can present with communication difficulties of varying extents. They may struggle with perceiving social cues, and/ or expressing themselves verbally, nonverbally or both. These communication difficulties challenge the social interactions of autistic people and can cause heightened anxiety (World Health Organization, 2020).

Repetitive Behaviours

Autistic people may display repetitive behaviours, inflexibility and experience difficulties adapting to change. These repetitive behaviours often serve as self-soothing, anxiety relief mechanisms. They may also have a narrow range of strong interests (World Health Organization, 2020).

Sensory Sensitivity

Autistic people may display hyper or hyposensitivity to sensory inputs. They may experience very strong reactions to aspects of their environment such as sounds, colours or textures, which overwhelm their senses and cause heightened distress (World Health Organization, 2020).

Gender Differences

Autism is more commonly identified in males and most clinical studies suggest a 4:1 male-to-female ratio, although this ratio may be more equal in autistic people who also have epilepsy (Maenner et al, 2020). However, it is increasingly being recognised that autism may be under recognised in females. Lack of identification of autistic females may be attributed to their having fewer difficulties at school and displaying fewer repetitive behaviours (Mandy et al 2012). Additionally, females may be more likely to mask or compensate for their autistic characteristics (Hull et al. 2020), and have their symptoms mislabelled (Schuck, Flores & Fung, 2019).

Co-occurring conditions

Autistic people are at a higher risk for other physical and mental health conditions such as epilepsy, diabetes, heart conditions, anxiety, ADHD, depression and motor coordination problems (McMorris et al, 2018; Lukmanji et al, 2019).

Understanding epilepsy

Epilepsy - one of the most common serious neurological conditions – is a brain disorder characterised by seizures that are brought on by excessive electrical activity. There are over 40 different types of epilepsy, and no two people’s experiences of the condition are the same. Epilepsy can affect anyone, at any age and from any walk of life. (Joint Epilepsy Council, 2011).

An epileptic seizure results from a sudden electrical discharge in the brain that causes changes in sensation, behaviour or consciousness. Seizure symptoms typically depend on where in the brain this abnormal burst of electrical activity happens. As a result, there are many different types of seizures. Most seizures usually last from a few seconds to a few minutes and usually stop without any treatment.

Approximately 60% of people have tonic-clonic seizures, 20% complex focal seizures, 12% have mixed tonic-clonic and focal seizures, 3% have simple focal seizures and less than 5% have absence seizures, myoclonic seizures and other types. Having epilepsy is usually defined by the presence of at least two seizures occurring 24 hours apart (Fisher et al 2014).

Approximately 600,000 people in the UK have epilepsy which is equivalent to around 1 in 103 people (Joint Epilepsy Council, 2011). The number of children and young people aged 18 years and under with epilepsy is near 1 in 220 (Joint Epilepsy Council, 2011). Shockingly, there are 21 epilepsy-related deaths in the UK every week (SUDEP Action, 2020).

Beyond seizures, there are higher rates of cognitive, developmental and behavioural disorders among young people with epilepsy, who are also four times more likely than their peers to experience mental health problems. Many of these problems remain unrecognised or unsupported and result in academic underachievement or school exclusion. There sadly remains significant social stigma about the condition and many young people feel isolated and anxious (Young Epilepsy, 2019).

The causes of epilepsy include:

Genetic factors

There are known genetic differences which lead to the development of seizures.

Structural

There is an abnormality in the brain thought to be causing seizures.

Metabolic

There is a metabolic disease (disease caused by some defect in the chemical reactions of the cells of the body) thought to be causing the seizures.

Immune

The seizures result from an immune disorder.

Infections

Epilepsy occurs as a result of an infection. This may not be so common in the UK, but is more common in other regions of the world.

Unknown

The cause is not yet known.

Diagnosis of epilepsy

An EEG (recording of brainwaves) can often help determine if there is epileptic activity in the brain, however there is no definitive test for epilepsy and diagnosis is based on medical history. Getting a diagnosis of epilepsy can often take some time and misdiagnosis is not uncommon i.e. a diagnosis of epilepsy given in error or not identified when it should be.

Epilepsy treatment

The main and first-line treatment for epilepsy is epilepsy medicine also called anti-seizure medicine (ASMs) or anti-epileptic drugs (AEDs). Sometimes an individual will need to try another medicine if the first one does not stop the seizures and sometimes will need to take a combination of two or even more medicines. ASMs usually stop seizures in 70% of cases. The other 30% will continue to experience seizures and other treatment options may need to be explored for these individuals who have medication resistant epilepsy.

Other types of treatment include epilepsy (brain) surgery, vagus nerve stimulation, and a special diet called the ketogenic diet. These other treatments do not work for, or may not be suitable for, all people with epilepsy. For around 30% of people with epilepsy, their seizures will not respond to treatment. This is known as refractory epilepsy.

While a seizure is not normally a medical emergency and the vast majority of seizures stop by themselves without the need for any treatment. Sometimes a medical emergency known as status epilepticus can occur. Epilepsy emergency medication may be prescribed if a child has previously experienced a seizure that has lasted for five minutes or more. ASMs may reduce seizures and also improve learning and behavioural difficulties. However, in some cases the side-effects of ASMs include learning and behavioural difficulties.

Epilepsy and co-occurring conditions

People with epilepsy are at increased risk for having a range of other conditions including autism, cerebral palsy, motor coordination difficulties, anxiety, depression, attention deficit hyperactivity disorder (ADHD), learning disabilities, difficulties with processing speed and memory difficulties. These conditions may be present before the individual develops epilepsy or be present even if the individual becomes seizure free.

These co-occurring conditions often affect the individual’s quality of life as much as or more than the epileptic seizures. The onset of epileptic seizures can in some cases lead to the development of, or exacerbate existing learning and behavioural difficulties.

Sudden Unexpected Death in Epilepsy (SUDEP)

Sudden unexpected death in epilepsy (SUDEP) is when a person with epilepsy dies suddenly and prematurely and no reason for death is found. Many of these deaths occur overnight. There may be obvious signs a seizure has happened, though this isn’t always the case. The cause of SUDEP is not yet known. SUDEP is rare occurs in approximately 1 per 1000 people with epilepsy (1 in 4,500 children) each year (SUDEP Action, 2020) Action, 2020).

Autism and epilepsy

The prevalence of epilepsy in autistic people is higher than in non-autistic people (Loussouarn, Dozieres-Puyravel & Auvin, 2019; Woolfenden et al, 2012). Co-occurring epilepsy contributes to decreased quality of life and increased risk of mortality among autistic patients (Capal et al, 2020; Woolfenden et al, 2012).

A systematic review of 74 studies including 283,549 autistic people found a 12.1% prevalence of epilepsy in autism (Lukmanji et al, 2019). The review also noted the prevalence of epilepsy was higher in females (Lukmanji et al, 2019).

Equally, people with epilepsy are more likely to be autistic than people without epilepsy. A systematic review of 19 studies found a prevalence of epilepsy in autism of 6.3% (Strasser et al, 2017). The review in this case notes males with epilepsy were more likely to be autistic than females.

Given the high co-occurrence of autism and epilepsy there is increasing interest in their possible shared biological causes. Understanding why autistic people have an increased risk for epilepsy at the biological level may allow for the development of treatments which can treat both seizures and lead to improvements in the quality of life of autistic people. There is already some evidence that early treatment of seizures in some children with medical and genetic conditions associated with both autism and epilepsy can lead to improvements in the children's development.

Part 1:

Risk factors of co-occurring epilepsy in autistic people

In order to determine risk factors for the occurrence of epilepsy in autism we undertook a systematic literature review. This is a type of review that examines all relevant research studies and summarises them to answer a research question, in this case we were looking at what the risk factors were for co-occurring epilepsy in autistic people. We did the review according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines (Liberati et al, 2009; Moher et al, 2009), which are the accepted way to carry out systematic reviews.

We searched electronic databases where scientific and academic papers are stored – PsycINFO, Medline, Web of Science, CINAHL and Cochrane – on 2 October 2020 using words associated with autism and epilepsy. The papers found were limited to those available in the English language and published from 2000 onwards. Following the screening of abstracts and full texts for relevance by two independent reviewers, 51 papers were included in the systematic review.

We decided to exclude studies where the majority of children had a neurodisability/neurogenetic condition (e.g. tuberous sclerosis complex, Dravet syndrome) associated with learning disability as these studies might bias our findings given the known high association with learning disability. The prevalence of epilepsy in studies with these syndromes is reported on separately from the main group of studies.

The search and screening process using the PRISMA guidelines is shown in **Figure 1** below.

Results

The 51 studies reviewed included a total of 452,268 autistic people, 48 of which included more males than females. Three studies did not report on the gender distribution of the sample.

From those that did report on gender, 69% (90,551) were male and 31% (45,331) were females. Of the 452,268 autistic participants it was possible to estimate epilepsy prevalence in 257,773 people and 18,135 (7%) had co-occurring epilepsy. In studies which focused on children with neurodisability/neurogenetic syndromes the prevalence of epilepsy in autistic people was 24%, highlighting that children with these syndromes are a particularly high-risk group for having co-occurring epilepsy.

The studies we found were conducted in 20 different countries across five continents. The most common country was the USA (19 studies), followed by Denmark (4) and the UK (4). In one study the location was not specified. Participant ages ranged between 0 and 72 years. Nine studies included adult participants only (aged 19 years or older); 22 studies included child participants only (aged 18 years or younger); and 11 studies included both child and adult participants. In nine studies, participant mean age and range were not reported.

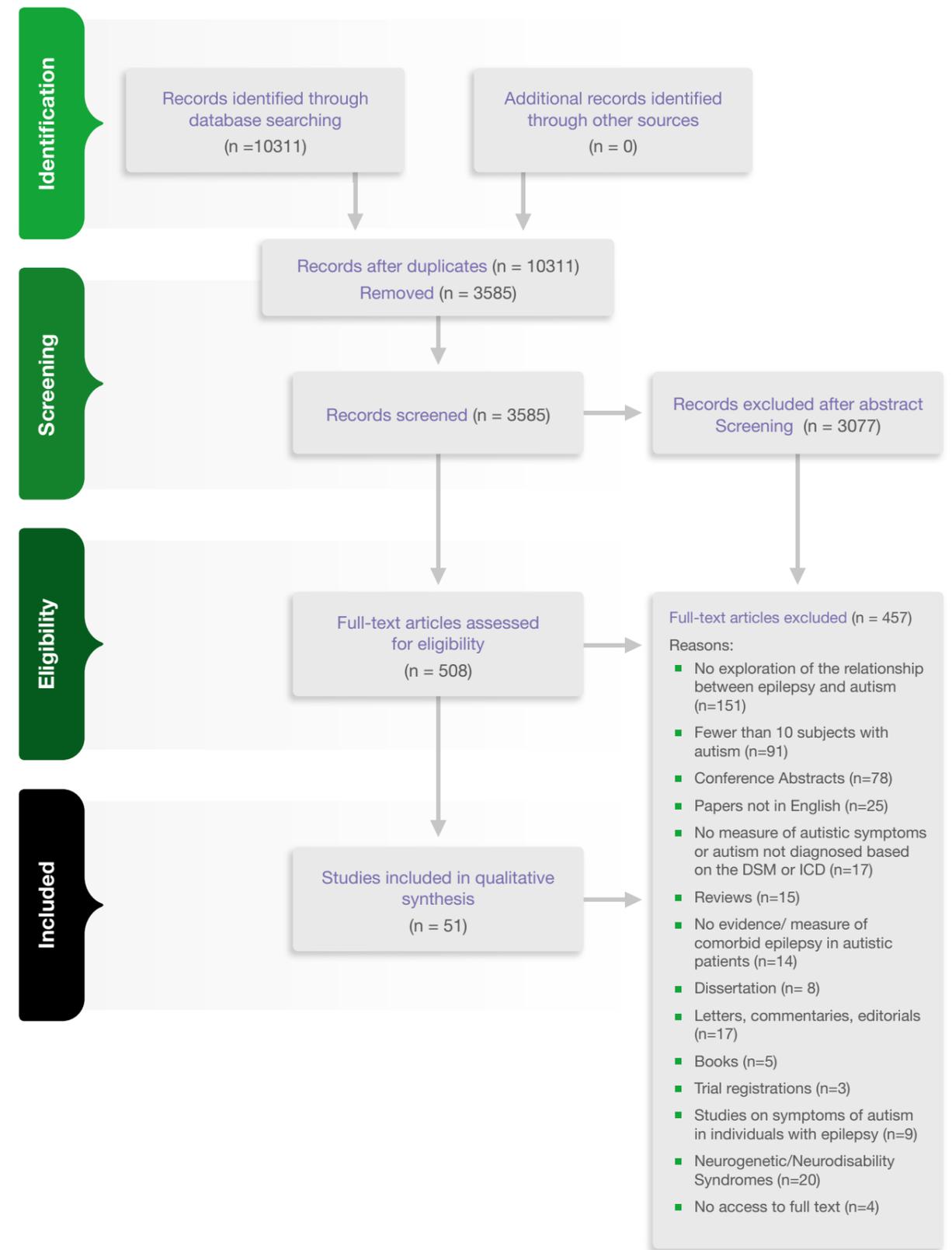
In all of the studies, factors associated to the occurrence of epilepsy in autistic people were deemed to be statistically significant if we felt 95% confident that there is an actual difference as opposed to just differences due to chance (or $p < 0.05$ level) meaning that the relationship between the factor and occurrence of epilepsy in autistic people was not likely to be due to chance.

There were six risk factors most often considered when we look at the occurrence of epilepsy in autistic people:

1. Learning disability and Learning (Cognitive) Difficulties

The factor most often significantly associated with the occurrence of epilepsy in autistic people was learning difficulties or intellectual (learning) disability. This factor was found to be significantly associated with the occurrence of epilepsy in autistic people in all 12 studies where it was considered. That means people with learning disability or learning difficulties and autism have a greater chance of also having epilepsy compared with autistic people without learning disability or learning difficulties.

Figure 1: PRISMA Diagram Search process for studies focusing on factors associated with epilepsy in autism



2. Gender

Another factor often found to be associated with the occurrence of epilepsy in autistic people was female gender – found in five of 10 studies. However, in one study male gender was found to be associated with the occurrence of epilepsy in autism and four studies found no significant relationships between gender the occurrence of epilepsy in autism.

3. Developmental Regression

The loss of previously acquired skill – developmental regression – has been noted in a significant minority of autistic people. The presence of developmental regression was significantly associated with an increased occurrence of epilepsy in autistic people in two of the seven studies where it was considered, but not significantly associated in the other five studies.

4. Additional behavioural/psychiatric conditions

Four of the seven studies where it was considered found that the presence of additional behavioural/psychiatric diagnoses was associated with an increase in the occurrence of epilepsy in autistic people. The other two studies found no significant relationships.

5. Chronological Age

Increasing age was associated with an increased occurrence of epilepsy in autism in four of seven studies where age was considered. However, in one study younger age was associated with an increased occurrence of epilepsy and in two studies no significant relationships were noted.

6. Injuries/Accidents

Two out of five studies that considered that there was an association between accidents and/or injuries and an increased risk for epilepsy in autistic people. The other three studies found no significant relationships.

Study quality

In addition to analysing all relevant studies with respect to the factors associated with the occurrence of epilepsy in autistic people, we examined all of them to look at their quality. Study quality refers to whether a study is carried out using appropriate methods and whether potential biases and errors have been minimised.

Study quality was evaluated by two of the research team based on commonly-used quality checklists¹ and all studies were given a rating of ‘good’, ‘moderate’ or ‘weak’. In total seven of the 51 studies were given a ‘good’ rating whilst the other studies were given either a ‘moderate’ or ‘weak’ rating.

You can see the seven ‘good’ studies in **Table 1** below, which also shows where we considered them to be statistically significant (denoted by the SIG in the relevant boxes) according to the $p < 0.05$ level we used to make sure that the relationships between the factor (the top row) and the occurrence of epilepsy in autistic people was not likely to be due to chance.

The abbreviations for the factors across the top row are:

BD/PD = Behavioral Disorders/ Psychiatric disorders

CL = Cognitive Level/ Learning disability

GEN = Gender

FC = Family Characteristics

IA = Injuries/Accidents

REG = regression

LANG = Language

SEV = Autism Severity

AB = Adaptive Behaviour

Table 1: Factors significantly associated with occurrence of epilepsy in autistic people in studies with a ‘good’ quality rating.

| Authors | YEAR | BD/PD | CL/ID | GEN | FC | IA | REG | LANG | SEV | AB |
|-------------------|------|-------|-------|-----|-----|-----|-----|------|-----|-----|
| Christensen et al | 2016 | | | | SIG | | | | | |
| Jokirant et al | 2014 | SIG | | | | | | | | |
| Jain et al | 2014 | | | | | SIG | | | | |
| Bolton et al | 2011 | | SIG | SIG | | | | SIG | | |
| Oslejskova et al | 2007 | | | | | | SIG | SIG | | |
| Danielsson et al | 2005 | | SIG | | | | | | | SIG |
| Pavone et al | 2004 | | SIG | | | | | | SIG | |

The following factors were significantly associated with the occurrence of epilepsy in autism in ‘good’ quality studies:

- Learning disability or learning difficulties
- Language difficulties
- Behavioural or psychiatric disorders
- Female gender
- Having an older sibling with epilepsy/autism or both
- More frequent injuries/accidents
- The presence of developmental regression
- Having more severe autistic symptoms
- Having a lower level of adaptive behaviour

Part 2:

Living with co-occurring autism and epilepsy

In order to describe the lived experiences of autistic people with epilepsy we started with a systematic literature review to identify previous research papers. We used the same electronic databases – PsycINFO, Medline, Web of Science, CINAHL and Cochrane – and searched systematically on 2 December 2020 using the search words associated with autism (eg, autism, ASD, Asperger, pervasive developmental disorder) and epilepsy (eg, epilepsy, seizure).

We combined these search words with the Scottish Intercollegiate Guidelines Network (SIGN) filters for studies on lived experience (eg, terms for quality of life, coping, attitudes to health and others). SIGN develops evidence-based clinical practice guidelines for the National Health Service (NHS) in Scotland. The papers retrieved were limited to those available in the English language and published from 2000 onwards.

Following title/abstract and full text screening by two independent reviewers, no relevant papers were found. That means the scientific literature we reviewed contained no previous studies of the lived experiences of autistic people with epilepsy.

At the same time as the systematic review, a Patient and Public Involvement (PPI) group was formed and met digitally three times during the project to discuss and identify key issues with regards to living with co-occurring autism and epilepsy. The group consisted of three autistic people with epilepsy and four parents of autistic people with epilepsy. All of the meetings were recorded and transcribed.

In addition to the three PPI meetings the participants were asked to contribute their thoughts via email regarding issues that had not been broached or fully discussed in the digital forum.

Two of our research team then did a thematic analysis (Braun & Clarke, 2006) to identify themes from the PPI meetings and email correspondences. Thematic analysis is one of the most common forms of analysis within qualitative research. It emphasises identifying, analysing and interpreting patterns of meaning within qualitative data.

The thematic analysis of the three PPI meetings resulted in 18 themes and 60 subthemes. You can see the 18 themes in **Figure 2** below. The subthemes and quotes from participants that help illustrate the themes are included after Figure 2.

Figure 2: Themes from the analysis of the PPI meetings.



Theme 1: Lack of support during assessment and after epilepsy diagnosis

Subthemes:

- 'Professionals would not believe us/me regarding symptoms of epilepsy'
- 'Nobody has explained what epilepsy is to me'

“ I was called a hysterical mother. ”

“ You get that epilepsy diagnosis and then you are kind of shown the door. ”

Theme 2: Lack of understanding of autism-epilepsy comorbidity

Subthemes:

- 'Lack of understanding of cumulative effect of having both conditions'
- 'Lack of appreciation that epilepsy and autism are often comorbid'

“ Their [professionals] inability to understand the epilepsy and autism being co-morbid. ”

“ When the evidence is so clear these conditions go hand in hand, how can those departments not talk to one another? ”

Theme 3: Lack of integration of care

Subthemes:

- 'Lack of communication between departments in hospital settings'
- 'Need to explain my child's/my health conditions over and over'
- 'Need for professionals knowledgeable about both conditions'



Theme 4: Failure to identify autism and subsequent lack of support after diagnosis

Subthemes:

- 'Lack of identification of autistic females leading to later diagnosis and later supports',
- 'Autism behaviour attributed to child's medication not autistic symptoms'
- 'Lack of support after diagnosis'



Theme 5: Assessment and investigations for epilepsy often difficult for autistic people

Subthemes:

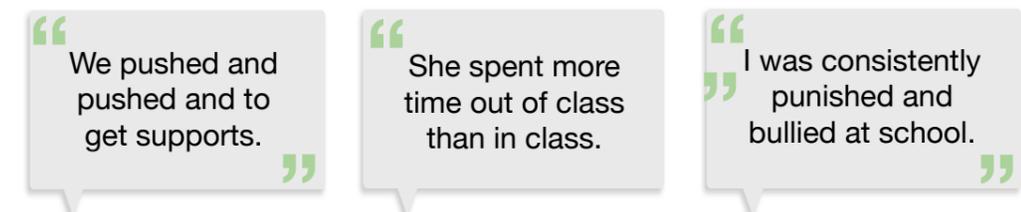
- 'Difficult experience for child/adult due to sensory aspects e.g., difficult to keep electrodes on head with EEG, child pulls out cannula, blood tests and MRI difficult experiences'
- 'Difficult to get child to hospital for assessment'
- 'Whole assessment experience was stressful for child and family'
- 'Much of preparation could be done over the phone'
- 'Difficult experiences leads to fear of hospitals'
- 'Lack of understanding of autism among epilepsy professionals'



Theme 6: Experiences at school often negative

Subthemes:

- 'Battle to get supports at school'
- 'Transitions at school are hard'
- 'Lack of understanding and necessary adaptations in mainstream schools - much better in special schools'
- 'Autistic people with epilepsy experience bullying in school'



“ Unless you absolutely can put your square peg in a round hole, mainstream school is not the place for a high functioning autistic [person]. ”

“ The level of service provision [in school system] is so poor across the board for the person who is nonverbal to the person who can self-advocate. ”

“ They don't understand epilepsy and don't understand autism [at school]. ”

“ I was kicked out of school because they did not want to support me. ”

Theme 7: Other co-occurring health conditions

Subthemes:

- 'Diagnostic overshadowing leading to lack of diagnosis'
- 'Perception among professionals is once you have autism you can't have anything more'

“ I am depressed - no you are not... you have autism. ”

“ Diagnostic overshadowing is big, big problem. ”

Theme 8: Potential difficulties with epilepsy medication including side effects and adherence

Subthemes:

- 'Difficult to know what it is what in terms of side-effects of medication or behaviour'
- 'Difficulty taking anti-seizure medication'

“ I don't know how 23 years of medication has affected my brain. ”

“ He has constipation but the lamotrigine exacerbates the constipation and that brings seizures. ”

“ We don't even know whether its epilepsy or not anymore, but we just keep giving it to him because it has a mood stabilising effect. ”

“ I used to have to keep spreadsheets of behaviour and medication and inputs to outputs to track it. Bloody nightmare. ”

Theme 9: Impact on siblings

Subthemes:

- 'Are very seizure aware'
- 'Very nurturing towards the individual with epilepsy'
- 'Sibling being bullied'
- 'Siblings concerns about their role when parents are gone'
- 'Sibling jealousy'

“ She [sibling] was having to care for me there because I was being bullied... she was really looking after me 24/7. ”

“ My daughter [sibling] dropped off school, she couldn't handle the stress. ”

“ She [sibling] was always on guard for me. ”

“ I got into status epilepticus. She [sibling] was so traumatised... and still has anxiety to this day. ”

“ His younger brother just came running up to me going, “You don't love me as much as you love him.” ”

Theme 10: Impact on parental wellbeing

Subthemes:

- 'Decided not to have more children'
- 'Parental conflict regarding how best to manage the child's epilepsy'
- 'Reduced social networks/ more restricted friendship network'
- 'General strain/stress on parental relationships can lead to relationship breakdown'

“ We decided we were not having any more children. ”

“ Our friends fell away very quickly. ”

“ Aside from my parents and my sister, I have only had 2 friends who have offered to take care of her over the years so my husband and I can have some time together. ”

Theme 11: Perceived understanding in the wider family of autism and epilepsy

Subthemes:

- ‘Lack of understanding of the child’s condition among the wider family’

“ I think he understands autism ... but he doesn’t see it in me. ”

“ For their grandmother, there is no autism. They’re just ill-behaved. ”

Theme 12: The autistic person’s perceptions of impact on the family

Subthemes:

- ‘Guilt over impact on the family’

“ I think it affects all of my family. I’ve definitely felt guilty over the years that it’s not my fault, but I feel it. ”

“ She’s always had this severe anxiety... and a lot of her anxiety stems back from that - sort of constantly being on guard for me. It’s difficult when I look back. ”

Theme 13: Economic impact on the autistic person

Subthemes:

- ‘Very difficult for autistic person in relation to accessing employment’
- ‘Navigating Benefits system difficult for autistic person’
- ‘Very hard to get a job if you mention epilepsy - autism is a little better’
- ‘Autistic person feels guilty – living off my parents or sponging off state’

“ I have less than a 35% chance of ever getting employed based on the statistics for people with autism and people with epilepsy separately in employment. ”

“ Adjustments [in workplaces] are free and small usually, but they are so often overlooked. ”

“ What’s the point in rights for being at work, if we can’t even get into work. ”

“ Employers and employees don’t understand or have a grasp of it, even if it’s in policies and contracts, a huge amount of awareness is totally needed every single time. ”

“ It is hard depending on the state to survive. ”

Theme 14: Economic impact on parents and the family

Subthemes:

- ‘Mother sacrificing career to look after children’
- ‘Affects parent’s confidence if they don’t work’
- ‘Need to future proof for child’s sake’
- ‘Paying for childcare (Limited available formal childcare & limited willingness from informal childcare)’

Theme 16: Learning and communication difficulties

Subthemes:

- 'Overestimate what child understands due to superficially good verbal ability leading to meltdowns'
- 'Child is nonverbal so people misunderstand receptive language abilities'

“ She does a good job of masking how little she understands. ”

“ We're stuck in a perpetual terrible twos that stage that neurotypical kids go through where they can't quite communicate what they need or want, and then rage instead, because they haven't got the language. ”

Theme 17: Epilepsy or autism has the greatest impact

Subthemes:

- 'Was epilepsy but now autism'
- 'Depends on frequency of seizures'

“ Autism is pushed to side when seizures were more frequent. ”

“ It is around what is the most pressing issue at the time. ”

“ The focus shifts depending on whether seizures are active or not. ”

“ Not being able to work has had a massive effect on my mom's confidence. ”

“ It is not unusual to end up paying for childcare you cannot use. ”

“ If anything happens to us in the future, who is going to look after our child? ”

“ It's interesting how so many childcare providers shy away from having a child with epilepsy. ”

“ I'm essentially a 1950s housewife. ”

Theme 15: Impact of behaviour that challenges

Subthemes:

- 'Parent/blaming - You are not a good parent'
- 'People ignore child as if they (the child) can't hear or understand'
- 'Can impact negatively on siblings'
- 'Can impact negatively on parents'
- 'Lack of understanding of child's needs leads to misunderstandings'
- 'Individual displays self-injury'
- 'Public misinterpret behaviour especially when child does not look physically different'

“ 'Parentsplaining' [others explaining to you what you should be doing as a parent] is common. ”

“ And even within the family you know there's just been so many examples of misinterpretation of behaviours to the point where sometimes you think it's willful. ”

“ The public at large misinterpret pretty much any kind of behaviour which they see as challenging and especially if your child doesn't look visibly disabled in any way the assumptions are made that they are just naughty, horrible, spoiled. ”

Theme 18: Sleep

Subthemes:

- 'Lack of parental sleep impacts parental wellbeing/function'
- 'Hard to put the child to sleep'
- 'Seizures impact sleep for autistic individual'

“ If we don't give her melatonin she doesn't settle to sleep. ”

“ When you're woken during the night repeatedly the desire and energy to do anything above and beyond what you have to do during the day decreases down to nothing. ”

“ When I fall asleep it's at that time when I start to have seizures... so it takes me a long time to get to sleep and it's just like a never-ending circle. ”

“ Digging ourselves an early grave [due to lack of sleep]. ”

“ Getting her to go to bed is a lot harder. ”

“ I was exhausted for the first 20 years of his life. ”

Part 3:

Economic analysis of the costs of co-occurring autism and

It's important to understanding the economic costs of co-occurring autism and epilepsy to make sure that adequate resources are in place to support affected people and their families. If inadequate financial resources are provided to the health and education sectors, it can lead to negative consequences.

The consequences might include things like increased financial burden for families in the form of indirect costs and inadequate access to needed health, care and educational resources. The indirect costs could include the increased need for informal care as well as negative impacts on ability to work and career progression.

Methods

We started by defining the search terms we would use for the review of the economic evidence in this area. Those were: terms associated with autism (autism, ASD, Asperger or pervasive developmental disorder) and epilepsy (epilepsy or seizure), combined with terms focused on cost and cost effectiveness analyses: economics, medical/ or Cost Benefit Analysis/ or Healthcare Costs/ or Cost of Illness/ or cost* or economic* or expense* or expenditure or finance* or willingness to pay or payment or DALY or disability adjusted life year or QALY or quality adjusted life year or net benefit or value or investment or patient reported outcome*.

Two researchers from the research team (TP and EZ) independently conducted comprehensive searches for peer-reviewed articles using online research databases – PsycINFO, Medline, Web of Science, CINAHL and Cochrane – and included any study looking at the cost-of-illness, resource use, or cost-effectiveness of relevant interventions that included autistic people who have epilepsy. The papers retrieved were limited to those available in the English language and published from 2000 onwards.

After removing duplicates, we had 274 abstracts, of which 10 were identified for full-text review. We used a simplified search based on the keywords listed above to search for studies in Google Scholar and screened resulting articles that might have been missed in the previous database searches. This search gave us 78 abstracts. Then we manually searched the references of the final included studies to capture additional studies that fit the inclusion criteria.

Results

A total of three papers met the inclusion criteria for this systematic review. All three of them were published relatively recently (ie, in the last decade), and were set in high income country settings in North America (US and Canada).

Due to the lack of evidence identified, greater flexibility was applied to the inclusion criteria for economic evidence than in the systematic review focusing on factors associated with co-occurring epilepsy in autistic people. In particular, one study focused on autism in people with epilepsy (Puka et al., 2016), and another study did not use ICD codes for autism or epilepsy, instead relying on diagnoses as reported by caregivers (Lavelle et al., 2014).

Across different contexts, each study examines only costs or resource use and none of the studies consider health outcomes. That means that no relevant economic evaluations of specific interventions targeted at autistic people who have epilepsy were found.

The systematic review can therefore be considered as exploratory, with a primary aim of establishing evidence gaps. Owing to the breadth of the methodology in the included studies, a formal and systematic approach to quality assessment and risk of bias that are usually applied to economic evaluation (eg, using the CHEERS statement; Husereau et al., 2013), was deemed inappropriate. Instead, the quality and limitations of each is assessed qualitatively in a narrative summary below.

Peacock et al. (2012)

Peacock et al. (2012) analyse Medicaid expenditure data from eight US states, comparing healthcare expenditure of children with and without autism. The dataset used consists of paediatric insurance claims for payments related to inpatient admissions, outpatient services and medication.

Children were eligible for Medicaid coverage either on the basis of low income or disability status. Around half of autistic children were eligible for Medicaid due to their disability status, compared to only 5% in the comparison group. The authors suggest this may mean that autistic children in the sample may require more medical treatment than other autistic children, and therefore may not be representative. They also suggest that those enrolled based on disability status may also have additional private coverage, though this is not clear from the available data.

Autistic children were identified based on International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes 299.00 and 299.80. Similarly, children with seizures and convulsions were identified based on ICD-9-CM codes 345 or 780.39. Children were eligible for inclusion in the analysis if they had either 1 inpatient admission or 2 outpatient encounters at least 30 days apart during the three years for which data was available. The final sample included 8,398 autistic children, and 1,464,383 children without autism. Amongst the autistic children, 13% (1,063) had seizures and convulsions, compared to 1.3% of children without autism.

Estimated costs are based on standardised Medicaid reimbursement rates in each state. Total annual expenditures per person for 2005 were estimated. Annual mean expenditure was \$10,709 for autistic children (12% inpatient, 22% drugs, 66% outpatient) compared to \$1,812 for children without autism (17% inpatient, 21% drugs, 62% outpatient).

Mean total annual expenditure for autistic children and no co-occurring conditions (in this study, epilepsy, learning disability or ADHD/hyperkinetic syndrome) was \$7,200, while mean expenditure was \$11,847 for children with both autism and epilepsy.

To isolate the effect of having epilepsy on expenditure, the authors ran two multivariate ordinary least squares (OLS) regressions, in order to control for the effect age, sex, ethnicity and type of health plan. This analysis suggests that epilepsy was associated with \$10,754 higher expenditures among those who were autistic and \$5,833 higher expenditures for those who were not autistic. However, a breakdown of the composition of this additional cost is not provided.

The authors note several limitations to their analysis. First, as noted above, the autistic children in the sample may be those with higher medical needs, and therefore higher medical expenditures.

Additionally, the study only includes children who have public insurance and have made medical claims in eight anonymous US states, and therefore are not representative of the autistic population in the US. It is therefore difficult to draw conclusions on the applicability of these estimates to settings outside of the US.

The authors do not state whether cost estimates are adjusted. It is assumed that the costs are reported in 2005 US dollars. Finally, children in the comparator group may not be generalisable to the wider population, as many children aged 1-17 may go up to 3 years without using any outpatient or inpatient healthcare services.

Puka et al. 2016

Puka et al. (2016) explore how health resource utilisation of children with epilepsy varies with comorbidities in Ontario, Canada. The authors use multiple linked administrative databases to identify children aged 0-18 years with epilepsy, based on ICD-10 code G40.x. Children with epilepsy who also had autism are identified also based on ICD-10 (F84).

Of the total of 19,035 children with epilepsy included in the study, only 290 (1.5%) of them were autistic. The authors note that this proportion may be lower than in other studies, and that this may be because comorbidities are underreported in the data used.

The annual number of neurologist visits, emergency department visits and hospitalisations were estimated for 2013. The association between having a comorbidity and health resource use was evaluated using Poisson regression, controlling for age, sex, residence and socioeconomic status. This analysis suggests that autism increased the risk of neurology visits¹ for children with epilepsy.

No estimates of the costs of healthcare utilisation are provided. In theory, these estimates could be combined with cost estimates from other studies to provide some estimate of the additional healthcare costs for children with epilepsy and autism. However, cost estimates in Peacock et al. (2012) are not directly comparable to this setting and are not broken down into component unit costs (ie, cost per visit).

Additionally, although Puka et al. (2016) report mean number of visits for the whole sample, estimated person-time at-risk is not reported, and the additional number of visits among autistic children remains unclear. Therefore, although it is clear that autism increases the risk of hospital visits in children with epilepsy, and that there is of course an additional cost associated with this, it is not possible to estimate the cost burden associated with these visits with the available data.

Lavelle et al. (2014)

Lavelle et al. (2014) use national data from two US surveys to estimate the economic burden associated with autism. One survey is used to estimate healthcare costs, while a second is used to estimate non-healthcare costs. None of the children in the first survey had epilepsy, so only non-healthcare costs from the second survey are described.

Members of an online market research panel who self-reported caring for an autistic child were emailed invitations to participate in the survey. A total of 137 autistic children were included in the sample for the second survey, only 10 of whom had epilepsy. The survey aimed to measure costs of school, therapy, family-coordinated services (including childcare and transportation), and caregiver time.

As a result, although the study provides detailed analysis on both healthcare and non-healthcare costs for autistic children, analysis for autistic children with epilepsy is limited. This amounts to a brief description of a sensitivity analysis:

“Healthcare costs were no longer significantly higher in the ASD group when we controlled for the presence of epilepsy or learning disability. The association between ASD and aggregate non-healthcare-costs decreased to \$10,508 (95% CI: \$725-\$20,586) when we controlled for these comorbidities”

However, these results are not presented in the paper or in the supplementary material so it is therefore difficult to draw any conclusions from them. The supplementary material suggests overall aggregate total non-healthcare costs for autistic children of \$14,060 [4390-24302], of which school costs represented \$8,610 [4390-24302]. However, none of the autistic children in the healthcare costs survey had epilepsy, so it is unclear how this could be controlled for.

1 Adjusted risk ratio (aRR) 1.91, 95% confidence interval (CI) [1.74-2.09], emergency department visits (aRR 1.26, 95% CI [1.13-1.40]) and hospitalizations (aRR 1.77, 95% CI [1.46-2.14])

Most importantly, although the results suggest that comorbidities are potentially an important determinant of non-healthcare costs for autistic children, it is unclear to what extent the additional base case costs are driven by learning disability or epilepsy. Additionally, only ten children in the sample had epilepsy, with clear implications for the ability to detect differences in costs in the sample. Finally, participating caregivers self-reported their child's diagnoses, and the term “autism” was used rather than ASD, which may lead to underestimates of ASD prevalence.

Summary

We've summarised the findings of our review in **Table 2**. There is an overall lack of economic evidence for the cost of epilepsy in autistic people and no specific, relevant healthcare interventions were identified for this population.

Although evidence suggests that autistic people will likely have greater healthcare utilisation, and therefore higher costs, it is difficult to comment on what drives differences in resource use or costs, based on the evidence reported.

Two of the studies focused on healthcare costs or utilisation. Although one study did look at non-healthcare costs of families, there is a lack of detail on epilepsy. None of the included studies looked at the longer-term economic impact of autism and epilepsy on families. For example, parents in the patient and public involvement (PPI) group discussions (see Part II) reported a reduction in the amount of time they were able to work and a need to save for their child's future, given the uncertainty in their child's long-term career prospects.

Despite both autism and epilepsy being associated with lower labour market participation (eg, Allers et al., 2015; Baldwin et al., 2014; Holwerda et al., 2012), we found no evidence regarding the impact of autism and epilepsy on children's future career prospects, even though this was a major concern reported by autistic people with epilepsy, and their caregivers.

Finally, in the PPI discussions, a sense of “dependency” was found to have an adverse effect on quality of life for both children and adults – who felt dependent on their parents or on the benefits system – and parents, who felt their children were dependent on them. This is another area that requires further research to benefit autistic people with epilepsy and their families. It will also have wider benefits for economic productivity and reduced welfare expenditure, as highlighted by reviews of enhancing work opportunities for autistic people (Hedley et al., 2015; Jacob et al., 2015).

Table 2: Factors significantly associated with occurrence of epilepsy in autistic people in studies with a 'good' quality rating.

| Author(s) | Objectives | Population | Methods | Results |
|---------------------|---|--|---|---|
| Lavelle et al. 2014 | To estimate the associations between autism spectrum disorder (ASD) diagnoses in children and health and non-health care costs. | Autistic children with epilepsy, whose caregiver responded to an online survey invitation (N=10) | Online survey asking respondents for non-health care costs. Generalised linear regression models were used to. | The association between autism spectrum disorders and total non-healthcare costs decreased from \$14,060 [95% CI: \$4,390-\$24,302], to \$10,508 [95% CI: \$725-\$20,586] when controlling for epilepsy and intellectual disability. |
| Peacock et al. 2012 | Estimate the impact of co-occurring conditions on annual medical care costs for children with autism spectrum disorders. | Children with autism spectrum disorders and seizures/convulsions, enrolled in Medicaid in 8 anonymous US states (N=1,063). | Analysis of paediatric insurance claims data for inpatient admissions, outpatient services and medication. The impact of epilepsy on overall costs was estimated using linear regression, controlling for age, sex, ethnicity and type of health care plan. | Mean total annual expenditure for children with ASD and no co-occurring conditions of \$7,200, compared to \$11,847 for children with both ASD and epilepsy. OLS analysis suggests that epilepsy was associated with \$5,833 higher expenditures for those with ASD. However, a breakdown of the composition of this additional cost is not provided. |
| Puka et al. 2016 | Estimate the association between comorbidities and health resource utilization amongst children with epilepsy in a universal health insurance system. | Children with epilepsy and autism spectrum disorders in Ontario, Canada (N=290). | The annual number of neurologist visits, emergency department visits and hospitalizations were estimated for 2013 using health administrative databases. The association between having a comorbidity and health resource use was evaluated using Poisson regression, controlling for age, sex, residence and socioeconomic status. | Autism spectrum disorders increased the risk of neurology visits (adjusted risk ratio (aRR) 1.91), emergency department visits (aRR 1.26) and hospitalizations (aRR 1.77) for children with epilepsy. |

Recommendations

After conducting our review, we have considered the implications of this work for supporting people with co-occurring autism and epilepsy in the future.

Improve awareness of the frequent co-occurrence in national guidelines and support organisations

The PPI group emphasised the need for improved awareness that autism and epilepsy are often co-occurring. It is important that the currently separate guidelines/toolkits (e.g. Royal College of General Practitioners, Royal College of Paediatrics and Child Health) and charity websites for supporting autistic people and people with epilepsy contain a section highlighting the frequent co-occurrence and its implications.

The guidelines/toolkits for each condition should also contain links to each other making it easy for professionals and caregivers to access information about both conditions. Support organisations should collaborate to ensure that guidelines for both conditions are integrated and support systems such as helplines can be shared to ensure access to support workers familiar with both conditions.

Make hospital visits more autism friendly

The PPI group highlighted that hospital visits for autistic people can be stress provoking. In particular, sensory sensitivities with respect to epilepsy-related investigations (eg, EEG and MRI) must be borne in mind when planning epilepsy-related visits.

It may be helpful to use telehealth where possible (eg, digital consultations, uploading seizure videos), to ensure in-person visits are as predictable as possible, and to provide visual supports (eg, visual schedules).

Epilepsy services need to ask autistic people and caregivers about the autistic person's preferences and needs including the best time of day for an appointment and sensory sensitivities.

Improve awareness of autism among epilepsy professionals

Lack of knowledge of the manifestation of autism among epilepsy professionals was highlighted as a particular concern by the PPI group.

Child and adult neurologists should be aware of the frequent co-occurrence of the conditions and the manifestations of autism at a group level, but also at the individual level. Professional bodies for doctors and nurses working in epilepsy care (e.g., Association of British Neurologists, British Paediatric Neurology Association) should invite autistic people with epilepsy to speak at training days and conferences.

Screen people with epilepsy for autism and other neurodevelopmental and mental health conditions

People with epilepsy have a much higher risk for autism than people without epilepsy. To ensure that all people with epilepsy and autism are identified, everyone with epilepsy should be screened for autism at or close to diagnosis.

Many studies have shown that autism is under recognised in epilepsy, leading to a lack of appropriate supports. Screening everyone will ensure that traditionally harder to identify groups such as females or people with frequent seizures, as highlighted by the PPI group, will be identified as early as possible.

Screening should be broad, focussing not only on autism but also other mental health and neurodevelopmental conditions. The PPI group indicated that they would like to know about potential co-occurring neurodevelopmental conditions at or close to epilepsy diagnosis.

Ensure that autistic people who have epilepsy have access to evidence-based therapies for co-occurring conditions

The PPI group emphasised that autistic people who have epilepsy often have other co-occurring health conditions, particularly mental health conditions and difficulties with sleep. These additional co-occurring difficulties often impact very negatively on the quality of life of the individuals and their families.

It is vital that people with both autism and epilepsy have access to evidence-based therapies for these conditions.

Future Research

The need for future research in co-occurring autism and epilepsy has been comprehensively identified in Autistica's 'Epilepsy Summit Report: How can research into autism and epilepsy save lives?'. This report highlights 13 keys areas where further research is needed, including:

- The need to better understand epilepsy onset in autistic people
- Seizure medication side-effects in autistic people
- Role of stress/anxiety and sleep difficulties in quality of life in people with both conditions
- Possible biomarkers associated with the co-occurrence
- Genetic aspects of the co-occurrence
- Risk factors for premature death in autistic people with epilepsy

In addition to these areas, we have highlighted the following areas where future research is needed:

Qualitative research with autistic people with epilepsy and their families

The lack of previously published research available on the lived experiences of autistic people with epilepsy and their families points to the necessity of conducting future qualitative research in this area.

Our PPI group has given valuable insights into the needs of this group but formal research is needed. In particular, it will be important to ensure that autistic people with epilepsy who also have learning difficulties/learning disability can be included.

Health Economics

Key relevant economic interventions for this population remain unclear and need to be identified. Interventions for this population may also go beyond healthcare, encompassing social care and education.

Economic evaluation of any identified interventions should take a societal perspective where possible, given the high direct and indirect costs borne by families of autistic children with epilepsy (see PPI discussion in Part II). If this is not possible, a provider perspective, including estimates of affordability, would still be valuable, given the lack of evidence. It may also be important to account for the quality-of-life for all household members, including siblings, in any economic evaluation, given the impact on the whole family.

Further research is needed on long-term non-healthcare costs. There remains uncertainty on how these differ for autistic people with epilepsy, as compared with autistic people who do not have epilepsy. These kind of questions could be addressed using a cohort study, measuring indirect costs, employment status, income and other opportunity costs to household members, including impact on leisure time.

Research is also needed on the impact that living with autism and epilepsy has on job/employment prospects for children when they grow up. Facilitating greater labour market participation will lead to benefits both for individuals and for society.

Conclusion

The prevalence of co-occurring epilepsy in autistic people is higher than in people without autism, as is the prevalence of autism in people with epilepsy. The factor most consistently associated with the co-occurrence is the presence of learning difficulties or learning disability.

There is a lack of data on the lived experience of people with both conditions. The PPI group in this project highlighted a range of needs that the people with both conditions have, including some aspects specific to individuals with both conditions. These specific aspects include difficulties for autistic people with respect to epilepsy related investigations and hospital visits, a lack of integrated healthcare, limited knowledge of autism among epilepsy professionals and potential impact of anti-seizure medicines on perception of autism symptoms and subsequent manifestation of symptoms.

There are few previous studies of the economic impact of having both conditions, although it is clear that the co-occurrence can increase the risk of hospital visits and economic cost. Additionally, analysis of responses from the PPI group suggest a potentially significant broad economic impact of having both conditions.

The lack of research and data on both the lived experience of people with both conditions and on the economic impact of having both conditions demonstrates the stark need for greater research investment in this area.

Key Papers

Amiet, C., Gourfinkel-An, I., Bouzamondo, A., Tordjman, S., Baulac, M., Lechat, P., Mottron, L., & Cohen, D. (2008). Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. *Biological psychiatry*, 64(7), 577–582.

A previous systematic review and meta-analysis that showed that main risk factors for epilepsy in autistic people are presence of learning disability and female gender.

Bolton, P. F., Carcani-Rathwell, I., Hutton, J., Goode, S., Howlin, P., & Rutter, M. (2011). Epilepsy in autism: features and correlates. *The British Journal of Psychiatry*, 198(4), 289-294.

A retrospective study that showed that learning disability, female gender and poor language skills are significant risk factors for the co-occurrence of epilepsy in autistic people.

Christensen, J., Overgaard, M., Parner, E. T., Vestergaard, M., & Schendel, D. (2016). Risk of epilepsy and autism in full and half siblings—A population-based cohort study. *Epilepsia*, 57(12), 2011-2018.

A population-based cohort study that found that having an older sibling with autism or epilepsy significantly increased the chances of co-occurring epilepsy in the younger autistic sibling.

Danielsson, S., Gillberg, I. C., Billstedt, E., Gillberg, C., & Olsson, I. (2005). Epilepsy in young adults with autism: a prospective population-based follow-up study of 120 individuals diagnosed in childhood. *Epilepsia*, 46(6), 918-923.

A population-based study that found that impaired cognitive level and adaptive behavior skills are significant risk factors for the co-occurrence of epilepsy in autistic people.

Jain, A., Spencer, D., Yang, W., Kelly, J.P., Newschaffer, C.J., Johnson, J., Marshall, J., Francisca, A., Tabb, L.P. & Dennen, T. (2014). Injuries Among Children With Autism Spectrum Disorder. *Academic Pediatrics*, 14(4), 390-397.

A retrospective study that showed that the presence of injuries/accidents are significantly associated with co-occurrence of epilepsy in autism.

Oslejskova, H., Dusek, L., Makovska, Z., & Rektor, I. (2007). Epilepsia, epileptiform abnormalities, non-righthandedness, hypotonia and severe decreased IQ are associated with language impairment in autism. *Epileptic Disorders*, 9(5), 9-18.

A retrospective study that showed that the presence of regression and poor language abilities (delayed speech and mutism) are significant risk factors for the co-occurrence of epilepsy in autism.

Pavone, P., Incorpora, G., Fiumara, A., Parano, E., Trifiletti, R. R., & Ruggieri, M. (2004). Epilepsy is not a prominent feature of primary autism. *Neuropediatrics*, 35(04), 207-210.

A study that showed that impaired cognitive abilities (low IQ scores) and autism severity are significant risk factors for the co-occurrence of epilepsy in autism.

Peacock, G., Amendah, D., Ouyang, L., & Grosse, S. D. (2012). Autism spectrum disorders and healthcare expenditures: the effects of co-occurring conditions. *Journal of Developmental & Behavioral Pediatrics*, 33(1), 2-8.

A study that analysed US health insurance databases to estimate the impact of co-occurring conditions on annual medical care costs for children with autism spectrum disorders.

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Young Epilepsy is the children and young people's epilepsy charity. We exist to create a society where children and young people with epilepsy are enabled to thrive and fulfill their potential. A society in which their voices are respected and their ambitions realised.

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