Introduction

Down syndrome is frequently associated with congenital anomalies, particularly of the cardiac system. People with Down syndrome are at higher risk than others for a range of conditions, including cardiac, respiratory, immunological, endocrine, and gastro-intestinal conditions. This physical phenotype puts people with Down syndrome at risk of dying at a younger age than the general population. In the mid-20th Century, average survival of a child with Down syndrome was to about 10 years of age, but this is thought to have increased markedly over subsequent decades, in particular due to access to treatments for congenital heart anomalies and improved surgical techniques and post-operative care (Hijii et al., 1997).

Changes in public attitudes have impacted on access to surgery and interventional care. As recently as the 1980s and 1990s there were reports of children with Down syndrome being offered conservative management rather than surgical interventions for congenital heart anomalies (Bull et al*.,* 1985; Kmietowicz, 2001); e.g. outcomes were presented for 67 children with Down syndrome and atrioventricular canal defects who were not given surgery (Bull et al., 1985). Others rejected this view and advocated for an equal provision of surgery (Wilson et al., 1985; Menahem & Mee, 1985). The British Medical Association *Handbook of Medical Ethics* (1984) at this time also endorsed the view that in certain circumstances severely malformed children could be allowed to die. A pivotal case in testing public attitudes was that of *R v Arthur*. In 1981 Dr. Leonard Arthur was acquitted of the murder of a baby with Down syndrome. The baby was rejected at birth by its parents and Dr. Arthur made a note “Parents do not

wish it to survive. Nursing care only", food was withheld and opioid pain relief (which has a side effect of respiratory suppression) was prescribed four hourly. The baby died after 69 hours with the cause of death recorded as bronchopneumonia. Clearly these practices are no longer acceptable, and technological and medical advancements related to treating congenital heart anomalies for people Down syndrome are likely to have influenced improved survival rates and older age of death (Coppus et al*.,* 2006; Glasson et al., 2016).

However this evidence needs further investigation. There is also a need for quantification of the extent of improved survival rates, and identification of causes of death and the factors influencing death.

We have been unable to identify any existing systematic review and synthesis of evidence on early deaths and specific causes of death for people with Down syndrome which could identify health inequality trends amongst people with Down syndrome, important for healthcare decision making and to inform strategies for reducing inequalities. The aim of this study was therefore to systematically review the evidence on early deaths amongst people with Down syndrome, determinants of early death, and the main causes of death.

Method

This review was conducted alongside a systematic review into early death and causes of death of people with intellectual disabilities. A clear search strategy and protocol was devised. The review protocol was registered with the International Prospective Register of Systematic Reviews (Prospero) (registration number: CRD42015020161).

CINAHL, MEDLINE, PsychINFO, Web of Science, and EMBASE online databases were searched for key words relating to intellectual disabilities and Down syndrome. These databases were also searched for key words relating to mortality, age of death and life expectancy (appendix 1). The search was completed on 20/10/16. The search results were filtered for English language and human. The following strict inclusion and exclusion criteria were applied when selecting the relevant studies.

Inclusion criteria

- Studies that report deaths or mortality rates of people with Down syndrome
- A minimum of 50% of participants have intellectual disabilities, if not reported separately
- Peer reviewed
- Primary research
- All ages
- All years
- All study designs.

Exclusion criteria

- Full paper not accessible in English
- Proportion of participants with intellectual disabilities unclear, or <50% of sample if not reported separately
- Studies that do not clearly report mortality outcomes separately for people with Down syndrome
- >50% of sample reside in institutional settings

- Studies reporting mortality rates/cause and age of death following relocation/resettlement
- Studies reporting post-operative and post-treatment deaths
- Case studies or case series for total sample of <20 participants
- Studies exclusively focussed on specialised populations such as those living in a specific type of residency only, or accessing a specific type of service only.

Study selection and data extraction

The titles that were identified from the five online databases were entered into the Endnote reference manager software. Duplicates were removed. Titles and abstracts were then assessed for inclusion. Five percent of these studies were then checked by a second reviewer. Disagreements or discrepancies were resolved with a third reviewer, until consistency was achieved between reviewers. Full papers were then assessed for inclusion by two reviewers.

Authors were contacted if the full paper could not be retrieved and if the reviewers were not clear about specific details of the study, to verify if the study met the inclusion criteria. Six authors were contacted for these purposes.

The reference lists of included studies were also searched in detail for any additional papers of relevance. Data were then systematically extracted from the included studies. This related to study characteristics, size, demographics, inclusions/exclusions, context, location, design, data source, comparator groups, analytical method, outcomes, findings and risk of bias. Information was tabulated in a database.

Meta-analysis and narrative analysis were two possible methods of synthesising this data. It has been argued that meta-analysis may be a more objective and less biased approach than narrative analysis (Cooper & Rosenthal, 1980). Different methods were used to measure life expectancy, age of death, and causes of death of the participants in these studies. Therefore it was not possible to use a meta-analysis in order to numerically synthesise the results of different studies (Glass et al*.,*1976), and narrative analysis was used. (Popay et al*.,* 2006).

The Critical Appraisal Skills Programme CASP (2013) guidelines were used to appraise the quality and rigour of the studies. This checklist scored the studies out of a possible 14 points based on their validity, reliability and generalisability. The CASP scores were checked with a 2nd researcher and any discrepancies were resolved with a 3rd reviewer. This approach helped to reduce any prospective bias associated with narrative analysis.

Results

Figure 1 illustrates the steps take in this review in order to identify relevant studies. A total of 24,702 references were retrieved from searching five databases. Two additional articles were identified from a reference in a relevant paper. N=19,111 of these articles were relevant after removing duplicates. These studies dated from 1796-2016.

N=17,010 were excluded, as these titles were not relevant to the purpose of population of the study. N=2101 abstracts were checked. N=322 of the abstracts were considered potentially relevant and these papers were read in depth. All reviewers agreed on the eligibility of the included studies. N=288 of the articles read in full did

not meet the inclusion criteria, whilst N=34 did. The findings from these studies were synthesised (tables 1-3).

- Insert tables 1-3 about here -

Country of studies

N=10/34 of the studies that were included in the narrative synthesis were undertaken within the USA (Scholl,1982; Eyman et al*.,* 1991; Strauss & Eyman, 1996; Singer & Straus, 1997; Friedman, 2001; Yang et al. 2002; Day et al., 2005; Rasmussen et al., 2006; Shin et al., 2007; Goldman et al., 2011). Six were conducted in Australia (Mulcahy, 1979; Malone, 1988; Leonard et al., 2000; Glasson et al., 2002; Bittles et al.,2007; Glasson et al.,2016); four were from the UK region (McGrother & Marshall,1990; Brookes & Alberman,1996; Bell et al., 2003; Kucik et al., 2013); and four were undertaken in Canada (Gallagher & Lowry, 1975; Baird & Sadovnick ,1987; Baird & Sadovnick, 1988; Baird & Sadovnick, 1990). Two studies were undertaken in each of Sweden (Frid *et al.,* 2004; Englund et al., 2012) and Denmark (Mikkelsen et al., 1990, Zhu et al., 2013). The remaining studies were from New Zealand (Bell *et al.,* 1989); Italy (Mastroiacovo et al., 1992); Ireland (Hayes et al., 1997); South America, specifically Argentina, Brazil, Chile, Paraguay, Uruguay (Castilla et al., 1998), Japan (Masaki et al., 1981), and Israel (Sadetzki et al.,1999). Hence all studies are from high income countries with the exception of one which included two upper middle income countries (Brazil and Paraguay).

Studies on early death

N=32/34 studies included in this review reported life expectancy, mortality rates or age of death of people with Down syndrome. A diverse range of methods were used to

assess age of death. This information is summarised on tables 1 and 2. These included measures of actual/predicted survival and median age of death. Some studied crude or standardised mortality rates. Studies also reported factors associated with early deaths, life expectancy and mortality rates. The majority of studies (N=17) only reported on mortality patterns and age of death in infants and childhood (<age 18 years) (see table 2). N=15 studies assessed age of death, life expectancy and mortality patterns of individuals with Down syndrome of all ages (table 1).

The diverse methods used to analyse deaths across these studies complicated the synthesis of the findings.

Mortality rate, life expectancy and age of death comparisons with the general population

Life expectancy and age of death was lower and mortality rates were higher for people with Down syndrome. For example Baird & Sadovnick (1988) identified that the life expectancy from birth of their cohort of N=1,610 individuals with Down syndrome was 28 years lower than the general population. Friedman (2001) reported that the median age of death within their sample of N=33,836 people with Down syndrome was 27 years younger than the general population. Glasson et al., (2002) reported that in their sample of N=1,332 individuals with Down Syndrome that the median age of survival was 17-23 years lower than for the general population. Day et al. (2005) reported that standardised mortality rates in their USA study of individuals with Down syndrome were 5.5 times higher than the general population, and Zhu et al., (2013) reported that the adjusted hazard ratio for mortality was 9.0 times higher in their Danish cohort of individuals with Down syndrome compared to the general population.

Several studies reported that infant mortality rates were significantly higher and survival rates were lower in Down syndrome compared to the general infant population (Mastroiacovo et al., 1992; Hayes et al., 1997; Sadetzki et al., 1999; Bell et al., 2003; Frid et al., 2004; Studies undertaken in the last decade reported that one year mortality rates were 6 to 8 times greater than that of the general population (Shin et al., 2007; Goldman et al., 2011). Earlier studies reported that one year Down Syndrome mortality rates were up to 24 time higher than that of the general population (Sadetzki et al., 1999). This figures show some improvement in survival rates over time.

Temporal trends in mortality patterns

Strikingly, studies consistently identified that infant mortality rates reduced, and life expectancy improved over time for children and adults with Down syndrome, particularly those with congenital heart anomalies (see Table 2). For example, Malone (1988) reported significant improvements in 5 year survival rates for their Australian cohort of children with Down syndrome and congenital heart anomalies from 1966-1976; Hayes et al., (1997) reported that that in Ireland, 1 year and 5 year survival rates were higher for children with Down syndrome who were born in 1985-1989, compared to children who were born in 1980-1984. Frid et al., (2004) and Shin et al., (2007) reported that 1 year mortality rates decreased by 12% and 41% respectively for infants with Down syndrome born in the 1970s compared to those born in the 1990s.

These improvements were also observed in studies that comprised individuals of all ages (see table 1). For example Bittles et al., (2007) reported a 9% reduction in age specific mortality trends for a cohort of individuals with Down syndrome born in 2000-2004, compared to earlier cohort born in 1980-1984. Englund et al., (1997) reported a very large increase in median age from 3.6 years to 56.8 years from 1969-2003.

The greatest temporal changes were reported for individuals with Down syndrome who also had congenital heart anomalies. For example, Kucik et al*.,* (2013) reported a great improvement in 1 year survival amongst a USA cohort of N=16,506 individuals with Down syndrome and congenital heart anomalies between 1983-2003 (see table 1). The influence of congenial heart anomalies on life expectancy and age of death was most apparent in earlier birth cohorts. For example Glasson et al., (2016) in comparing five year survival rates between birth cohorts within a Western Australian context identified that the earliest birth cohort, born in 1980-1985 had a 93% survival rate to age five for children with Down syndrome without congenital heart anomalies, and a 72% survival rate to age five for children with Down syndrome with congenital heart anomalies. These differences were smaller for the later birth cohort, born in 2006-2010, which had a 95% survival rate for children with Down syndrome without congenital heart anomalies, and a 92% survival rate for children with Down syndrome with congenital heart anomalies.

Factors associated with mortality rates and early deaths

Congenital heart anomalies: Consistently, mortality probabilities were reported to be higher and survival probabilities were lower for infants and children with congenital heart anomalies (Mulcahy et al*.,* 1979; Masaki et al., 1981; Malone, 1988; Mikkelsen et al., 1990; Leonard et al*.,* 2000; Rasmussen et al., 2006), and actual survival rates were lower and mortality rates were higher for children with Down syndrome and congenital heart anomalies (Mastroiacovo et al*.,*1992, Hayes et al.,1997; Castilla et al., 1998; Bell et al., 2003; Shin et al., 2007). This association also emerged in some of the studies comprising individuals of all ages (Baird & Sadovnick, 1987). Day et al., (2005) reported that age specific mortality rates were higher for their sample of people with Down syndrome and congenital heart anomalies compared to the general

population, significantly so for those aged <50years, but not significantly so for those aged >50years.

Age: Several studies reported that mortality rates in Down syndrome were the highest in infancy and early childhood compared to older children and young adults (Gallagher & Lowry, 1975; Baird & Sadovnick,1988), particularly so in early infancy (Mulcahy, 1979; Malone, 1988; Masaki et al., 1981).

Ethnicity: Race and ethnicity also had an influence on mortality patterns and age of death in both infant and child/adult studies (see tables 1 and 2). White ethnicity appeared to be associated with lower mortality rates and improvements in life expectancy over time compared to other ethnic groups, whilst black ethnicity was associated with lower survival probability (Rasmussen et al*.,* 2006; Kucik et al*.,*2013) and high mortality rates (Day et al., 2005; Shin et al., 2007). Leonard et al., (2000) identified how aboriginal ethnicity was associated with lower one year survival probability amongst their cohorts of Australian infants with Down syndrome, whilst Glasson et al., (2016) identified that aboriginal ethnicity was associated with lower survival rates among their sample of 1,378 adults with Down syndrome. In the USA Friedman (2001) and Yang et al., (2002) revealed that an increase in median age of death for individuals with Down syndrome over time was greatest amongst individuals from a white ethnic background.

Other factors: Higher mortality rates were also associated with severe level of intellectual disabilities (Strauss & Eyman, 1996; Singer & Straus, 1997), and presence of medical conditions (Sadetzki et al., 1999). Co-morbidities particularly feeding and mobility impairments appeared to reduce life expectancy (Eyman et al., 1991). Low birth weight increased mortality rates (Sadetzki et al., 1999) and reduced survival

length (Leonard et al., 2000; Rasmussen et al*.,* 2006) amongst children with Down syndrome (Sadetzki et al., 1999), and low parental education also lowered survival rates of the Down syndrome offspring (Eyman et al., 1991).

Three studies also identified that survival rates were lower for individuals with Down syndrome, compared to individuals with intellectual disabilities (no Down syndrome) (Baird & Sadovnick, 1987; Eyman et al., 1991; Singer & Strauss, 1997).

Studies on causes of death

Primary, underlying, and contributory causes of death

It was difficult to determine consistent trends in primary, underlying and contributory causes of death and to ascertain whether the pattern of causes of death have changed over time, due to a variation in recording of causes of death across regions. Also, there was a relatively small number of studies that recorded primary and underlying causes of death, and only five studies recorded contributory causes. This limited capacity to identify whether and how cause of death may have changed over time by age group. However, some trends appeared (see table 3).

Congenital heart anomalies: These were reported as leading primary or underlying cause of mortality in the majority of the studies, accounting for 30%-50% of causes of death in studies that were undertaken in USA, Denmark and Australia comprised of children and adults combined (Scholl et al., 1982; Baird & Sadovnick, 1990; Zhu et al., 2013; Glasson et al*.*, 2016). They were reported as accounting for a large proportion of deaths in studies that comprised infants and children with Down syndrome only in studies undertaken in Australia, Denmark, UK, Ireland and USA (Bell et al., 1989; Mikkelsen et al., 1990; McGrother & Marshall 1990; Hayes et al*.*, 1997; Shin et al.,

2007). These specific cause of death rates ranged from 33.9% in the most recent study undertaken by Shin et al., (2007) of infant deaths (born 1979-2003) to 65% in an older study conducted by McGrother and Marshall (1990) on a birth cohort of children born 1976-1985.

Incidences of congenital heart anomalies as a cause of mortality were reported to be lower amongst white ethnic groups in two USA studies (Yang et al., 2002; Rasmussen et al., 2006).

Respiratory conditions: These were reported as another common underlying or primary cause of death in studies comprising adults and children accounting for 34% of a Canadian sample of deaths (Baird & Sadovnick, 1990), and 20% in a more recent Danish study (Zhu et al., 2013). Bittles et al., (2007) reported that respiratory illness death rates were highest for individuals aged over 41 (39.6%) and lowest for individuals aged 0-18 years (33.1%) in their Australian sample of N=298 deaths of people with Down syndrome.

Respiratory conditions were also reported as an underlying or primary cause of death in studies comprising infants and children. They accounted for 5% of 20 main causes of death in a UK sample of children born 1976-1985 (McGrother & Marshall, 1990). Hayes *et al.,(*1997) reported that respiratory illness in the absence of congenial heart anomalies accounted for 9.1% in an Irish sample of 63 deaths of infants that were born in 1980-1989.

Pneumonia was identified as one of the main respiratory causes of death in Australian and Danish studies that comprised infants and children (Mulcahy, 1979; Mikkelsen et al., 1990), and USA, Australian and Swedish studies that comprised all ages (Scholl

et al., 1982; Day et al., 2005; Bittles et al., 2007; Englund et al., 2012; Glasson et al., 2016).

Other conditions: Circulatory disease accounted for 24% of 1,930 deaths at all ages in a Swedish study (Englund et al., 2012), 12.1% of 3,272 deaths at all ages in a Danish study (Zhu's et al. 2013), and 1.5% of 324 deaths up to age 32 in a US study (Baird & Sadovnick, 1990). Cardiac failure accounted for 33% of 55 infant deaths in an Australian study (Mulcahy et al., 1979), and 18.8% of 16 reported causes of death up to age 5 in a UK study (Brookes & Alberman, 1996). These conditions were likely to be associated with congenital heart anomalies. Bittles et al., (2007) reported that cardiac/renal and respiratory failure deaths decreased with age in their Australian study. They reported that they accounted for 11.5% of causes of death in their sample of individuals aged 0-18 years and 9% of causes of death in their sample aged 40+ years.

Other less common causes of death were leukaemia, which accounted for 2-13% of the main causes of death across nine studies undertaken in Australia, USA, UK, Denmark, Ireland and Sweden (Mulcahy, 1979; Scholl et al., 1982; Bell et al., 1989; Mikkelsen et al., 1990, Brookes & Alberman, 1996; Hayes et al., 1997; Englund *et al*., 2012; Glasson et al., 2016). Whilst being a less common cause of death, leukaemia therefore clearly occurred more commonly than it does in the general population. Accidental deaths accounted for a small proportion (2-6%) of primary causes of death in studies undertaken in Australia, USA and Ireland (Mulcahy et al., 1979; Scholl et al., 1982; Baird & Sadovnick, 1990; Hayes et al., 1997; Bittles et al., 2007; Shin et al., 2007). Down syndrome was reported as a primary or underlying cause of death in some studies undertaken in the USA (Baird & Sadovnick, 1990; Day et al., 2005;

Rasmussen et al., 2006; Shin et al., 2007), Sweden (Englund et al., 2012) and Australia Glasson et al., 2016). Perinatal conditions and complications were also reported as accounting for a small proportion of causes of death in two USA studies (Baird & Sadovnick, 1990; Shin et al., 2007) and one Danish study (Mikkelsen et al*.,* 1990)

Contributory and intermediate causes of death were not recorded in most studies, so it was difficult to capture the sequence of events leading to mortality (see table 3). Down syndrome was recorded as a contributory cause of death in 93.8% by Brookes & Alberman (1996) and 44% by Shin et al*.,* (2007). Down syndrome was reported to account for 51.5% of multiple cause of death in a USA study undertaken by Goldman et al., (2011). Other contributory cause of death included dementia in an Australian study undertaken by Bittles et al., (2007), respiratory disease/infections or complications in Australian, UK, Irish and US studies (Bell et al., 1989; Brookes & Alberman, 1996; Hayes et al*.,*1997; Goldman et al., 2011). Table 3 outlines other less common causes of death reported in individual studies.

Comparisons of causes of death with the general population

Congenital heart anomalies were substantially more common as a cause of death in Down syndrome than the general population (Scholl et al., 1982; Yang et al., 2002; Day et al., 2005). Englund et al*.* (2012) reported that Standardised Mortality Odds Ratios were 80 times higher in their sample of N=3,956 children with Down syndrome, compared to the general population.

Pneumonia was also a lot more common cause of death amongst people with Down syndrome than in the general population. Day et al*.,* (2005) reported Standardised Mortality Ratios of 140.4 for aspiration pneumonia as a cause of death amongst

individuals with Down syndrome compared with the general population, whilst Yang et al., (2002) identified aspiration pneumonia or influenza to be 7.6 times more common, with this difference increasing with age, and Englund et al., (2012) reported that respiratory illness (including pneumonia) was 5.6 times more common.

Two USA studies identified dementia/Alzheimer disease to be more common causes of death amongst people with Down syndrome compared to the general population. Day et al., (2005) reported an SMR of 154.6, and Yang et al*.,* (2002) reported a SMOR of 21.1 at age >40 years.

Three studies undertaken within the USA and Sweden reported that rates of leukaemia deaths were higher for people with Down syndrome than the general population. Scholl et al., (1982) reported that proportional mortality ratios for leukaemia were significantly higher compared to the general population for children with Down syndrome aged 2-4 years and adults aged 20-34 years. Yang et al*.,* (2002) and Englund et al. (2012) identified that SMORs for leukaemia were 1.6 and 1.7 times higher for people with Down syndrome compared to the general population in their respective studies. Yang et al., (2002) reported that SMORS were highest at age <10 years.

Less common causes of death amongst people with Down syndrome compared to the general population included ischaemic heart disease (Scholl et al*.,* 1982; Yang et al., 2002) and cancers such as digestive/genital/ breast and lung cancer (Scholl et al., 1982; Day et al*.,* 2005).

Discussion

Principal findings

People with Down syndrome have a life expectancy about 28 years lower than the general population; their life expectancy has increased over time, this is particularly true for infant mortality, and for those who additionally have congenital heart anomalies (more so for white than non-white ethnicity). Survival rates are lower in the first year of life, than in childhood or young adult life. Survival is poorer for those with congenital heart anomalies, non-white ethnicity, more severe intellectual disabilities, low birth weight, additional medical conditions, feeding and mobility problems, and for offspring of younger mothers and parents with lower educational levels. The pattern of cause of deaths differs from the general population, with cardiac and respiratory deaths most common and occurring substantially more so than in the general population. Solid tumours are less common causes of death than for the general population, but leukaemia, whilst not a common cause of death in people with Down syndrome is considerably more common than in the general population. This is the first systematic review to synthesise these studies of death of people with Down syndrome across the life span.

The increase in life expectancy and age of death was most apparent for individuals with congenital heart anomalies. This improvement is likely to be due to early diagnosis and better-quality health care intervention for individuals with congenital heart anomalies, in particular access to surgical intervention, and better surgical technique and post-operative care (Bernier et al., 2010). The ethnic differences in survival could possibly reflect a poorer access to surgery and/or poorer care, and if so would be an inequality that could be amenable to improvements in health care. Clearly this needs further investigation, and action if inequitable health care is found. Other cultural factors may also be important in accounting for average age of death or life expectancy of individuals from black or minority ethnic backgrounds not improving at

the same rate as for individuals from white ethnic backgrounds. None of the studies explained the reasons for the racial disparity in life expectancy or survival rates. Their suggestions included under-ascertainment or under-reporting of congenital heart anomalies in white ethnic groups compared to black and minority ethnic groups (Yang et al., 2002; Rasmussen et al., 2006; Shin et al., 2007). Friedman (2001) also suggested that differences in factors associated with improved health such as community support or access to preventative health care may account for this disparity.

As for people with intellectual disabilities who do not have Down syndrome, comorbidities and severe intellectual disabilities were associated with lower life expectancy and earlier death, highlighting the importance of health care for infants, children and adults with Down syndrome. Antenatal care is also clearly important due to the finding on lower birth weight, and younger maternal age; as is support for parents thereafter, demonstrated by the association of poorer outcomes for the Down syndrome offspring with lower educational achievements of parents.

This review has identified different cause of mortality patterns in people with Down syndrome compared to the general population. Respiratory illness (particularly pneumonia) was a significantly more common cause of death for people with Down syndrome compared to the general population, due to their anatomical and physiological differences. However, aspiration pneumonia is a preventable cause of death with the right support and health care, and points to the need for greater awareness and training on this for professionals, support staff and families; and pneumonia is amenable to health care. People with Down syndrome require prolonged periods of treatment in order to overcome respiratory infection (Ram & Chinen, 2011).

Individuals with Down syndrome were more likely to die from amenable causes such as pneumonia and some congenital cardiac anomalies. Synthesis of these studies also revealed that individuals with Down syndrome were less likely to die from causes that could be prevented through public health interventions such as certain cancers and accidents. These findings echoed findings from that of another systematic review that revealed that individuals with intellectual disabilities in general were more likely to die from amenable than preventable causes (O'Leary et al., 2017).

There is an increased recognition of dementia as an issue for the ageing population of people with Down syndrome (McCarron et al., 2014). Only two of the studies in this review reported dementia as an underlying cause of death, probably reflecting the small population sizes of people with Down syndrome at old age included in the studies.

Health gains and areas for improvement

The findings from this review have demonstrated that the age of death and life expectancy of a subset of people with Down syndrome has improved over time. This may reflect an improvement in medical intervention and health care particularly for individuals with congenital defects. However health care improvements need to be further improved and better tailored to the needs of specific subgroups, so that they can achieve a longer life expectancy; including people with repeated respiratory infections and/or cardiac anomalies. This is important in order to reduce risk of avoidable causes of death and increase life expectancy for all individuals with Down syndrome.

Limitations of studies

This review aimed to synthesise evidence for mortality patterns of comparable samples of individuals with Down syndrome. However, some studies were limited through reliance on administrative data, omission of infants and young children with Down syndrome, or through identifying people with Down syndrome via entries on death certificates which is highly likely to undercount the population. (Others were population-based birth cohorts, or identified the people with Down syndrome via multiple sources). All studies except one were conducted in high income countries, restricting generalisation to within such countries.

The accuracy of underlying /primary and contributory cause of death results was compromised by the reliance on death certificates, which are completed by many doctors. Death certificates are subject to coding errors, as physicians are often not familiar with the coding rules for completing death certificates (Landes & Peek, 2013). This may lead to the risk of incorrect attribution of an easily identifiable condition such as Down syndrome as an underlying cause of death (Baird & Sadovnick, 1990). Also, the cause of death recording process is often not undertaken consistently by medical practitioners working in different regions. Therefore, it may be difficult to obtain a consistent picture of the leading and underlying causes of death across different countries and regions.

Also, reliability of findings in two of the cause of death studies may be critiqued by the fact that they were limited by 20 or less deaths (McGrother & Marshall, 1990; Brookes & Alberman, 1996), and four studies provided very limited or incomplete details in relation to causes of death (Bell et al*.,* 1989; Mikkelsen et al., 1990; Hayes 1997; Glasson et al*.,* 2016). As there was a limited number of studies that investigated causes of death and limited sample sizes, it was also difficult to determine how cause

of death has changed over time. For this reason, it was also difficult to extrapolate patterns in cause of death by specific age groups, countries or health care systems.

There was limited information in relation to the morbidity sequence leading to mortality in most of these studies. For example, Goldman et al., (2011) did not distinguish between underlying and multiple cause of death in their study and grouped both causal categories together. Similarly, Englund et al., (2012) did not distinguish between main and contributory causes in their study and only six studies reported intermediate or contributory causes of death. Hence it is not possible to build a clear and consistent picture of the chain of events leading to mortality for individuals with Down syndrome from all of the studies included in the systematic review.

The analysis of the results was limited in most studies, as they did not adjust for potential confounding factors such as gender, so it is difficult to determine whether these variables influenced age or cause of death. Comparison groups did not all take age into account.

Strengths and limitations of the review

The Methodological Quality of Systematic Reviews checklist (AMSTAR, 2015) was used to assess the quality of the systematic review. The research protocol and objectives were registered with the International Prospective Register of Systematic Reviews. This ensured that the aims of the study were rigorously adhered to. This protocol informed a comprehensive search strategy comprising specific keywords, and papers were selected against pre-defined eligibility criteria.

The majority of the studies were undertaken in high income countries and were restricted to English publications. This limits global generalisability, and capacity to

elucidate culture distinctions amongst individuals with Down syndrome related to life expectancy, age, and causes of death. This is a notable limitation as it is predicted that the improvements in life expectancy and age of death for individuals with congenital heart anomalies may not emerge across specific low and middle-income countries. This may be because surgical and care interventions for individuals with congenital heart anomalies are complex and resource-intensive, and therefore may not be accessible to individuals in such regions (Bernier *et al.,* 2010, but the lack of representation of low and middle income countries precluded distinctions on the basis of different health care systems.

Although studies that reported post-treatment or post-treatment deaths were not included in this review, some included studies may have some participants who had cardiac surgery. Therefore this may have influenced survival outcomes for some of the participants in these studies.

The findings from this review had to be synthesised using narrative analysis, due to the incomparable nature of the studies in the review. This approach carries the risk of being more biased than a meta-analysis (Cooper & Rosenthal, 1980). However quality appraisal was ensured through checking a proportion of study titles, abstracts and full papers with a 2nd reviewer. The critical appraisal (CASP) checklist was also used to reduce this bias, as each specific study was given a formal quality assessment score, and this was verified with a 2nd and 3rd reviewer: the quality of studies varied, including with regards to representativeness.

This appraisal of the strengths and limitations of the review was conducted by the team who completed the review, and so may be subject to unintentional bias.

Conclusions

This review has revealed that people with Down syndrome are now living longer and die up to 28 years younger than the general population in high income countries. Age of death has notably increased in recent years, particularly for individuals with congenital heart anomalies. This may be due to improvements in diagnosing and treating these conditions. However, these improvements have not been observed across all sub groups of individuals with Down syndrome, and ethnic differences in particular warrant further investigation. The pattern of cause of death differed from the general population, with congenital heart anomalies and respiratory illness being most common, some of which may be amenable to improved healthcare. There is a need for improved standardisation and rigorous reporting of the underlying, primary and contributory causes of death across countries.

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