Journal of **Policy and Practice in Intellectual Disabilities**

Journal of Policy and Practice in Intellectual Disabilities
Volume 7 Number 1 pp 70–81 March 2010

Aging in Down Syndrome: Morbidity and Mortality

Jennifer Torr*, Andre Strydom†, Paul Patti‡, and Nancy Jokinen§
*Centre for Developmental Disability Health Victoria, Monash University, Notting Hill, Victoria, Australia; †Department of Mental Health Sciences, University College London, UK; ‡George Jervis Clinic, Institute for Basic Research in Developmental Disabilities, Staten Island, New York, USA; §University of Calgary, Calgary, Alberta, Canada

Abstract The life expectancy of adults with Down syndrome has increased dramatically over the last 30 years, leading to increasing numbers of adults with Down syndrome now living into middle and old age. Early-onset dementia of the Alzheimer type is highly prevalent in adults with Down syndrome in the sixth decade, and this has overshadowed other important conditions related to aging among adults with Down syndrome. The authors' aim was to update and summarize current knowledge on these conditions, and examine causes of morbidity and mortality in older people with Down syndrome by conducting a systematic review of the published literature for the period: 1993–2008. They reviewed English-language literature drawn from searches in the electronic databases Medline, CINAHL, and PsycINFO, as well as supplementary historical papers. The authors conclude that functional decline in older adults with Down syndrome cannot be assumed to be due only to dementia of the Alzheimer type (which is not inevitable in all adults with Down syndrome). Functional decline may be the result from a range of disorders, especially sensory and musculoskeletal impairments. Given the high rates of early-onset age-related disorders among adults with Down syndrome, programmatic screening, monitoring, and preventive interventions are required to limit secondary disabilities and premature mortality. With respect to assessment and treatment, in the absence of specialist disability physicians, geriatricians have a role to play.

Keywords: aging, Down syndrome, health, morbidity, mortality

INTRODUCTION

Down syndrome is due to trisomy 21 in 95% of cases, the remaining 5% being due to mosaic trisomy 21 and various translocations of chromosome 21 (Mulcahy, 1979). Triplication of the 225 genes encoded by chromosome 21 (Hattori et al., 2000) disrupts normal gene expression, affecting the structure and function of all body systems. This has consequences for the health and well-being of people with Down syndrome over the lifespan, as well as reducing life expectancy relative to those with other intellectual disabilities (ID). The early onset and high prevalence of Alzheimer's disease in adults with Down syndrome is well known, overshadowing the other disorders of aging that result in significant morbidity, functional decline, and early mortality.

Our aim is to provide a descriptive update and summary of the current knowledge on the health disorders of aging in adults with Down syndrome through a systematic review of the published literature between 1993 and 2008. The review focuses on the causes of mortality and age-related morbidity in people with Down syndrome aged 40 years and over; it does not specifically address general non-age related conditions associated with Down syndrome, nor the pathophysiology of the disorders of aging in Down syndrome. For a comprehensive review of Alzheimer's disease in Down syndrome, see Strydom et al. (in press).

Received January 28, 2009; accepted November 7, 2009
Correspondence: Jennifer Torr, Centre for Developmental Disability Health Victoria, Monash University, Building One, Omnico Business Centre, 270 Ferntree Gully Rd, Notting Hill VIC 3065 Australia. Tel: +61 39501 2400; Fax: +61 38575 2270; E-mail: jenny.torr@med.monash.edu.au

LITERATURE SEARCHES AND SELECTION OF PAPERS

Online searches of Medline, CINAHL and [PsycINFO] using the exploded MESH term "Down syndrome," as well as keyword searches for equivalent terms (Down syndrome, Down's syndrome, trisomy 21). The search was limited to papers published in the English language between 1993–2008. Additional limits to the search included a focus on middle-aged and aged groups. The search was undertaken at the end of April 2008. This strategy delivered over 1,200 citations; abstracts for these citations were read, and papers relating to life expectancy, mortality, and age-related morbidity were selected. Papers were also limited to epidemiological and clinical studies, and the pathophysiology of aging in Down syndrome was not covered. The review was conducted within the context of the changing demographics of Down syndrome, the recent increases in life expectancy to almost 60 years, and the associated increases in the numbers of adults with Down syndrome in their 50s, 60s, and 70s. Thus, an

illustrative review of population prevalence and changing life expectancy over the last century was obtained. The review was also supplemented by relevant papers identified from reference lists, as well as some targeted searches outside initial search limits when current literature was scant (e.g., for hip disease).

There is great variability in the methodology of the identified research (Table 1). No meta-analysis of data has been conducted, and many studies are relatively small and based on convenience samples in clinical and social service settings. The categorization of what are considered "older adults" with Down syndrome varied from 40 to 50 or more years. Comparison groups included the general population, people with other ID, or younger adults with Down syndrome. The country and regional locality of studies varied considerably, but studies were predominantly done in Western countries. Given this, caution is required in the interpretation and generalization of findings. However, large population studies, such as those of sensory impairment in people with ID conducted in the Netherlands, have confirmed the findings of smaller nonrepresentative samples.

DEMOGRAPHICS

The population prevalence of Down syndrome in developed countries is in the order of 6–8 per 10,000 (Besser, Shin, Kucik, & Correa, 2007; Mantry et al., 2008; Steele & Stratford, 1995), accounting for 10–18% of people with ID (Glasson et al., 2002; Mantry et al., 2008; Singer & Strauss, 1997). Down syndrome occurs in about 1 per 650–1,000 live births (Bittles, Bower, Hussain, & Glasson, 2007). Reported live birth rates vary greatly between countries from 0.23 per 1,000 in Taiwan (Jou et al., 2005), to 2.98 in Ireland (O'Nuallain, Flanagan, Raffat, Avalos, & Dineen, 2007), reflecting differences in maternal age, access to antenatal diagnosis, and social attitudes toward termination of pregnancy. While live birth rates with Down syndrome have declined in Taiwan (Jou et al., 2005), Singapore (Lai et al., 2002), and France (Khoshnood, De Vigan, Vodovar, Goujard, & Goffinet, 2004), live birth rates are increasing in Ireland (O'Nuallain et al., 2007), Japan (Takeuchi et al., 2008), and Hungary (Metneki & Czeizel, 2005). The overall prevalence of people with Down syndrome is expected to increase for some time due to dramatic increases in median and average life expectancy, even where there is a drop in live birth rates.

Life expectancy of people with Down syndrome was just 9 years in 1929 (Penrose, 1949), but is now approaching 60 years. The mean age at death of people with Down syndrome at the Stoke Park Hospitals in the UK increased from 10–14 years in the 1930s, to 15–19 years in the 1940s, 20–31 years in the 1950s, 32–35 years in the 1960s, and 42–55 years in the 1970s (Carter & Jancar, 1983). There has been a gradual increase in life expectancy from the mid-50s in the 1980s (Strauss & Eyman, 1996), to the mid- to late 50s from the 1990s (Bittles et al., 2007; Coppus et al., 2008; Jancar & Jancar, 1996; Puri, Lekh, Langa, Zaman, & Singh 1995). This dramatic increase in life expectancy is attributable to improvements in general and medical care resulting in the survival of the majority of people with Down syndrome into adulthood, as mortality associated with the leading causes of death in Down syndrome, such as congenital heart disease and infections secondary to impaired immunity, has diminished.

Improvements in accommodations and deinstitutionalization, antibiotic treatments, and vaccinations have contributed to the reduction of death from pneumonia and other infections. In the 1950s, death from respiratory infections in people with Down syndrome was six times greater than for the general population (Oster, Mikkelsen, & Nielsen, 1975; Ugazio, Maccario, Notarangelo, & Burgio, 1990). Recent research has shown that the standardized mortality ratio (SMR) for respiratory infection in Down syndrome has dropped to 7.6 (Yang, Rasmussen, & Friedman, 2002).

Congenital heart disease remains a leading cause of death among persons with Down syndrome, with a reported SMR of 29 (Yang et al., 2002). However, due to access to and advances in pediatric cardiac surgery (Formigari et al., 2004; Kabbani et al., 2005) the median age at death for people with Down syndrome in the U.S. has increased from just 2 years in 1968, to 25 years in 1983, and 49 years in 1997 (Friedman, 2001; Yang et al., 2002). One-year survival rates in Australia have increased from 46% in the 1940s to 80% in the late 1960s and early 1970s (Mikkelsen, 1981), to 90% in the 1990s (Leonard et al., 2000). Nonetheless, there are differential survival rates for disadvantaged groups in developed countries. African Americans with Down syndrome had a median life expectancy of under 25 years in 1997 (Friedman, 2001). Only 78% of Aboriginal Australians with Down syndrome survived their first year in the 1990s (Leonard et al., 2000).

This exponential rise in early survival over the last 40–50 years has resulted in a rapid rise in the numbers of older people with Down syndrome. The average age of people with Down syndrome in Scotland is now 40 years (Mantry et al., 2008). Steffelaar and Evenhuis (1989) reported the number of people with Down syndrome, aged 40 years and over, in institutional care in the Netherlands increased from 16 to 1,150 between 1958 and 1983. They predicted that between 1990 and 2010, the number of people with Down syndrome aged 40 years and over would increase by 75%, while the number aged 50 years and over would increase by 200%. In one institutional setting in the Netherlands, more than 70% of the 96 adults with Down syndrome were over the age of 40 years (Van Buggenhout et al., 1999). Twenty years ago, Baird and Sadovnick (1988) predicted that of live-born infants with Down syndrome, about 44% would live to 60 years and 13.6% to 68 years. This prediction has proved prescient. By 2000, 75% of people with Down syndrome in Western Australia had survived to age 50 years, 50% to 58.6 years, and 25% to 62.9 years (Glasson et al., 2002). In Norway, mean age at death for people with Down syndrome has increased from 12.6 years in 1970 to 50.0 years in 2005. This is attributed to a relative decrease in newborn and infant mortality more so than a significant extension of longevity. The number of people with Down syndrome 40 years and older is projected to increase by 100% by 2045 (Larsen & Kirkevold, 2008). Furthermore, there are reports of people with Down syndrome living into their late 60s and 70s (Chicoine & McGuire, 1997; Glasson et al., 2002; Jancar & Jancar, 1996; Krinsky-McHale et al., 2008; Mantry et al., 2008; Royston et al., 1994; van Allen et al., 1999).

TABLE 1
Age-related morbidity, other than Alzheimer's disease, in adults with Down syndrome

Authors, year	Study design	Location	Source	Sample	Age	Condition/s	Outcomes/findings
Menopause							
Carr & Hollins (1995)	Questionnaire survey	UK	Wandsworth Register for People with Learning Disabilities	45 women with DS 126 women non-DS ID	18 years plus	Menopause	87% of DS menopause by 46 years 69% non-DS ID by 46 years 100% DS menopause by 51 years 100% non-DS ID menopause by 54 years
Cosgrave, Tyrrell, McCarron, Gill, & Lawlor (1999)	Prospective semistructured interview of subjects and carers	Ireland	Longitudinal cohort	78/143 women with DS	Mean age 46.1 years	Menopause	Average age of menopause 44.7 years
Schupf et al. (1997)	Semistructured interview	New York State, USA	New York Office of Mental Retardation and Developmental Disabilities	157 women with DS 187 women with non-DS ID	40 years plus	Menopause	DS vs. non-DS ID age adjusted odds ratio for menopause = 2.3
Schupf et al. (2003)	Restrospective	New York State, USA	New York state developmental disabilities services system	121/163 postmenopausal women with DS	40–60 years	Menopause	Age at menopause <46 years, $n = 65$ >46 years, $n = 46$
Milberger, Leroy, Lachance, and Edelson (2002)	Questionnaire	Michigan, USA	Community agencies	23 postmenopausal women with DS	44–77 years Mean 54.7 years	Menopause	Age at menopause 40–53 years Mean = 45.2 years years
Musculoskeletal disorders							
Center, Beange, and McElduff (1998)	Examination by endocrinologist Lumbar DEXA	Australia	Community based 90%	Females DS $n = 12$ Non-DS ID $n = 41$ Males DS $n = 8$ Non-DS ID $n = 33$	Females mean age = 35 years Males Mean age = 35 years	Osteoporosis	Females with DS lower BMD than non-DS females $p = 0.03$ Males with DS lower BMD than non-DS ID males $p = 0.009$
van Allen, Fung, and Jurenka (1999)	Review of comprehensive annual medical assessments and acute care notes from medical records	British Columbia, Canada	Provincial residential center	Adults with DS $N = 38$	<50 years $n = 18$ vs. >50 years $n = 20$	Vertebral crush fracture Osteoarthritis (OA) spine OA other Fractures long bones Fractures other bones	<50 years vs. >50 years 0/18 vs. 6/20 4/18 vs. 8/20 0/18 vs. 5/20 — vs. 11/20 NI vs. 6/20
Angelopoulou, Souftas, Sakadamis, and Mandroukas (1999)		Greece		9 males with DS 12 females with DS Compared with age matched controls	Mean age = males 26 years; females 24 years	BMD of spine *t*-score with respect to scanner reference database	Males DS vs. controls Lower BMD $p < 0.001$ *t*-score = –2.62 Females DS vs Controls Lower BMD $p < 0.001$ *t*-score = –1.56

Angelopoulou et al. (2000)	BMD	Greece		8 males with DS 8 males with non-DS ID 10 male controls	Mean age = 24 years Mean age = 24 years Mean age = 25 years	BMD of spine *t*-score with respect to scanner reference group	DS T score = –2.66 Non-DS ID *t*-score = –0.15 Control *t*-score = –0.06
Tyler, Snyder, and Zyzanski (2000)	Screening Heel DEXA	Ohio, USA	Community training center for adults with developmental disabilities	31 females with DS 15 females with non-DS ID	40–60 years	BMD Osteoporosis	10 variable multiple regression analysis of BMD DS standardized beta coefficient –0.28, $p = 0.005$
Milberger et al. (2002)	Bone mineral density, questionnaire Comparison with norms for general population	Michigan, USA	Community agencies	23 postmenopausal women with DS	44–77 years Mean 54.7 years	Osteoporosis	Spine($n = 23$) 39% osteoporosis 48% osteopenia Relative lifetime fracture risk 2.5 Hip ($n = 20$) 35% osteoporosis 45% osteopenia Relative lifetime fracture risk 6.6 Proximal forearm ($n = 15$) 20% osteoporosis 40% osteopenia Relative lifetime fracture risk 4.4
Baptista, Varela, and Sardinha (2005)	Cross-sectional clinical assessment	Portugal	Community vocational and educational centers	DS $n = 67$ Female $n = 33$ Male = 34 Controls $n = 67$ Female $n = 33$ Male $n = 34$	14–44 years	Volumetric BMD adjusted for bone area, height and age	DS risk factor for low volumetric BMD and diminished bone strength
Schrager, Kloss, and Ju (2007)	Retrospective chart review	Wisconsin, USA	Family medicine clinics	23 women with DS 70 women with non-DS ID	18–60 plus years	Fractures	Average age for first fracture 41.7 years Average age for any fracture 45.08 years Adjusted odds ratio Postmenopausal 10.344 ($p = 0.011$) Anticonvulsant use 3.669 ($p = 0.043$)
Guijarro, Valero, Paule, Gonzalez-Macias, and Riancho (2008)	Cross-sectional Clinical assessment	Spain	Clinical population Convenience sample	DS $n = 39$ Male $n = 18$ Female $n = 21$ Controls $n = 78$ Male $n = 36$ Female $n = 42$	18–45 years Mean age 26 years 19–47 years Mean age 27 years	Volumetric BMD	Multivariate regression analysis DS, control Lumbar vs. BMD 0.26 (0.001) Femoral vs. BMD not significant
Hresko, McCarthy, and Goldberg (1993)	Review of clinical records		Community and institutional	DS $n = 65$ out of 125 Male $n = 36$ Female $n = 29$	14–70 years Mean age 40 years	Orthopedic abnormalities Osteoarthritis	22% hips abnormal 5% hips dislocated Osteoarthritis in older group
van Allen et al. (1999)	Review of comprehensive annual medical assessments and acute care notes from medical records	British Columbia, Canada	Provincial residential center	Adults with DS $n = 38$	<50 years $n = 18$ vs >50 years $n = 20$	Osteoarthritis Spine Other joints	<50 years vs. >50 years 4/18 vs. 8/20 0/20 vs. 5/20

TABLE 1 *Continued*

Authors, year	Study design	Location	Source	Sample	Age	Condition/s	Outcomes/findings
Kioschos, Shaw, & Beals (1999)	Clinical	Oregon, USA	Community	Adults with DS $N = 6$	22–47 years Mean age 36 years	Osteoarthritis	Arthroplasty on 9 hips
Sensory disorders							
Meuwese-Jongejeugd et al. (2006)	Cross-sectional epidemiological study Direct clinical assessment	Netherlands	Stratified (age and DS) random sample of 1,598 people from base population of 9,012	Non-DS ID $n = 1,178$ <50 years $n = 744$ >50 years $n = 434$ DS $n = 420$ <50 years $n = 257$ >50 years $n = 163$	>18 years	Hearing loss	>60 years DS vs. non-DS ID Odds ratio for hearing loss = 5.18
van Splunder, Stilma, Bernsen, and Evenhuis (2004)	Cross-sectional epidemiological study Direct clinical assessment	Netherlands	Stratified (age and DS) random sample of 1,598 people from base population of 9,012	non-DS ID $n = 1,178$ <50 years $n = 744$ >50 years $n = 434$ DS $n = 420$ <50 years $n = 257$ >50 years $n = 163$	>18 years	Vision impairment and blindness	DS >50 years Odds Ratio for vision impairment, including blindness = 4.08 (95% confidence interval 2.28–7.29) $p = 0.0005$ Non-DS ID >50 years Odds ratio for vision impairment including blindness = 1.60 (95% confidence interval 1.07–2.38) $p = 0.010$
Castane, Boada-Rovira, & Hernandez-Ruiz (2004)	Cross-sectional general clinical assessment	Italy		Adults with DS $n = 49$	40–62 years	Vision impairment	Myopias 61.4% Astigmatisms 45.8% Hyperopias 32.1% Crystalline opacities 25% Nystagmus 13.5% Keratoconus 6.2%
Van Buggenhout et al. (1999)	Cross-sectional general clinical assessment	Belgium	Institutional setting of 591 adults with intellectual disability	Adults with DS $n = 96$	>40 years $n = 70$	Vision impairment	50–59 years half had moderate to severe vision loss <50 years one-third had moderate vision loss
van Schrojenstein Lantman-de Valk et al. (1994)	Retrospective clinical file questionnaire	Netherlands	Epidemiological age stratified cohort	Adults with ID $n = 1,583$ DS $n = 307$ Non-DS ID $n = 1,117$ Vision data $n = 1,309$ Hearing data $n = 1,312$	0–60+ years	Vision impairment Hearing impairment	DS >50 years 46% Non-DS ID >50 years 13% DS>60 years 45% Non-DS ID >60 years 16%
Meuwese-Jongejeugd et al. (2006)	Clinical assessment	Netherlands	Epidemiological age stratified cohort	Adults with ID $n = 1,583$ DS $n = 307$ Non-DS ID $n = 1,117$	0–60+ years	Hearing impairment	Onset of age related hearing impairment three decades earlier in DS
Mental health							
Mantry et al. (2008)	Clinical assessment	Scotland	Population based longitudinal cohort	Adults with DS $n = 186$	16 = years	Mental ill health	No difference in rates of mental ill health excluding dementia in 16–45 years and >45 year age groups.
Patti and Tsiouris (2006)	Clinical assessment	New York, USA	Outpatient clinical sample	Adults with DS $n = 206$	20–71 years	Psychiatric disorder	Decreasing behavior disorder with age

DS = Down syndrome; ID = intellectual disabilities; BMD = bone mineral density; OA = osteoarthritis; DEXA = dual energy X-ray absorptiometry.

PREMATURE MORTALITY IN OLDER PEOPLE WITH DOWN SYNDROME

In spite of the increasing life expectancy of people with Down syndrome, these gains have started to plateau over the last two decades. Mortality increases sharply after the age of 40 years (Day, Strauss, Shavelle, & Reynolds, 2005; Dupont, 1986; Eyman, Call, & White, 1991; Strauss & Eyman, 1996; Strauss & Shavelle, 1998). Differential life expectancy between people with Down syndrome and other ID is a consistent finding across time (Baird & Sadovnick, 1988; Carter & Jancar, 1983; Maaskant, Gevers, & Wierda, 2002; Penrose, 1949). Singer and Strauss (1997) reported that in California (in the U.S.), the population mortality rates for adults with Down syndrome are similar to those of people with other ID up until the age of 35 years. After the age of 35 years, the annual mortality rate for adults with Down syndrome doubled every 6.3 years compared with 9.6 years for adults with other ID. In a study of mid-life adults (mean age 33 years) living with their families, those with Down syndrome had four times the risk of mortality compared with adults of other intellectual disability etiologies (Esbensen, Seltzer, & Greenberg, 2007).

Studies of mortality in adults with Down syndrome fall into two main categories: cause of death and risk factors for mortality. Large population studies have relied on causes of death recorded on death certificates, which will generally document proximate cause of death, such as pneumonia, but may not note an underlying cause of death, such as Alzheimer's disease (Bittles et al., 2007; Yang et al., 2002). For example, in a population-based study in Western Australia, Alzheimer's disease was listed as a contributing cause of death in only three cases, but pneumonia was reported as the cause of death in 40% of people with Down syndrome aged 40 years plus (Bittles et al., 2007). This highlights the serious limitations of death certificate analysis. Pneumonia is a major cause of death associated with dementia (Keene, Hope, Fairburn, & Jacoby, 2001). Given high rates of dementia in older people with Down syndrome, it is expected that Alzheimer's disease would be an important secondary cause of death. In a smaller study of 92 adults with Down syndrome (Margallo-Lana et al., 2007), bronchopneumonia was listed as the cause of death in 61% of cases, Alzheimer's disease in 21%, and epilepsy in 14%. Of note, 68% of those who died had a diagnosis of dementia.

Bearing in mind limitations of death certificate data, there is a different pattern of mortality between younger and older adults with Down syndrome. The leading causes of death recorded on death certificates among adults aged 19–40 years with Down syndrome in Western Australia are congenital heart disease (33%) and respiratory infection (23%). After the age of 40 years, the leading cause of death was respiratory infection (44%).

Another population-based study, in the U.S., reported the standardized mortality odds ratios (SMOR) for people with Down syndrome compared with the general population. The SMOR for pneumonia was higher in the over 40 year age groups, peaking at 14 in the 50–59 year age group. In this study, dementia was found to be a significant cause of death with an SMOR of 116 in the 40–49 year age group and a SMOR of 67 in the 50–59 year age group. The SMOR for congenital heart disease fell across the over 40 year age groups from 43 to 19. This compares with SMOR for congential heart disease of 86 and 74 for the 20–29 and 30–39 year age groups, respectively (Yang et al., 2002).

Of note, cardiovascular disease and solid tumor cancers, which are major causes of death in older people in the general population, are minor causes of death in older people with Down syndrome. This is a consistent finding across a number of studies. In the Western Australian population study, the recorded cause of death in adults with Down syndrome over 40 years was coronary artery disease in 10% and solid cancers 5%. In the U.S. population study, the SMOR for ischemic heart disease for adults with Down syndrome in the over 40 years age group was 0.42 or less. The SMOR for malignancies (not leukemia) for the older group was 0.09 or less. Of note, the SMOR for leukemia falls below 1 in the 40 year plus age group with Down syndrome. This indicates that Down syndrome is in some way protective against ischemic heart disease and solid malignancies. With respect to ischemic heart disease, this apparent protection occurs in the context of high rates of obesity and sedentary life styles in adults with Down syndrome (Henderson et al., 2007; Janicki et al., 2002; Melville, Cooper, McGrother, Thorp, & Collacott, 2005; van den Akker, Maaskant, & van der Meijden, 2006; van Schrojenstein Lantman-de Valk, Haveman, & Crebolder, 1996).

Coppus et al. (2008) examined risk factors for mortality according to morbidity at baseline in a prospective longitudinal study of almost 500 people with Down syndrome in the Netherlands, followed up on average over 4.5 years. Hazard ratios between 2 and 3 were found for epilepsy, vision impairment, mobility restriction, dementia, as well as for onset of dementia during follow-up. In a review of 98 published case reports, the mean duration of Alzheimer's disease in people with Down was 6 years (range 0.5–21) (Prasher & Krishnan, 1993). If the two extreme cases of duration of dementia over 15 years are removed, then mean duration of life is 4.8 years. Life expectancy following the onset of seizures in people with Down syndrome and dementia was less than 2 years (Prasher & Corbett, 1993). Adverse reactions of phenytoin treatment of late-onset seizures were found to be possible contributors to shortened life expectancy after the onset of seizures in persons with Down syndrome who were diagnosed with dementia (Tsiouris, Patti, Tipu, & Raguthu, 2002). Strauss and Zigman (1996) found increased mortality associated with age-related decline in eating, toileting, and ambulatory skills in adults with Down syndrome aged 40 years plus. Behavior change and functional decline are further risks for mortality for mid-life adults with Down syndrome (Esbensen et al., 2007).

The Apo E genotype is related to the risk of developing Alzheimer's disease in Down syndrome, as well as in the general population. The presence of the allele Apo E2 is protective against Alzheimer's disease in people with Down syndrome, and is also associated with increased longevity into the late 60s and early 70s (Royston et al., 1994). The presence of the Apo E4 allele is not only associated with an increased risk of Alzheimer's disease in Down syndrome, but with an increased risk of mortality (Coppus et al., 2008) even in individuals without dementia (Coppus et al., 2008; Zigman, Jenkins, Tycko, Schupf, & Silverman, 2005).

Severe and profound intellectual disability in Down syndrome is associated with higher rates of mortality (Coppus et al., 2008; Strauss & Eyman, 1996). The relationship between sex and mortality in older adults with Down syndrome is not clear. Some studies have found a higher life expectancy of 2–3 years for men (Carter & Jancar, 1983; Glasson et al., 2003), while other studies have found longer life expectancies of 3–7 years for women

(Janicki, Dalton, Henderson, & Davidson, 1999; Puri et al., 1995). Coppus et al. (2008) found sex was not a factor in mortality risk, although they did note that there were fewer female participants in their study suggesting possible earlier mortality.

DISORDERS OF AGING IN DOWN SYNDROME

Dementia of Alzheimer's type is a most important age-related disorder in middle-aged adults with Down syndrome, and is associated with substantial comorbidity and mortality. However middle-aged adults with Down syndrome also face considerable levels of other age related morbidity and disability, especially sensory impairments and musculoskeletal disorders, which are earlier in onset and of greater prevalence than among people with other ID and the general population (Table 1).

Psychiatric Disorders

Psychiatric conditions among people with Down syndrome are less prevalent than for people with other ID. A population-based study in Glasgow, Scotland, assessed the mental health status of 186 adults with Down syndrome (Mantry et al., 2008). There was no significant difference in the point prevalence of mania (0%), psychosis (0%), depression (2–3%), and behavior disorders (10%) between those adults with Down syndrome aged 16–44 years and those aged more than 45 years. In a New York (U.S.) outpatient clinic sample of 206 adults with Down syndrome between the ages of 20 and 71 years, mood and sleep disturbances and behavior rituals were the most frequent psychiatric signs and symptoms reported. The incidence of aggressive and disruptive behaviors was found to decrease with advancing age. Across all age groups, mood and anxiety disorders were the principal psychiatric diagnoses, whereas the incidence of psychotic disorders was low (Patti & Tsiouris, 2006). Adults with Down syndrome and dementia often have a past history of depression (Coppus et al., 2006), and depression is common in early stage dementia (McCarron, Gill, McCallion, & Begley, 2005a). However, depressive disorders are often mistaken for dementia when an adult with Down syndrome presents with functional and cognitive decline, and can be reversed with appropriate treatment with antidepressant medications and electroconvulsive therapy (Patti & Tsiouris, 2006; Tsiouris & Patti, 1997; Warren, Holroyd, & Folstein, 1989).

A number of studies indicate that behavior change may precede decline in functioning and cognition (Ball et al., 2006; Deb, Hare, & Prior, 2007; Holland, Hon, Huppert, & Stevens, 2000; Nelson, Orme, Osann, & Lott, 2001). Behavioral and psychological symptoms of diagnosed dementia are common, including mood changes and depression, daytime wandering, restlessness, resistiveness, aggressive behaviors, sleep disturbance, incontinence, amotivation, slowness, and social disengagement (Cooper & Prasher, 1998; Coppus et al., 2006; Huxley, Van-Schaik, & Witts, 2005; McCarron, Gill, McCallion, & Begley, 2005b; Prasher & Filer, 1995; Urv, Zigman, & Silverman, 2008). A diagnosis of dementia is predictive of maladaptive behavior (Prasher & Chung, 1996) and increased psychotropic drug use (Coppus et al., 2006). Behavioral and psychological symptoms of dementia in Down syndrome are covered in more detail by Strydom et al. (in press).

Dementia of the Alzheimer Type

It is well established that adults with Down syndrome have very high rates of dementia of the Alzheimer type, with average age of diagnosis in the early to mid-50s. A prospective, longitudinal study in the Netherlands of 506 adults with Down syndrome aged 45 years and older found the prevalence of dementia by age group to be: up to 49 years—16.8%; 50–54 years—17.7%; 55–59 years—32.1%; 60 years plus—25.6%. The prevalence of dementia doubled every 5 years up to 60 years. After the age of 60 years, there was no actual decrease in the incidence of dementia, and the fall in prevalence was attributed to the increased mortality (Coppus et al., 2006). In a hospital-based cohort of 92 adults with Down syndrome (Margallo-Lana et al., 2007), the reported prevalence of dementia was 0% under 45 years, 10% between 45 and 49 years, 26% between 50 and 54 years, 35% between 55 and 59 years, and 42% over 60 years. The incidence rate of dementia per 100 person years increased from 0 in the under age 45 group to 3.4 in the 50–54 year group, to just over 7 in the 55–59 year and 60 year plus groups. See Strydom et al. (in press) for a more detailed review of dementia prevalence and incidence in people with Down syndrome.

There is substantial comorbidity associated with dementia of the Alzheimer type in people with Down syndrome, increasing support needs and carer burden (Coppus et al., 2006; McCarron et al., 2005b; Prasher & Filer, 1995). A study of 211 adults with ID found that adults with Down syndrome in the sixth decade, particularly those with dementia, experienced significantly more life events, including relocations, losses or separations, and medical events than age peers without Down syndrome (Patti, Amble, & Flory, 2005).

In an Irish study, the amount of time formal caregivers spent meeting day-to-day care needs of people with Down syndrome increased with the onset of dementia, but did not increase significantly from early-stage to end-stage dementia, although the nature of caregiving did change with dementia progression (McCarron et al., 2005a). In another Irish study of 124 individuals with Down syndrome over the age of 35 years, there was a marked increase in immobility, feeding problems, pneumonia, and epilepsy from the group without dementia to mid-stage and then late-stage dementia. There was no difference in immobility between the no dementia and mid-stage dementia groups, but by end-stage dementia, 88% were completely immobile. Tube feeding was given to 36% of those at end stage. Lung disease, including breathing difficulties and recurrent chest infections, was 8% in the no dementia group, 33% by mid-stage dementia, and 92% by end-stage dementia. Prevalence of epilepsy increased from 11% for those without a diagnosis of dementia to 39% at mid-stage and 84% at end stage. This compares with a prevalence of epilepsy of about 10% in dementia of Alzheimer type in the general population (McCarron et al., 2005b). Rates of seizures among adults with Down syndrome affected by dementia in order of 80% have been reported by other researchers (Evenhuis, 1997; Prasher & Corbett, 1993).

Pulmonary Disorders

Annual health assessments of two cohorts of adults with Down syndrome in a residential care facility, 18 middle-aged individuals (30–43 years) and 20 elderly individuals (47–58 years), identified pneumonia as an equally common problem in both groups, occurring in 55% overall. Recurrent pneumonia occurred more often as mobility declined. Of concern was the identification of chronic interstitial lung changes on X-ray in 30% of the elderly group. This was attributed to recurrent aspiration (van Allen et al., 1999).

In a literature review, Lazenby (2008) noted that disorders of eating, drinking, and swallowing lead to malnutrition, dehydration, asphyxiation, aspiration, pneumonia, and eventual death. Most studies on disorders of eating, drinking, and swallowing have been done on the pediatric population with Down syndrome and have identified a range of anatomical and neuromuscular abnormalities. No studies on the effects of aging on eating, drinking, and swallowing in older adults with Down syndrome were identified through this review. This is a surprising given that pneumonia remains a leading cause of death in older people with Down syndrome.

Menopause

Menopause was reported to occur earlier in women with Down syndrome than among women with other ID and among women in general. Carr and Hollins (1995) found 87% of women with Down syndrome had stopped menstruating by 46 years of age (compared with 69% of women with other ID), and all had stopped by 51 years (compared with 54 years for women with other ID). A study of 143 Irish women with Down syndrome found the average age at menopause to be 44.7 years (Cosgrave et al., 1999). Schupf et al. (1997) report an age adjusted odds ratio of 2.3 for menopause in women with Down syndrome compared with women with other ID. No association has been found between thyroid disease and early menopause in women with Down syndrome (Schupf et al., 1997; Seltzer, Schupf, & Wu, 2001). There are few studies of the consequences of premature menopause, such as osteoporosis, but no specific guidance on the benefits and risks of hormone replacement therapy in women with Down syndrome. However, a number of studies have found an association between age of menopause and age of onset of Alzheimer's disease in women with Down syndrome (Cosgrave et al., 1999; Patel et al., 2004; Patel, Seltzer, Wu, & Schupf, 2001; Schupf et al., 2003; Schupf et al., 2006). Women with Down syndrome who have low levels of bioavailable oestradiol at baseline are four times more likely to develop Alzheimer's disease and do so about 3 years earlier—after adjusting for age, level of intellectual disability, body mass index, hypothyroidism, and Apo E4 (Schupf et al., 2006).

Sensory Impairments

Adults with Down syndrome have high rates of sensory impairments and are at further risk of age-related decline in sensory function. A large-scale population-based epidemiological study of 1,598 adults with ID, living in both institutional and community settings in the Netherlands, employed rigorous assessments of hearing and vision (Meuwese-Jongejeugd et al., 2006; van Splunder, Stilma, Bernsen, & Evenhuis, 2006). The results showed that older people with Down syndrome have higher rates of sensory impairments than people with other ID.

The odds ratios for specific ocular diagnoses for Down syndrome compared with other ID were reported to be 2.16 for refractive errors, 2.47 for strabismus, 8.27 for lens opacity, 7.65 for keratoconus, and 2.70 for corneal opacity. Risk for ocular hypertension was reduced with an odds ratio of 0.21 (van Splunder, Stilma, Bernsen, & Evenhuis, 2004). There is a strong association between increasing age and prevalence of vision impairment in people with Down syndrome and a less clear relationship with severity of intellectual disability, which is the opposite for adults with other ID. Down syndrome is the strongest risk factor for vision impairment in people with ID over 50 years. Vision impairment was found in more than a third of adults with Down syndrome aged 50 years plus and in two-thirds of those adults with profound intellectual disability. These rates are substantially higher than reported for comparison groups with other ID (van Splunder et al., 2006). A small sample study of 49 adults with Down syndrome aged between 40 and 62 years who were referred for dementia assessment found 61% had myopias, 46% astigmatisms, 23% hyperopias, 67% strabismus and altered motility, 59% crystalline opacities, 25% nystagmus, and 6% keratoconus, with 14% receiving interventions due to cataracts. No association between vision impairment and diagnosis of Alzheimer's disease was found (Castane, Boada-Rovira, & Hernandez-Ruiz, 2004). Similarly, Van Buggenhout et al. (1999) reported an increase in vision impairment with age in an institutional sample of adults with Down syndrome.

The prevalence of hearing impairments in people with Down syndrome over 50 years, in the Netherlands population study, was 28% compared with 8% for the older group with other ID (van Schrojenstein Lantman-de Valk et al., 1994). Hearing impairment was found in 38% of people with Down syndrome under 50 years of age, and 62% for those over 50 years and 100% over 60 years (Meuwese-Jongejeugd et al., 2006). Van Buggenhout et al. (1999) also report an increase in hearing impairment with age in an institutional sample of adults with Down syndrome.

Musculoskeletal Disorders

A number of studies have found significantly lower bone mineral density (BMD) in young adults with Down syndrome compared with age peer controls with other ID (Angelopoulou et al., 1999; 2000; Baptista et al., 2005; Center et al., 1998; Guijarro et al., 2008; Sepulveda et al., 1995) and controls without intellectual disability (Center et al., 1998). Higher rates of osteoporosis are reported for older adults with Down syndrome, from the age of 40 years, compared with the general population (Milberger et al., 2002; Tyler et al., 2000; van Allen et al., 1999). van Allen et al. (1999) reported vertebral crush fractures in 30% and long bone fractures in 55% in 20 people with Down syndrome age 50 plus years compared with no fractures in 18 people with Down syndrome age less than 50 years. This is one of the few studies on osteoporosis and fractures to include males. There is a greater rate of fractures in postmenopausal women with Down syndrome

compared with expected rates for the U.S. general population for the same age and ethnicity (Milberger et al., 2002). A study by Schrager et al. (2007) of fracture risk in women with ID found increased risk related to anticonvulsants and being postmenopausal, but overall risk for fractures was not related to having Down syndrome. Multiple risk factors have been postulated for the increased risk in osteoporosis in Down syndrome, including lower bone density development, small body size, thyroid disease, seizure disorder, low muscle mass and strength, low activity levels, and early menopause. However there is early evidence that triplication of certain genes on chromosome 21 confers a unique risk for osteopaenia and osteoporosis (Tumer et al., 2005).

A range of major orthopedic problems are common in Down syndrome. Lax ligaments and hypermobility of joints can result in instability, subluxation, and dislocation of joints, in particular the atlanto-occipital joint, patella, and hip (Diamond, Lynne, & Sigman, 1981), as well as contributing to degenerative joint disease. Osteoarthritis of the spine and hips is common in older adults with Down syndrome (Diamond et al., 1981; Hresko, McCarthy, & Goldberg, 1993; van Allen et al., 1999; Van Dyke & Gahagan, 1988). Degenerative changes in the cervical spine, including osteophyte and spur formation, narrowing of the foramina, and narrowing of the disc inner space, are apparent from the mid-20s (Van Dyke & Gahagan, 1988). Hip abnormalities occur in 8–28% of people with Down syndrome, with an increased incidence of dysplasia, Perthe's disease, dislocation, slipped epiphysis, and avascular necrosis (Kioschos, Shaw, & Beals, 1999). Hip instability can progress over time, and the prevalence of hip dysplasia and subluxation can increase with age (Hresko et al., 1993). Severe, debilitating, and painful degenerative disease of the hip can occur in relatively young adults, and hip joint degeneration can occur quickly over a few years in mid-adult life (Kioschos et al., 1999; Skoff & Keggi, 1987). Degenerative hip disease is an important cause of disability and pain in older adults with Down syndrome (Diamond et al., 1981). Total hip joint replacements have been successfully performed on adults with Down syndrome. Skoff and Keggi (1987) described eight total hip joint replacements in five people with Down syndrome, with a mean age of 46 years, with excellent results, no infection, loosening, or dislocation at mean follow-up of 4.3 years. Similarly Kioschos et al. (1999) describe nine hip replacements in six adults with Down syndrome aged 22–47 years, with good functional outcome and control of pain, maintained over an average follow-up time of 7 years. In spite of good anesthetic, surgical and functional outcomes of hip joint replacement, there are reports of people with Down syndrome being denied corrective surgery for no clinically justifiable reason (Gill et al., 2006).

A range of studies by Carmeli et al. (Carmeli, Ayalon, Barchad, Sheklow, & Reznick, 2002; Carmeli, Barchad, Lenger, & Coleman, 2002; Carmeli, Kessel, Bar-Chad, & Merrick, 2004; Carmeli, Kessel, Coleman, & Ayalon, 2002; Carmeli & Merrick, 2006; Carmeli, Merrick, Kessel, Masharawi, & Carmeli, 2003) found older adults with ID tended to be smaller, more obese, with lower muscle strength than adults in the general population. Older people with Down syndrome had greater muscle weakness, slower walking speed, poorer balance, and more impaired functional and sensorimotor performance. However, muscle strength and balance improved over 6 months with treadmill and physical activity training.

DISCUSSION

Down syndrome is the most common genetic cause of intellectual disability accounting for 10–20% of the identified population with ID. The number of people with Down syndrome over the age of 50 years has increased rapidly over the last two to three decades, and these numbers will be sustained and indeed will increase in many developed nations in the coming decades.

The dramatic gains in life expectancy since the 1920s appear to have plateaued due to the increased mortality associated with the development of dementia of Alzheimer type predominantly in the sixth and seventh decades. Average life expectancies of people with Down syndrome may not increase much beyond 60 years until preventive or disease modifying treatments for Alzheimer's disease become available.

Dementia of the Alzheimer type among adults with Down syndrome is associated with high levels of morbidity. However, this overshadows very high rates of early onset age-related disorders, especially sensory impairments and musculoskeletal disorders. These are important disorders because of the associated functional disability, pain, and distress, as well as the increased risk of mortality associated with vision and mobility impairments. Functional decline in older adults with Down syndrome cannot be automatically assumed to be due to dementia of the Alzheimer type, which is not inevitable in all adults with Down syndrome.

Some researchers have provided guidance on annual screening in older people with Down syndrome. Evenhuis, Theunissen, Denkers, Verschuure, and Kemme (2001) recommend annual hearing and vision checks, and van Allen et al. (1999) have provided guidelines on annual health assessment of older people with Down syndrome. However, further research is required with respect to general screening and the institution of preventive measures in particular with regards to disorders of eating, drinking and swallowing, and musculoskeletal functioning.

The model of care in many developed countries has split services for people with ID from health services with the general expectation that generic health services will meet the specific health needs of people with ID. Furthermore, as most aged social care and geriatric health services generally have an eligibility of service age of either 60 or 65 years, this often precludes specialized aging-related service provision to adults with Down syndrome with early-onset age-related disorders. The potential complex of multiple morbidities in aging adults with Down syndrome, as well as other ID, is an argument for engaging specialist physicians and providing for multidisciplinary teams in ID. In the absence of specialist adult physicians in intellectual disability, geriatricians are well placed to assess and manage the complex mix of disorders presenting in older people with Down syndrome. Training of geriatricians needs to address the healthcare needs of older adults with Down syndrome and other ID. Policy (or legislation) needs to be changed to permit provision of a range of aged care services to people with Down syndrome from the age of 40 years. In addition, programmatic proactive screening, monitoring, and preventive interventions are required to limit disability and premature death in older people with Down syndrome. When preventive and disease modifying treatments become available for Alzheimer's disease, the average life expectancy of people with Down syndrome could increase well beyond 60 years, and the

numbers of elderly people with Down syndrome will increase substantially beyond current expectations, posing new challenges to social and healthcare services.

REFERENCES

Akker, M. van den, Maaskant, M. A., & Meijden, R. J. van der. (2006). Cardiac diseases in people with intellectual disability. *Journal of Intellectual Disability Research, 50*, 515–522.

Allen, M. I. van, Fung, J., & Jurenka, S. B. (1999). Health care concerns and guidelines for adults with Down syndrome. *American Journal of Medical Genetics, 89*, 100–110.

Angelopoulou, N., Matziari, C., Tsimaras, V., Sakadamis, A., Souftas, V., & Mandroukas, K. (2000). Bone mineral density and muscle strength in young men with mental retardation (with and without Down syndrome). *Calcified Tissue International, 66*, 176–180.

Angelopoulou, N., Souftas, V., Sakadamis, A., & Mandroukas, K. (1999). Bone mineral density in adults with Down's syndrome. *European Radiology, 9*, 648–651.

Baird, P. A., & Sadovnick, A. D. (1988). Life expectancy in Down syndrome adults. *Lancet, 2*, 1354–1356.

Ball, S. L., Holland, A. J., Hon, J., Huppert, F. A., Treppner, P., & Watson, P. C. (2006). Personality and behaviour changes mark the early stages of Alzheimer's disease in adults with Down's syndrome: Findings from a prospective population-based study. *International Journal of Geriatric Psychiatry, 21*, 661–673.

Baptista, F., Varela, A., & Sardinha, L. B. (2005). Bone mineral mass in males and females with and without Down syndrome. *Osteoporosis International, 16*, 380–388.

Besser, L. M., Shin, M., Kucik, J. E., & Correa, A. (2007). Prevalence of down syndrome among children and adolescents in metropolitan Atlanta. *Birth Defects Research, 79*, 765–774.

Bittles, A. H., Bower, C., Hussain, R., & Glasson, E. J. (2007). The four ages of Down syndrome. *European Journal of Public Health, 17*, 221–225.

Carmeli, E., Ayalon, M., Barchad, S., Sheklow, S. L., & Reznick, A. Z. (2002). Isokinetic leg strength of institutionalized older adults with mental retardation with and without Down's syndrome. *Journal of Strength and Conditioning Research, 16*, 316–320.

Carmeli, E., Barchad, S., Lenger, R., & Coleman, R. (2002). Muscle power, locomotor performance and flexibility in aging mentally-retarded adults with and without Down's syndrome. *Journal of Musculoskeletal and Neuronal Interactions, 2*, 457–462.

Carmeli, E., Kessel, S., Bar-Chad, S., & Merrick, J. (2004). A comparison between older persons with Down syndrome and a control group: Clinical characteristics, functional status and sensorimotor function. *Down Syndrome: Research and Practice, 9*, 17–24.

Carmeli, E., Kessel, S., Coleman, R., & Ayalon, M. (2002). Effects of a treadmill walking program on muscle strength and balance in elderly people with Down syndrome. *Journals of Gerontology Series A-Biological Sciences and Medical Sciences, 57*, M106–M110.

Carmeli, E., & Merrick, J. (2006). Physical activity for aging persons with Down syndrome. *International Journal on Disability and Human Development, 5*, 343–345.

Carmeli, E., Merrick, J., Kessel, S., Masharawi, Y., & Carmeli, V. (2003). Elderly persons with intellectual disability: A study of clinical characteristics, functional status, and sensory capacity. *Scientific World Journal, 3*, 298–307.

Carr, J., & Hollins, S. (1995). Menopause in women with learning disabilities. *Journal of Intellectual Disability Research, 39*, 137–139.

Carter, G., & Jancar, J. (1983). Mortality in the mentally handicapped: A 50 year survey at the Stoke Park group of hospitals (1930–1980). *Journal of Mental Deficiency Research, 27*, 143–156.

Castane, M., Boada-Rovira, M., & Hernandez-Ruiz, I. (2004). Trastornos oculares propios del síndrome de Down en mayores de 40 años [Eye conditions as features of Down's syndrome in patients over 40 years of age]. *Revista de Neurologia, 39*, 1017–1021.

Center, J., Beange, H., & McElduff, A. (1998). People with mental retardation have an increased prevalence of osteoporosis: A population study. *American Journal of Mental Retardation, 103*, 19–28.

Chicoine, B., & McGuire, D. (1997). Longevity of a woman with Down syndrome: A case study. *Mental Retardation, 35*, 477–479.

Cooper, S. A., & Prasher, V. P. (1998). Maladaptive behaviours and symptoms of dementia in adults with Down's syndrome compared with adults with intellectual disability of other aetiologies. *Journal of Intellectual Disability Research, 42*, 293–300.

Coppus, A. M. W., Evenhuis, H. M., Verberne, G. -J., Visser, F. E., Oostra, B. A., Eikelenboom, P., et al. (2008). Survival in elderly persons with down syndrome. *Journal of the American Geriatrics Society, 56*, 2311–2316.

Coppus, A., Evenhuis, H., Verberne, G. -J., Visser, F., van Gool, P., Eikelenboom, P., et al. (2006). Dementia and mortality in persons with Down's syndrome. *Journal of Intellectual Disability Research, 50*, 768–777.

Cosgrave, M. P., Tyrrell, J., McCarron, M., Gill, M., & Lawlor, B. A. (1999). Age at onset of dementia and age of menopause in women with Down's syndrome. *Journal of Intellectual Disability Research, 43*, 461–465.

Day, S. M., Strauss, D. J., Shavelle, R. M., & Reynolds, R. J. (2005). Mortality and causes of death in persons with Down syndrome in California. *Developmental Medicine and Child Neurology, 47*, 171–176.

Deb, S., Hare, M., & Prior, L. (2007). Symptoms of dementia among adults with Down's syndrome: A qualitative study. *Journal of Intellectual Disability Research, 51*, 726–739.

Diamond, L. S., Lynne, D., & Sigman, B. (1981). Orthopedic disorders in patients with Down's syndrome. *Orthopedic Clinics of North America, 12*, 57–71.

Dupont, A. (1986). Mortality and life expectancy of Down's syndrome in Denmark. *Journal of Mental Deficiency Research, 30*, 111–120.

Esbensen, A. J., Seltzer, M. M., & Greenberg, J. S. (2007). Factors predicting mortality in midlife adults with and without Down syndrome living with family. *Journal of Intellectual Disability Research, 51*, 1039–1050.

Evenhuis, H. M. (1997). The natural history of dementia in ageing people with intellectual disability. *Journal of Intellectual Disability Research, 41*, 92–96.

Evenhuis, H. M., Theunissen, M., Denkers, I., Verschuure, H., & Kemme, H. (2001). Prevalence of visual and hearing impairment in a Dutch institutionalized population with intellectual disability. *Journal of Intellectual Disability Research, 45*, 457–464.

Eyman, R. K., Call, T. L., & White, J. F. (1991). Life expectancy of persons with Down syndrome. *American Journal on Mental Retardation, 95*, 603–612.

Formigari, R., Di Donato, R. M., Gargiulo, G., Di Carlo, D., Feltri, C., Picchio, F. M., & Marino, B. (2004). Better surgical prognosis for patients with complete atrioventricular septal defect and Down's syndrome. *Annals of Thoracic Surgery, 78*, 666–672.

Friedman, J. M. (2001). Racial disparities in median age at death of persons with Down syndrome—United States, 1968–1997. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report, 50*, 463–465.

Gill, C. E., Taylor, H. M., Lin, K. T., Padaliya, B. B., Newman, W. J., Abramovitch, A. I., et al. (2006). Difficulty in securing treatment for degenerative hip disease in a patient with Down syndrome: The gap remains open. *Journal of the National Medical Association, 98*, 93–96.

Glasson, E. J., Sullivan, S. G., Hussain, R., Petterson, B. A., Montgomery, P. D., & Bittles, A. H. (2002). The changing survival profile of people

with Down's syndrome: Implications for genetic counselling. *Clinical Genetics, 62*, 390–393.

Glasson, E. J., Sullivan, S. G., Hussain, R., Petterson, B. A., Montgomery, P. D., & Bittles, A. H. (2003). Comparative survival advantage of males with Down syndrome. *American Journal of Human Biology, 15*, 192–195.

Guijarro, M., Valero, C., Paule, B., Gonzalez-Macias, J., & Riancho, J. A. (2008). Bone mass in young adults with Down syndrome. *Journal of Intellectual Disability Research, 52*, 182–189.

Hattori, M., Fujiyama, A., Taylor, T. D., Watanabe, H., Yada, T., Park, H. S., et al. (2000). The DNA sequence of human chromosome 21. *Nature, 405*, 311–319.

Henderson, A., Lynch, S. A., Wilkinson, S., Hunter, M., Henderson, A., Lynch, S. A., et al. (2007). Adults with Down's syndrome: The prevalence of complications and health care in the community. *British Journal of General Practice, 57*, 50–55.

Holland, A. J., Hon, J., Huppert, F. A., & Stevens, F. (2000). Incidence and course of dementia in people with Down's syndrome: Findings from a population-based study. *Journal of Intellectual Disability Research, 44*, 138–146.

Hresko, M. T., McCarthy, J. C., & Goldberg, M. J. (1993). Hip disease in adults with Down syndrome. *Journal of Bone and Joint Surgery—British Volume, 75*, 604–607.

Huxley, A., Van-Schaik, P., & Witts, P. (2005). A comparison of challenging behaviour in an adult group with Down's syndrome and dementia compared with an adult Down's syndrome group without dementia. *British Journal of Learning Disabilities, 33*, 188–193.

Jancar, J., & Jancar, P. J. (1996). Longevity in Down syndrome: A twelve year survey (1984–1995). *Italian Journal of Intellective Impairment, 9*, 89–92.

Janicki, M. P., Dalton, A. J., Henderson, C. M., & Davidson, P. W. (1999). Mortality and morbidity among older adults with intellectual disability: Health services considerations. *Disability and Rehabilitation, 21*, 284–294.

Janicki, M. P., Davidson, P. W., Henderson, C. M., McCallion, P., Taets, J. D., Force, L. T., et al. (2002). Health characteristics and health services utilization in older adults with intellectual disability living in community residences. *Journal of Intellectual Disability Research, 46*, 287–298.

Jou, H. -J., Kuo, Y. -S., Hsu, J. -J., Shyu, M. -K., Hsieh, T. -T., & Hsieh, F.-J. (2005). The evolving national birth prevalence of Down syndrome in Taiwan. A study on the impact of second-trimester maternal serum screening. *Prenatal Diagnosis, 25*, 665–670.

Kabbani, M. S., Giridhar, S., Elbarbary, M., Elgamal, M., Najm, H., & Godman, M. (2005). Postoperative cardiac intensive care outcome for Down syndrome children. *Saudi Medical Journal, 26*, 943–946.

Keene, J., Hope, T., Fairburn, C. G., & Jacoby, R. (2001). Death and dementia. *International Journal of Geriatric Psychiatry, 16*, 969–974.

Khoshnood, B., De Vigan, C., Vodovar, V., Goujard, J., & Goffinet, F. (2004). A population-based evaluation of the impact of antenatal screening for Down's syndrome in France, 1981–2000. *BJOG: An International Journal of Obstetrics and Gynaecology, 111*, 485–490.

Kioschos, M., Shaw, E. D., & Beals, R. K. (1999). Total hip arthroplasty in patients with Down's syndrome. *Journal of Bone and Joint Surgery—British Volume, 81*, 436–439.

Krinsky-McHale, S. J., Devenny, D. A., Gu, H., Jenkins, E. C., Kittler, P., Murty, V. V., et al. (2008). Successful aging in a 70-year-old man with down syndrome: A case study. *Intellectual and Developmental Disabilities, 46*, 215–228.

Lai, F. M., Woo, B. H., Tan, K. H., Huang, J., Lee, S. T., Yan, T. B., et al. (2002). Birth prevalence of Down syndrome in Singapore from 1993 to 1998. *Singapore Medical Journal, 43*, 70–76.

Larsen, F., & Kirkevold, O. (2008). The ageing population with Down syndrome in Norway, 1969–2045. *Journal of Intellectual Disability Research, 52*, 644.

Lazenby, T. (2008). The impact of aging on eating, drinking, and swallowing function in people with Down's syndrome. *Dysphagia, 23*, 88–97.

Leonard, S., Bower, C., Petterson, B., & Leonard, H. (2000). Survival of infants born with Down's syndrome: 1980–96. *Paediatric and Perinatal Epidemiology, 14*, 163–171.

Maaskant, M. A., Gevers, J. P. M., & Wierda, H. (2002). Mortality and life expectancy in Dutch residential centres for individuals with intellectual disability, 1991–1995. *Journal of Applied Research in Intellectual Disabilities, 15*, 200–212.

McCarron, M., Gill, M., McCallion, P., & Begley, C. (2005a). Alzheimer's dementia in persons with Down's syndrome: Predicting time spent on day-to-day caregiving. *Dementia, 4*, 521–538.

McCarron, M., Gill, M., McCallion, P., & Begley, C. (2005b). Health co-morbidities in ageing persons with Down syndrome and Alzheimer's dementia. *Journal of Intellectual Disability Research, 49*, 560–566.

Mantry, D., Cooper, S. A., Smiley, E., Morrison, J., Allan, L., Williamson, A., et al. (2008). The prevalence and incidence of mental ill-health in adults with Down syndrome. *Journal of Intellectual Disability Research, 52*, 141–155.

Margallo-Lana, M. L., Moore, P. B., Kay, D. W. K., Perry, R. H., Reid, B. E., Berney, T. P., et al. (2007). Fifteen-year follow-up of 92 hospitalized adults with Down's syndrome: Incidence of cognitive decline, its relationship to age and neuropathology. *Journal of Intellectual Disability Research, 51*, 463–477.

Melville, C. A., Cooper, S. A., McGrother, C. W., Thorp, C. F., & Collacott, R. (2005). Obesity in adults with Down syndrome: A case-control study. *Journal of Intellectual Disability Research, 49*, 125–133.

Metneki, J., & Czeizel, A. E. (2005). Increasing total prevalence rate of cases with Down syndrome in Hungary. *European Journal of Epidemiology, 20*, 525–535.

Meuwese-Jongejeugd, A., Vink, M., van Zanten, B., Verschuure, H., Eichhorn, E., Koopman, D., et al. (2006). Prevalence of hearing loss in 1598 adults with an intellectual disability: Cross-sectional population based study. *International Journal of Audiology, 45*, 660–669.

Mikkelsen, M. (1981). Epidemiology of trisomy 21: population, peri- and antenatal data. *Human Genetics, 2*, 211–226.

Milberger, S., LeRoy, B., Lachance, L., & Edelson, G. (2002). Osteoporosis and women with Down syndrome. *Journal of Intellectual and Developmental Disability, 27*, 273–280.

Mulcahy, M. T. (1979). Down's syndrome in Western Australia: Cytogenetics and incidence. *Human Genetics, 48*, 67–72.

Nelson, L. D., Orme, D., Osann, K., & Lott, I. T. (2001). Neurological changes and emotional functioning in adults with Down Syndrome. *Journal of Intellectual Disability Research, 45*, 450–456.

O'Nuallain, S., Flanagan, O., Raffat, I., Avalos, G., & Dineen, B. (2007). The prevalence of Down syndrome in County Galway. *Irish Medical Journal, 100*, 329–331.

Oster, J., Mikkelsen, M., & Nielsen, A. (1975). Mortality and life-table in Down's syndrome. *Acta Paediatrica Scandinavica, 64*, 322–326.

Patel, B. N., Pang, D., Stern, Y., Silverman, W., Kline, J. K., Mayeux, R., et al. (2004). Obesity enhances verbal memory in postmenopausal women with Down syndrome. *Neurobiology of Aging, 25*, 159–166.

Patel, B. N., Seltzer, G. B., Wu, H. S., & Schupf, N. (2001). Effect of menopause on cognitive performance in women with Down syndrome. *Neuroreport, 12*, 2659–2662.

Patti, P. J., Amble, K. B., & Flory, M. J. (2005). Life events in older adults with intellectual disabilities: Differences between adults with and without Down syndrome. *Journal of Policy and Practice in Intellectual Disabilities, 2*, 149–155.

Patti, P. J., & Tsiouris, J. A. (2006). Psychopathology in adults with Down syndrome: Clinical findings from an outpatient clinic. *International Journal on Disability and Human Development, 5*, 357–364.

Penrose, L. S. (1949). The incidence of Mongolism in the general population. *Journal of Mental Science, 95*, 685–688.

Prasher, V. P., & Chung, M. C. (1996). Causes of age-related decline in adaptive behavior of adults with Down syndrome: Differential diagnoses of dementia. *American Journal on Mental Retardation, 101*, 175–183.

Prasher, V. P., & Corbett, J. A. (1993). Onset of seizures as a poor indicator of longevity in people with Down syndrome and dementia. *International Journal of Geriatric Psychiatry, 8*, 923–927.

Prasher, V. P., & Filer, A. (1995). Behavioural disturbance in people with Down's syndrome and dementia. *Journal of Intellectual Disability Research, 39*, 432–436.

Prasher, V. P., & Krishnan, V. H. (1993). Age of onset and duration of dementia in people with Down syndrome; Integration of 98 reported cases in the literature. *International Journal of Geriatric Psychiatry, 8*, 915–922.

Puri, B. K., Lekh, S. K., Langa, A., Zaman, R., & Singh, I. (1995). Mortality in a hospitalized mentally handicapped population: A 10-year survey. *Journal of Intellectual Disability Research, 39*, 442–446.

Royston, M. C., Mann, D., Pickering-Brown, S., Owen, F., Perry, R., Raghavan, R., et al. (1994). Apolipoprotein E e2 allele promotes longevity and protects patients with Down's syndrome from dementia. *Neuroreport, 5*, 2583–2585.

Schrager, S., Kloss, C., & Ju, A. W. (2007). Prevalence of fractures in women with intellectual disabilities: A chart review. *Journal of Intellectual Disability Research, 51*, 253–259.

Schrojenstein Lantman-de Valk, H. M. van, Haveman, M. J., & Crebolder, H. F. (1996). Comorbidity in people with Down's syndrome: A criteria-based analysis. *Journal of Intellectual Disability Research, 40*, 385–399.

Schrojenstein Lantman-de Valk, H. M. van, Haveman, M. J., Maaskant, M. A., Kessels, A. G., Urlings, H. F., & Sturmans, F. (1994). The need for assessment of sensory functioning in ageing people with mental handicap. *Journal of Intellectual Disability Research, 38*, 289–298.

Schupf, N., Pang, D., Patel, B. N., Silverman, W., Schubert, R., Lai, F., et al. (2003). Onset of dementia is associated with age at menopause in women with Down's syndrome. *Annals of Neurology, 54*, 433–438.

Schupf, N., Winsten, S., Patel, B. N., Pang, D., Ferin, M., Zigman W. B., et al. (2006). Bioavailable estradiol and age at onset of Alzheimer's disease in postmenopausal women with Down syndrome. *Neuroscience Letters, 406*, 298–302.

Schupf, N., Zigman, W., Kapell, D., Lee, J. H., Kline, J., & Levin, B. (1997). Early menopause in women with Down's syndrome. *Journal of Intellectual Disability Research, 41*, 264–267.

Seltzer, G. B., Schupf, N., & Wu, H. S. (2001). A prospective study of menopause in women with Down's syndrome. *Journal of Intellectual Disability Research, 45*, 1–7.

Sepulveda, D., Allison, D. B., Gomez, J. E., Kreibich, K., Brown, R. A., Pierson, R. N., Jr, et al. (1995). Low spinal and pelvic bone mineral density among individuals with Down syndrome. *American Journal of Mental Retardation, 100*, 109–114.

Singer, R. B., & Strauss, D. (1997). Comparative mortality in mentally retarded patients in California, with and without Down's syndrome, 1986–1991. *Journal of Insurance Medicine, 29*, 172–184.

Skoff, H. D., & Keggi, K. (1987). Total hip replacement in Down's syndrome. *Orthopedics, 10*, 485–489.

Splunder, J. van, Stilma, J. S., Bernsen, R. M. D., & Evenhuis, H. M. (2004). Prevalence of ocular diagnoses found on screening 1539 adults with intellectual disabilities. *Ophthalmology, 111*, 1457–1463.

Splunder, J. van, Stilma, J. S., Bernsen, R. M., & Evenhuis, H. M. (2006). Prevalence of visual impairment in adults with intellectual disabilities in the Netherlands: Cross-sectional study. *Eye, 20*, 1004–1010.

Steele, J., & Stratford, B. (1995). The United Kingdom population with Down Syndrome: Present and future projections. *American Journal on Mental Retardation, 99*, 664–682.

Steffelaar, J. W., & Evenhuis, H. M. (1989). Life expectancy, Down syndrome and Dementia. *The Lancet, 333*, 492–493.

Strauss, D., & Eyman, R. K. (1996). Mortality of people with mental retardation in California with and without Down syndrome, 1986–1991. *American Journal of Mental Retardation, 100*, 643–653.

Strauss, D., & Shavelle, R. (1998). Life expectancy of persons with chronic disabilities. *Journal of Insurance Medicine, 30*, 96–108.

Strauss, D., & Zigman, W. B. (1996). Behavioral capabilities and mortality risk in adults with and without Down syndrome. *American Journal on Mental Retardation, 101*, 269–281.

Strydom, A., Shooshtari, S., Lee, L., Raykar, V., Torr, J., Tsiouris, J., et al. (in press). Dementia in older adults with intellectual disabilities: Epidemiology, presentation and diagnosis. *Journal of Policy and Practice in Intellectual Disability*.

Takeuchi, A., Ehara, H., Ohtani, K., Maegaki, Y., Nanba, Y., Nagata, I., et al. (2008). Live birth prevalence of Down syndrome in Tottori, Japan, 1980–1999. *American Journal of Medical Genetics, 146A*, 1381–1386.

Tsiouris, J. A., & Patti, P. J. (1997). Drug treatment of depression associated with dementia or presented as "pseudodementia" in older adults with Down syndrome. *Journal of Applied Research in Intellectual Disabilities, 10*, 312–322.

Tsiouris, J. A., Patti, P. J., Tipu, O., & Raguthu, S. (2002). Adverse effects of phenytoin given for late-onset seizures in adults with Down syndrome. *Neurology, 59*, 779–780.

Tumer, Z., Henriksen, A. M., Bache, I., Brixen, K., Kalscheuer, V., Illum, N., et al. (2005). Eponymous Jacobsen syndrome: Mapping the breakpoints of the original family suggests an association between the distal 1.1 Mb of chromosome 21 and osteoporosis in Down syndrome. *American Journal of Medical Genetics, 135A*, 339–341.

Tyler, C. V., Jr, Snyder, C. W., & Zyzanski, S. (2000). Screening for osteoporosis in community-dwelling adults with mental retardation. *Mental Retardation, 38*, 316–321.

Ugazio, A. G., Maccario, R., Notarangelo, L. D., & Burgio, G. R. (1990). Immunology of Down syndrome: a review. *American Journal of Medical Genetics, 7*, 204–212.

Urv, T. K., Zigman, W. B., & Silverman, W. (2008). Maladaptive behaviors related to dementia status in adults with Down syndrome. *American Journal on Mental Retardation, 113*, 73–86.

Van Buggenhout, G. J., Trommelen, J. C., Schoenmaker, A., De Bal, C., Verbeek, J. J., Smeets, D. F., et al. (1999). Down syndrome in a population of elderly mentally retarded patients: Genetic-diagnostic survey and implications for medical care. *American Journal of Medical Genetics, 85*, 376–384.

Van Dyke, D. C., & Gahagan, C. A. (1988). Down syndrome. Cervical spine abnormalities and problems. *Clinical Pediatrics, 27*, 415–418.

Warren, A., Holroyd, S., & Folstein, M. (1989). Major depression in Down's syndrome. *British Journal of Psychiatry, 155*, 202–205.

Yang, Q., Rasmussen, S. A., & Friedman, J. M. (2002). Mortality associated with Down's syndrome in the USA from 1983 to 1997: A population-based study. *Lancet, 359*, 1019–1025.

Zigman, W. B., Jenkins, E. C., Tycko, B., Schupf, N., & Silverman, W. (2005). Mortality is associated with apolipoprotein E epsilon4 in nondemented adults with Down syndrome. *Neuroscience Letters, 390*, 93–97.