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Mortality in people with intellectual disabilities and epilepsy: a systematic review

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Abstract

Background. Epilepsy is highly prevalent in people with intellectual disabilities and mortality is increased in people with epilepsy generally. This review summarises research on the comparative risk of mortality in people with intellectual disabilities and epilepsy compared to the general population, people with intellectual disabilities without epilepsy, and people with epilepsy without intellectual disabilities.

Method. Studies were identified via electronic searches using Medline, Cinahl and PsycINFO and cross-citations. Information extracted from studies was tabulated and reviewed narratively.

Results. 16 studies met the inclusion criteria. Epilepsy was associated with increased mortality in people with intellectual disabilities in most studies, particularly in those experiencing recent seizures. Further research is needed to substantiate some of the reported findings.

Conclusion. Services must be equipped with the skills and information needed to manage this condition in order to minimise the risk of death in people with intellectual disabilities and epilepsy.

Keywords: epilepsy; mortality; intellectual disabilities

Introduction

Epilepsy is one of the most common serious brain disorders, affecting over 50 million people worldwide (WHO, 2005). The prevalence of epilepsy has been estimated at approximately 0.5% to 1.0% of the general population (Forsgren *et al.*, 2005, Linehan *et al.*, 2010, Joint Epilepsy Council, 2011). In people with intellectual disabilities, estimates of the prevalence of epilepsy vary due to differences in the methods used and inherent population biases (Lhatoo and Sander, 2001). Despite this variation, it is clear that the prevalence of epilepsy in people with intellectual disabilities is much greater than in the general population (Deb, 2000). Reported rates range, for example, from 16.1% of 1,595 people with intellectual disabilities identified in South Wales (Morgan *et al.*, 2003) to 30.7% in a random sample of 753 people with intellectual disabilities aged 40 or more from Ireland's National Intellectual Disability Database (NIDD) (McCarron *et al.*, 2014). In a systematic review of the prevalence of chronic health conditions in children with intellectual disabilities, the most common condition was epilepsy (Oeseburg *et al.*, 2011) with prevalence rates in the 14 studies identified ranging from 5.5% to 35.0%, with an overall weighted mean prevalence rate of 22.0% (95% CI 20.8, 23.2).

Mortality is increased in people with epilepsy, with a recent systematic review and meta-analysis of 38 epilepsy cohorts including over 165,000 patients finding a pooled relative risk of death of 3.3 (95% CI 2.83, 3.92) compared to the general population (Nevalainen *et al.*, 2014). Risk of premature death was lowest in idiopathic epilepsy and in people with epilepsy who had attained seizure freedom.

People with epilepsy may have elevated mortality from external causes such as accidents including drowning (Bell *et al.*, 2008). However, Sudden Unexpected Death in Epilepsy (SUDEP) is the most important category of epilepsy related death (Kiani *et al.*, 2014). In the UK it is estimated that 500 deaths per annum are SUDEP (Hanna *et al.*, 2002). Overall findings regarding the risk of SUDEP in

people with intellectual disabilities are inconsistent. One systematic review of risk factors for SUDEP based on 27 studies found that 'mental retardation' was not a risk factor for SUDEP (Monté *et al.*, 2007). However, it is not clear how many studies in the review included intellectual disability as a risk factor. A more recent review identified 23 articles which considered intellectual disability and SUDEP of which 14 found intellectual disability to be a risk factor for SUDEP and none found intellectual disability to be a protective factor in SUDEP (Young *et al.*, 2014).

For people with intellectual disabilities, epilepsy or convulsions has been identified as an important and to some extent potentially preventable cause of death (Glover and Ayub, 2010). The study looked at ages and causes of death recorded on death certificates for people with intellectual disabilities, or conditions that can cause intellectual disabilities, who died between 2004 and 2008 in England. Epilepsy or unspecified convulsions were involved in 948 deaths (13% of those identifiable) of people with intellectual disabilities or possibly associated conditions. In other people, they were involved in 0.4%. Based on Standardised Mortality Odds Ratios (an approximation of the Standardised Mortality Ratio), adjusting for ages at death, people where death involved epilepsy or unspecified convulsions were 9.7 times more likely than others to have an intellectual disability-related condition (95% confidence interval 9.1, 10.4).

The high prevalence of epilepsy in people with intellectual disabilities, combined with the increased risk of mortality in people with epilepsy, makes the topic of mortality in people with intellectual disabilities and epilepsy a pertinent one. This review aims to summarise studies on mortality in the general population of people with intellectual disabilities and epilepsy and as such it excludes studies on specific syndromes associated with intellectual disabilities. However, the review does include information relating to people with Down syndrome which is by far the most common chromosomal disorder associated with intellectual disability with a prevalence of approximately 1 in 700 live births (Hatton, 2012). Most early studies of mortality in people with intellectual disabilities

and epilepsy were hospital based, with an early search of the literature finding no population based-studies including all types of intellectual disabilities on the influence of epilepsy on mortality (Forsgren *et al.*, 1996). Since that time, further studies have been conducted, including population-based studies. In this review, we summarise existing research published from 1990 that quantifies the mortality of people with intellectual disabilities and epilepsy using a comparative statistic relative to either the general population, people with intellectual disabilities who do not have epilepsy, or people with epilepsy who do not have intellectual disabilities. The statistics reported are defined in Table One. For all of these, a value of one implies no difference between the two groups, a value of more than one indicates that the risk is greater in the target group, and a value of less than one indicates that the risk is less in the target group. For example, a hazard ratio of two implies double the risk of dying in the target group than in the comparison group. If the hazard ratio is 0.5 then the relative risk of dying in the target group is half the risk of dying in the comparison group. For all of these statistics, the value can be considered statistically significant at $p<.05$ if the 95% confidence interval does not include one.

Table One Here

Method

Electronic literature database searches were conducted in Medline, Cinahl and PsycINFO on EBSCO. In addition, the reference lists of articles meeting the inclusion criteria were searched and articles from authors' personal collections included. The reference lists of key book chapters were also searched (Blake and Kerr, 2014, Brown, 2008, Cardoza and Kerr, 2010). Searches were completed on 19 June 2014. Searches included terms relating to both mortality and prevalence to create a pool of articles on mortality or prevalence, with articles on prevalence being retained for a separate review. Searches combined terms for epilepsy, intellectual disabilities, and mortality/prevalence with the Boolean operator 'and'. Full details of the search terms are given in Appendix One.

Inclusion Criteria

- Peer reviewed
- English Language full text
- Published from 1990; articles published before this date were excluded as they predate both improvements in epilepsy treatment and major changes in service provision for people with intellectual disabilities (Emerson, 2004).
- Primary research.
- Presents a comparative statistic (e.g. relative risk, standardized mortality ratio (SMR), hazard ratio) on mortality in adults or children with intellectual disability and epilepsy compared to the general population, people with intellectual disability without epilepsy, or people with epilepsy without intellectual disability
- Samples of adults or children with intellectual disabilities or samples where 50% or more have intellectual disabilities or mixed samples where results are disaggregated for people with intellectual disabilities

Exclusion Criteria

- Case studies
- Case series
- Narrative reviews
- Studies based on neonates (new born infants up to 28 days after birth), all other age groups were included
- Studies on conditions where intellectual disabilities cannot be assumed (e.g. cerebral palsy, autistic spectrum disorder (ASD)) where results were not disaggregated for people with intellectual disabilities
- Studies on specific syndromes associated with intellectual disabilities with the exception of Down syndrome. Less common syndromes were excluded, such as Fragile X syndrome

which has a prevalence of 1 in 4,000 males and 1 in 8,000 females (Cornish *et al.*, 2012) and is not always associated with intellectual disabilities (Hatton, 2012).

- Does not present a comparative statistic approximating relative risk (e.g. presents only descriptive statistics, presents chi-squared analysis).

Initially, titles and abstracts were used to exclude those studies which were obviously not within the scope of reviews on prevalence or mortality. Those retained for further screening were those for which relevance could not be assessed without accessing full text, or those that were chosen as potentially within scope. These studies were screened by the first and second author and discussed until consensus was reached on whether or not they met the inclusion criteria in relation to mortality in people with intellectual disabilities and epilepsy.

Where multiple articles used the same sample or samples were likely to have considerable overlap (e.g. Day *et al.*, 2003, Day *et al.*, 2005), only the most recent study was included unless the studies were looking at different topics within the same sample (e.g. Strauss et al 2003 and Day et al 2005 are based on the same sample source but one looks at causes of death, and one looks at whether seizure severity increases mortality).

Information from the included studies was extracted by the first author in relation to: authors; year of publication; country of study; study design and study period; sample description; definition of epilepsy; sample size and number of deaths for those with intellectual disabilities and epilepsy; sample size and number of deaths for any comparison group; group that people with intellectual disabilities and epilepsy are compared to; statistic used (e.g. SMR); and main results. This information was tabulated (see Table Two). Formal quality assessments were not undertaken as the intention was to include all studies reporting relevant comparative statistics and as such the review does not adhere to PRISMA guidelines (Moher *et al.*, 2009). However, elements of studies relevant

to quality and risk of bias (i.e. sample representativeness, definition used for ascertainment of epilepsy, sample size) are summarised for each study in Table Two. Differences in the main characteristics of samples included in the studies and in the definition of epilepsy used were such that it was not possible to conduct meta-analysis to combine estimates of the risk of mortality.

Results

The process of identifying studies for inclusion is summarised in Figure One. Electronic database searches identified a total of 1,332 references, with 1,099 remaining after removal of duplicates. Following the first examination of studies, 144 remained in a pool of articles relating to mortality or prevalence. After examination of full text articles from this pool and the addition of articles cited within these and from authors' personal collections, 16 articles met the criteria for inclusion in relation to mortality in people with intellectual disabilities and epilepsy.

Figure One here – identification of studies here

Country

All studies were from high income countries. There were five studies based on samples from the United States (Day *et al.*, 2005, Decouflé and Autry, 2002, Nickels *et al.*, 2012, Strauss *et al.*, 2003, Walczak *et al.*, 2001); four from the United Kingdom (UK) (Derby *et al.*, 1996, Hermon *et al.*, 2001, Kiani *et al.*, 2014, Nashef *et al.*, 1995); three from Finland (Mölsä, 1994, Patja *et al.*, 2000, Sillanpää and Shinnar, 2010); and one from each of the Netherlands (Coppus *et al.*, 2008), Sweden (Forsgren *et al.*, 1996), Sweden and Denmark (Hill *et al.*, 2003), and Japan (Ohwada *et al.*, 2013). The studies are summarised in Table Two. Figures for 95% confidence intervals are given in parentheses after the point estimate.

Table Two Here: Summary of Studies

Sample Representativeness

Few studies were based on samples that could be considered representative of the general population of people with intellectual disabilities and epilepsy. Three studies were based on samples of people with Down syndrome (Coppus *et al.*, 2008, Hermon *et al.*, 2001, Hill *et al.*, 2003). Two articles using the same data source included those with mild developmental disabilities (Day *et al.*, 2005, Strauss *et al.*, 2003). One study included those with refractory epilepsy (Derby *et al.*, 1996). Other studies were based on samples from specific settings where samples may have been skewed towards those with more severe epilepsy, including those attending one school for those with epilepsy and intellectual disabilities (Nashef *et al.*, 1995), an institution for those with the most severe disabilities (Ohwada *et al.*, 2013), inpatients and outpatients at one centre for people with intellectual disabilities (Mölsä, 1994) and patients at three epilepsy centres (Walczak *et al.*, 2001).

Two studies included comprehensive samples of people with epilepsy including those with and without intellectual disabilities. One study ascertained all children with epilepsy in one US county (Nickels *et al.*, 2012). Similarly, one study ascertained all children with epilepsy in the catchment area of one hospital (Sillanpää and Shinnar, 2010). One study used a population based cohort of people with developmental disabilities but this study did not give exact details for the number of people with intellectual disabilities and epilepsy in the sample, with the result given in Table Two relating to those with epilepsy and an additional unspecified developmental disability (Decouflé and Autry, 2002). Three studies included representative samples of people with intellectual disabilities both with and without epilepsy including all those in one province of Finland (Forsgren *et al.*, 1996), those on the Leicestershire Intellectual Disability Register (Kiani *et al.*, 2014), and a nationwide population based sample from Finland (Patja *et al.*, 2000).

All cause mortality in cohorts with intellectual disabilities: comparison of those with or without epilepsy to the general population

In a small number of studies, figures are given in relation to all cause mortality for people with intellectual disabilities compared to the general population separately for those with and without epilepsy, or the entire sample including both those with and without epilepsy. For those with mild developmental disabilities (excluding those unable to walk well or with degenerative conditions), the SMR for those with remote symptomatic epilepsy was 4.0 (95% CI 3.6, 4.3) compared to 1.9 (95% CI 1.8, 2.0) for those without epilepsy (Day *et al.*, 2005). For a representative sample of people with intellectual disabilities from Sweden, the SMR was 5.0 (95% CI 3.3, 7.5) for those with intellectual disabilities and epilepsy compared to 2.0 (95% CI 1.7, 2.3) for the entire sample (Forsgren *et al.*, 1996). In this latter study, SMRs are also given in relation to seizure type and frequency: seizure free in the preceding year 2.0 (95% CI 0.9, 4.7); seizures weekly or fewer 4.7 (95% CI 2.8, 7.9); seizures more than weekly 16.8 (95% CI 10.7, 26.5); partial seizures without seizures secondarily generalized 3.7 (95% CI 1.0, 13.6); seizures secondarily generalized 5.0 (95% CI 2.3, 11.0); and seizures generalized from onset 8.1 (95% CI 5.7, 11.5). In a sample from England, the SMRs for people with intellectual disabilities and epilepsy were 3.2 (95% CI 2.7, 3.8) for men and 5.6 (95% CI 4.6, 6.7) for women, whilst the overall SMRs for the entire sample were 2.2 (95% CI 2.0, 2.4) for men and 2.8 (95% CI 2.5, 3.1) for women (Kiani *et al.*, 2014). Finally, the SMR for overall mortality in a study of pupils at one school for those with severe epilepsy and intellectual disabilities compared to the general population was 15.9 (95% CI 10.6, 23.0) (Nashef *et al.*, 1995).

All cause mortality in cohorts with intellectual disabilities: comparison of those with and without epilepsy

More commonly, studies compare the mortality of people with intellectual disabilities and epilepsy to people with intellectual disabilities who do not have epilepsy in the same cohort. For people with mild developmental disabilities (excluding those unable to walk well or with degenerative

conditions) and remote symptomatic epilepsy, compared to those in the cohort without epilepsy, SMRs were: 1.1 (95% CI 0.8, 1.5) for those who had not had a seizure in the last year; 2.4 (95% CI 1.9, 3.0) for those who had had seizures in the last year but not generalised tonic-clonic (GTC) seizures; 2.9 (95% CI 2.4, 3.4) for those who had had GTC seizures in the last year; and 3.7 (95% CI 2.5, 5.4) for those who had experienced status epilepticus in the last year (Strauss *et al.*, 2003). In this cohort, those without epilepsy had an SMR of 1.7 (95% CI not stated) compared to the general population. In a later analysis employing the same sample source and exclusions, the overall ratio SMR (the SMR for those with epilepsy divided by the SMR for those without epilepsy) was 2.1 (95% CI 1.9, 2.3) (Day *et al.*, 2005).

In a cohort of inpatients and outpatients of one centre for people with intellectual disabilities, the hazard ratio was 0.87 (95% CI 0.48, 1.61) for inpatients with epilepsy and 1.79 (95% CI 0.76, 4.25) for outpatients with epilepsy (Mölsä, 1994). When type of residence was considered for outpatients, the risk of death due to status epilepticus was more than doubled for those in hostels. In a cohort living in one institution for people with severe intellectual disabilities (excluding those with severe motor disabilities), the hazard ratio for those with epilepsy compared to those without was 2.39 (95% CI 1.17, 4.92) (Ohwada *et al.*, 2013). This remained significant in a multivariate analysis with a hazard ratio of 2.79 (95% CI 1.21, 6.41). In a nationwide population based sample, epilepsy was associated with reduced survival in those who were aged 2 to 9 in 1962 (hazard ratio 95% CI 0.38, 0.84, point estimate not stated) and those who were aged 10 to 19 in 1962 (hazard ratio 95% CI 0.10, 0.81, point estimate not stated) (Patja *et al.*, 2000). Finally, one study gives a hazard ratio of 2.29 (95% CI 1.50, 3.48) for those with epilepsy compared to those without epilepsy in a cohort of people with Down syndrome aged 45 or more (Coppus *et al.*, 2008). However, in multivariate survival analysis, age, presence of dementia, and mobility restrictions were the most important predictors of mortality.

All cause mortality in cohorts with epilepsy: comparison of those with or without intellectual disabilities

In other studies, figures are given for cohorts of people with epilepsy depending on whether or not they have an intellectual disability. For those with epilepsy and an additional developmental disability (including but not necessarily intellectual disabilities) the all cause SMR (compared to the general population) was 13.2 (95% CI 7.6, 21.5); for those with epilepsy and no other developmental disability the SMR was 1.5 (95% CI 0.3, 4.3) (Decouflé and Autry, 2002). In a population based cohort of children with epilepsy, the hazard ratio for those with intellectual disability compared to those with epilepsy without intellectual disability was 20.86 (95% CI 2.76, 157.97) although only abnormal neurological examination was statistically significant in a multivariate model (Nickels *et al.*, 2012). Similarly, for those with remote symptomatic epilepsy the hazard ratio for those with severe cognitive impairment was 4.1 (95% CI 2.0, 8.3) (Sillanpää and Shinnar, 2010). However, only lack of 5-year terminal remission was significant in multivariate analysis.

Causes of Death

A small number of studies have considered specific causes of death. One study looked at causes of death in people with mild developmental disabilities (excluding those unable to walk well or with degenerative conditions) and remote symptomatic epilepsy which was noted to be epilepsy occurring in persons with developmental delay or identified brain lesions and excluding idiopathic epilepsy. Ratio SMRs were obtained for those with epilepsy compared to those without epilepsy in the cohort for numerous causes of death including: epilepsy/seizures 53.1 (95% CI 28.0, 101.0); convulsions 25.2, (95% CI 11.7, 54.2); brain cancer 5.2 (95% CI 2.2, 12.1); accidents 2.7 (95% CI 1.9, 3.7); respiratory diseases 1.7 (95% CI 1.2, 2.5) including aspiration pneumonia and accidental inhation 3.0 (95% CI 1.5, 6.0); suicide 1.5 (95% CI 0.3, 6.5); and circulatory diseases 1.3 (95% CI 1.0, 1.7) (Day *et al.*, 2005). Accidental drowning was noted to be the single most significant cause of accidental death. The ratio SMR for accidental drowning, which was included as part of the total

accidents figures, was 12.8 (95% CI 7.0, 23.2). The ratio SMR for accidental drowning in those with recent seizures was 15.8 (95% CI 7.2, 34.7). Compared to the general population, the SMR for accidental drowning for those with recent seizures was 35.9 (95% CI not stated) compared to 2.3 (95% CI not stated) for those with no history of epilepsy. The authors note that the excess numbers of deaths due to some causes (e.g., seizures, aspiration, and accidental drowning) must at least in part be attributable to epilepsy. For suicide, the SMR compared to the general population was 0.3 (95% CI not stated) for those with epilepsy and 0.2 for those without epilepsy. Finally, two studies have looked at epilepsy as a cause of death in people with Down syndrome compared to the general population, with one reporting a SMR of 17.3 (95% CI 7.4, 34.0) (Hermon *et al.*, 2001) and one reporting a SMR of 30.4 (95% CI 13.9, 57.7) (Hill *et al.*, 2003).

SUDEP

SUDEP as a cause of death is considered in a small number of studies. In a sample from England, SMRs for SUDEP in people with intellectual disabilities compared to the general population were 37.6 (95% CI 21.9, 60.2) for men and 52.0 (95% CI 23.8, 98.8) for women (Kiani *et al.*, 2014). A study of pupils at one school for pupils with severe epilepsy and intellectual disabilities found an incidence of SUDEP of 1:295/year (Nashef *et al.*, 1995). It was noted that all 14 cases of SUDEP occurred when the pupils were not under the close supervision of the school and most were unwitnessed. In a study of those with refractory epilepsy aged under 50, the relative risk of SUDEP was 1.4 (95% CI 0.3, 8.0) for those with a computer recorded history of intellectual disabilities compared to those without (Derby *et al.*, 1996). Finally, for patients at 3 epilepsy centres intellectual disability was a risk factor for SUDEP after adjustment for seizure frequency (odds ratio 4.6 (95% CI 1.2, 18.0)) (Walczak *et al.*, 2001).

Discussion

People with intellectual disabilities have an elevated risk of death compared to the general population, and the studies reviewed here indicate that this risk is elevated further in those who have co-occurring epilepsy. The risk of death in people with intellectual disabilities and epilepsy has been found to be greater than in the general population by between 3.2 times for men on the Leicestershire Intellectual Disability Register (Kiani *et al.*, 2014) and 16.8 times for those having seizures more than weekly (Forsgren *et al.*, 1996). In comparison, the pooled estimate for mortality in cohorts of people with epilepsy generally has been given as 3.3 (95% CI 2.83-3.92) (Nevalainen *et al.*, 2014). However, there are only four studies which provide a comparative statistic for those with intellectual disabilities and epilepsy compared to the general population (Forsgren *et al.*, 1996, Day *et al.*, 2005, Kiani *et al.*, 2014, Nashef *et al.*, 1995).

In a number of studies comparing mortality in people with intellectual disabilities and epilepsy to those with intellectual disabilities without epilepsy in the same cohort, the risk of death has been found to be two or more times greater (Ohwada *et al.*, 2013, Day *et al.*, 2005, Coppus *et al.*, 2008), although in the latter study only dementia, age at baseline and restricted mobility were significant in multivariate analysis. Further, the risk appears to be associated with seizure type and frequency with those who had not had a seizure in the last year not having an elevated risk of mortality (Strauss *et al.*, 2003).

For studies involving cohorts of people with epilepsy, increased risk for those with intellectual disabilities has been reported (Decouflé and Autry, 2002, Nickels *et al.*, 2012). However, in one of these studies, the risk associated with intellectual disabilities was not significant in multivariate analysis, with abnormal neurological examination being the only significant factor (Nickels *et al.*, 2012). Similary, severe cognitive impairment was associated with increased risk in those with remote symptomatic epilepsy but on multivariate analysis only lack of five year terminal remission

was significant (Sillanpää and Shinnar, 2010). This suggests that, although mortality in those with intellectual disabilities and epilepsy is significantly elevated, some of this excess is related to underlying conditions, rather than epilepsy per se. As noted in a previous review, the higher mortality in those with intellectual disabilities and epilepsy is partly due to epilepsy being a marker of the severity of disability, and the severity of disability being a predictor of mortality (Morgan *et al.*, 2001).

This issue is considered in the design of one study where it is noted that in the absence of a controlled comparison, it may not be possible to separate the effect of epilepsy on mortality from the effect due to the underlying condition (Strauss *et al.*, 2003). To address this, Strauss et al (2003) included only those with mild developmental disabilities with minimal motor dysfunction who did not have degenerative conditions. Based on a sample of over 80 thousand, they conclude that epilepsy per se is associated with an increased mortality rate, with the increased mortality risk being evident mainly in those with ongoing seizures.

Causes of Death

For people with mild developmental disabilities and remote symptomatic epilepsy the risk of death related to drowning in those with epilepsy compared to those without epilepsy in the cohort was 12.8 times higher (Day *et al.*, 2005). Compared to the general population, the SMR for drowning was 28.7 for those with remote symptomatic epilepsy, increasing to 35.9 for those with recent seizures. This compared to 2.3 for those with no history of epilepsy. In the general population of people with epilepsy, the SMR for drowning has been estimated as 18.7 (95% CI 15.0, 23.1) in a meta-analysis of 51 cohorts (Bell *et al.*, 2008). These figures suggest that the risk of drowning may be greater for people with mild developmental disabilities and epilepsy than for the general population of people with epilepsy, although this is based on just one study in which the 95% confidence interval around the point estimate is not given.

Over the period 1993 to 2010, SUDEP was the second most common cause of death among adults with epilepsy and intellectual disabilities on the Leicestershire Intellectual Disability Register (Kiani *et al.*, 2014). Twenty-six people with intellectual disabilities died from probable or definite SUDEP. The SMRs for SUDEP in adults with intellectual disabilities were 37.6 for men and 52.0 for women. The authors acknowledge that this is partly attributable to the higher prevalence of epilepsy among people with intellectual disabilities compared to the general population (the prevalence being 19% in the cohort) but that even taking this into account, people with intellectual disabilities appear to be disproportionately disadvantaged. Similarly, intellectual disability has been found to be a risk factor for SUDEP even after adjusting for seizure frequency (Walczak *et al.*, 2001). However, for those with refractory epilepsy on the General Practice Research Database (GPRD, a database including over 4 million people registered with a GP in the UK), the relative risk of SUDEP was not significantly increased in people with a history of intellectual disability (Derby *et al.*, 1996). The authors acknowledge that with a small number of sudden deaths, confidence intervals are wide and that ascertainment of intellectual disability may not have been complete.

Finally, Day et al (2005) found that in people with developmental disabilities and remote symptomatic epilepsy death rates were elevated for a number of causes including aspiration pneumonia. However, the rate for suicide was lower than that for the general population (although the confidence interval for this estimate is not given). Overall, in relation to cause of death in people with intellectual disabilities and epilepsy, there is a need for more research on cause of death and to facilitate this there is a need for better, detailed recording of death so that cause of death can be determined with some certainty.

Limitations

There are a number of limitations to this review. Whilst studies were identified from a range of countries, the review is restricted to English language publications. Very little information was identified regarding mortality for people with intellectual disabilities and epilepsy in low and middle income (LAMI) countries. However, this is not surprising as there is little information available regarding mortality for people with epilepsy as a whole from LAMI countries. This lack of data has been attributed to the fact that in LAMI countries, incidence studies are difficult, death certificates are not very reliable, autopsies are not easy to obtain, and the cause of death is not usually known with certainty (Carpio *et al.*, 2005).

The review has included studies relating to mortality in people with intellectual disabilities and epilepsy generally but has only included the most common syndrome associated with intellectual disability (Down syndrome). People with intellectual disabilities are a highly heterogeneous group. Whilst all have a significant general impairment in intellectual functioning that is acquired during childhood, they differ in relation to the cause and severity of the intellectual disability which may result from a complex interaction between biomedical, social, behavioural and educational factors (Hatton, 2012). Further, life expectancy can vary markedly between specific syndromes associated with intellectual disabilities. For example, mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) is associated with early death, generally during the second or third decade of life (Valstar *et al.*, 2008), whilst life expectancy in fragile X syndrome is not greatly reduced (Sabaratnam, 2006). Future reviews could consider the issue of mortality in other syndromes that are associated with intellectual disabilities. It is evident that research related to epilepsy in such syndromes, although not necessarily in relation to mortality, does exist (e.g. Leung and Ring, 2013).

All data was extracted by one reviewer and extraction of data by two reviewers independently would have reduced the possibility of errors. Ideally, the same definition of epilepsy should be used across studies to allow comparison of mortality rates. However, the studies identified use a variety of definitions of epilepsy as shown in Table Two. Further, for some studies the confidence intervals around point estimates are extremely wide.

Finally, many of the studies include cohorts for time periods that preceded the development of more recent anti-epileptic drugs (AEDs). It has been noted that after a 15 year period with no new treatments, five drugs for epilepsy were approved from 1993 to 1997 (McKee and Bodfish, 2000). As such, the relevance of early cohorts to current practice may be restricted. As poor seizure control appears to be a risk factor for mortality, future studies may show a diminished risk of mortality due to wider variety of treatment options.

Conclusion

The evidence base identified for this review is small and further research is needed to substantiate some of the findings reported here. However, the evidence suggests that people with intellectual disabilities and epilepsy do have a substantially increased risk of mortality, particularly where seizures are ongoing. It is important that services are equipped with the information and skills needed to manage epilepsy in this population. A recent report provides information on reasonable adjustments that can be made to improve epilepsy care for people with intellectual disabilities (Marriott *et al.*, 2014) The ideas, information and examples of good practice in relation to reasonable adjustments provided within this report should help services improve provision for this highly prevalent condition and potentially reduce the excess deaths associated with epilepsy in people with intellectual disabilities.

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England.

Table One: Definitions for statistics reported

Term	Definition
Standardised mortality ratio (SMR)	Number of observed deaths in the target population divided by the number of deaths that would be expected based on death rates of a chosen standard population
Relative risk or risk ratio	The risk of an event (e.g. death) in the target population divided by the risk in the comparison group
Hazard ratio	A specific type of relative risk which is obtained using the Cox Proportional Hazards Model, a regression model that takes into account time until the event occurs
Odds ratio	The odds (number of times an event happens divided by the number of times it does not happen) of an event occurring in one group divided by the odds of the same event in another group

Table Two: Summary of studies on comparative risk of mortality in people with intellectual disabilities and epilepsy

Author	Country	Design & study period	Sample Description	Epilepsy definition	Sample size ID & epilepsy	Sample size other group	Comparison group	Statistic	Results (& 95% confidence interval). All cause mortality unless otherwise stated
Coppus, Evenhuis, Verberne et al 2008	Nether-lands	Prospective longitudinal cohort, enrolled 1999 to 2003, end date Jan 1st 2007	All with DS aged 45 or more (n=499) living in community or institutions in 4 regions	Epilepsy (past or present) at baseline	109 with epilepsy, 40 deaths	390[c] without epilepsy, 69[c] deaths	Those without epilepsy in sample	Hazard ratio	2.29 (1.50, 3.48) Not significant in multivariate survival analysis
Day, Wu, Strauss et al 2005 (see also Strauss et al 2003)	US	Retrospective analysis of records 1988 to 2002	People with mild DD (defined as disabling condition closely related to ID) receiving services from State of California Dept of Developmental Services. Excluded more severe disabilities (unable to walk climb stairs without support, severe or profound ID, degenerative conditions)	History of remote symptomatic epilepsy (idiopathic epilepsy excluded)	10,030 DD & epilepsy (65,126 person years). 406 deaths	96,163 DD & no epilepsy (656,632 person years). 1,991 deaths	Those without epilepsy in sample	Ratio SMR (SMR those with epilepsy/ SMR those with no epilepsy)	2.1 (1.9, 2.3). Cause specific (based on ICD-9 codes): Epilepsy/seizures 53.1 (28.0, 101.0); Convulsions 25.2, (11.7, 54.2); Brain cancer 5.2 (2.2, 12.1), Respiratory 1.7 (1.2, 2.5) Aspiration pneumonia 3.0 (1.5, 6.0) Circulatory diseases 1.3 (1.0, 1.7), Suicides 1.5 (0.3, 6.5) Accidents 2.7 (1.9, 3.7), especially Drowning 12.8 (7.0, 23.2). Drowning those with recent seizures 15.8 (7.2, 34.7)
As above same study, compared to General Population	As above	As above	As above	As above	As above	As above	California general population (GP)	SMR	DD & epilepsy 4.0 (3.6 to 4.3) DD no epilepsy 1.9 (1.8 to 2.0) Suicide DD & epilepsy 0.3 (ns) Suicide DD no epilepsy 0.2 (ns) Drowning those with recent seizures 35.9 (ns) Drowning no history of epilepsy 2.3 (ns)

Author	Country	Design & study period	Sample Description	Epilepsy definition	Sample size ID & epilepsy	Sample size other group	Comparison group	Statistic	Results (& 95% confidence interval). All cause mortality unless otherwise stated
Decouflé & Autry 2002	US	Population-based cohort 1985 to 1995	People with DD ascertained at 10 years of age from schools, hospitals, other health & social services, total 1584 with DD aged 10-19 of whom 67% had 'mental retardation'. 34% had epilepsy, number with ID & epilepsy ns	Epilepsy, ns	ns. 181 'epilepsy multiple' (has epilepsy as well as an additional DD). 16 deaths	354 'epilepsy isolated' (has epilepsy but no additional DD), 3 deaths	General population	SMR^{MR}	Epilepsy & additional DD 13.2 (7.6 to 21.5), Epilepsy but no additional DD 1.5 (0.3 to 4.3)
Derby, Tennis & Jick 1996	UK sample authors US	Nested case-control study 1989 to 1992	Those with refractory epilepsy under 50 years of age identified in General Practice Research Database (GPRD) (> 4 million people registered with GP) - ID those with computer recorded history of ID	Refractory; received prescriptions for two or more AEDs within 30 days of each other	ns (2 exposed cases)	Total sample 4150, total 15 SUDEP	Those in sample without ID	Relative risk	SUDEP 1.4 (0.3-8.0) (Paper uses acronym 'SUD' but criteria used are consistent with criteria for SUDEP)
Forsgren, Edvinsson, Nyström et al 1996	Sweden	Prospective cohort 1987 to 1992	All registered with Board for Provision & Services to the Mentally Retarded (BPSMR) in one province, almost total ID population in study area. Total sample of 1478. Males 821, females 657. All levels of ID & ages. Of these 296 with active epilepsy	Active epilepsy. Last SZ in last 5 years &/or on AEDs	296 of whom 30 deaths	ID without epilepsy 1182 of whom 94 deaths	General population	SMR	Entire ID sample 2.0 (1.7 to 2.3). ID with epilepsy 5.0 (3.3 to 7.5) ID, epilepsy & CP 5.8 (3.4 to 9.8). SZ free in preceding year 2.0 (0.9 to 4.7) SZ weekly or fewer 4.7 (2.8 to 7.9), SZ more than weekly 16.8 (10.7 to 26.5). Partial SZ without SZ secondarily generalized 3.7 (1.0 to 13.6) SZ secondarily generalized 5.0 (2.3 to 11.0) SZ generalized from onset 8.1 (5.7 to 11.5)

Author	Country	Design & study period	Sample Description	Epilepsy definition	Sample size ID & epilepsy	Sample size other group	Comparison group	Statistic	Results (& 95% confidence interval). All cause mortality unless otherwise stated
Hermon, Alberman, Beral et al 2001	England & Scotland	Cohort study, mortality followed up to July 1997	1425 persons with DS born before 1990 identified from records of five collaborating genetic units in England and Scotland, total 346 deaths	ICD 9 - cause of death epilepsy (code 345)	ns - focus is epilepsy as cause of death; 8 deaths	General population	General population	SMR	Epilepsy as cause of death 17.3 (7.4 to 34.0)
Hill, Gridley, Cnattingius et al 2003	Sweden & Denmark	Hospitalization data linked to registries of mortality & cancer for those with diagnosis of DS at discharge 1965 to 1993 Sweden & 1977 to 1989 Denmark. Follow-up to end 1993	Combined cohort of 4872 from Sweden & Denmark with hospital discharge diagnosis of DS who survived at least 12 months after date of discharge, total 742 deaths	ICD 9 - cause of death epilepsy (code 345)	ns - focus is epilepsy as cause of death; 9 deaths	General population	General population	SMR	Epilepsy as cause of death 30.4 (13.9 to 57.7)
Kiani, Tyrer, Jesu et al 2014	England	Retrospective cohort 1993 to 2010, epilepsy related deaths identified, case notes of 20 SUDEP cases investigated	5391 adults (20+) with ID on the Leicestershire Intellectual Disability Register database (LIDR) of whom 1027 had epilepsy (19%)	Diagnosis of epilepsy	1027, total 244 all cause deaths, 26 definite or probable SUDEP	Population approx 700,000; 607 deaths potentially from epilepsy; 83 definite or probable SUDEP	General population of Leicester City, Leicester-shire & Rutland	SMR	Men with ID 2.2 (2.0 to 2.4) Women with ID 2.8 (2.5 to 3.1). Men with ID & epilepsy 3.2 (2.7 to 3.8) Women with ID & epilepsy 5.6 (4.6 to 6.7) SUDEP men with ID 37.6 (21.9 to 60.2) SUDEP women with ID 52.0 (23.8 to 98.8)

Author	Country	Design & study period	Sample Description	Epilepsy definition	Sample size ID & epilepsy	Sample size other group	Comparison group	Statistic	Results (& 95% confidence interval). All cause mortality unless otherwise stated
Mölsä 1994	Finland	Cohort followed for 20 years 1971 to 1991	212 Inpatients & 217 outpatients of a centre for 'mentally handicapped', 53% & 54% with epilepsy respectively. All ages & from mild to profound ID. Total 88 deaths, 53 inpatients & 35 outpatients	Epilepsy yes/no	229[c] (approx; no of deaths ns)	Without epilepsy 220[c] (approx; no of deaths ns)	Those without epilepsy in sample	Hazard ratio[RR]	Outpatients 1.79 (0.76 to 4.25), Inpatients 0.87 (0.48 to 1.61) Outpatients subdivided by type of residence, for those in hostels risk of death due to status epilepticus more than doubled
Nashef, Fish, Garner et al 1995	England	Cohort enrolled at special school 1970 to 1993, follow-up included time after leaving school	310 pupils with epilepsy & ID at special residential school for children & adolescents with epilepsy & ID	Most had severe epilepsy, most more than one seizure a week	310 of whom 28 deaths, 14 of which SUDEP	General population	General population	SMR	All cause 15.9 (10.6-23.0) All 14 sudden deaths occurred when the pupils were not under the close supervision of the school and most were unwitnessed (incidence 1:295/year)
Nickels, Grossardt & Wirrell 2012	US	Review of records of population-based cohort of children with epilepsy 1980 to 2009	All children age 1 month to 17 years diagnosed with epilepsy while resident in one County (n=467). 'Abnormal cognitive function' in 192 (109 mild to moderate ID; 83 severe ID)	Diagnosed with new-onset epilepsy; being predisposed to unprovoked seizures	192 of whom 15 died	275 of whom 1 died	Those without ID in sample	Hazard ratio	20.86 (2.76-157.97) In multivariable Cox regression model only abnormal neurological examination remained statistically significant

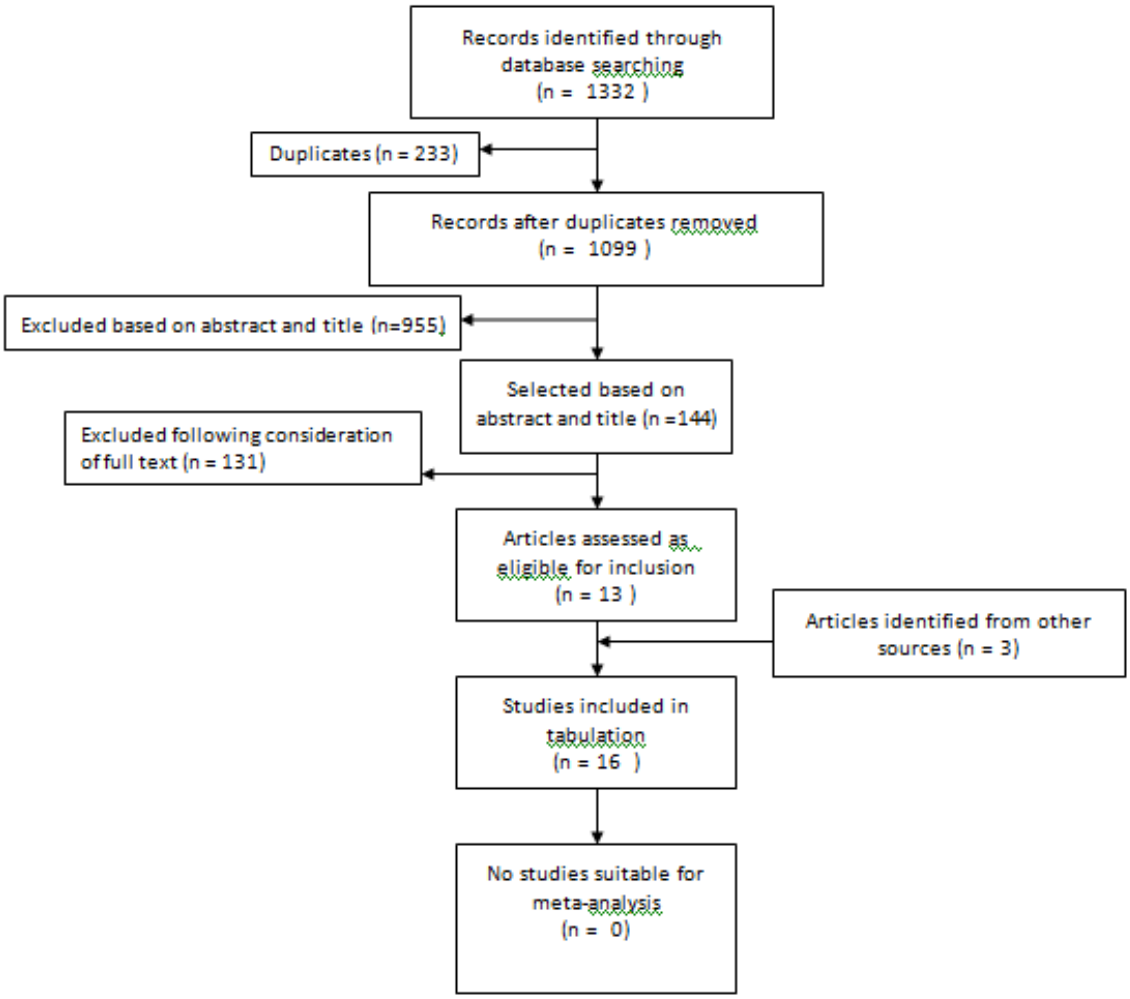
Author	Country	Design & study period	Sample Description	Epilepsy definition	Sample size ID & epilepsy	Sample size other group	Comparison group	Statistic	Results (& 95% confidence interval). All cause mortality unless otherwise stated
Ohwada, Nakayama, Tomono et al 2013	Japan	Retrospective cohort 1984 to 2007	316 people (ages 18–69 years) living in an institution where 90% judged to have severe ID. Excludes those with severe motor disabilities. Total 44 deaths	Presence or absence of epilepsy	85 (deaths ns)	231[c] (deaths ns)	Those without epilepsy in sample	Hazard ratio	2.39 (1.17 to 4.92) Multivariate analysis with forced procedures HR 2.79 (1.21-6.41)
Patja, Iivanainen, Vesala et al 2000	Finland	Prospective cohort 1963 to 1997	Nationwide population based sample of 2366 people with ID with 35 year follow-up (61 689 person years). 1108 died	Epilepsy yes/no	ns	ns	Those without epilepsy in sample	Hazard ratio[RR]	Cox regression found epilepsy was associated with reduced survival for the following: 2-9 years old in 1963 ns (0.38-0.84) 10-19-years old in 1963 ns (0.10-0.81)
Sillanpää & Shinnar 2010	Finland	Prospective cohort 1964 to 2002	All children < 16 yrs in catchment area of a University Hospital in 1964 with a diagnosis of epilepsy (n=245), number with 'severe cognitive impairment' not stated	At least 2 unprovoked SZ; classification based on ILAE	ns	Total sample 245, number with ID not stated, 60 deaths	Those without severe cognitive impairment in sample	Hazard ratio[RR]	For those with remote symptomatic epilepsy (n=123 of whom 45 deaths), severe cognitive impairment was associated with increased mortality 4.1 (2.0 to 8.3) Only lack of 5-year terminal remission significant in multivariate analysis

Author	Country	Design & study period	Sample Description	Epilepsy definition	Sample size ID & epilepsy	Sample size other group	Comparison group	Statistic	Results (& 95% confidence interval). All cause mortality unless otherwise stated
Strauss, Day, Shavelle et al 2003 (see also Day et al 2005)	US	Retrospective analysis of records 1988 to 1999	People with mild DD receiving services from State of California, 71% with 'other DD' of whom majority had mild or moderate ID. Excluded if unable to walk well alone at least 20 feet & balance well, unable to climb stairs without support, severe or profound ID. Degenerative conditions excluded.	Remote symtomatic epilepsy, idiopathic epilepsy excluded	8,156 of whom 266 deaths (some of sample not ID)	72,526 without epilepsy of whom 1257 deaths (some of sample not ID)	Those without epilepsy in sample	SMR	Epilepsy no SZ in last year 1.1 (0.8 to 1.5) Seizures not GTC in last year 2.4 (1.9 to 3.0), GTC seizures in last year 2.9 (2.4 to 3.4), Status epilepticus in last year 3.7 (2.5-5.4) Compared to the California general population those with no history of epilepsy had an SMR of 1.7 (ns)
Walczak, Leppik, D'Amelio et al 2001	US	Prospective cohort 1991 to 1996	Patients at 3 epilepsy centres enrolled prospectively, ID defined as Full-Scale Wechsler IQ < 70 or not considered testable. Total 4,578 patients (16,463 patients years). 20 SUDEP cases out of 111 deaths.	ns, enrolled at epilepsy centre	ns, 7 of 20 SUDEP cases were those with ID	ns, 13 of 20 SUDEP cases were those without ID	4 controls randomly selected for each SUDEP case from patients enrolled in same month at same centre (total 80)	Odds Ratio (OR)	ID a risk factor for SUDEP after adjustment for SZ frequency, OR 4.6 (1.2-18.0)

[c] Computed from available data, not reported directly; [RR] study reports 'relative risk' or 'rate ratio' based on Cox Proportional Hazards Regression, entered in the table as 'hazard ratio'; [MR] study reports 'mortality ratio', description of method consistent with SMR.

AED antiepileptic drug: CP cerebral palsy: DD developmental disabilities; DS Down syndrome; GPRD general practice research database; GTC generalised tonic-clonic; ICD-9 International Classification of Diseases 9th Edition; ID intellectual disabilities; ILAE International League Against Epilepsy; ns not stated; SMR standardised mortality ratio; SUDEP Sudden Unexpected Death in Epilepsy; SZ seizures.

Figure One: Flowchart of Study Identification



Appendix One: Electronic Search Strategy

MEDLINE AND CINAHL

Limits: 1990; English; Human

(TI (learning N1 (disab* or difficult* or handicap*)) OR TI (mental* N1 (retard* or disab* or deficien* or handicap* or disorder*)) OR TI (intellectual* N1 (disab* or impair* or handicap*)) OR TI development* N1 disab* OR TI (multipl* N1 (handicap* or disab*)) OR TI "Down* syndrome" OR (MH "Developmental Disabilities/EP/MO") OR (MH "Intellectual Disability+/EP/MO") OR (MH "mentally disabled persons")) OR (AB (learning N1 (disab* or difficult* or handicap*)) OR AB (mental* N1 (retard* or disab* or deficien* or handicap* or disorder*)) OR AB (intellectual* N1 (disab* or impair* or handicap*)) OR AB development* N1 disab* OR AB (multipl* N1 (handicap* or disab*)) OR AB"Down* syndrome")

AND

(MH "Epilepsy+/MO/EP") OR (TI epilep* OR TI seizure* OR TI convulsi* OR AB epilep* OR AB seizure* OR AB convulsi*)

AND

(TI incidence OR TI prevalence OR TI mortality OR TI death OR AB incidence OR AB prevalence OR AB mortality OR AB death) OR (MH "Incidence") OR (MH "Prevalence") OR (MH "Mortality+")

PSYCINFO

Limits: 1990, Peer review, English, Exclude dissertations

DE "Epilepsy" OR DE "Epileptic Seizures" OR (DE "Seizures" OR DE "Audiogenic Seizures" OR DE "Epileptic Seizures" OR DE "Grand Mal Seizures" OR DE "Petit Mal Seizures" OR DE "Status Epilepticus") OR (TI epilep* OR TI seizure* OR TI convulsi* OR AB epilep* OR AB seizure* OR AB convulsi*)

AND

(TI incidence OR TI prevalence OR TI mortality OR TI death OR AB incidence OR AB prevalence OR AB mortality OR AB death) OR DE "Epidemiology" OR DE “death and dying” OR DE “mortality rate”

AND

DE "Intellectual Development Disorder" OR DE "mental retardation" OR DE "developmental disabilities" OR (TI (learning N1 (disab* or difficult* or handicap*)) OR TI (mental* N1 (retard* or disab* or deficien* or handicap* or disorder*)) OR TI (intellectual* N1 (disab* or impair* or handicap*)) OR TI development* N1 disab* OR TI (multipl* N1 (handicap* or disab*)) OR TI "Down* syndrome") OR AB (mental* N1 (retard* or disab* or deficien* or handicap* or disorder*)) OR AB (intellectual* N1 (disab* or impair* or handicap*)) OR AB development* N1 disab* OR AB (multipl* N1 (handicap* or disab*)) OR AB "Down* syndrome"

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