OULU 2011
D 1141

ACTA
UNIVERSITATIS OULUENSIS

Tuomo Määttä

DOWN SYNDROME, HEALTH AND DISABILITY

A POPULATION-BASED CASE RECORD AND FOLLOW-UP STUDY

UNIVERSITY OF OULU,
FACULTY OF MEDICINE,
INSTITUTE OF HEALTH SCIENCES, PUBLIC HEALTH;
JOINT AUTHORITY FOR KAINUU;
RINNEKOTI RESEARCH CENTRE;
UNIVERSITY OF HELSINKI,
FACULTY OF MEDICINE, DEPARTMENT OF CHILD NEUROLOGY

ACTA UNIVERSITATIS OULUENSIS
D Medica 1141

TUOMO MÄÄTTÄ

DOWN SYNDROME, HEALTH AND DISABILITY

A population-based case record and follow-up study

Academic dissertation to be presented with the assent of the Faculty of Medicine of the University of Oulu for public defence in the Martti Hela Hall of the Research and Development Centre of Kajaani (Seminaarinkatu 2), on 16 December 2011, at 12 noon

UNIVERSITY OF OULU, OULU 2011

Acta Univ. Oul. D 1141, 2011

Supervised by
Professor Anja Taanila
Doctor Markus Kaski
Professor Matti Iivanainen

Reviewed by
Docent Maija Castrén
Professor Sirpa Hartikainen

ISBN 978-951-42-9708-3 (Paperback)
ISBN 978-951-42-9709-0 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

JUVENES PRINT
TAMPERE 2011

Määttä, Tuomo, Down syndrome, health and disability. A population-based case record and follow-up study

University of Oulu, Faculty of Medicine, Institute of Health Sciences, Public Health, P.O. Box 5000, FI-90014 University of Oulu, Finland; Joint Authority for Kainuu, P.O. Box 400, FI-87070 Kainuu, Finland; Rinnekoti Research Centre, Rinnekodintie 10, FI-02980 Espoo, Finland; University of Helsinki, Faculty of Medicine, Department of Child Neurology, P.O. Box 20, FI-00014 University of Helsinki

Acta Univ. Oul. D 1141, 2011
Oulu, Finland

Abstract

The present study surveyed medical problems and mental health in an unselected population-based series of people with Down syndrome (DS). All people with DS identified in the Intellectual Disability Service Register in the Kainuu region (n=138) were included, and their health and disability case records in the public services were analysed. The severity of intellectual disability was related to age, gender, and recorded medical problems. Adaptive behaviour changes were assessed among adults repeatedly during ten years using the Adaptive Behaviour Scale - Residential and Community, Part I. The study evaluated health surveillance and practices were compared to the national Current Care guidelines.

Numerous medical problems and behavioural symptoms were recorded in this population. Surgical treatments were used extensively. The number of medical problems varied to a great degree among participants. Health problems were extensive from birth to old age. Many health concerns were age-related. The degree of intellectual disability related to visual and neurological impairments. Depression, and among participants in their forties and older, Alzheimer's disease were the most common underlying reasons for changes in adaptive behaviour. A gradual functional decline and dementia affected many participants at a relatively early age.

Visual acuity and hearing should be regularly monitored in all individuals with DS because of a high prevalence of visual impairment and hearing loss in this population. There was a general lack of evidence that the health care guidelines initiated five years ago were being followed. This suggests that possibilities to enhance health have not been optimally implemented. Therefore, further efforts are needed to diagnose and treat medical problems in people with DS.

Keywords: ageing, Alzheimer's disease, Down syndrome, health, health services, intellectual disability, medical records, morbidity

Määttä, Tuomo, Terveys ja vammaisuus Downin oireyhtymässä . Väestöpohjainen sairauskertomus- ja seurantatutkimus

Oulun yliopisto, Lääketieteellinen tiedekunta, Terveystieteiden laitos, Kansanterveystiede, PL 5000, 90014 Oulun yliopisto; Kainuun maakunta -kuntayhtymä, PL 400, 87070 Kainuu; Rinnekodin tutkimuskeskus, Rinnekodintie 10, 02980 Espoo; Helsingin yliopisto, Lääketieteellinen tiedekunta, Lastenneurologia, PL 20, 00014 Helsingin yliopisto

Acta Univ. Oul. D 1141, 2011
Oulu

Tiivistelmä

Tutkimuksessa kuvattiin todettujen terveysongelmien yleisyyttä ja terveysseurannasta annettujen suositusten toteutumista Downin oireyhtymässä. Nykyisin Kainuussa elävien Down -henkilöiden tietojen lisäksi alueella aiemmin asuneiden saatavissa olevat sairaus- ja huoltokertomustiedot analysoitiin (n=138). Kehitysvammaisuuden vaikeusasteen, iän, sukupuolen ja todettujen sairauksien yhteyksiä selvitettiin. Aikuisten ja ikääntyvien Down -henkilöiden toimintakykyä seurattiin kymmenen vuoden ajan käyttäen Adaptiivisen käyttäytymisen asteikkoa. Käypä hoito -suosituksen toteutumista terveysseurannan osalta arvioitiin.

Down -henkilöillä oli todettu lukuisia terveysongelmia ja käytösoireita kaikissa ikäryhmissä. Kirurgisia hoitoja oli tehty paljon. Yksilölliset erot sairastavuudessa ja toimintakyvyssä olivat erittäin huomattavat. Monet terveysongelmista liittyivät tiettyyn ikään. Vaikeasti kehitysvammaisilla todettiin enemmän silmäsairauksia ja näön ongelmia sekä neurologisia sairauksia kuin lievästi tai keskivaikeasti kehitysvammaisilla. Masennus ja yli 40 vuoden ikäisillä Alzheimerin tauti olivat yleisimmät toimintakyvyn heikentymisen syyt. Toimintakykvyn heikentyminen alkoi usein 40 ikävuoden jälkeen ja moni sairastui suhteellisen nuorena dementiaan.

Kaikkien Down -henkilöiden kuuloa ja näköä tulisi seurata säännöllisesti, koska kuulon alentuminen ja näön ongelmat ovat yleisiä ja jäävät usein toteamatta. Hoitosuositukset eivät toteutuneet ainakaan säännöllisen kuulon ja kilpirauhasen toiminnan seurannan osalta viiden vuoden kuluessa suositusten antamisesta. Terveysseurannan parempi toimeenpano terveyden edistämiseksi on mahdollista. Down henkilöiden sairauksien toteamisen ja hoidon kehittäminen vaatii edelleen työtä.

Asiasanat: Alzheimeirin tauti, Downin oireyhtymä, kehitysvammaisuus, sairastavuus, sairauskertomukset, terveys, terveyspalvelut, vanheneminen

Acknowledgements

I wish to express my gratitude to Professor Risto Pelkonen for his wise guidance to Finnish colleagues and his deep interest to the provision of good care for all citizens, including people with intellectual disabilities.

The work was carried out during the years 2000 – 2011 at the Service Centre of Kuusanmäki, Joint Authority for Kainuu since 2005, formerly Joint Municipal Authority for Social and Specialized Health Services for Kainuu.

I wish to express my thanks to Professor Matti Iivanainen, Department of Child Neurology, University of Helsinki, for the continuous support and encouragement. He suggested this work and without his expertise and efforts as supervisor this work would never have been finished. I am deeply grateful for his initiative to my participation in European Health Indicator Projects *Pomona I and II* during years 2002-2008 lead by Professor Patricia Noonan Walsh. These projects helped to connect with researchers in the field of intellectual disability.

I am grateful to MD, PhD Markus Kaski, Director and Chief Physician, Rinnekoti Research Centre for supervising and for sharing his long experience and enthusiasm in the field of intellectual disability medicine. I thank for his invitation to the group updating the Current Care guideline: appropriate treatment of medical problems associated with Down's syndrome. My special thanks are addressed to Professor Lea Hyvärinen, MD, PhD Jorma Komulainen and MD Maija Wilska.

Professor Anja Taanila, Institute of Health Sciences, University of Oulu, provided invaluable advice as my supervisor. Professor Sirkka Keinänen-Kiukaanniemi, Institute of Health Sciences, University of Oulu, participated as supervisor in the early stages of this study.

Docent Maija Castrén, University of Helsinki, and Rinnekoti Research Centre, and Professor Sirpa Hartikainen, University of Eastern Finland, reviewed the manuscript. Their contribution was invaluable to finalise the work.

I am grateful to Professor Matti Sillanpää, Research professor Tytti Solantaus and MD, PhD Ilkka Kunnamo for their advice and friendship.

I thank members of The Finnish Association of Doctors in Developmental Disability, dear colleagues including Docent Maria Arvio, Marja-Leena Hassinen, Markus Kaski, Jarmo Körkkö, Hannu Westerinen, Esko Pulkkinen, Ari W Sulin, and Maija Wilska for support and friendship. I express my sincere thanks to colleagues in Kainuu for their support and for the good care of their patients including people with DS. Furthermore, I am grateful for numerous professional

and cultural events which they have organized. I address special thanks to Esa Ahonen, Päivi Cheney, Aune Hirvasniemi, Taina Huusko, Elena Hakala, Jukka Juvonen, Jouko Kotimäki, Antto Miettinen, Raisa Mäkäräinen, Johanna Rantala, Jouko Siivola and Pertti Varimo.

I owe my warmest thanks to all present and former members of the expert team for specialized intellectual disability services in the Kainuu for sharing your expertise and friendship. Special thanks are addressed to Tiina Ahava, Pirjo Herrala, Mirja Hujanen, Ritva Kaikkonen, Heli Katajamäki, Tiia Kemppainen, Rauha Kärkkäinen, Helena Mikkonen, Irma Ohtonen, Ulla Rissanen, Kristiina Taskinen and Markus J Viljanen. I thank my clients with intellectual disabilities, including participants with Down syndrome, their parents and siblings and professionals supporting them, for sharing experiences.

I am deeply thankful to my parents, Nikke and Elvi Määttä for their love and support. I am deeply grateful to my mother-in-law Hilja Tervo for her continuous support.

I express my warmest thanks to Eira Jansson-Verkasalo, Raimo Verkasalo and Pentti Heikkinen for your help and friendship.

I would like to express my warmest gratitude to my wife Tuula Tervo-Määttä for her participation, endless support and understanding. Our children Milla, Joonas, Aleksi and Roope have provided valuable advice and a lot of joy to our life.

The study was supported financially by The Finnisch Cultural Foundation, Rinnekoti Research Foundation and The Finnish Medical Society Duodecim.

Kajaani 14.11. 2011 Tuomo Määttä

Abbreviations

AAIDD	the American Association of Intellectual and Development Disabilities
AD	Alzheimer's disease
ABS-RC	Adaptive Behaviour Scale – Residential and Community
APOE	apolipoprotein E
ARDA	Alzheimer's Disease and Related Disorders Association
CAMDEX	Cambridge Examination for Mental Disorders of the Elderly
CD	celiac disease
CI	confidence interval
dB	decibel
DS	Down syndrome
DSM	Diagnostic and Statistical Manual of Mental Disorders
E2	estradiol
GABA	gamma amino butyric acid
HLA	human leukocyte antigen
HR	hazard ratio
ICD-10	the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ID	intellectual disability
ICF	the International Classification of Functioning, Disability, and Health
IQ	intelligence quotient
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
n	number
OR	odds ratio
p	significance probability
RR	risk ratio
SIR	standardised incidence ratio
SMR	standardised mortality ratio
SNP	single nucleotide polymorphism
TC	total cholesterol
WHO	the World Health Organization

List of original publications

I Määttä T, Kaski M, Taanila A, Keinänen-Kiukaanniemi S & Iivanainen M (2006) Sensory impairments and health concerns related to the degree of intellectual disability in people with Down syndrome. Downs Syndr Res Pract 11(2): 78–83.

II Määttä T, Määttä J, Tervo-Määttä T, Taanila A, Kaski M & Iivanainen M (2011) Healthcare and guidelines: A population-based survey of recorded medical problems and health surveillance for people with Down syndrome. J Intellect Dev Disabil. 36(2): 118–26.

III Määttä T, Tervo-Määttä T, Taanila A, Kaski M & Iivanainen M (2006) Mental health, behaviour and intellectual abilities of people with Down syndrome. Downs Syndr Res Pract 11(1): 37–43.

IV Määttä T, Tervo-Määttä T, Taanila A, Kaski M & Iivanainen M (2011) Adaptive behaviour change in adults with Down syndrome, a prospective clinical follow-up study. Manuscript.

Contents

1 Introduction

Down syndrome (DS) is the most common known genetic cause of intellectual disability. DS is caused by the trisomy of chromosome 21 and it is characterised by recognisable facial features, short stature, abnormalities in learning, memory, and language, and impairment of intellectual functioning. DS affects approximately 1 / 650–1000 live births. Most individuals (95%) with trisomy 21 have three free copies of chromosome 21; in about 5% of patients, one copy or part of one copy is translocated to another chromosome. In 2–4% of cases with free trisomy 21, there is recognizable mosaicism for a trisomic and a normal cell line. Updated information on genetic aspects of Down syndrome is available in an Online Catalog of Human Genes and Genetic Disorders, the Online Mendelian Inheritance in Man at the website http://omim.org/entry/190685 (Johns Hopkins University 2011).

People with DS have an increased incidence of congenital heart defects, leukaemia, thyroid disease, celiac disease, diabetes, depression, and Alzheimer's disease (Roizen & Patterson 2003). Individuals with DS are affected by these phenotypes to a variable extent; some genetic causes of this variation have been previously identified (Wiseman *et al.* 2009). There is a need for better understanding of the health concerns of this population (Rasmussen 2008).

The birth prevalence of people with Down syndrome has remained relatively stable (Collins *et al.* 2008), their survival has improved (Weijerman *et al.* 2008), and the life expectancy of individuals with DS has increased during the last decades in developed countries (Janicki *et al.* 1999, Merrick 2000). However, due to higher morbidity, for example, individuals with Down syndrome die at an earlier age than do adults with intellectual disabilities and adults in the general population (Janicki *et al.* 1999, Bittles *et al.* 2007). It is expected, however, that the number of aged patients with DS will further increase in the near future (Steffelaar & Evenhuis 1989). Furthermore, the co-morbidity of Down syndrome and Alzheimer’s disease is common due to increased life expectancy and the very early onset of Alzheimer’s disease in this population (Zigman *et al.* 1996, Zigman *et al.* 2004, Coppus *et al.* 2006).

Comprehensive medical services are essential to ensure good quality of life for people with DS (Roizen & Patterson 2003). People with DS are predisposed to a number of health impairments (Davidson 2008, Weijerman & Winter 2010, Torr *et al.* 2010) and are at risk of insufficient health surveillance (Krahn *et al.*

2006, Hendersson *et al.* 2007, Virji-Babul *et al.* 2007, Fergeson *et al.* 2009, Wecsler *et al.* 2009, Creavin & Brown 2010).

National recommendations for good health care for individuals with Down syndrome were provided to health professionals in Finland in September 2004 (Kaski *et al.* 2005) and they are available on-line for physicians, among other evidence-based Current Care guidelines. It is not known to what extend the guidelines for individuals with Down have been followed in clinical practice. The health service use of adults with DS is largely unknown.

The present study describes the recorded medical problems, intellectual disabilities, and their associations in a cohort of people with DS. Health surveillance of this cohort is compared to recommendations provided in the Finnish Current Care guidelines. The study describes the adaptive behaviour changes of adults with DS and suspected dementia and evaluates the possible use of adaptive behaviour assessment in the detection and follow-up of dementia.

2 Review of literature

2.1 Concepts and definitions

Health

The present study focuses on recorded medical problems. These are described based on the tenth edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) by the World Health Organization (WHO), which has been used in Finland since 1.1.1996. WHO defines health as complete physical, mental, and social well-being, and not merely the absence of disease. ICD-10 and the earlier editions of ICD form the basis of recorded diagnoses in medical case records. The use of a common international classification, including ICD-10, is essential for international comparisons and research. ICD-10 is available at the website http://apps.who.int/classifications/apps/icd/icd10online/ (World Health Organization 2006).

Intellectual Disability

Intellectual disability (ID) is a condition that begins during childhood or before the age of 18 years and that significantly limits intelligence and adaptive skills. ICD-10 uses the term mental retardation (F70-F79), defined as "a condition of arrested or incomplete development of the mind, which is especially characterized by impairment of skills manifested during the developmental period, skills which contribute to the overall level of intelligence, i.e. cognitive, language, motor, and social abilities" (World Health Organization 2006).

The concepts of disability have been further developed and refined during the last decades (Buntinx & Schalock 2010). The WHO has developed a model of human functioning, disability, and health in its International Classification of Functioning, Disability, and Health (ICF) for use as the international standard to describe and measure health and disability. It includes environmental factors like activity and participation, in addition to descriptions of body functions and structure. The ICF was officially endorsed by all WHO Member States 2001 and it is available at the website http://www.who.int/classifications/icf/en/ (World Health Organization 2001).

The American Association on Intellectual and Development Disabilities (AAIDD) developed a conceptual framework for human functioning and added supports, including services, as important components influencing human functioning (Schalock *et al.* 2010). Intellectual abilities, adaptive behaviour, health, participation, and context are also seen in this model as main determinants of human functioning. The AAIDD definition and classification of intellectual disability, including systems of supports, is used by professionals in the disability field for assessments of service needs of people with intellectual disability. The ICD-10 definition of intellectual disability and the conceptual framework of the AAIDD were used in the present study, whereas the ICF classification was not applied.

Adaptive behaviour

Adaptive behaviour, one of the skills mentioned in the ICD-10 criteria of intellectual disability, is a central concept in the field of intellectual disabilities where several methods have been developed for the assessment of adaptive behaviour. A significant impairment of conceptual skills, social skills, and practical skills during development is needed to diagnose intellectual disability and impairments in exhibited adaptive skills are critical factors in determining a person's required school, work, community, and home supports. The Adaptive Behaviour Scale developed by the AAIDD (formerly the American Association on Mental Retardation, AAMR) has separate measures for adaptive and maladaptive behaviour (Nihira *et al.* 1993). Correspondingly, ICD-10 has two subdivisions for use with categories F70-F79 to identify the extent of impairment of behaviour requiring attention or treatment: no or minimal vs. significant.

Dementia

ICD-10 defines dementia as follows: "Dementia (F00-F03) is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. This syndrome occurs in

Alzheimer's disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain."

Alzheimer's disease

According to ICD-10, "Alzheimer's disease is a primary degenerative cerebral disease of unknown aetiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years".

2.2 Epidemiology of Down syndrome

The incidence of DS at conception is highly dependent upon the maternal, but not the paternal, age distribution and age-specific pregnancy rates. Between 1920 and the early 1980s, DS live-birth prevalence decreased in many populations due to declining fertility rates, particularly among older women. As the median age of populations and birth rates among older women steadily increased since 1980s, the decreasing trend began to reverse (Olsen *et al.* 2003).

Prenatal diagnosis was introduced in the early 1970s. There are large differences in screening policies and in prenatal detection rates for DS among countries in Europe according to the survey of Boyd *et al.* (2008). Sixty-eight percent of DS cases (range 0–95%) were detected prenatally in European countries, of which 88% resulted in termination of pregnancy.

2.2.1 Incidence and prevalence

The birth prevalence of people with DS is relatively similar in most countries, 1 / 650–1000 live births, and has remained relatively stable during the last decades (Collins *et al.* 2008).

The incidence of DS was 3.2 per 1,000 live births in the Northern Finland Birth Cohort in 1966 (Rantakallio *et al.* 1986) and 1.70 per 1,000 in the Northern Finland Birth Cohort in 1986 (Heikura *et al.* 2005). Down syndrome was the most common identified aetiology of intellectual disability and was seen in 13.4% of children with intellectual disability followed until the age of 11.5 years in the Northern Finland Birth Cohort of 1986 (Heikura *et al.* 2005).

The prevalence of DS in births, including 5.3% stillbirths, in Finland during 1993–2008 was on average 12.7/10,000 and the live birth prevalence was 12.0/10,000 (National Institute for Health and Welfare & Official Statistics of Finland 2011). DS prevalence estimates beyond infancy are needed to assess health service needs. In metropolitan Atlanta in 2003, there were 13.0 per 10,000 live births with DS and 8.3 per 10,000 survivors with DS under the age of twenty (Besser *et al.* 2007). Expectations were that the number of aged patients with DS in The Netherlands would be highest between 2005 and 2020, and would increase at least to numbers 50% above the numbers reached in 1990 (Steffelaar & Evenhuis 1989).

Based on eight national health and social benefit registers, the prevalence of intellectual disability in Finland was 0.70% in 2000 (Westerinen *et al.* 2007). Persons with intellectual disability were identified in these registers (36 053 in a total population of 5 184 980), among them 3 676 (10.2%) with DS (Westerinen 2004). The prevalence of DS in Finland counted from this data was 7.1/10,000 in 2000.

2.2.2 Survival

During the last decades, early childhood survival in DS has improved, as shown in Table 1, due largely to advances in cardiac surgery (Hijii *et al.* 1997, Day *et al.* 2005) and in general health management (Leonard *et al.* 2000, Weijerman *et al.* 2008). Neonatal and infant mortality in DS in 2003 were still higher than in mainstream children – 1.65% versus 0.36% and 4% versus 0.48%, respectively, in The Netherlands (Weijerman *et al.* 2008). The standardized mortality ratio for persons with DS in California between 1988 and 1999 was 5.5; Afro-Americans were at greater risk than were Caucasians, Hispanics, or Asians (relative risk = 1.5) (Day *et al.* 2005).

Table 1. Survival of people with Down syndrome.

Study; population	Survival 1 year (%)	Survival 10 years (%)
Hayes *et al.* 1997; Dublin, 1980–1989	88%	82%
Leonard *et al.* 2000; Western Australia, 1996	91%	85%
Rasmussen *et al.* 2006; Metropolitan Atlanta, 1979–1998	92.9%	88.6%
Wejerman *et al.* 2008; Netherlands, 2003	96%	

2.2.3 Life expectancy

Life expectancy has increased to nearly 60 years of age during the last two generations in developed countries (Janicki *et al.* 1999, Merrick 2000, Glasson *et al.* 2002). However, individuals with DS die at an earlier age than do adults with intellectual disabilities (Janicki *et al.* 1999) and adults in the general population (Bittles *et al.* 2007).

In the United States, the median age at death increased from 25 years in 1983 to 49 years in 1997 among people with DS (Yang *et al.* 2002). Among adults with intellectual disabilities, aged 40 and older, the average age at death for adults with DS was 55.8 years compared to 66.1 years for adults with intellectual disabilities (Janicki *et al.* 1999). Another study reported a life expectancy of 58.6 years, 3.3 years longer for males than for females with DS in Western Australia; 25% lived to 62.9 years (Glasson *et al.* 2002).

2.2.4 Causes of death

Table 2 summarizes the causes of death and standardised mortality ratios (SMR) among people with Down syndrome. Individuals with DS have a substantially increased risk of mortality due to congenital anomalies, including heart defects, infectious diseases, leukaemia, and dementia (Yang *et al.* 2002, Hill *et al.* 2003, Day *et al.* 2005). Pneumonia was the most common cause of death (23% of deaths in adulthood, 40% in senescence), while congenital heart defects were common causes in childhood (13%) and adult (23%) deaths in Western Australia (Bittles *et al.* 2007). Congenital anomalies, respiratory illnesses, leukaemia, and

circulatory diseases accounted for most of the excess mortality in California (Day *et al.* 2005). Better survival rates in persons with DS older than 45 years were associated with relative preservation of cognitive and functional abilities; dementia, mobility restrictions, visual impairment, and epilepsy were the most important disorders related to mortality (Coppus *et al.* 2008).

Table 2. Causes of death and standardised mortality ratios among individuals with Down syndrome.

Study; population	Cause of death, standardised mortality ratios, SMR (95% confidence intervals)
Yang *et al.* 2002; United States, 1983–1997	heart defects 29.1 (27.8–30.4)
	dementia 21.2, (19.6–22.7)
	hypothyroidism 20.3 (18.5–22.3)
	leukaemia 1.6 (1.4–1.8)
	malignant neoplasms other than leukaemia 0.07 (0.06–0.08)
Hill *et al.* 2003; Sweden, 1965–1993 and Denmark, 1977–1989	dementia and Alzheimer disease 54.1 (27.9–94.4)
	epilepsy 30.4 (13.9–57.7)
	congenital anomalies 25.8 (21.0–31.4)
	other heart disease 16.5 (11.0–23.7)
	infectious diseases 12.0 (6.0–21.4)
	cerebrovascular disease 6.0 (3.5–9.6)
	stomach cancer 6.4 (1.7–16.4)
	ischemic heart disease 3.9 (2.7–5.4)
Day *et al.* 2005; California, 1988–1999.	congenital anomalies 72[a]
	respiratory illnesses 27
	leukaemia 17
	circulatory diseases 5.3
	mortality, all causes 5.5

[a]SMR (95% confidence intervals not reported)

2.3 Health services

The provision of adequate health care for people with intellectual disabilities is critical to improve their health and presents challenges worldwide, as reviewed by Krahn *et al.* 2006. Primary health care and family physicians have an important role in health surveillance. However, all children with DS require many different specialists, often repeatedly, including cardiologists and ophthalmologists, to

meet their special needs (Davidson 2008, Weijerman & Winter 2010). Guidelines have been developed and implemented to help inform proxies and professionals. Some countries, including the Netherlands and Finland, have organized special services for people with intellectual disabilities; Italy and Israel have organised services tailored specifically for people with DS. However, numerous researchers in developed countries like the Netherlands, United States, England, and Israel have detected and reported inadequacies in health care and surveillance for people with intellectual disabilities (Hendersson *et al.* 2007, Virji-Babul *et al.* 2007, Fergeson *et al.* 2009, Wecsler *et al.* 2009, Creavin & Brown 2010).

2.3.1 Health care

Children with DS had substantially higher rates (threefold or higher, compared with children without intellectual disabilities) for nearly all health and special education service use measures in the 1997–2005 national health interview survey in Atlanta, United States (Schieve *et al.* 2009). Hospital admission and medication use rates in young infants with DS are very high, mainly because of congenital heart and gastrointestinal disease and acquired respiratory disease (van Trotsenburg *et al.* 2006a). Health care expenditures for infants and young children with DS in a privately insured population (Atlanta, USA) were 12 to 13 times higher than for children without DS; for infants with DS and congenital heart defects, the costs were 5 to 7 times higher than for infants with DS who did not have congenital heart defects (Boulet *et al.* 2008).

2.3.2 Health surveillance

Davidson (2008) reviewed health care guidelines for children with DS and presented an update of the current evidence behind these guidelines. Weijerman & de Winter (2010) and Bull & Committee on Genetics (2011) provided up-dated reviews of clinically important medical problems and a recommendations of medical assessments for children with DS. To ensure the best possible long-term outcomes for these patients, clinicians should be well aware of comorbid conditions.

Health assessment programmes have improved health outcomes among people with intellectual disabilities (Cooper *et al.* 2006, Lennox *et al.* 2007, Romeo *et al.* 2009) and reduced the costs of care compared with standard care costs (Romeo *et al.* 2009). Medical management of DS requires an organised

approach of assessment, monitoring, prevention, and vigilance (Weijerman & Winter 2010). Comprehensive medical services are essential to ensure good quality of life (Roizen & Patterson 2003, Torr *et al.* 2010).

2.4 Intellectual disability

Degrees of intellectual disability are conventionally estimated by standardized intelligence tests, supplemented by assessments of social adaptation in a given environment. According to ICD-10, mild intellectual disability is characterized by an IQ range of 50 to 69 in adults, which translates to a mental age from 9 to 12 years, and some learning difficulties in school, but it is also characterized by an ability to work, maintain good social relationships, and contribute to society. Moderate intellectual disability (IQ range of 35 to 49 in adults, translating to a mental age from 6 to 9 years) is likely to result in marked developmental delays in childhood and some degree of dependence for self-care and adequate communication in adulthood; adults will need varying degrees of support to live and work in the community. People with severe intellectual disability (IQ range of 20 to 34 in adults, translating to a mental age from 3 to 6 years) are likely to need continuous support, while people with profound intellectual disability (IQ under 20 in adults, with a mental age below 3 years) often have severe limitations in self-care, continence, communication, and mobility. (World Health Organization 2006).

2.4.1 Brain development

Lott & Dierssen (2010) reviewed current understanding of the pathogenesis of cognitive deficits in individuals with DS. Brain development and functioning are variably affected in all individuals with DS. Relative volumes of the frontal and temporal lobes (including the hippocampus) and the cerebellum are reduced more than the total brain volume is. Dendritic development is affected during early childhood. Changes in synaptic density, length, and synaptic contact zones have been described. Reduced or abnormally connected neuronal networks might limit information processing and decreased synaptic plasticity, in all likelihood, limits behavioural flexibility. Cognitive functions that require intracortical processing or wide neural circuits, including connections of the cerebellum, cortical, and

subcortical areas, may be impaired in DS; these include executive functions, language learning, and working memory.

Early degeneration of cholinergic basal forebrain neurons is well documented in DS and this may affect the brain development, specifically of the cortical areas and the hippocampus as reviewed by Berger-Sweeney (1998). The basal cholinergic forebrain system is important for cortical differentiation, and later it has a role in selective attention and processing of new information. Furthermore the impairment of the cholinergic function associates with memory deficits in aging and Alzheimer's disease (Schliebs & Arendt 2011).

2.4.2 Cognitive abilities

Children with Down syndrome show marked individual differences in cognitive abilities (Tsao & Kindelberger 2009) and skills (Dykens *et al.* 2006, van Duijn *et al.* 2010). Both genetic and environmental effects contribute to these differences (Shepperdson 1995, Turner *et al.* 2008). Eight-year-old Duch children with DS had an average developmental delay of four years; mean developmental age was significantly lower among boys than girls, 3.9 and 4.2 years respectively (van Gameren-Oosterom *et al.* 2011).

Individuals with DS have a delay in cognitive development with specific deficits in speech, language production, and auditory short-term memory (Chapman & Hesketh 2000). Laws *et al.* (2004) identified short-term memory functions as predictors of language and comprehension skills in children with Down syndrome. Overall intellectual disability and relative weaknesses in expressive language, syntactic processing and verbal working memory may influence the cognitive performance of individuals with DS (Silverman 2007). A meta-analytic review confirmed that children with DS have broad language deficits not restricted to expressive language, and associated verbal short-term memory deficits (Naess *et al.* 2011).

Adults with DS perform significantly more poorly in tasks assessing the phonological loop of working memory compared to people with mixed aetiology of intellectual disability (Numminen *et al.* 2001). The impairments in working memory and executive functioning have been identified as core problems among people with intellectual disabilities in general and even more so among people with DS. Lanfranchi *et al.* (2010) described characteristic broad impairments of

executive functions in tasks assessing set shifting, planning/problem-solving, working memory and inhibition/perseveration in adolescents with DS.

2.4.3 Adaptive behaviour

Children with DS acquire their motor, daily living, communicative, and social behavioural skills at a slower pace than typically developing children, mainly by 12 years of age (Dykens *et al.* 2006, van Duijn *et al.* 2010). However, adaptive skills increase, and adults from 20 to 30 years show the highest performance for all age groups among individuals with DS (Dressler *et al.* 2010, Bertoli *et al.* 2011). Carr (2008) followed a birth cohort of people with DS in England from childhood to 40 years of age, interviewing repeatedly the parents and/or carers about the participant's health, independence, activities, and social relationships. The surviving participants continued to have reasonably good health, but most had limited independence and sparse social lives, mainly determined by the person's level of cognitive ability.

The Adaptive Behaviour Scale – Residential and Community (Nihira *et al.* 1993) has been widely used in research. Cross-sectional studies have demonstrated lower scores from people with DS older than 40 years compared to younger participants with DS (Collacott 1992). Prospective studies have confirmed age-related decline in adaptive behaviour, and its association to dementia (Rasmussen & Sobsey 1994, Prasher & Chung 1996, Prasher *et al.* 1998). Zigman *et al.* (2002) described the temporal patterns of adaptive behaviour changes in aging adults with intellectual disabilities with and without DS. The cumulative incidence of decline in adaptive behaviour started to increase rapidly in the late fifties in participants with DS. Vocational and domestic activities declined at an early stage of aging whereas language and communication abilities declined later. Rasmussen & Sobsey (1994) found stability of adaptive behaviour in adults with DS younger than 40 years and declines in self-help and communication skills in several individuals with DS older than 40, including declines in dressing, receptive language, and vocational and domestic behaviour.

2.5 Sensory impairment

Visual impairment (Stephen *et al.* 2007, Creavin & Brown 2009) and hearing loss (Buchanan 1990, van Schrojenstein Lantman-de Valk *et al.* 1994, Meuwese-

Jongejeugd *et al.* 2006) are frequent among people with DS at all ages. Visual impairments are more frequent in people with severe and profound intellectual disability than in persons with mild or moderate intellectual disability (van Schrojenstein Lantman-de Valk *et al.* 1994, Evenhuis *et al.* 2001, Evenhuis *et al.* 2009).

Organized visual and hearing assessments have been recommended by many (van Schrojenstein Lantman-de Valk *et al.* 1994, Jonelid *et al.* 2002, Creavin & Brown 2009) but they remain difficult to implement (Evenhuis *et al.* 2004). The establishment of ophthalmic screening has improved ocular surveillance, and possibly improves developmental and functional outcomes in DS patients (Stephen *et al.* 2007).

2.5.1 Hearing loss

Table 3 summarizes the findings of studies on hearing loss in DS. Conventional behavioural testing of hearing shows that children with DS have a high prevalence of hearing deficits. Roizen *et al.* (1993) evaluated hearing levels using auditory brain-stem responses of 47 unselected patients 2 months to 3 1/2 years of age. Only thirty-four percent of children with DS had normal hearing levels. Hildmann *et al.* (2002) found hearing deficiencies in 56% of children with DS seen and checked for hearing disorders in an outpatients unit for hearing disorders; hearing loss was most often conductive.

Harigai (1994) reported longitudinal observations of the hearing and speech development of 110 children with DS during a 10-year period. Middle ear infection with effusion was detected in 34 (63%) of the 54 children with moderate hearing loss. Active treatment with medication or minor surgery, such as a myringotomy or insertion of a ventilation tube, resulted in improvement in hearing in 76% of the children with middle ear infections. Harigai (1994) emphasized appropriate medical care and management of hearing impairment, including the use of hearing aids for patients' emotional and linguistic development.

Shott *et al.* (2001) reported audiologic results at the end of the first year of a longitudinal study. Aggressive, 'state of the art' treatment was provided to a group of children, (n = 48), entered into the study at an age under 2 years. After treatment of reversible hearing loss from middle ear infections, 98% of the children had normal hearing levels.

Good hearing ability during early childhood is critical for language and cognitive development in children with DS (Marcell & Cohen 1992, Marcell *et al.* 1995, Harigai 1994, Laws 2004, Lott & Dierssen 2010). Early diagnosis and treatment of illnesses, such as middle ear infections, which can cause hearing impairment, provides significantly improved hearing levels compared to delayed diagnosis and treatment (Harigai 1994, Shott *et al.* 2001).

Bone anchored hearing aids should be considered for amplification in the overall management of individuals with DS, but only after conventional hearing aids and/or ventilation tubes have been considered or already unsuccessfully attempted (Sheehan & Hans 2006, McDermott *et al.* 2008). Better hearing improves social and physical functioning in DS, as it does in normal populations.

Table 3. Hearing impairment in people with Down syndrome.

Study; participants	Methods	Results
Roizen *et al.* 1993; 47 children, age 2 mo–3,5 years	Auditory brain-stem responses	34% normal hearing 28% unilateral hearing loss 38% bilateral hearing loss
Harigai 1994; 110 children	Otomicroscopy, behavioural audiometry, auditory brain stem response audiometry and tympanometry	32% hearing level (0–39 dB) 49% hearing level (40–79 dB) 19% hearing level above 80 dB.
Hildmann *et al.* 2002; 102 children	Assessment in an outpatients unit for hearing disorders	56% hearing loss 88% conductive hearing loss 7% combined hearing loss 5% sensory hearing loss
Shott *et al.* 2001; 48 children, age under 2 years	Active medical and surgical treatment with pressure-equalizing tubes	98% normal hearing levels after treatment of reversible hearing loss from chronic middle ear infection
Meuwese-Jongejeugd *et al.* 2006; 409 adults with DS	Audiologic screening	100% (95% CI: 79.4–100%) prevalence of hearing loss in adults over 60 years of age

Pure tone threshold data were reported as a function of age for 152 subjects with DS (age range: 5.4 years to 59.1 years) by Buchanan (1990). The results revealed that persons with DS have an early onset of age related hearing loss (presbyacusis). Adults with DS also experience difficulty during the central pre-

attentive auditory processing that underlies stimulus detection (Pekkonen *et al.* 2007). Sinusoidal tones were presented to DS patients and healthy controls, and auditory-evoked fields were measured with a whole-head magnetoencephalography system. Patients with DS had significantly delayed and attenuated N100m, and delayed but not attenuated P50m responses.

A cross-sectional epidemiological study on the prevalence of hearing loss was carried out in an age- and DS-stratified random sample of 1598 persons, representing the Dutch adult population of intellectual disability service users (Meuwese-Jongejeugd *et al.* 2006). The prevalence of hearing loss was 30.3% (95% CI 27.7–33.0%). DS (OR 5.18, 95% CI 3.80–7.07) and age were confirmed to be risk factors. Subgroup prevalence in adults over 60 years of age with DS was 100% (95% CI 79.4–100%). Age-related increase in prevalence in persons with DS appeared to occur approximately three decades earlier than in the general population, and in persons with intellectual disabilities from other causes, approximately one decade earlier.

2.5.2 Visual impairment in children

Creavin & Brown (2009) systematically reviewed the literature on paediatric ophthalmology in DS including 23 of 230 identified articles. Refractive error was a common finding, particularly hyperopia. Strabismus was also reported regularly, particularly esodeviation. Other frequent findings were poor visual acuity, nystagmus, and blepharitis, whereas cataract and glaucoma were less common.

Prevalence of the most common ocular disorders found in 123 Korean (Kim *et al.* 2002), 60 Malaysian (Liza-Sharmini *et al.* 2006), 157 Italian (Fimiani *et al.* 2007), and 81 English (Stephen *et al.* 2007) children with DS are summed in Table 4.

The implementation of ocular surveillance resulted in the earlier prescription of glasses for refractive errors (mean age 5 y 6 mo before guidelines, 3 y 6 mo after, $p < 0.001$) (Stephen *et al.* 2007). At school age, 43% of the study population had significant refractive errors. The locally implemented protocol for ophthalmic screening included neonatal eye examination by an ophthalmologist and a comprehensive ophthalmological examination by at least the age of 3 years, followed by preschool follow-up as indicated. The authors anticipated that developmental and functional outcomes in DS would improve.

Table 4. Ocular disorders among children with Down syndrome.

Ocular disorder[a]	Children with the given ocular disorder (%)
Hyperopia	44
Strabismus	33
Esotropia+exotropia	23+7
Astigmatism	28
Nasolacrimal obstruction	20
Myopia	17
Nystagmus	17
Blepharitis	9
Cataract	9

[a]Combined data of 412 children with DS from four studies: Kim *et al.* 2002, Liza-Sarmini *et al.* 2006, Fimiani *et al.* 2007 and Stephen *et al.* 2007.

Accommodation

Many children with DS have impaired accommodative responses. More than 75% of children with DS failed to accommodate accurately on near targets resulting in optically blurred images for near work (Woodhouse *et al.* 2000).

Stewart *et al.* (2005) evaluated the controlled use of bifocal spectacles as an aid to near focusing. Thirty-four children with DS of primary school age (5–11 years) took part. The study provided the treatment group with bifocal spectacles with a +2.50 addition, and the control group with single-vision lenses to correct any clinically significant refractive errors. The treatment group showed consistently more accurate accommodation than the control group, not only through the bifocal segment, but through the distance part of the lens as well. The authors recommended that eye examinations of children with DS should routinely include a measure of near accommodation, and that bifocal spectacles should be considered for those who show under-accommodation.

Nandakumar & Leat (2010) investigated the impact of bifocals on visual function and visual perceptual and early literacy skills in a group of schoolchildren with DS. Children were followed for 5 months with single-vision lenses after which bifocals were prescribed if required, based on their accommodative responses. Visual acuity, accommodation, and perceptual and literacy skills were measured after adaptation to bifocals and 5 months later. The study assessed educational progress and compliance with spectacle wear. Bifocals provided clearer near vision with less but quicker accommodation. The improvement in visual acuity resulted in improvements in early literacy skills.

Cortical function

Suttle & Turner (2004) compared transient visual evoked potentials from children with DS with those recorded from children developing normally. Response latency was similar in the two groups, but the N75 component was diminished or undetectable in responses from children with DS suggesting a cortical impairment. Little *et al.* (2009) evaluated the integrity of higher visual processing. Participants were 29 children aged 9 to 16 years who had DS and 68 age-matched developmentally normal children as controls. All wore best refractive correction, and none had clinically significant ocular abnormalities. Mean Vernier acuity was reduced in DS indicating that cortical visual function was compromised.

2.5.3 Visual impairment in adults

Visual impairment and eye conditions reported in two studies in adults with DS are summarised in Table 5. Castane *et al.* (2004) determined the refractive status and ocular health of a group of adults with DS between 40 and 62 years of age. Refractive errors were found in most participants, myopias being most common (61%); 31.2% of participants needed prescription to improve near sight. Puri & Singh (2007) performed ophthalmological examinations for the presence of cataracts on 68 adults with DS, aged between 28.9 and 83.3 years. The prevalence of cataract was 16.2%, with no significant difference in the prevalence between males (17.1%) and females (15.2%).

Table 5. Visual impairment and eye conditions in adults with Down syndrome.

Study; population	Visual impairment	Eye conditions
Castane *et al.* 2004;	68.7% visual acuity in long	66.7% strabismus
49 participants with DS, age	distance sight below 0.5	61.4% myopias,
40–62 years	48% visual acuity below 0.4 in	59.4% crystalline opacities
	near sight	45.8% astigmatisms
		25% nystagmus
		23% hyperopias
		13.5% interventions due to
		cataracts,
		6.2% keratoconus
van Splunder *et al.* 2006;	11.5%, under 50 years	2.6% blindness, under 50 years
227 participants with DS	33.3%, 50 years or more	7.4% blindness,50 years or more

Van Splunder *et al.* (2006) reported population-based prevalence figures on visual impairment and blindness in a random sample of 1598 adult users of intellectual disability services screened in The Netherlands. Results were related to degree of intellectual disability, occurrence of DS, and age. Weighted prevalence of visual impairment in the total Dutch population of adult users of intellectual disability services was 13.8% (95% CI, 9.3–18.4). The prevalence of visual impairment was 33% among people with DS older than 50 years, and 66.7% (95% CI, 41.0–86.7) in older adults (50 years or older) with profound intellectual disabilities and DS. Visual impairment or blindness had remained undiagnosed in 106/261 (40.6%) persons. Physicians of this population reported visual impairment in 46% of individuals with DS older than 50 years, and in 13% of people with other causes of intellectual disability of the same age (van Schrojenstein Lantman-de Valk *et al.* 1994).

Assessments of visual function seem to be easier to organize than assessments of hearing. Evenhuis *et al.* (2004) obtained complete and reliable data to diagnose visual impairment for 1358/1598 (85%) and data to diagnose hearing impairment for 1237/1598 (77%) of adult participants with intellectual disability.

Combined sensory impairment

Meuwese-Jongejeugd *et al.* (2008) reported combined sensory impairment (deaf-blindness) in five percent of adults with intellectual disabilities in the Dutch sample of adults with intellectual disabilities. The risk was higher among people with severe intellectual disability. Prevalence of combined sensory impairment was 27.8% (95% CI, 16.5–41.6) in older adults (50 years or older) with DS. A complete diagnosis had been identified previously in only 12% of the cases.

Regular organized visual assessments using appropriate methods are needed for people with DS at all ages to detect and treat visual impairment (van Schrojenstein Lantman-de Valk *et al.* 1994, Jonelid *et al.* 2002, Evenhuis *et al.* 2004, Stephen *et al.* 2007, Meuwese-Jongejeugd *et al.* 2008, Creavin & Brown 2009).

2.6 Other medical problems

The rates of reported medical issues are high in clinical samples among children and teenagers (Yam *et al.* 2008) and adults (Henderson *et al.* 2007, Kerins *et al.*

2008) as well as in population-based health studies (Murphy *et al.* 2005, Schieve *et al.* 2009). Congenital heart defects occur in half of children born with DS and the mortality of people with severe heart defects was high before modern heart surgery (Hijii *et al.* 1997). Hospital admission and medication use rates in young infants with DS are still very high, mainly because of congenital heart and gastrointestinal diseases and respiratory infections (van Trotsenburg *et al.* 2006a).

Bloemers *et al.* (2010) reviewed studies on the immune system in DS; they concluded that the high incidence of respiratory tract infections in children with DS is at least partly explained by disturbances in the immune system. Additionally, congenital heart defects, abnormal airway anatomy and physiology, hypotonia, and aspiration may contribute. Immunological impairments may also contribute to the increased incidence of leukaemia and autoimmune diseases like hypothyroidism, celiac disease, and diabetes in DS. Gillespie *et al.* (2006) studied the frequency of islet autoantibodies and found an increased frequency of subclinical islet autoimmunity in DS. Juj & Emery (2009) identified 9 cases of DS and juvenile idiopathic arthritis; the prevalence of arthropathy was 8.7/1000, more than 6 times higher than in the general population.

Goldacre *et al.* (2004) analysed hospital and death records to determine the risk of cancers and selected immune related diseases in people with DS in the Oxford health region of England from 1963 to1999. They compared a cohort of 1453 people with DS and a cohort of 460,000 people with other conditions. Significantly elevated risks (ratios of rates of disease) in people with DS were found for leukaemia (19, 95% CI 10.4–31.5), celiac disease (4.7, 1.3–12.2), acquired hypothyroidism (9.4, 3.4–20.5), other thyroid disorders, and type 1 diabetes (2.8, 1.0–6.1).

2.6.1 Heart defects

Half of children born with DS have congenital heart defects, the most common of which are atrioseptal defects and ventricular septal defects (Vis *et al.* 2009). The mortality of people with severe heart defects was high before such defects could be surgically corrected (Baird & Sadovnick 1987). By the turn of the century, survival at age 24 years for patients without heart defects was 92.2% (Hijii *et al.* 1997). Survival to age 24 years for those with heart defects was 74.6%, while survival was 87.8% for those who underwent surgery for cardiovascular lesions. The survival rate for those not undergoing surgery was 41.4%. Surgical correction of atrio-ventricular septal defect can be achieved with low mortality and little

need for reoperation, regardless of DS or not (Dodge-Khatami *et al.* 2008). The presence of DS does not increase the risk in complete atrioventricular septal defect repair (Lange *et al.* 2007).

Vis *et al.* (2010) reported a high prevalence of un-recognised heart defects among adults with DS in The Netherlands. While 16% of adults living in residential centres had previously known congenital heart defects, a screening echocardiography performed on those with unknown cardiac status revealed congenital heart defects in 17% of those screened. Additionally, valvular regurgitation of one or more valves was found in 77% of screened participants.

2.6.2 Malignancies

Patients with DS display a unique spectrum of malignancies, with a 10- to 20-fold higher risk of acute leukaemias, and a markedly lower incidence of solid tumours (Rabin & Witlock 2009). Approximately 10% of the neonates with DS exhibit transient neonatal leukaemia and twenty percent of children with transient leukaemia subsequently develop myeloid leukaemia (Webb *et al.* 2007, Zwaan *et al.* 2008, Malinge *et al.* 2009, Rabin & Witlock 2009).

In a Danish register study (Hasle *et al.* 2000), leukaemia constituted 60% of the cases of malignant disease in DS overall and 97% of the cases in children. The cumulative risk for leukaemia by the age of 5 years was 2.1% and by 30 years was 2.7%. Risks of testicular cancer and liver cancer are elevated (Hill *et al.* 2003, Goldacre *et al.* 2004, Patja *et al.* 2006). Standardised risk ratios, the ratios of rates of disease in people, for leukaemia and cancer in DS are given in Table 6.

Table 6. Risk ratio for leukaemia and cancer among people with Down syndrome.

Register study	Standardised incidence ratio (95% confidence interval)	
	Leukaemia	Cancer
Hasle *et al.* 2000	leukaemia 56 (38–81) at age 0–4 years, 10 (4–20) at 5–29 years	solid malignant tumours 0.50 (0.32–0.75)
Hill *et al.* 2003	acute nonlymphocytic leukaemia 28.2 (15.7–48.3) acute lymphocytic leukaemia 24.2 (15.2–36.6)	liver cancer 6.0 (1.2–17.5) testicular cancer 3.7 (1.0–9.4)
Goldacre *et al.* 2004	leukaemia 19 (10.4–31.5)	testicular cancer 12.0 (2.5–35.6) cancers combined 1.2 (0.6–2.2)
Patja *et al.* 2006	leukaemia 10.5 (6.6–15.8)	testicular cancer 4.8 (1.8–10.4)

2.6.3 Respiratory infections

Acute respiratory tract infection is a common reason for hospitalization in children with DS. Respiratory syncytial virus is the single most important cause of lower respiratory tract infections in children and DS is a risk factor for severe cases of these infections (Bloemers *et al.* 2007). Bruijn *et al.* (2007) reported elevated incidences of severe courses of respiratory infections in children with DS (acute lung injury, OR 9.4, 95% CI 3.9–22.6 and acute respiratory distress OR 11.9, 95% CI 4.8–29.8). Children with DS and sepsis had a significantly elevated risk of mortality (mortality rate ratio 1.30, 95% CI 1.06–1.59) after adjusting for potential confounding factors including demographics, pathogens, and concomitant conditions (Garrison *et al.* 2005).

2.6.4 Thyroid disorders

Hypothyroidism may affect adaptive behaviour (Bhaumik *et al.* 1991) and cognitive functions in DS (Lott & Dierssen 2010). As a group, infants with DS have a persistent mild congenital hypothyroidism (van Trotsenburg *et al.* 2006b). The prevalence of thyroid disease increases to 7% during childhood (Gibson *et al.* 2005, Unachak *et al.* 2008, Murphy *et al.* 2008) and further during adulthood (Prasher & Gomez 2007). Among 140 children in Thailand with DS, aged from 3

days to 13 years 9 months, fifty-six children (40%) had abnormal thyroid functions (Unachak *et al.* 2008). Sub-clinical hypothyroidism accounted for 32.9% of all cases. Ten patients (7.1%) were diagnosed with overt thyroid disease.

Transient and persistent thyroid dysfunction was common in 200 adults with DS over a 10-year period in annual thyroid function tests (Prasher & Gomez 2007). The 5- and 10-year incidence of definite hypothyroidism was 0.9–1.64% and 13.6%, respectively. Subclinical hypothyroidism was not found to be an early sign for definite hypothyroidism.

Guidelines have increased detection and treatment of thyroid disease (Carroll *et al.* 2008). Screening for hypothyroidism annually has been recommended for children (American Academy of Paediatrics 2001, Bull & Committee on Genetics 2011) and every one to two years for adults (Kaski *et al.* 2005).

2.6.5 Celiac disease

The diagnosis of celiac disease depends on histological evaluation of intestinal biopsies. Numerous studies demonstrate an increased prevalence of celiac disease in individuals with DS (Table 7).

Bonamico *et al.* (2001) performed a large multicenter study in Italy and described clinical characteristics of celiac disease in DS. In celiac patients, diarrhoea, vomiting, failure to thrive, anorexia, constipation, abdominal distension, and low levels of haemoglobin, serum iron, and calcium were more common than in patients without celiac disease. The diagnosis of celiac disease was made after a mean period of 3.8 years from the initiation of symptoms. Sixty-nine percent of patients showed a classic presentation, 11% had atypical symptoms, and 20% had silent celiac disease. Autoimmune disorders were frequent (30.9%, controls 15%, $P < 0.05$).

The prevalence of celiac disease varied from 3.6% to 18.6% (total 6.6%) among children and adolescents with DS (Carlsson *et al.* 1998, Zachor *et al.* 2000, Carnicer *et al.* 2001, Rumbo *et al.* 2002, Nisihara *et al.* 2005, Hansson *et al.* 2005, Shamaly *et al.* 2007). The prevalence rates (2.7–16.9%, total 5.3%) have been shown to be comparable in studies including adults (Zubillaga *et al.* 1993, Jansson & Johansson 1995, Gale *et al.* 1997, Pueshel *et al.* 1099, Bonamico *et al.* 2001, Sciberras *et al.* 2004, Uibo *et al.* 2006, Cerqueira *et al.* 2010).

Table 7. Prevalence of celiac disease (CD) among people with Down syndrome.

Study	Country	n	n of CD	CD, %
Children				
Shamaly *et al.* 2007	Israel (arabs)	52	2	3.8
Hansson *et al.* 2005	Sweden	72	4	5.6
Nisihara *et al.* 2005	Brazil	71	4	5.6
Rumbo *et al.* 2002	Argentine	56	2	3.6
Carnicer *et al.* 2001	Spain	284	18	6.3
Zachor *et al.* 2000	USA	75	5	6.7
Carlsson *et al.* 1998	Sweden	43	8	18.6
Sum of previous studies		653	43	6.58
Children and adults				
Cerqueira *et al.* 2010	Portugal	98	9	9.2
Uibo *et al.* 2006	Estonia	134	5	3.7
Sciberras *et al.* 2004	Malta	100	8	8
Bonamico *et al.* 2001	Italy	1202	55	4.6
Pueschel *et al.* 1999	USA	105	4	2.7
Gale *et al.* 1997	Australia	51	2	3.9
Jansson & Johansson 1995	Sweden	65	11	16.9
Zubillaga *et al.* 1993	Spain	70	3	4.3
Sum		1825	97	5.32
All studies		2478	140	5.65

Several authors recommend universal screening of children with DS for celiac disease (Zachor *et al.* 2000, Carnicer *et al.* 2001, Bonamico *et al.* 2001, Sciberras *et al.* 2004, Cerqueira *et al.* 2010). Screening with antiendomysium antibody and IgA for all children with DS is recommended, even if there are no gastrointestinal symptoms (Zachor *et al.* 2000). Wouters *et al.* (2009) recommended HLA-DQ2/8 typing from buccal swabs during the first year of life and initiating serologic screening of children with DS in whom test results are positive for HLA-DQ2 or DQ8 at age 3 years.

2.6.6 Oral health

Morgan (2007) reviewed studies on periodontal disease, which is significantly more prevalent and more severe among people with DS. A series of studies have reported periodontal disease in 58% to 96% of persons with DS younger than 35 years of age. Chaushu *et al.* (2007) detected reduction (> 92%) in the bacterial specific salivary antibodies of adults with DS compared to age-matched controls.

The severe immunodeficiency in the secretion rate of the specific salivary IgA response in DS individuals intensified with age.

Parents have highlighted a need for appropriate and timely oral health information early in childhood and access to dentists who are sympathetic, good communicators and well informed about DS (Kaye *et al.* 2005).

2.6.7 Cholelithiasis

Cholelithiasis is considered uncommon in infancy, childhood, and adolescence. Toscano *et al.* (2001) performed a prospective, controlled study showing that children with DS have a significantly higher prevalence of cholelithiasis (4.7%) compared with controls (0.2%). Boechat *et al.* (2007) performed abdominal ultrasound examination of 547 children with DS (53.2% male, 46.8% female) at ages of between one day and three years (mean: five months). In 50 patients (9.1%), the ultrasound demonstrated gallbladder abnormalities (6.9% lithiasis and 2.1% biliary sludge). Spontaneous resolution occurred in 66.7% of the patients with biliary sludge and in 28.9% with lithiasis. Cholecystectomy was carried out on 26.3% of the patients with gallstones. Boechat *et al.* (2007) suggest monitoring children with DS throughout the neonatal period because of the risk of developing lithiasis and biliary sludge.

2.6.8 Urological problems

Mercer *et al.* (2004) reviewed the literature of genitourinary pathology in DS. Defects throughout the genitourinary tract that may associate with DS were reported with renal hypoplasia, obstructive uropathy, and glomerular microcysts being the most common renal anomalies. The testicular abnormalities most frequently reported were cryptorchidism, testicular cancer (Hill *et al.* 2003, Coldacre *et al.* 2004, Patja *et al.* 2006), and infertility. Vachon *et al.* (2006) found a high prevalence of testicular microlithiasis in individuals with DS. The prevalence was 29%, which is significantly higher ($P < 0.0001$) than the 7% found in patients without DS. The prevalence increased with advancing age.

2.6.9 Atlantoaxial instability

Atlantoaxial instability and occult spinal canal stenosis due to C-1 hypoplasia in persons with DS may significantly increase the risk of myelopathy. In a study by

Matsunaga *et al.* (2007), eight children (6.7%) developed atlantoaxial subluxation associated with myelopathy among 102 children ranging in age from 10 to 15 years. Bull & the Committee on Genetics (2011) provide a review and suggest at least biennial discussions with parents of young children with DS at age one to five years to instruct parents about the warning symptoms of possible spinal cord impingement. They do not recommend routine radiological evaluation of the cervical spine in asymptomatic children. However, children with new onset neck pain, change in gait or use of arms or hands, weakness, change in bowel or bladder function, or signs of myelopathy must undergo cervical spine radiography and be referred to specialist for evaluation of atlantoaxial instability.

2.7 Mental health and behaviour

In his review, Dykens (2007) summarizes key findings on the behaviour and emotional problems in children, adolescents, and adults with DS. These include relatively low rates of severe problems in children, and well-documented risks of depression and Alzheimer's disease in older adults. Although children with DS are at lower risk for psychopathology than are others with intellectual disabilities (Haveman *et al.* 1994), they do show more problems than typically developing children (Dykens *et al.* 2002, van Gameren-Oosterom *et al.* 2011).

2.7.1 Mental health and behaviour in children

Childhood psychiatric and behaviour disorders in individuals with DS have good early prognoses (McCarthy & Boyd 2001). However, childhood psychopathology and functioning associate with severe behaviour disorders in young adults (McCarthy 2008). Externalizing behaviours (dominance, opposing/refusing, impulsiveness, inattention, and increased motor activity) were significantly higher in the group of children at the age of 5–10 years, whereas internalizing behaviours (shy/insecure, low self-confidence, decreased motor activity) where more prevalent in adolescents and young adults (Dykens *et al.* 2002, Nicham *et al.* 2003).

Gilmore & Cuskelly (2009) studied motivation in children with DS in early childhood and adolescence and found an association of early task persistence with later persistence and academic competence in adolescence. Compulsive-like behaviour (including ritualistic habits and perfectionist behaviours) was more

frequent in children with DS compared to mental age-matched controls (Evans & Gray 2000).

Lowenthal *et al.* (2007) found a 15.6% prevalence of autism spectrum disorder (5.58% of autism and 10.05% of pervasive developmental disorder non-autism) among 180 children and adolescents with DS using the Autism Screening Questionnaire. Prevalences of autism spectrum disorders in DS from 5% to 39% have been published; autism spectrum disorders are common in many genetic syndromes and associate with the severity of intellectual disability (Moss & Howling 2009).

Sleep disorders

Parents of children with DS reported significantly greater bedtime resistance, sleep anxiety, night waking, parasomnias, sleep disordered breathing and daytime sleepiness compared to published data for typically developing populations (Carter *et al.* 2009). Amongst children 4 years and older, 66% rarely fell asleep in their own beds, 55% were always restless during sleep, and 40% usually woke at least once during the night. Importantly, 78% seemed tired during the day at least 2 days per week, suggesting inadequate sleep.

Sleep apnoea is a common sleep disorder characterized by sleep fragmentation, oxygen desaturation, and daytime somnolence. Fizgerald *et al.* (2007) found obstructive sleep apnoea in 97% of 33 children with DS, mean age 4.9 years, who snored, using diagnostic overnight polysomnograms. None of participants had had adenotonsillectomies, and 91% were non-obese. Shott *et al.* (2006) completed overnight polysomnography on fifty-six children with DS between 4 and 63 months of age. 57% of the children displayed abnormal results and evidence of obstructive sleep apnoea syndrome. Because of the high incidence of obstructive sleep apnoea syndrome in young children with DS, and because of the poor correlation between parental impressions of sleep problems and clinical findings, polysomnography was recommended for all children with DS at age 3 to 4 years by Shott *et al.* (2006).

2.7.2 Mental health and behaviour in adults

Mantry *et al.* (2008) conclude that mental ill health is less prevalent in adults with DS than in adults with other intellectual disabilities. Point prevalence of mental ill-health of any type, excluding specific phobias, in adults with DS was 23.7%

according to clinical measures, 19.9% according to Diagnostic Criteria for Psychiatric Disorders for use with Adults with Learning Disabilities/Mental Retardation (DC-LD), 11.3% according to ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research (DCR-ICD-10) and 10.8% according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Revised (DSM-IV-TR) criteria (Mantry *et al.* 2008). Depression and dementia were more common diagnoses in adults with DS than in adults with intellectual disabilities due to other aetiologies while conduct disorder, personality disorder, or schizophrenia/paranoid state were less common in adults with DS (Collacott *et al.* 1992, Haveman *et al.* 1994, Collacott *et al.* 1998).

Depression

Myers and Pueschel (1995) described symptoms of depression in people with DS. Depression commonly appears as crying, depressed appearance or mood lability, severe withdrawal and mutism, psychomotor retardation, decreased appetite, weight loss, and insomnia. Verbal expressions of suicide, death, self-depreciation, or guilt are infrequent. Hallucinations may be prominent. This pattern of vegetative symptomatology with few verbal complaints and prominent hallucinations may be related to intellectual disability rather than specifically to DS.

Behavioural symptoms

Depression and behavioural disorders in adults may precede the onset of dementia (Burt *et al.* 1992, Burt *et al.* 1998, Urv *et al.* 2008, Urv *et al.* 2010). Depression and indifference, decline in social discourse and verbal expression in social contexts and literal understanding are common in adults with DS and suspected Alzheimer's disease (Nelson *et al.* 2001). Individuals in the early stages of dementia may display increased aggression, fearfulness, sadness, sleep problems, social inadequacy, stealing, and general regressive behaviour (Urv *et al.* 2008).

Cooper & Prasher (1998) compared the behavioural symptoms of dementia in individuals with DS and intellectual disabilities due to other causes. The group with DS had a higher prevalence of low mood, restlessness or hyperactivity, disturbed sleep, uncooperativeness, and auditory hallucinations. Aggression occurred with greater frequency in the subjects with intellectual disabilities due to

other causes (Cooper & Prasher 1998, Cooper *et al.* 2009). The presence of dementia did not predict aggression in individuals with DS (Cosgrave *et al.* 1999).

The functional decline in adults with Down syndrome starts decades earlier, compared to the mainstream population and other people with intellectual disabilities (Zigman *et al.* 1996, Zigman *et al.* 2004, Strydom *et al.* 2007). The coping skills necessary for daily life, social interactions, and work are gradually lost during the progression of dementia (Margallo-Lana *et al.* 2007). The absence of a medical illness predicts a higher level of adaptive behaviour, while dementia is associated with increased maladaptive behaviour (Prasher & Chung 1996, Cooper *et al.* 1998) and psychiatric symptoms (Urv *et al.* 2010).

2.8 Neurological disorders

Cognitive deficits and neurological complications in individuals with DS were reviewed by Lott & Dierssen (2010). Seizures are associated with cognitive decline and seem to cause additional decline in cognitive functioning, particularly in people with DS, and comorbid disorders such as autism (Goldberg-Stern *et al.* 2001, Eisermann *et al.* 2003). Infantile spasms, other central nervous system diseases, and gastrointestinal anomalies associated with developmental age delays at the age of 24 months (van Trotsenburg *et al.* 2006a). Systemic diseases may potentially affect cognitive functions by interfering with the circulation, nutrition, or metabolism of the brain. Central nervous system infections, stroke, and accidents are additional risks to cognitive abilities.

Alzheimer's disease may cause early loss of abilities in the later lives of individuals with DS (Prasher and Chung 1996). The cognitive impairment in adults with DS has similarities to early cognitive changes in Alzheimer's disease (Brugge *et al.* 1994, Ball *et al.* 2010). Increasing age associates with decreasing cognitive and language abilities (Carr 2005), but the deterioration with age is largely explained by the presence of Alzheimer's disease (Iacono *et al.* 2010). The co-morbidity of DS and Alzheimer's disease is increasing because of longer life expectancy and the very early onset of Alzheimer's disease in this population (Collacott 1993, McCarron *et al.* 2005, Torr *et al.* 2010).

2.8.1 Epilepsy

Goldberg-Stern *et al.* (2001) found that epileptic seizures had been experienced by 8% of 350 children and adolescents with DS aged 0–20 years. Infantile spasms (32% of seizures) associated with poor developmental outcomes even with good seizure control. However, treatment of infantile spasms and of children with DS and epilepsy, started within two months had better treatment responses and cognitive development compared to those with delayed treatment (Eisermann *et al.* 2003). Adult-onset seizures are relatively rare in young adults with DS, but the prevalence increases with advancing age (Lott & Dierssen 2010). Myocolonic seizures are seen in the late stages of Alzheimer´s disease whereas partial or tonic clonic seizures may be seen before other symptoms of cognitive decline (Menendez 2005).

2.8.2 Alzheimer's disease

People with DS are at high risk for early Alzheimer's disease and premature ageing (Coppus *et al.* 2006, Zigman & Lott 2007). Dementia that resembles Alzheimer's disease (AD) is common in adults with DS, whereas the rates of dementia in adults with intellectual disabilities without DS are comparable with general population rates (Zigman *et al.* 2004). However, in a study by Strydom *et al.* (2007), investigating individuals with intellectual disabilities without DS, aged 60 years and older, the prevalence of Alzheimer's dementia was 8.6% (95% CI 5.2–13.0), almost three times greater than expected.

Neuropathological lesions characteristic of Alzheimer's disease are found in all the brains of patients with trisomy 21 who die after age 40 years (Wisniewski *et al.* 1985). Depending on diagnostic criteria, 17–55% of them develop clinical dementia after that age (Franceschi *et al.* 1990, Johanssen *et al.* 1996, Holland *et al.* 1998, Janicki & Dalton 2000, Tyrrell *et al.* 2001, Coppus *et al.* 2006). The reported prevalence of dementia in people with DS is summarised in Table 8.

Table 8. Prevalence of dementia in individuals with Down syndrome.

Study; population, criteria	Prevalence of dementia (age group years)
Franceschi *et al.* 1990;	18% (20–52 years)
50 patients with DS and mild intellectual disability,	0% (20–29)
NINCDS/ADRDA criteria	33% (30–39)
	55% (40–52)
Johannsen *et al.* 1996;	Possible dementia
A population-based study,	6% (23–29)
clinical assessment	24% (50–60)
	Definite clinical dementia
	24% (50–60)
Holland *et al.* 1998;	3.4% (30–39)
A population-based study,	10.3% (40–49)
modified Cambridge Examination for Mental Disorders	40% (50–59)
of the Elderly (CAMDEX)	
Janicki & Dalton 2000;	22% (40–)
A state-wide survey	56% (60–)
	In the general population:
	3% (40–)
	6% (60–)
Tyrrell *et al.* 2001;	13.3% (35–74).
285 people with DS (Age 35–74 years),	
DSMIV criteria	
Coppus *et al.* 2006;	8.9% (45–49)
506 people with DS, aged 45 years and above,	17.7% (50–54)
ICD-10 Symptom Checklist for Mental Disorders	32.1% (55–59)
	25.6% (60–)

Coppus *et al.* (2006) performed a population-based study of dementia and mortality among 506 people with DS, aged 45 years and above. A standardized assessment of cognitive, functional, and physical status was repeated annually. If deterioration occurred, the patients were examined to confirm the diagnosis. The overall prevalence of dementia was 16.8%. Up to the age of 60, the prevalence of dementia doubled with each 5-year interval. In the age category of 60 and above, there was a small decrease in the prevalence of dementia. The lack of increase after the age of 60 may be explained by the increased mortality among elderly demented patients (44.4%) in comparison with non-demented patients (10.7%) who were observed during a 3.3-year follow-up. Patients with dementia were more frequently treated with antiepileptic, antipsychotic, and antidepressant drugs. A history of depression was strongly associated with dementia.

Diagnostic aspects

Diagnosing Alzheimer's dementia in DS can be problematic for a number of reasons including the large intra-individual variability in cognitive functioning, the different diagnostic and methodological procedures used, and the difficulty to assess cognitive and behavioural change in adults with DS. Niuwenhuis-Mark (2009) explored recent developments and provided recommendations, which may aid clinicians in their attempts to diagnose Alzheimer's dementia in the early stages in the DS population. Identification of persons with risk of early dementia remains a challenge (Niuwenhuis-Mark 2009). Direct assessments of cognitive functions of people with intellectual disabilities may be difficult. Informant-based assessments are useful as complementary or alternative methods in clinical work (Ball *et al.* 2004, Niuwenhuis-Mark 2009). Experimental approaches have also been developed (Nelson *et al.* 2001, Nelson *et al.* 2007).

Personality and behaviour changes (Ball *et al.* 2006), executive dysfunction (Ball *et al.* 2008), and selective attention deficits (Krinsky-McHale *et al.* 2008) are early signs of dementia in adults with DS followed by an increase in characteristics associated with frontal lobe dysfunction and/or deterioration in memory. Frontal-like dementia can be diagnosed in 33% in of DS individuals in their thirties (Holland *et al.* 2000). Informant-reported personality/behaviour changes were a significant predictor of performance on executive function and two 'executive memory' tests but not on episodic memory tests (Ball *et al.* 2008).

Teipel *et al.* (2003) analyzed magnetic resonance imaging scans of non-demented adults with DS. They found comparable decreases of the corpus callosum and hippocampal size with age. The size of the corpus callosum correlated with cognitive performance. Corpus callosum atrophy has been established as a marker of neocortical neuronal loss in Alzheimer's disease. Age-related atrophy in DS resembles the pattern of brain atrophy evident in the early stages of AD. DS has been proposed as a model to study the predementia stages of AD (Teipel & Hampel 2006).

Margallo-Lana *et al.* (2007) followed 92 hospitalized persons with DS from 1985 to 2000. At outset, 87 participants were dementia-free, with a median age of 38 years. Eighteen patients (21%) developed dementia during follow-up, with a median onset age of 55.5 years (range 45–74). Clinical dementia associated with the neuropathological features of Alzheimer's disease, and neocortical neurofibrillary tangle densities.

Risk of dementia

Several risk factors of dementia among people with DS have been identified Participants with APOE epsilon 4 allele had a 1.8 higher risk of developing dementia (1.12–2.79) than did those without the allele, an earlier onset of dementia, (55.0 vs. 57.0 years), and a more rapid progression (Prasher *et al.* 2008). Margallo-Lana *et al.* (2004) found a 13-year difference in the age at onset of dementia associated with the number of tetranucleotide repeat alleles in amyloid precursor protein (APP). Those in the middle and highest tertiles of plasma Beta-amyloid peptide Abeta (42) levels were more than 2 times as likely to develop dementia as those in the lowest tertile (Schupf *et al.* 2007).

Patel *et al.* (2010) found significant associations of single nucleotide polymorphisms (SNPs) in five genes with dementia in DS, namely APOE, SORL1, BACE1, RUNX1, and ALDH18A1. Homozygosity for the minor T allele and for the minor C allele of the sortilin-related receptor gene (SORL1) associated with later age at onset of dementia and reduced risk of dementia (Lee *et al.* 2007).

Participants with total cholesterol 200mg/dL or more were more likely to develop dementia than those with lower total cholesterol (Zigman *et al.* (2007); participants who used statins had a non-significant reduction in their risk of dementia (0.402; 0.138–1.173).

Early age at menopause has been associated with an increased risk, RR 1.82 (1.31–2.52), of dementia in women with DS (Coppus *et al.* 2010). Women with low levels of estradiol (E2) had dementia, on average, 3 years earlier, than did those with high levels of E2 (Schupf *et al.* 2006). Women with C allele of estrogen receptor-alpha had an almost 3-fold increase in the risk of dementia, compared with women without the C allele (Schupf *et al.* 2008).

Treatment

There is some evidence of the benefit of medical treatment on the outcome of Alzheimer's disease (Prasher *et al.* 2002), but larger randomized controlled studies with longer follow-ups are required. Studies on cholinergic medications in DS are precented in more detail in chapter 2.9. *Recent research on Down syndrome*, page 49.

Accurate measures are important for the follow-up and evaluation of treatments. It is necessary to find and use valid, reliable, and sensitive methods for assessments of adults and ageing people with Down syndrome and Alzheimer's disease. Repeated assessments of adaptive behaviour in people at risk of functional decline might help to confirm the change, lead to necessary additional evaluations of the underlying reasons, and help in follow-up. It is also important to recognize and treat all health co-morbidities in ageing persons with DS and Alzheimer's disease (McCarron *et al.* 2005, Kerins *et al.* 2008, Torr *et al.* 2010).

2.8.3 Stroke

The incidence rate of stroke is unknown in people with DS. The incidence of atherosclerotic vascular disease and its complications such as myocardial infarction is low in subjects with DS (Vis *et al.* 2009, Lott & Dierssen 2010). However, cerebral infarcts and amyloid angiopathy are common findings in autopsies performed on adult people with DS (Wisniewsky *et al.* 1985). Moyamoya syndrome is associated with DS and it should be considered in the evaluation of patients who present with transient ischemic attack-like symptoms. Cerebral revascularization surgery seems to protect against additional strokes in this patient population (Jea *et al.* 2005).

2.9 Recent research on Down syndrome

The research on DS is active and published literature is abundant. Therefore, information on numerous specific health concerns is available. Basic research has rapidly increased the understanding of genetic, developmental, and functional aspects during recent years (Wiseman *et al.* 2009). Trisomic and transgenic mouse models for DS have been used to study neurodevelopmental and cognitive disorders (Robertoux & Carlier 2010, Fillat *et al.* 2010) and to test treatments (Bianchi *et al.* 2010).

2.9.1 Molecular biology and genes

Rachidi & Lopes (2010) review recent advances in research including altered molecular pathways that are important in understanding the molecular basis of intellectual disability pathogenesis in DS. They discuss the effects of the gene

dosage imbalance on DS phenotypes. Studies have shown up- or down-regulations of genes located on chromosome 21 and the other chromosomes. Park *et al.* (2008) summarized the recent findings of two key genes, which are thought to be closely associated with the typical features of DS, and their role in neural development and neuropathology. DYRK1A phosphorylates several transcriptional factors, endocytic complex proteins, and AD-linked gene products. RCAN1 is an inhibitor of calcineurin A, and its unbalanced activity is linked to neuronal and/or non-neuronal functions in DS and AD. These genes contribute to the learning and memory deficit, altered synaptic plasticity, impaired cell cycle regulation, and AD-like neuropathology in DS. The understanding of the genetic mechanisms is essential for development of therapies to improve developmental and cognitive outcome of people with DS in the future.

2.9.2 Medications

Thyroxin

The effects of thyroxin on the early development of children with DS were examined by van Trotsenburg *et al.* (2005). Neonates were randomized to treatment for 2 years with thyroxine or a placebo. At age 24 months, the thyroxine-treated children had a 0.7-month smaller delay in motor developmental age (95% confidence interval, −1.4 to 0). The mental developmental age delay was also 0.7 months smaller in the thyroxine group (95% confidence interval, −1.5 to 0.2), but the difference was not statistically significant. Thyroxine-treated children had also grown faster.

Piracetam

Piracetam, a cyclic derivative of gamma amino butyric acid (GABA), the main inhibitory transmitter in the brain, has been used to improve cognitive function in children with DS. However, piracetam therapy (80–100 mg/kg per day, 4 months) was shown not to improve cognitive performance in a randomized, double-blind, placebo-controlled crossover study in children with DS aged 6.5–13 years (Lobaugh *et al.* 2001).

Cholinergic medications

Individuals with DS exhibit a cholinergic deficiency similar to that found in Alzheimer's disease. Some evidence support the use of early cholinergic medication to improve cognitive functioning or adaptive behaviour in adult individuals with DS (Prasher *et al.* 2002, Kondoh *et al.* 2011).

Prasher *et al.* (2002) found a small but statistically not significant slowing in the progression of deterioration in participants with DS and Alzheimer`s disease in a 24-week double-blind, placebo-controlled trial (Donepezil, 5–10 mg daily). Heller *et al.* (2003) reported improvement in expressive language performance following donepezil therapy (5–10 mg once daily) in adults with DS in a small 24-week non-controlled open study. Johnsson *et al.* (2003) also reported improvement on language but no other scores during donepezil therapy (5–10 mg) in adults with DS in a small 12-week placebo-controlled study. Kishnani *et al.* (2009) did not find significant efficacy of donepezil (5–10 mg daily) in young adults with DS (123 participants, age 18–35 years) in a 12-week randomized, double-blind, placebo-controlled large-scale multicenter study. However, the therapy was safe and well tolerated. Kondoh *et al.* (2011) reported improvements in females with DS and severe cognitive impairment in abilities of daily living, assessed by the ICF scaling system in a 24-week randomized, double-blind, placebo-controlled trial (donepezil; 3 mg daily). The conflicting findings support the need for longer, double-blind studies of the efficacy of cholinesterase inhibitors in adults with DS.

The first investigation of the safety and efficacy of rivastigmine (an acetyl and butyryl cholinesterase inhibitor) on specific cognitive domains in adolescents with DS (n = 11, age 10–17 years) reported improvements in overall adaptive function, attention, memory, and language domains (Heller *et al.* 2006). In a study of the safety and cognitive efficacy of donepezil hydrochloride (2.5–5 mg) in seven children (8–13 years) with DS, some children showed improvement on measures of memory and sustained attention to tasks although increased irritability and/or assertiveness were noted in some patients (Spiridigliozzi *et al.* 2007). Kishnani *et al.* (2010) performed a 10-week, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of donepezil (2.5–10 mg/day) in children aged 10–17 years with DS and mild to moderate intellectual disability. This study failed to demonstrate any benefit of donepezil versus placebo for treatment of cognitive dysfunction. The between-group differences in

improvements measured by the Vineland-II Adaptive Behaviour Scales and Parent/Caregiver Rating Forms were not statistically significant.

Fluoxetine

Bianchi *et al.* (2010) reported promising results of treatment with fluoxetine on brain development and behaviour in the mouse model for DS: a treatment given daily during the two first weeks after birth corrected impaired proliferation of neurons and memory impairment completely. Fluoxetine is currently used as an antidepressant in adults and children.

2.9.3 Nutritional supplements, vitamins, antioxidants

The activities of serum acetyl- and butyrylcholinesterase were low in children with DS compared to age-matched healthy children, and improved after six months of supplementation of zinc in combination with antioxidant vitamins and minerals (Lakshmi *et al.* 2008). The authors claimed improvement in observed cognitive skills and behaviour, but did not provide data to support this statement.

In a randomised controlled trial (Ellis *et al.* 2008), antioxidants, folinic acid, or both did not improve the psychomotor and language development of children with DS. Infants with DS without severe cardiac defects or long-term illness, aged less than 7 months (n = 156), were randomised in four groups at a mean age of 4 months. Daily oral supplementation with antioxidants (selenium 10 mg, zinc 5 mg, vitamin A 0.9 mg, vitamin E 100 mg, and vitamin C 50 mg), folinic acid (0.1 mg), antioxidants and folinic acid combined, or placebo was used for 18 months.

Blehaut *et al.* (2010) investigated the effect of oral folate supplementation on cognitive functions in children with DS, aged from 3 to 30 months. They received 1 mg/kg leucovorin or placebo daily, for 12 months, in a single-centre, randomised, double-blind study. A per-protocol analysis revealed a positive effect of leucovorin on developmental age. This effect was particularly strong in patients receiving concomitant thyroxin treatment.

3 Aims of the study

The associations of health impairments, intellectual disability, adaptive behaviour change in ageing, and health surveillance of people with DS are interesting and clinically important. The study was prompted by the belief that health surveillance and successful treatment of medical problems of people with DS, based on objective data regarding their health risks and impairments, intellectual disability, and adaptive behaviour, improve their health and quality of life. Based on this background, this study explores the aspects mentioned above in a Kainuu cohort and sets out to answer four specific questions about people with DS:

1. What are the frequencies of the recorded medical problems in general and especially related to age?
2. Is the severity of intellectual disability related to health impairments?
3. How does the adaptive behaviour change in ageing?
4. How does the health surveillance follow the recent guidelines given in Finland?

4 Participants and methods

One hundred and thirty-eight persons with DS were identified in the Specialized Service Register of the Kainuu region. The study analysed the case records of these persons, for both specialized and primary health care and disability services.

4.1 Participants

In the first stage of the study, 129 case records of individuals with DS were identified and analysed in March 2004. Data was collected from the archives of the Intellectual Disability Service Register and the Central Hospital of Kainuu. The medical and disability case records of the participants from birth to the data collection date were surveyed for any clinically significant medical problems (survey 2004, n = 129).

The second survey of case records took place in January 2009. Persons born after the first survey (n = 8) were included. The study population was composed of the cases from the first (n = 129) and from the second (n = 8) survey (survey 2009, n = 137). The second survey was conducted on-line from the regional computerized case records that were used for at least five years in primary and specialized health and disability services. The study included the data of health surveillance, primary health care, and dental care and reviewed laboratory examinations performed during the preceding five years.

A third survey was performed in March 2011 to assess the vital statistics. This survey was limited to updating the subgroups according to their presence in the region. Data of one person who had moved to the region were included. The data of the third survey (survey 2011, n = 138) were used for a comparison of health data from the previous surveys in the updated groups of deceased and living persons. An analysis of medical problems recorded in the 2009 survey by age was performed, including the data of all identified participants.

The combined data of these surveys were used for analysis. The detected health impairments were related to age and to the severity of intellectual disability. The data of persons who moved from the region were analysed for the time they lived in the region and in the local registers only.

The data of deceased and re-located people (people who had moved from the region) are presented separately in the results. The data of these groups are compared to the present population (n = 84). Table 9 presents the numbers and

percentages of the deceased, relocated, and present subgroups. Most of the deceased persons were more than 40 years old.

Table 9. The numbers and percentages of participants in the present, deceased and relocated subgroups. survey 2011.

Age	Present		Deceased		Relocated		All	
	n	%	n	%	n	%	n	%
0–9	16	11.6	3	2.2	6	4.3	25	18.1
10–19	15	10.9	1	0.7	2	1.4	18	13.0
20–29	16	11.6	4	2.9	3	2.2	23	16.7
30–39	21	15.2	5	3.6	3	2.2	29	21.0
40–49	13	9.4	12	8.7	1	0.7	26	18.8
50–59	3	2.2	9	6.5	0		12	8.7
60+	0		5	3.6	0		5	3.6
Total	84	60.9	39	28.3	15	10.9	138	100.0

The data of a combined subgroup of deceased and re-located people (past subgroup) were compared to the present population for description of changes over time. The only conspicuous differences between the two groups were no participants who were deceased or not living in the region in the present subgroup and a shorter time had passed from the last contact for that group compared to the past subgroup. Table 10 shows characteristics of the present and past subgroups in the survey 2009.

Table 10. Characteristics of the past (deceased or re-located) and present subgroups, survey 2009.

Characteristic of the group	Past *n* = 53	Present *n* = 84
Males, n (%)	28 (52)	49 (59)
Age years, mean (range)	35.1 (0.1–67.9)	34.5 (0.6–59.2)
Age group of 0–29 years, n (%)	20 (38)	30 (36)
30-year-old age group, n (%)	33 (62)	54 (64)
Time from last contact or death years (range)	13.5 (0.3–34)	3.6 (0.1–23.6)
Deceased participants, n (mean age at death)	32 (43.3)	0
Participants no longer in target region, n (mean age at last contact)	21 (22.7)	0

4.2 Coding of recorded data

Data was coded as described in detail below. Frequencies were reviewed and data were recoded to fewer categories for descriptive statistics. The most common symptoms and diseases, including hypothyroidism, seizures, epilepsy, depression, and Alzheimer's disease, were coded separately. The time of last contact in disability and health services and the time of death were recorded.

Intellectual disability had been determined by repeated psychological assessments based on the diagnostic criteria of the International Classification of Diseases and Related Health Problems (ICD-10, World Health Organisation 1992). The ICD-10 criteria for intellectual disability include adaptive behaviour in addition to cognitive abilities.

The severity of intellectual disability was scored from 1 to 4 according to the best level achieved by each individual as follows: mild (IQ 50–69) 1, moderate (IQ 35–49) 2, severe (IQ 20–34) 3, profound intellectual disability (IQ < 20) 4. Categories 1 and 2 were recoded to mild/moderate and 3 and 4 to severe/profound intellectual disability.

The study used speech production as an index of verbal communication abilities and speech impairment was scored as follows: relatively fluent speech with extensive vocabulary – 0, communicative speech with long sentences – 1, short sentences – 2, single words – 3, and no verbal communication – 4. Speech production was recoded to good/moderate (0, 1 or 2), limited (3) and no verbal communication (4).Visual impairment was scored as follows: visual acuity of the better eye with or without correction of refraction at least 0.8 – 0, visual acuity 0.4–0.7 – 1, visual acuity not known – 2, visual acuity 0.1–0.3 or cataracts or corneal opacities – 3, visual acuity less than 0.1 – 4, bilateral blindness – 5. Visual impairment was recoded to good (0 or 1), unknown (2), and impaired visual acuity (3, 4 or 5).

Hearing loss and ear disease were scored as follows: hearing thresholds at frequencies of 0.5–1 kHz in the better ear less than 20 dB in audiometry – 0, hearing thresholds less than 30 dB by screening audiometry at 1.0 Hz – 1, hearing not determined or evaluated as normal – 2, hearing thresholds 20–49 dB in audiometry or less than 50 dB by screening audiometry, recurrent middle ear infections, glue ear or perforation of tympanic membrane – 3, hearing thresholds 50–70 dB in audiometry or less than 70 dB by screening audiometry or hearing aids needed – 4, hearing thresholds more than 70 dB – 5. The Pocket Audiometry Tester (PAT225 of Madsen electronics) was used for screening audiometry.

Hearing and ear disease was recoded to no/minor hearing loss and no recurrent middle ear infections (0 or 1), unknown (2), and hearing loss or recurrent middle ear infections (3, 4, or 5).

Oral health scoring was based on the number of lost permanent teeth as follows: no loss of permanent teeth – 0, loss of 1–4 permanent teeth – 1, loss of 5–9 permanent teeth or the number of lost teeth unknown – 2, loss of 10 or more permanent teeth with more than 5 remaining teeth, or repeated treatments under general anaesthesia needed – 3, only 1–5 permanent teeth left or severe caries or chronic periodontal infection – 4, loss of all permanent teeth – 5. Oral health was recoded to good (0, 1 or 2), moderate (3 or 4) and poor (5). The number of teeth was drawn from the records and based on visual inspection only, thus remaining residual teeth were scored as lost.

Immune diseases were scored according to the number of autoimmune and related diseases, including atopic dermatitis, asthma, celiac disease, thyroid disease, psoriasis, alopecia, rheumatoid arthritis, and diabetes. Immune diseases were recoded to none (0) and one or more (1 or more).

Infectious diseases other than dental or upper respiratory infections or ear infections were scored as follows: no episodes of pneumonia, urinary tract infections, abdominal or skin infections – 0, one or two episodes – 1, three or more episodes, chronic infection, or very serious (septic) infections – 2.

The epilepsy and stroke score was defined as the sum of the following items: recurrent fainting – 1, epilepsy – 1, total number of episodes of stroke during life 0–5, unilateral pareses – 1, bilateral involvement – 2, visual impairment – 1 and speech loss – 1. The score was used as an index of neurological symptoms (including fainting, epilepsy and stroke), possibly or definitely related to impairment of brain circulation.

Behavioural and mental health problems were separately scored for severity as follows: Mood, anxiety: no problems – 0, mild depression/withdrawal – 1, moderate depression, anxiety or fears – 2, severe depression, anxiety, somatic symptoms – 3, very severe depression, psychotic symptoms or severe self-injury – 4. Behaviour: no problems – 0, occasional difficulties – 1, occasional aggressive outbursts, destruction of material objects – 2, severe irritability, disturbing behaviour, attacking others – 3, difficult to manage, dangerous to others – 4. Combined behavioural or mental health problems were recoded to no/minor (0 or 1, sum 0–3) and yes (2, 3 or 4, sum 4–8). The presence of depression was separately recoded to no/mild (0 or 1) and yes, severe (3 or 4).

The data was analysed using the Microsoft Excel and SPSS Statistics 17.0 for Windows software packages. Descriptive statistics, cross-tabulations with Chi-square test (Chi2-test) for statistical significance, and non-parametric correlation (Spearman) and partial correlation to control for age effects were used.

4.3 Adaptive behaviour assessments

The proxies of people with DS were informed about the possibility of early aging and the risk of dementia and encouraged to contact professionals of the service centre for assessment in case of any concern. Informant evaluations regarding observed changes in behaviour were recorded repeatedly. The closest relatives or carers who lived or worked with the participants and had known the persons and their daily skills for a long time performed the adaptive behaviour assessments.

Assessments of adaptive behaviour were conducted with 42 adult persons with DS. Assessments were performed over ten years, beginning in 2000. Seventeen persons were assessed once (age range 18–65 years). An additional 25 persons had repeated assessments. These person's proxies had noticed a change of mood, behaviour, or performance.

The coping skills for daily living were assessed using the Adaptive Behaviour Scale – Residential and Community, ABS-RC: 2 1993, Part I (Nihira *et al.* 1993). The Adaptive Behaviour Scale (ABS) was chosen because the reliability and validity of this method are well established. The first part of ABS focuses on personal independence and includes ten domains or subscales: Independent Functioning, Physical Development, Economic Activity, Language Development, Numbers and Time, Domestic Activity, Prevocational/Vocational Activity, Self-Direction, Responsibility and Socialization. The ABS Manual reports that factor analysis has found three Part-one factors: Personal Self-Sufficiency, Community Self-Sufficiency, and Personal–Social Responsibility.

The principal investigator did clinical evaluations. These included interviews of the proxies, referrals for differential diagnostics and specialist consultations, and prescriptions and assessments of medications. Additional clinical data was drawn from the case records of the health centres, the central hospital, and the service centre regarding all persons with DS in the region. The data of medical treatments for Alzheimer's disease, depression, behavioural problems, epilepsy, and other major health concerns possibly affecting adaptive behaviour were analyzed. The age at the time of the first observation of functional decline was calculated.

Informant ratings on the ABS were scored and analysed. Total scores, scores for the ten subscales and three factors of ABS, and changes of scores from the first to the last evaluation were counted. The ABS score changes were calculated as percentages per three years for subgroups of participants with and without Alzheimer's disease, depression, epilepsy, hypothyroidism, and antipsychotic medication use for challenging behaviour.

At the time of the first evaluation, subjects' age range was 24–61 years, with a mean of 45.8 and a SD of +/− 8.4; at the time of the last evaluation, the corresponding figures were 25–65.5, 48.8, and +/− 8.4 years, respectively. The mean time of follow-up was, thus, 3.0 years (range 0–8 years). Five participants died during the follow up. Twenty participants (80%) of the 25 were 40 years or older at the time of the first evaluation.

The ethics committee of Kainuu Hospital District approved the study plan. The Finnish Ministry of Social Affairs and Health gave permission for the linkage of social and health register data needed in the study.

5 Results

5.1 Recorded medical problems

The data available in the social and medical records varied greatly. Carefully recorded social, psychological, and medical evaluations were available for most persons. The majority of visits of adults to medical services related to assessments of symptoms and follow-up of detected medical problems.

The most extensive recorded data belonged to some teenagers and young adults. Young participants had received more recorded services than older ones. The weight of the medical records of participants in the Central Hospital may reflect their health needs but also the availability of these services in the region because services were available only for the last 40 years, since 1969 when the current Central hospital was built.

Most people with Down syndrome had several severe health concerns. The health concerns of 129 persons identified in the first survey (survey 2004) included visual impairment with visual acuity of 0.3 or less in 30 individuals (23%), hearing loss with hearing thresholds of 20 dB or more or recurrent middle ear infections in 42 (33%), loss of at least 10 permanent teeth, severe caries, or periodontal disease in 47 (36%), at least one immune disease in 47 (36%), and at least one episode of infection (excluding upper respiratory and ear infections) treated in hospital in 56 (43%).

Two children had acute leukaemia. Three participants lost their mobility because of spinal cord injuries, two of them had anomalies of the upper cervical spine, and the third had degenerative changes of the middle part of the cervical spine. Five participants had diabetes; three were treated with insulin. Fractures occurred in 12 participants (9%). Sleep disorders had not been actively searched and none had been diagnosed.

Diseases related to old age, Alzheimer's disease, epilepsy, and stroke were more common among the deceased participants in comparison to the still living participants. Severe medical conditions like septic infections and severe heart defects had affected many of them, too.

The weight of medical records in specialized health care was extremely variable among all age groups as shown in Figure 1.

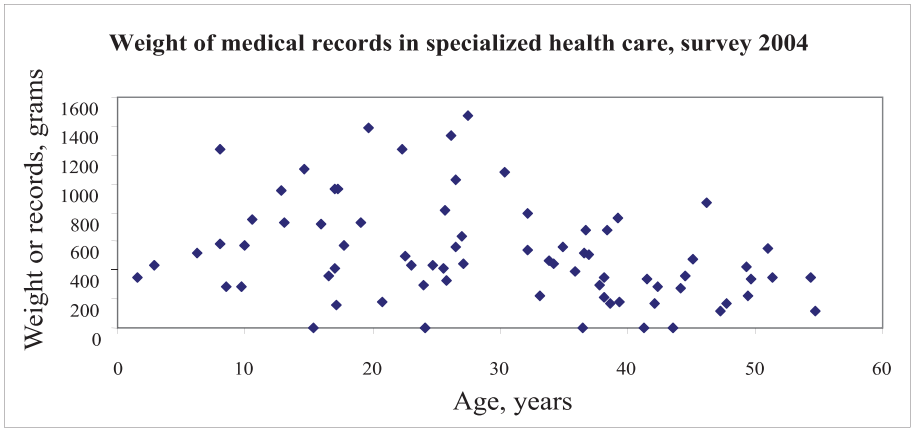

Fig. 1. Weight of medical records by age.

Table 11 shows main medical problems and percentages of affected people in the present population with DS (n = 84) and in the subgroups of 32 deceased participants and 21 participants who had lived in the region earlier but moved elsewhere (re-located).

Table 11. Medical problems of people with Down syndrome in subgroups, survey 2009.

Medical problem	Re-located n = 21 %	Deceased n = 32 %	Present n = 84 %	Total n = 137 %
Heart defect	19	34	26	27
Middle ear infections	5	16	44	31
Hearing loss	10	16	27	22
Eye concerns	43	47	70	61
Cataracts	14	19	15	16
Keratoconus	10	3	5	5
Blindness	5	6	2	4
Skin disease	19	13	14	15
Asthma	0	31	2	9
Hypothyroidism	19	22	26	24
Celiac disease	0	3	4	3
Psychiatric or behavioural problem	19	19	37	30
Depression and/or anxiety	14	19	29	24
Challenging behaviour	10	9	24	18
Autistic features	5	9	8	8
Panic	0	9	10	8
Seizures, fits or fainting	33	59	43	45
Fainting	10	22	18	18
Epilepsy	0	44	7	15
Pneumonia	33	53	27	34
Septic infection	5	13	2	5
Stroke	5	44	2	12
Alzheimer´s disease	10	41	18	22

Surgical treatments

About half (48%) of all participants had received major surgical treatments during their lifetimes. Forty-seven (56%) of the currently living participants had at least one major surgical operation, and 37 (27%) of all participants had had several operations, even when adenoidectomies, tonsillectomies, grommet insertions, and ophthalmologic and dental operations were not counted. Common indications for operative treatments were musculoskeletal (habitual dislocations of the knee, fractures, and various hernias), gastrointestinal (gall stones, which were operated on in five of the nine detected, and duodenal obstructive anomalies),

cardiovascular (congenital heart defects), and genitourinary problems (foreskin and other urinary tract strictures in males).

Medical problems and age

The detected health impairments related to age. Health data of participants in all subgroups (n = 137) were combined to describe medical problems experienced by participants and recorded from birth to the defined ages. Main medical problems and percentages of affected people in age groups of participants divided into three age groups and are presented in Table 12.

Middle ear infections were mostly experienced by young people, while epilepsy, stroke, and Alzheimer's disease were more frequent among older people. Severe infections had affected participants in all age groups. Congenital heart defects were seen in 24 (47%) of participants younger than 30 years, but in only 2 (6%) of those 50 years or older.

Suspected or confirmed hearing loss with at least 20 dB hearing thresholds was evident in 30 (22%) of the participants. Pure tone audiometry to determine hearing loss accurately had seldom been performed successfully. Four of the 84 participants (5%) in the present population used hearing aids.

Table 12. Medical problems of people with Down syndrome in the Kainuu region divided to three age groups, survey 2009.

Medical problem	Age groups			
	0–29	30–49	50+	Total
	n = 51	n = 55	n = 31	n = 137
	%	%	%	%
Congenital heart defect	47	20	6	27
Middle ear infections	51	31	0	31
Hearing loss	16	31	16	22
Eye concerns	49	67	68	61
Cataracts	6	15	35	16
Keratoconus	2	9	3	5
Blindness	2	5	3	4
Skin disease	10	13	26	15
Asthma	12	7	6	9
Hypothyroidism	8	40	23	24
Celiac disease	4	4	0	3
Psychiatric or behavioural problem	22	24	55	30
Depression and/or anxiety	16	16	52	24
Challenging behaviour	10	18	32	18
Autistic features	6	13	3	8
Panic	0	9	19	8
Seizures, fits or fainting	33	42	71	45
Fainting	14	13	32	18
Epilepsy	4	15	32	15
Pneumonia	39	36	23	34
Septic infection	10	2	3	5
Stroke	4	15	23	12
Alzheimer´s disease	0	13	74	22

Eye concerns, including refractive errors and eye diseases were more common in the older participants (67%) compared to younger participants (50%). Glasses to correct refractive errors were widely distributed. Cataracts were detected in 3 (6%) of participants younger than 30 years, and in 19 (22%) of participants older than 30 years.

Epilepsy was diagnosed in 21 (15%) of participants. Dementia was diagnosed only in persons older than 30 years. Acute loss or disturbance of consciousness had affected 62 (45%) of the participants. Fainting was the most common diagnosis, recorded in 25 (18%) of participants. Acute anxiety symptoms, hyperventilation, and panic attacks mimicked epileptic seizures.

Recurrent middle ear infections had been experienced by 31% of participants, mainly during childhood. However, recorded data on middle ear problems were seldom found for participants older than 50 years (Table 13). Impairment of visual acuity was common in all age groups and most frequent in the oldest age groups (Table 13).

Table 13. Problems related to hearing loss and visual impairment, survey 2011.

Age years	Number of participants	Recurrent middle ear infections		Visual impairment	
		N	%	N	%
0–9	25	5	20.0	1	4.0
10–19	18	11	61.1	2	11.1
20–29	23	10	43.5	5	21.7
30–39	29	10	34.5	8	27.6
40–49	26	5	19.2	8	30.8
50–59	12	0	0	4	33.3
60+	5	1	20.0	2	40.0
Total	138	42	30.4	30	21.7

Psychiatric disorders and behavioural problems were frequent in all age groups. Psychiatric disorders or challenging behaviours were recorded for 30% of all participants. A specific diagnosis of depression or anxiety, for example, was not easily achieved. An assessment based on recorded symptoms gave higher rates of psychiatric disorders and behavioural problems than the actually recorded diagnoses or severe symptoms (Table 14).

Table 14. Severe psychiatric and behavioural problems, survey 2011.

Age years	Number of participants	Psychiatric or Behavioural Problem		Severe depression	
		N	%	N	%
0–9	25	0	0	0	0
10–19	18	2	11.1	2	11.1
20–29	23	5	21.7	3	13.0
30–39	29	4	13.8	0	0
40–49	26	7	26.9	5	19.2
50–59	12	5	41.7	3	25.0
60+	5	1	20.0	1	20.0
Total	138	24	17.4	14	10.1

Mental health (depression/anxiety) and behaviour based on recorded data could be scored for 108 persons (84% of the 129 persons of the first survey). For 48 persons (44% of the 108 evaluated) no problems related to behaviour had been recorded, while 36 (33%) had experienced occasional difficulties. Ten (9%) had exhibited occasional aggressive behaviour, and another 10 (9%) had shown severe irritability and disturbing behaviour. Four (4%) had been difficult to manage or even dangerous to others.

For 66 persons (61% of the 108 evaluated) no problems related to mood or anxiety had been recorded, whereas 18 (17%) had experienced mild depression/withdrawal, 12 (11%) moderate depression, anxiety or fears, 9 (8%) severe depression, anxiety and somatic symptoms, and 3 (3%) severe depression, psychotic symptoms or severe self-injury. No differences in mental health appeared between males and females. Depression was sometimes diagnosed only after long and elaborate investigations.

Eleven of the 33 patients (33%) with repeated psychological evaluations during childhood had displayed behaviour suggestive of attention deficit hyperactivity disorder. Depression had been identified and treated mainly in people with mild to moderate disability. Severe self-injurious behaviour and aggressive behaviour were sometimes difficult to treat. Autistic behaviour was seen in 9 persons (8 males, 1 female) with profound intellectual disability. Behavioural changes were common in adults with early stages of Alzheimer's disease. Maladaptive challenging behaviour was often an early sign of Alzheimer's disease.

Neurological problems

Rates of Alzheimer's disease and seizures increased with increasing age. More than half of the participants had early dementia already in their forties and had experienced seizures by their fifties. Neurological problems of younger participants, including infantile spasms, other epilepsies, stroke, and central nervous system infections were less frequent, as shown in Table 15.

Table 15. Neurological problems, survey 2011.

Age years	Number of participants	Participants with Neurological Problems[a]		Alzheimer's disease		Seizures	
		N	%	N	%	N	%
0–9	25	3	12.0	0	0	3	12.0
10–19	18	2	11.1	0	0	0	0
20–29	23	4	17.4	0	0	2	8.7
30–39	29	5	17.2	2	6.9	2	6.9
40–49	26	15	57.7	14	53.8	9	34.6
50–59	12	11	91.7	10	83.3	6	50.0
60+	5	4	80.0	4	80.0	4	80.0
Total	138	42	30.4	30	21.7	26	18.8

[a]Neurological problems include seizures, epilepsy, brain infections, stroke and Alzheimer's disease

Stroke

Strokes, even repeated strokes, had caused permanent disabilities for some of the young and many of the old participants. Stroke and suspected stroke had been seen in 20 (15.8%) of these 126 persons with DS so far. Four had recurrent episodes of stroke. Many strokes occurred during childhood. Acute-onset hemiparesis and loss of speech were the most common presentations. Severe functional and cognitive impairment followed partial recovery of mobility in children. Elderly people had less dramatic presentations with a gradual decline of adaptive skills and stroke often co-occurring with Alzheimer's disease and epilepsy. Table 16 presents the clinical data of identified patients with stroke and suspected stroke.

Table 16. Subjects with stroke and suspected stroke: presentation and outcome, survey 2004.

Case	Gender	Age (years)	Recurrences	Hemiparesis	Speech loss	Outcome
1	female	2	no	yes	no	slow partial recovery
2	male	2.5	no	no	yes	autism, no speech
3	male	3.5	no	no	yes	autism, no speech
4	male	10	no	yes	no	slow recovery
5	male	11	no	yes	no	recovery
6	male	14	at 15	yes	yes	recovery of mobility, speech impairment
7	female	20	at 23, 36, 37, 48	bilateral	yes	severe motor and visual impairment
8	male	23	no	yes	unconscious	death within days
9	male	24	at 30	bilateral	no	partial recovery, no speech
10	male	35	no	no	yes	permanent loss of speech
11	male	37	at 37	bilateral	yes	severe motor and visual impairment
12	male	40	no	yes	no	autism, no speech, slow deterioration
13	female	47	no	yes	no	slow deterioration
14	female	47	no	facial	transient	quick recovery
15	female	47	no	suspected	no	slow deterioration
16	male	59	no	suspected	no	slow deterioration
17	female	59	no	transient	no	slow deterioration
18	male	61	no	suspected	no	slow deterioration
19	female	64	no	yes	yes	partial slow recovery
20	female	66	no	yes	no	slow deterioration

Medical problems of old age had been more frequent among the deceased than the living participants (Table17).

Table 17. Comparison of recorded medical problems in deceased and living people, survey 2011.

Medical problem	Alive n = 101 %	Deceased n = 37 %	Total %	Pearson Chi-Square (Asymp.Sig. 2-sided) Value	P
Neurological problems[a]	19.8	59.5	30.4	20.116	< 0.001
Alzheimer's disease	13.9	45.9	22.5	16.005	< 0.001
Seizures . epilepsy	12.9	35.1	18.8	8.778	0.003
Other brain disorders	8.9	29.7	14.5	9.471	0.002
Medical problems	6.9	16.2	9.4	10.066	0.007

[a]Neurological problems include seizures, epilepsy, brain infections, stroke and Alzheimer's disease

The age at death varied greatly, as shown in Figure 2. There was a trend of increasing overall age during the decades surveyed.

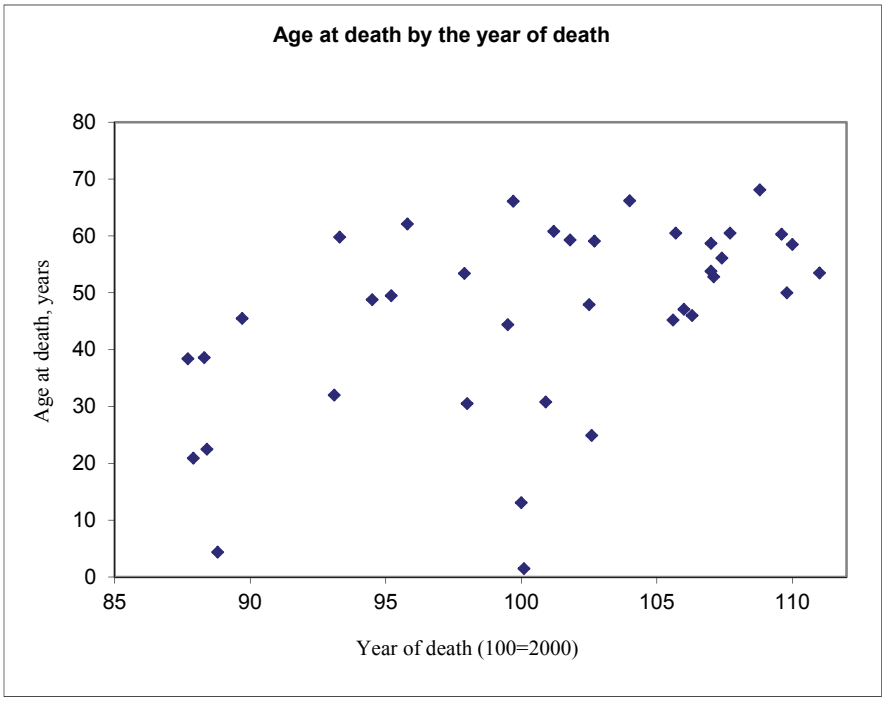

Fig. 2. Age at death by the year of death, survey 2011.

5.2 Intellectual disability

Intellectual disability had been assessed in 131 (95%) of all participants. Children and adolescents had a higher incidence of mild intellectual disability compared to adults. Most children and young adults had mild or moderate intellectual disability, while more than half of the older adults had severe or profound intellectual disability. 82% of people evaluated under the age of 20 years and 35% of those older than 20 years had mild or moderate intellectual disability (Table 18).

Table 18. Intellectual disability in different age groups, survey 2009.

Age	Number of	Intellectual disability (ID)							
years	individuals	Profound ID		Severe ID		Moderate ID		Mild ID	
		N	%	N	%	N	%	N	%
0–9	22	1	4.5	1	4.5	4	18.2	16	72.7
10–19	18	1	5.6	4	22.2	8	44.4	5	27.8
20–29	21	5	23.8	3	14.3	10	47.6	3	14.3
30–39	28	6	21.4	15	53.6	4	14.3	3	10.7
40–49	26	6	23.1	14	53.8	4	15.4	2	7.7
50–59	12	3	25.0	5	41.7	4	33.3	0	0
60+	4	1	25.0	1	25.0	2	50.0	0	0
Total	131	23	17.6	43	32.8	36	27.5	29	22.1

Participants with severe intellectual disability were compared to those with mild or moderate intellectual disability. They were significantly older and they had more age related medical problems (Table 19).

Table 19. Comparison of the group of individuals with severe intellectual disability to the group of individuals with mild/moderate intellectual disability, survey 2009.

Clinical data: age group, medical problem	Severe intellectual disability (n = 66) %	Mild/ Moderate intellectual disability (n = 65) %	Total (n = 131) %	Pearson Chi-Square (Asymp.Sig. 2-sided) Value	P
Age					
0–29	22.7	70.8	46.6		
30+	77.3	29.2	53.4	30.377	<0.001
Oral health					
1 good	43.9	87.7	65.6		
2 moderate	36.4	10.8	23.7		
3 poor	19.7	1.5	10.7	28.719	<0.001
Neurological problems	47.0	16.9	32.1	13.573	<0.001
Visual acuity					
1 good	12.1	27.7	19.8		
2 moderate	53.0	61.5	57.3		
3 severe visual impairment	34.8	10.8	22.9	12.706	0.002
Brain diseases	40.6	15.4	27.9	10.211	0.001
Other brain disorders	22.7	6.2	14.5	7.254	0.007
Alzheimer's disease	33.3	13.8	23.7	6.884	0.009
Seizures, epilepsy	27.3	12.3	19.8	4.610	0.032

Communication abilities, spoken language

Almost 80% of 115 participants evaluated after early childhood produced speech: single spoken words (35%) or at least short sentences (44%). Speech production was statistically significantly better in women compared to men ($p<0.05$).

Intellectual disability related to communication and health

The partial correlations controlling for age between intellectual disability, speech impairment, and medical problems were used to assess the effects of health impairments on intellectual disability. Significant correlations of intellectual disability were found with visual impairment, dental loss, and hearing impairment. Speech impairment correlated with intellectual disability, hearing impairment, epilepsy & stroke scores and dental loss (Table 20).

Table 20. Partial correlation coefficients between salient clinical data (controlling for age at last visit and birth year), survey 2004.

Medical problem	Intellectual disability	Speech impairment
Intellectual disability	1.000	0.702(**)
Speech impairment	0.702(**)	1.000
Visual impairment	0.328(**)	0.191(*)
Hearing impairment	0.171(*)	0.279(**)
Dental loss	0.252(**)	0.197(*)
Epilepsy & stroke	0.094	0.208(*)

** Correlation is significant at the 0.01 level (1-tailed).

* Correlation is significant at the 0.05 level (1-tailed).

5.3 Adaptive behaviour change

Assessments of adaptive behaviour using the Adaptive Behaviour Scale (ABS) were conducted repeatedly with 25 adults with DS (ABS follow-up group). These persons' proxies had noticed changes of mood, behaviour, or performance. An additional 15 participants had single ABS assessments.

The number of people with Down syndrome living in the area was well known and their morbidity data was available for comparison. The participants in the follow-up group with repeated ABS assessments were older than were the participants with single assessments. Dementia, medication use for challenging behaviour, depression, and epilepsy were more common in the follow-up group than among other adults with Down syndrome living in the region. Alzheimer's disease with dementia was diagnosed in 15 (60%) out of the 25 participants assessed repeatedly. Four of them died during the survey. Most (15/17, 88%) of the Down individuals with diagnosed or suspected dementia in the present population participated in this study and had repeated ABS assessments.

A decline of daily functioning was observed by informants regarding 19 of 25 persons between the ages of 37 and 51 years with a mean of 44.9 and SD +/− 4 years in persons with full trisomy of chromosome 21. The mean ABS total scores for the 25 participants with multiple assessments declined from 161 to 126 (21.8%) during the mean 3.0 years between the first and last assessments. The decline of ABS total scores associated very strongly to Alzheimer's disease: there was no decline in the mean ABS total scores in the group of participants with no suspected or confirmed Alzheimer's disease.

The mean rates of ABS score change were higher in participants with Alzheimer's disease (33.6% in three years), and depression (32.0%) compared to

participants without these conditions (0.6% and 13.9%, respectively). The mean rates of change were similar in participants with and without epilepsy, antipsychotic medication, and hypothyroidism.

The biggest mean declines were seen in the subscales Domestic Activity, Responsibility, and Self-Direction, 35.2, 48.8, and 49.7%, respectively. The mean changes of scores for the ABS factors Personal Self-Sufficiency, Community Self-Sufficiency, and Personal–Social Responsibility were 22.2, 27.9, and 36.8%, respectively.

5.4 Health care and surveillance

Most children with DS had regular health and developmental assessments. Comprehensive preventive health assessments of adults with DS were not organized and therefore seldom performed and recorded. Specialists assessed visual and hearing acuity infrequently compared to guideline recommendations. Dental care was the only preventive intervention that had been relatively regularly offered by health services to most adults with DS.

Oral health

Fifty percent of the present population had visited a dentist or oral hygienist during the last three years: 78% of the younger (<30 years) participants and 35% of the older (> 30 years) participants. Fifty percent of the younger participants and 19% of the older participants had visited during the last year. The oral health of the younger participants was satisfactory. Chronic periodontal infection was the main concern and cause of dental loss during adulthood. Corrective dental care was performed under general anaesthesia for 44 (32%) of the participants, whose fearfulness prevented the usual care.

Screening for hypothyroidism and search for celiac disease

Guidelines recommend thyroid tests every two years throughout life. Thyroid-stimulating hormone (TSH) determination had been performed for only 45 (54%) of the participants in the present population during the preceding five years. Hypothyroidism had been diagnosed in 33 (24%) of the cases: it was more common in older (33%) than younger (8%) participants. Laboratory examinations to detect celiac disease were recommended when even the slightest suspicion

arose. Celiac disease had been diagnosed in three (4%) of the participants, and screening tests had been performed for 16 (19%) of the participants in the present population. Significantly, more participants in the present and older subgroups had participated in screenings for hypothyroidism and celiac disease than in the deceased or relocated, and young subgroups.

6 Discussion

The present study surveyed medical problems and mental health in an unselected population-based series of people with DS. The severity of intellectual disability related to age and recorded medical problems. A large variety of medical problems and behavioural symptoms were common in this population. Adequate health care is needed to improve health and well-being of individuals with DS.

6.1 Discussion of results

Numerous medical problems were recorded in this population. Individual differences in health and disability were obvious. The degree of intellectual disability related to visual and neurological impairments. Depression and, among participants in their forties and older, Alzheimer's dementia were the most common underlying reasons for changes in adaptive behaviour. A gradual functional decline and dementia affected many participants at a relatively early age.

6.1.1 Medical problems

People with DS had high risks for heart defects, visual impairment, hearing loss, depression, infections, hypothyroidism, epilepsy, and Alzheimer's disease. The spectrum and frequencies of recorded health concerns and medical problems were very similar to those described in the literature (Murphy *et al.* 2005, Henderson *et al.* 2007, Coppus *et al.* 2007, Yam *et al.* 2008, Kerins *et al.* 2008, Schieve *et al.* 2009, Torr *et al.* 2010). However, morbidity rates not addressed in the earlier literature for fainting and stroke were high. Health problems were extensive from birth to old age. Many of the health concerns were age-related. Dementia affected many participants at a relatively early age. Epilepsy was common among the oldest participants, too.

The data available in the social and medical records varied greatly. The number of recorded medical problems varied to a great degree between participants. The individual differences in medical problems and health service needs were obvious during the survey of the medical records. The weight of medical records of participants in specialized health care was extremely variable in all age groups.

The most extensive recorded data were found among young adults. Heart defects of young participants had been addressed surgically, when necessary. Heart surgery has been available for less than 40 years. Surgical treatments performed for other indications were extensively offered for the participants, too. The health needs of young participants were perhaps more adequately met during the last four decades due to the developed operative treatments for heart defects and many other severe medical problems. This may also reflect a better availability of specialized medical services in the region for the last 40 years since the building of the Central Hospital of Kainuu in 1969.

The relatively modest amount of records for older participants in specialized health services may reflect the more stable health of these people, a naturally selected group of healthy survivors. Older people with DS are definitely a selected group, with few survivors among those with severe congenital heart defects (Baird & Sadovnick 1987, Hijii *et al.* 1997). The primary health care services were able to meet most health needs of adults and elderly participants and specialized health care was not very often needed by them.

Stroke was recorded mainly in the records of deceased participants suggesting poor prognosis. No published population-based epidemiological studies of stroke in people with DS were available. The pathogenesis of stroke in Down syndrome is different from that in the general population. Hypertension and atherosclerotic vascular disease are rare (Vis *et al.* 2009) but amyloid depositions in the arteries of the brain are common in DS (Wisniewsky *et al.* 1985, Jea *et al.* 2005).

Some health needs may not have been identified in the local population. Searches for sleep disorders of young children and osteoporosis were noticeably lacking, and consequently, these were seldom recorded. Hearing loss among older participants was also quite seldom investigated and not often identified. The high frequency of fainting in the local population was a new finding. Possible explanations include low blood pressure and undetected heart defects, which are common in older people with DS (Vis *et al.* 2010). Some epileptic seizures may have been falsely interpreted as fainting. However, the recorded frequency of epilepsy was comparable to that reported in earlier research.

Behavioural changes or loss of function may be the only indications of medical illnesses. Presently, people with DS live longer, and therefore, are becoming prone to health problems and diseases of old age. A careful evaluation of the life situations and comprehensive assessments of physical and mental health are necessary when carers describe a decline in everyday functioning – a

difficulty in accomplishing daily tasks, which the individual would normally complete with ease (Ball *et al.* 2006). This is also needed in care for the elderly with established Alzheimer's disease because of common co-morbidities (McCarron *et al.* 2005, Torr *et al.* 2010). In the case of a rapid deterioration of function, the underlying reasons should be assessed.

Mental health, behaviour

Diagnostic challenges were evident for behavioural and mental health problems. Many participants could not express depression or anxiety verbally. Sometimes panic symptoms were first erroneously assessed as epileptic symptoms. Although mental health and behavioural problems were common, most participants did not have major mental illnesses or serious behavioural issues.

Depression was the most common mental health problem seen in young adults in the present study, as it has also been in earlier studies (Myers & Pueschel 1991, Collacott *et al.* 1992). Depression had been recognised mainly in people with mild to moderate intellectual disabilities. This may be explained by the difficulty to diagnose mental health problems, including depression, in participants with severe to profound intellectual disabilities.

Many researchers have discussed the possible link between depression and Alzheimer's disease (Burt *et al.* 1992, 1998, Nelson *et al.* 2001, Urv *et al.* 2008 2010). Depression and Alzheimer's disease are common in people with DS and the symptoms overlap. Antidepressants and cholinesterase inhibitors are safe and well tolerated and may be considered even when the diagnosis of depression or Alzheimer's disease is only suspected. Management of behavioural and mental health problems is beneficial not only to the individual served, but also to the family's and carers' well-being.

6.1.2 Intellectual disability

A wide range in the degree of intellectual disability from severe to mild was seen among children and adults. Cognitive functions, learning, and adaptive behaviour were variably affected in all participants. Advancing age was associated with more severe intellectual disability. The degree of intellectual disability was sometimes estimated only during adulthood, when ageing may already have affected the person's abilities.

Recent studies have reported increasing inter-individual variability and early stagnation of cognitive development (Dykens 2006, Tsao *et al.* 2009) and the development of adaptive skills (van Duijn *et al.* 2010) in children with DS. The increasing variance in adaptive behaviour begins at approximately six or seven years (Dykens *et al.* 2006) and a ceiling of adaptive skills appears by about twelve years (van Duijn *et al.* 2010). Tsao & Kindelberger (2009) identified four common cognitive profiles in children with Down syndrome based on their relative strengths in verbal and nonverbal abilities. The present study supports the earlier findings of wide variability in the degree of language difficulties, cognitive impairment, and skills among individuals with Down syndrome.

The severity of intellectual disability correlated with difficulty in verbal communication. Higher levels of cognitive abilities associated with more developed speech production. Females showed milder degrees of intellectual disability, more developed speech, and less challenging behaviour compared to males. People with mild to moderate intellectual disability and better speech are often able to express their feelings verbally, which may be helpful to behavioural adaptation, and thus, decrease maladaptive aggressive behaviour.

Research has provided limited evidence of hearing loss affecting cognitive functions in people with DS (Harigai 1994, Laws 2004, Lott & Dierssen 2010). The difficulty to administer accurate hearing assessments has resulted in insufficient recorded data for an assessment of the possible contribution of hearing loss to the degree of intellectual disability. However, this study detected associations between the score of hearing problems/ear disease, and speech problems, thus supporting the importance of early detection and treatment of hearing loss. Middle ear infections were common at a young age when language learning is still ongoing. The treatment policy for middle ear infections was active. However, regular assessments of hearing acuity in adults and aging individuals, as recommended in the guidelines, had not been implemented.

Memory impairment is a common finding in people with DS; it has even been regarded as an aspect of the behavioural phenotype of DS (Chapman & Hasketh 2001). The impairment of auditory short-term memory is thought to contribute to difficulties in language acquisition, speech, and cognition even more than to hearing impairment (Jarrold *et al.* 2002). Observations of memory impairment in children with DS had been repeatedly recorded systematically in the surveyed records in recent years only. The contribution of memory impairment to the level of intellectual disability, language, and adaptive behaviour was not assessed in the present study. Only recently Edgin *et al.* (2010) found a

relation between verbal immediate memory and intelligence quotient, and a relation between spatial associative memory and adaptive behaviour in adolescents and young adults with DS.

Visual impairment was more common in people with severe to profound intellectual disability than in those with mild to moderate intellectual disability. This supports the findings reported earlier (van Schrojenstein Lantman-de Valk *et al.* 1994, Evenhuis *et al.* 2001) and suggests a contribution of poor vision to cognitive impairment. The present study confirms the association between visual impairment and the degree of intellectual disability, as shown in Tables 19 and 20. Evenhuis et al (2009) found a similar association between visual impairment and intellectual disability among adults with intellectual disabilities. Furthermore, they report a widespread impairment of daily living skills, communication, and language associated with visual impairment. However, intellectual disability was the most important determinant of adaptive behaviour in adults with intellectual disabilities. Visual impairment did not associate with any apparent emotional or behavioural problems and had often remained undetected.

Neurological problems were more common among those with severe in comparison to mild/moderate intellectual disability, and affected almost half of participants with severe intellectual disability. Seizures and epilepsy, specifically infantile spasms, may potentially affect development in children with DS (Goldberg-Stern *et al.* 2001, Aisermann *et al.* 2003). Stroke in young people associated with poor cognitive outcomes, suggesting that stroke may contribute to cognitive impairment in individuals with DS. These findings are easy to understand because the crucial importance of brain functions to cognitive and adaptive behaviour has been well established by earlier research (Lott & Dierssen 2010).

The association between oral health and intellectual abilities found in the present study has many possible explanations. Dental loss was associated with older age, and hence, with a more severe degree of intellectual disability. However, the association remained when the age effects were controlled, as shown in Table 20. Periodontal disease, a chronic infection, is the main cause of dental loss in individuals with DS. Thus, the possibility of a common immunological background to chronic periodontal infection and poor cognitive development may be hypothesized. DS affects immune functions and increases the risk to bacterial and viral infections and autoimmune diseases (Kusters *et al.* 2009, Bloemers *et al.* 2010). However, the implications of immune functions to brain development have not been established. Adults with intellectual disability

and poor ability to co-operate with dental treatment and those with DS have an increased risk for impaired oral health (Gabre *et al.* 2001).

6.1.3 Adaptive behaviour, ageing

A long-term prospective follow-up of adults with DS, suspected or confirmed dementia, and description of the change in their adaptive behaviour was reported. The participants were adults with DS and behavioural changes were perceived by carers. Depression and, among participants in their forties and older, Alzheimer's dementia were the most common underlying reasons for the behavioural change. Most people with DS and diagnosed Alzheimer's dementia in this population were identified and participated in the follow-up of adaptive behaviour.

A change of behaviour or adjustment had been noticed by their proxies before the diagnosis of Alzheimer's dementia. A decline in ABS scores was also seen in most participants after their early forties. This supported the suspicion of Alzheimer's disease, led to differential diagnostic assessments, and helped in monitoring the progression of the disease. Age-related decline in adaptive behaviour has been established in adults with DS (Rasmussen & Sobsey 1994, Prasher *et al.* 1998). The clinical use of ABS to monitor aging and dementia from the early, non-symptomatic phase to the advanced stages at various levels of abilities proved to be possible and helpful for the clinician. Repeated prospective assessments overcame memory errors compared to retrospective evaluations. The possibility of performing an assessment in various settings without special professional expertise is a benefit of this approach.

The decline of the ABS total scores associated strongly to Alzheimer's disease; therefore, the described declines in the ABS subscale scores probably reflect changes attributable to Alzheimer's disease as well. The speed of change was higher in Domestic Activity, Responsibility, Self-Direction, and Vocational Activity subscale scores, as compared to other domains of adaptive behaviour. This may reflect the early impairment of frontal lobe functions among people with DS (Holland *et al.* 2000), including executive dysfunction in the development of Alzheimer's disease (Ball *et al.* 2008).

Individual differences of the functional skills assessed by ABS scores were considerable. Decline of skills with aging started at very different ages among participants in this study. A considerable proportion of people with DS do not develop clinical dementia at all (Coppus *et al.* 2006). People with DS differ in their risk of dementia (Zigman & Lott 2007, Prasher *et al.* 2008, Patel *et al.*

2008). There is a need to gain a better understanding of the genetic and environmental influences associated with individual age-related differences among people with DS. Recent research has identified genetic mechanisms modifying the individual risk of early dementia in DS (Margallo-Lana *et al.* 2004, Lee *et al.* 2007, Jones *et al.* 2008, Prasher *et al.* 2008, Schupf *et al.* 2008, Patel *et al.* 2010).

Improvements in adaptive behaviour were seen in some participants during the treatment of Alzheimer's disease and co-morbidities. Repeated assessments of adaptive behaviour and careful clinical evaluations are suggested to detect early dementia in adults with DS. An active treatment of Alzheimer's disease and co-morbidities may benefit many people with DS.

6.1.4 Health surveillance

Everyone residing in Finland is entitled to receive good quality public health care within set timeframes. A complete paediatric evaluation is performed for all children born with DS after birth. The child welfare clinics and disability services provide developmental assessments to all people with DS from early childhood to adulthood. However, there is no systematic follow-up program after the neonatal period in the specialized health care for these children.

The Finnish guideline's (Kaski *et al.* 2005) recommendations to screen for specific health concerns in DS were not strictly followed. Health surveillance remained insufficient. The present study found no evidence that the health care guidelines have been followed during the last five years, since the guidelines were implemented. Specialists did not regularly assess the visual and hearing acuity of adults and aging people of this population in the public services. Probably not all persons with hearing impairment could be identified. A reliable evaluation of hearing had been performed and recorded for a minority of people in this population. The perceived lack of compliance was addressed in the update on the Finnish Current Care guideline "Appropriate treatment of medical problems associated with Down syndrome" (Kaski *et al.* 2011).

The guidelines were available to health care professionals, but not used for organising services. The attitudes of Finnish healthcare professionals towards clinical care guidelines are positive and about half of professionals indicated intentions to use guidelines in clinical decision making (Kortteisto *et al.* 2010). The main reasons for infrequent health surveillance of the persons with DS might

be that the need for such surveillance was not recognised by the patients, their proxies, or the professionals. The clients, their proxies, and the service providers were perhaps not aware of the recommendations to participate in regular health screening. Special services for people with intellectual disabilities are provided. However, health and social service providers use separate case records and registers. Even within specialized health care, somatic and mental health services have their own case records. Therefore, the health and social professionals may have a limited knowledge of the medical problems and treatments of a person with DS. Shared patient records for health (primary, specialized, physical, and mental health) and disability services (local and regional) could improve the coordination of services.

Visual acuity and hearing should be regularly monitored in all adults with DS because of the high prevalence of visual impairment (van Splunder *et al.* 2006) and hearing loss (Meuwese-Jongejeugd *et al.* 2006, Meuwese-Jongejeugd *et al.* 2008) and the high tendency of these impairments to remain unrecognised (Evenhuis *et al.* 2001). The more severe the degree of intellectual disability in people with DS is the more probable sensory and neurological impairments are. Visual impairment and neurological impairments seem to affect cognitive functions and adaptive behaviour adversely and increase the degree of intellectual disability (Evenhuis *et al.* 2009, Lott & Dierssen 2010).

Low adherence to national health care guidelines for people with DS has been recently reported in several other studies (Virji-Babul *et al.* 2007, Fergeson *et al.* 2009, Wechsler *et al.* 2009, Creavin & Brown 2010). The tendency for hearing loss and visual impairment to go unnoticed in people with intellectual disabilities is considerable (Evenhuis *et al.* 2001, Splunder *et al.* 2001). Henderson *et al.* (2007) assessed current practice regarding medical surveillance in adults with DS in England. Data were obtained from the primary care records. Complications such as hypothyroidism, celiac disease, and obesity occurred frequently but surveillance was infrequent. In this study, 33% had not had a medical assessment in the previous 3 years. Wechsler *et al.* (2009) assessed the adequacy of medical surveillance of individuals with DS in Israel. The caregivers of 150 individuals were interviewed and the medical records were reviewed. Only 42.7% and 63.3% had been tested for auditory or visual acuity, respectively, and 39.3% of the study population had documented auditory deficits while the reported prevalence is 75%.

An active provision of health care and monitoring for this vulnerable group is needed. The possibilities to enhance health, learning, and adaptation have not

been optimally implemented so far. Therefore, further efforts are needed to diagnose and treat medical problems in people with DS. Better identification of the health needs of this population, to avoid preventable and treatable disabilities and to optimise their cognitive and functional performance is possible.

A meeting entitled "Setting a Public Health Research Agenda for DS" identified the following as priority areas for future public health research: identification of risk and preventive factors for physical health and cognitive outcomes, improved understanding of comorbid conditions, identification of mental health comorbidities and of the risk and protective factors for their development, development of strategies for conveying up-to-date information to parents and health professionals, identification of interventions to improve cognition, language, mental health, and behaviour, understanding the impact of educational and social services and supports, and identification of improved methods for diagnosis of and interventions for Alzheimer disease (Rasmussen *et al.* 2008).

Increasing knowledge and understanding will most certainly benefit many people with DS in the near future. The research on DS is active and published literature is abundant. Therefore, published data on numerous specific health concerns is available. The basic research has rapidly increased the understanding of genetic, developmental, and functional aspects during recent years. It is already possible to identify people with increased risk for celiac disease and early dementia among people with DS. Medical interventions to enhance cognitive development in DS are being investigated and may be available relatively soon.

6.2 Methodological considerations

Case records were used as a source of information to survey health concerns and medical problems. The recorded data was abundant, original, and informative but it had not initially been recorded for research purposes. Therefore, the available data was variable and unsystematic. It was hard to extract any data for quantitative analysis beyond birth and visit dates and the weight or hard copies of medical records. Perhaps the recorded data would have been more suitable for qualitative description and analysis than for attempts to extract numeric information. However, frequencies of the most common medical problems experienced by participants were available. A national register study could perhaps give more powerful quantitative data of the major recorded health problems and use of health and disability services.

A description of naturally accumulated clinical case record data was chosen to describe the health of participants. A formal cross-sectional survey or organized prospective follow-up study could have had advantages and would have complemented the recorded data. No formal systematic health assessments or interventions were arranged for this study. Many participants were familiar to the researcher through personal clinical contacts. Perhaps a continuous long-term service contact with many of the participants and caregivers compensated to some degree for the lack of an organised survey.

6.2.1 Validity

The public health services are accessible to all citizens and most participants of this study used these services. Thus, the diseases identified and recorded in the analysed case records reflect identified medical problems and interventions undertaken. Detected health problems and interventions had been carefully recorded in the case records. Observations of the proxies, symptoms and signs, laboratory and other examinations, diagnoses, treatments including medications, diets, and surgical interventions were recorded in detail.

Inclusion of people who had died or had moved out of the area to the analysis of age-related health concerns and combining data of these different groups was problematic to the interpretation of results. People who had died had more health problems, while the same was not true for people who had moved away. The data of persons who moved from the region were analysed for the time they lived in the region and in the local registers only. To overcome some of the difficulties of interpretation, health data was presented for each of the subgroups.

The differences in the morbidity, health care, and health surveillance between the subgroups were used to describe recent changes of health services, because there was a ten-year mean difference between the subgroups in the time since the last recorded data. However, the differences in the availability of data and the morbidities of the deceased participants in the past subgroup may have contributed to the perceived group differences.

6.2.2 Reliability

All people with DS identified in the Intellectual Disability Service Register in the Kainuu region were included to avoid selection bias. The health and disability case records in the public services were analysed. Data for the majority of life

spans could be surveyed using the original paper records of the disability and specialized health care archives. A second survey of case records was performed on line five years later for the preceding five years. A third update was performed two years later to update the demographic data.

The researcher surveyed all the recorded data. The survey of the records was repeated by the same person to update current health information and to enhance the reliability of the study.

Stable scores in clinically stable participants between repeated evaluations supported the reliability of ABS, when used by proxy informants. The informants with a close and long familiarity to their proxies observed and reported subtle changes in daily life and completed adaptive behaviour questionnaires without obvious difficulty.

6.2.3 Limitations

The paper describes only those health concerns reported in health and disability records, not necessarily all those relevant to people with DS. The data that was not reviewed or recorded may have been just as important. The findings reflect local clinical services and do not necessarily generalise to other populations and service arrangements.

The recorded data relates to clinical and social service needs experienced by the participants, their proxies, and professionals. Therefore, actual health status was not uniformly recorded in the case records. Health behaviour, exercise, nutrition, weight indexes, and physical fitness were not uniformly assessed and recorded in a way to allow inclusion in the analysis.

Family and social situations and supports were variably recorded and were not analysed. Important health determinants thus remained largely unknown. Mental health and behaviour were assessed based on recorded descriptive data only. Direct evaluations of cognitive functions were not possible in this study due to the limited neuropsychological resources available.

Data on health services provided to this population by private specialists, including private ophthalmologists, were not available for the study. Thus, the extent of consultations with private ophthalmologists and assessments by optometrists for glass correction of refractive errors remained unknown.

6.3 Conclusions

1. Medical problems are frequently observed and recorded among people with DS. Many medical problems of elderly people in the general population affect people with DS at an earlier age.
2. Individual differences in cognitive abilities are evident in childhood. Visual impairment and neurological problems associate to severe intellectual disability.
3. Aging affects individuals with DS differently. The decline of adaptive behaviour starts at different ages and many do not have signs of early decline at all.
4. Regular health assessments, as recommended in the Finnish Current Care guidelines for health surveillance of people with DS, need to be organised and implemented.

References

American Academy of Pediatrics. Committee on Genetics (2001) American Academy of Pediatrics: Health supervision for children with Down syndrome. Pediatrics 107(2): 442–449.

Baird PA & Sadovnick AD (1987) Life expectancy in Down syndrome. J Pediatr 110(6): 849–854.

Ball SL, Holland AJ, Hon J, Huppert FA, Treppner P & Watson PC (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. Int J Geriatr Psychiatry 21(7): 661–673.

Ball SL, Holland AJ, Huppert FA, Treppner P, Watson P & Hon J (2004) The modified CAMDEX informant interview is a valid and reliable tool for use in the diagnosis of dementia in adults with Down's syndrome. J Intellect Disabil Res 48(Pt 6): 611–620.

Ball SL, Holland AJ, Treppner P, Watson PC & Huppert FA (2008) Executive dysfunction and its association with personality and behaviour changes in the development of Alzheimer's disease in adults with Down syndrome and mild to moderate learning disabilities. Br J Clin Psychol 47(Pt 1): 1–29.

Ball SL, Holland AJ, Watson PC & Huppert FA (2010) Theoretical exploration of the neural bases of behavioural disinhibition, apathy and executive dysfunction in preclinical Alzheimer's disease in people with Down's syndrome: potential involvement of multiple frontal-subcortical neuronal circuits. J Intellect Disabil Res 54(4): 320–336.

Berger-Sweeney J (1998) The effects of neonatal basal forebrain lesions on cognition: towards understanding the developmental role of the cholinergic basal forebrain. Int J Dev Neurosci 16(7–8): 603–612.

Bertoli M, Biasini G, Calignano MT, Celani G, De Grossi G, Digilio MC, Fermariello CC, Loffredo G, Luchino F, Marchese A, Mazotti S, Menghi B, Razzano C, Tiano C, Zambon Hobart A, Zampino G & Zuccala G (2011) Needs and challenges of daily life for people with Down syndrome residing in the city of Rome, Italy. J Intellect Disabil Res 55(8): 801–820.

Besser LM, Shin M, Kucik JE & Correa A (2007) Prevalence of down syndrome among children and adolescents in metropolitan Atlanta. Birth Defects Res A Clin Mol Teratol 79(11): 765–774.

Bhaumik S, Collacott RA, Garrick P & Mitchell C (1991) Effect of thyroid stimulating hormone on adaptive behaviour in Down's syndrome. J Ment Defic Res 35 (Pt 6)(Pt 6): 512–520.

Bianchi P, Ciani E, Guidi S, Trazzi S, Felice D, Grossi G, Fernandez M, Giuliani A, Calza L & Bartesaghi R (2010) Early pharmacotherapy restores neurogenesis and cognitive performance in the Ts65Dn mouse model for Down syndrome. J Neurosci 30(26): 8769–8779.

Bittles AH, Bower C, Hussain R & Glasson EJ (2007) The four ages of Down syndrome. Eur J Public Health 17(2): 221–225.

Blehaut H, Mircher C, Ravel A, Conte M, de Portzamparc V, Poret G, de Kermadec FH, Rethore MO & Sturtz FG (2010) Effect of leucovorin (folinic acid) on the developmental quotient of children with Down's syndrome (trisomy 21) and influence of thyroid status. PLoS One 5(1): e8394.

Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ, van den Ende K, Kimpen JL, Strengers JL & Bont LJ (2007) Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis–a prospective birth-cohort study. Pediatrics 120(4): e1076–81.

Bloemers BL, Broers CJ, Bont L, Weijerman ME, Gemke RJ & van Furth AM (2010) Increased risk of respiratory tract infections in children with Down syndrome: the consequence of an altered immune system. Microbes Infect 12(11): 799–808.

Boechat MC, Silva KS, Llerena JC,Jr & Boechat PR (2007) Cholelithiasis and biliary sludge in Downs syndrome patients. Sao Paulo Med J 125(6): 329–332.

Bonamico M, Mariani P, Danesi HM, Crisogianni M, Failla P, Gemme G, Quartino AR, Giannotti A, Castro M, Balli F, Lecora M, Andria G, Guariso G, Gabrielli O, Catassi C, Lazzari R, Balocco NA, De Virgiliis S, Culasso F, Romano C & SIGEP (Italian Society of Pediatric Gastroenterology and Hepatology) and Medical Genetic Group (2001) Prevalence and clinical picture of celiac disease in italian down syndrome patients: a multicenter study. J Pediatr Gastroenterol Nutr 33(2): 139–143.

Boulet SL, Molinari NA, Grosse SD, Honein MA & Correa-Villasenor A (2008) Health care expenditures for infants and young children with Down syndrome in a privately insured population. J Pediatr 153(2): 241–246.

Boyd PA, Devigan C, Khoshnood B, Loane M, Garne E, Dolk H & EUROCAT Working Group (2008) Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG 115(6): 689–696.

Brugge KL, Nichols SL, Salmon DP, Hill LR, Delis DC, Aaron L & Trauner DA (1994) Cognitive impairment in adults with Down's syndrome: similarities to early cognitive changes in Alzheimer's disease. Neurology 44(2): 232–238.

Bruijn M, van der Aa LB, van Rijn RR, Bos AP & van Woensel JB (2007) High incidence of acute lung injury in children with Down syndrome. Intensive Care Med 33(12): 2179–2182.

Buchanan LH (1990) Early onset of presbyacusis in Down syndrome. Scand Audiol 19(2): 103–110.

Bull MJ & Committee on Genetics (2011) Health supervision for children with Down syndrome. Pediatrics 128(2): 393–406.

Buntinx WH & Schalock (2010) Models of Disability, Quality of Life, and Individualized Supports: Implications for Professional Practice in Intellectual Disability. J Policy Practice Intellect Disabil 7(4): 283–294.

Burt DB, Loveland KA & Lewis KR (1992) Depression and the onset of dementia in adults with mental retardation. Am J Ment Retard 96(5): 502–511.

Burt DB, Loveland KA, Primeaux-Hart S, Chen YW, Phillips NB, Cleveland LA, Lewis KR, Lesser J & Cummings E (1998) Dementia in adults with Down syndrome: diagnostic challenges. Am J Ment Retard 103(2): 130–145.

Carlsson A, Axelsson I, Borulf S, Bredberg A, Forslund M, Lindberg B, Sjoberg K & Ivarsson SA (1998) Prevalence of IgA-antigliadin antibodies and IgA-antiendomysium antibodies related to celiac disease in children with Down syndrome. Pediatrics 101(2): 272–275.

Carnicer J, Farre C, Varea V, Vilar P, Moreno J & Artigas J (2001) Prevalence of coeliac disease in Down's syndrome. Eur J Gastroenterol Hepatol 13(3): 263–267.

Carr J (2005) Stability and change in cognitive ability over the life span: a comparison of populations with and without Down's syndrome. J Intellect Disabil Res 49(Pt 12): 915–928.

Carr J (2008) The everyday life of adults with Down syndrome. J Applied Res Intellect Disabil 21:389–397.

Carroll KN, Arbogast PG, Dudley JA & Cooper WO (2008) Increase in incidence of medically treated thyroid disease in children with Down Syndrome after rerelease of American Academy of Pediatrics Health Supervision guidelines. Pediatrics 122(2): e493–8.

Carter M, McCaughey E, Annaz D & Hill CM (2009) Sleep problems in a Down syndrome population. Arch Dis Child 94(4): 308–310.

Castane M, Boada-Rovira M & Hernandez-Ruiz I (2004) Eye conditions as features of Down's syndrome in patients over 40 years of age. Rev Neurol 39(11): 1017–1021.

Cerqueira RM, Rocha CM, Fernandes CD & Correia MR (2010) Celiac disease in Portuguese children and adults with Down syndrome. Eur J Gastroenterol Hepatol 22(7): 868–871.

Chapman RS & Hesketh LJ (2000) Behavioral phenotype of individuals with Down syndrome. Ment Retard Dev Disabil Res Rev 6(2): 84–95.

Chaushu S, Chaushu G, Zigmond M, Yefenof E, Stabholz A, Shapira J, Merrick J & Bachrach G (2007) Age-dependent deficiency in saliva and salivary antibodies secretion in Down's syndrome. Arch Oral Biol 52(11): 1088–1096.

Collacott RA (1992) The effect of age and residential placement on adaptive behaviour of adults with Down's syndrome. Br J Psychiatry 161: 675–679.

Collacott RA (1993) Epilepsy, dementia and adaptive behaviour in Down's syndrome. J Intellect Disabil Res 37 (Pt 2)(Pt 2): 153–160.

Collacott RA, Cooper SA, Branford D & McGrother C (1998) Behaviour phenotype for Down's syndrome. Br J Psychiatry 172: 85–89.

Collacott RA, Cooper SA & McGrother C (1992) Differential rates of psychiatric disorders in adults with Down's syndrome compared with other mentally handicapped adults. Br J Psychiatry 161: 671–674.

Collins VR, Muggli EE, Riley M, Palma S & Halliday JL (2008) Is Down syndrome a disappearing birth defect? J Pediatr 152(1): 20–4, 24.e1.

Cooper SA, Morrison J, Melville C, Finlayson J, Allan L, Martin G & Robinson N (2006) Improving the health of people with intellectual disabilities: outcomes of a health screening programme after 1 year. J Intellect Disabil Res 50(Pt 9): 667–677.

Cooper SA & Prasher VP (1998) Maladaptive behaviours and symptoms of dementia in adults with Down's syndrome compared with adults with intellectual disability of other aetiologies. J Intellect Disabil Res 42 (Pt 4)(Pt 4): 293–300.

Cooper SA, Smiley E, Jackson A, Finlayson J, Allan L, Mantry D & Morrison J (2009) Adults with intellectual disabilities: prevalence, incidence and remission of aggressive behaviour and related factors. J Intellect Disabil Res 53(3): 217–232.

Coppus A, Evenhuis H, Verberne GJ, Visser F, van Gool P, Eikelenboom P & van Duijin C (2006) Dementia and mortality in persons with Down's syndrome. J Intellect Disabil Res 50(Pt 10): 768–777.

Coppus AM, Evenhuis HM, Verberne GJ, Visser FE, Eikelenboom P, van Gool WA, Janssens AC & van Duijn CM (2010) Early age at menopause is associated with increased risk of dementia and mortality in women with Down syndrome. J Alzheimers Dis 19(2): 545–550.

Coppus AM, Evenhuis HM, Verberne GJ, Visser FE, Oostra BA, Eikelenboom P, van Gool WA, Janssens AC & van Duijn CM (2008) Survival in elderly persons with Down syndrome. J Am Geriatr Soc 56(12): 2311–2316.

Cosgrave MP, Tyrrell J, McCarron M, Gill M & Lawlor BA (1999) Determinants of aggression, and adaptive and maladaptive behaviour in older people with Down's syndrome with and without dementia. J Intellect Disabil Res 43 (Pt 5)(Pt 5): 393–399.

Creavin AL & Brown RD (2009) Ophthalmic abnormalities in children with Down syndrome. J Pediatr Ophthalmol Strabismus 46(2): 76–82.

Creavin AL & Brown RD (2010) Ophthalmic assessment of children with Down syndrome: is England doing its bit? Strabismus 18(4): 142–145.

Cregg M, Woodhouse JM, Pakeman VH, Saunders KJ, Gunter HL, Parker M, Fraser WI & Sastry P (2001) Accommodation and refractive error in children with Down syndrome: cross-sectional and longitudinal studies. Invest Ophthalmol Vis Sci 42(1): 55–63.

Davidson MA (2008) Primary care for children and adolescents with Down syndrome. Pediatr Clin North Am 55(5): 1099–111, xi.

Day SM, Strauss DJ, Shavelle RM & Reynolds RJ (2005) Mortality and causes of death in persons with Down syndrome in California. Dev Med Child Neurol 47(3): 171–176.

Deb S & Braganza J (1999) Comparison of rating scales for the diagnosis of dementia in adults with Down's syndrome. J Intellect Disabil Res 43 (Pt 5)(Pt 5): 400–407.

Dodge-Khatami A, Herger S, Rousson V, Comber M, Knirsch W, Bauersfeld U & Pretre R (2008) Outcomes and reoperations after total correction of complete atrio-ventricular septal defect. Eur J Cardiothorac Surg 34(4): 745–750.

Dressler A, Perelli V, Feucht M & Bargagna S (2010) Adaptive behaviour in Down syndrome: a cross-sectional study from childhood to adulthood. Wien Klin Wochenschr 122(23–24): 673–680.

Dykens EM (2007) Psychiatric and behavioral disorders in persons with Down syndrome. Ment Retard Dev Disabil Res Rev 13(3): 272–278.

Dykens EM, Hodapp RM & Evans DW (2006) Profiles and development of adaptive behavior in children with Down syndrome. Downs Syndr Res Pract 9(3): 45–50.

Dykens EM, Shah B, Sagun J, Beck T & King BH (2002) Maladaptive behaviour in children and adolescents with Down's syndrome. J Intellect Disabil Res 46(Pt 6): 484–492.

Edgin JO, Pennington BF & Mervis CB (2010) Neuropsychological components of intellectual disability: the contributions of immediate, working, and associative memory. J Intellect Disabil Res 54(5): 406–407.

Eisermann MM, DeLaRaillere A, Dellatolas G, Tozzi E, Nabbout R, Dulac O & Chiron C (2003) Infantile spasms in Down syndrome–effects of delayed anticonvulsive treatment. Epilepsy Res 55(1–2): 21–27.

Ellis JM, Tan HK, Gilbert RE, Muller DP, Henley W, Moy R, Pumphrey R, Ani C, Davies S, Edwards V, Green H, Salt A & Logan S (2008) Supplementation with antioxidants and folinic acid for children with Down's syndrome: randomised controlled trial. BMJ 336(7644): 594–597.

Evans DW & Gray FL (2000) Compulsive-like behavior in individuals with Down syndrome: its relation to mental age level, adaptive and maladaptive behavior. Child Dev 71(2): 288–300.

Evenhuis H, van Splunder J, Vink M, Weerdenburg C, van Zanten B & Stilma J (2004) Obstacles in large-scale epidemiological assessment of sensory impairments in a Dutch population with intellectual disabilities. J Intellect Disabil Res 48(Pt 8): 708–718.

Evenhuis HM, Sjoukes L, Koot HM & Kooijman AC (2009) Does visual impairment lead to additional disability in adults with intellectual disabilities? J Intellect Disabil Res 53(1): 19–28.

Evenhuis HM, Theunissen M, Denkers I, Verschuure H & Kemme H (2001) Prevalence of visual and hearing impairment in a Dutch institutionalized population with intellectual disability. J Intellect Disabil Res 45(Pt 5): 457–464.

Fergeson MA, Mulvihill JJ, Schaefer GB, Dehaai KA, Piatt J, Combs K, Bright BC & Neas BR (2009) Low adherence to national guidelines for thyroid screening in Down syndrome. Genet Med 11(7): 548–551.

Fillat C, Dierssen M, de Lagran MM & Altafaj X (2010) Insights from mouse models to understand neurodegeneration in Down syndrome. CNS Neurol Disord Drug Targets 9(4): 429–438.

Fimiani F, Iovine A, Carelli R, Pansini M, Sebastio G & Magli A (2007) Incidence of ocular pathologies in Italian children with Down syndrome. Eur J Ophthalmol 17(5): 817–822.

Fitzgerald DA, Paul A & Richmond C (2007) Severity of obstructive apnoea in children with Down syndrome who snore. Arch Dis Child 92(5): 423–425.

Franceschi M, Comola M, Piattoni F, Gualandri W & Canal N (1990) Prevalence of dementia in adult patients with trisomy 21. Am J Med Genet Suppl 7: 306–308.

Gabre P, Martinsson T & Gahnberg L (2001) Longitudinal study of dental caries, tooth mortality and interproximal bone loss in adults with intellectual disability. Eur J Oral Sci 109(1): 20–26.

Gale L, Wimalaratna H, Brotodiharjo A & Duggan JM (1997) Down's syndrome is strongly associated with coeliac disease. Gut 40(4): 492–496.

Garrison MM, Jeffries H & Christakis DA (2005) Risk of death for children with down syndrome and sepsis. J Pediatr 147(6): 748–752.

Gibson PA, Newton RW, Selby K, Price DA, Leyland K & Addison GM (2005) Longitudinal study of thyroid function in Down's syndrome in the first two decades. Arch Dis Child 90(6): 574–578.

Gillespie KM, Dix RJ, Williams AJ, Newton R, Robinson ZF, Bingley PJ, Gale EA & Shield JP (2006) Islet autoimmunity in children with Down's syndrome. Diabetes 55(11): 3185–3188.

Gilmore L & Cuskelly M (2009) A longitudinal study of motivation and competence in children with Down syndrome: early childhood to early adolescence. J Intellect Disabil Res 53(5): 484–492.

Glasson EJ, Sullivan SG, Hussain R, Petterson BA, Montgomery PD & Bittles AH (2002) The changing survival profile of people with Down's syndrome: implications for genetic counselling. Clin Genet 62(5): 390–393.

Goldacre MJ, Wotton CJ, Seagroatt V & Yeates D (2004) Cancers and immune related diseases associated with Down's syndrome: a record linkage study. Arch Dis Child 89(11): 1014–1017.

Goldberg-Stern H, Strawsburg RH, Patterson B, Hickey F, Bare M, Gadoth N & Degrauw TJ (2001) Seizure frequency and characteristics in children with Down syndrome. Brain Dev 23(6): 375–378.

Hansson T, Dahlbom I, Rogberg S, Nyberg BI, Dahlstrom J, Anneren G, Klareskog L & Dannaeus A (2005) Antitissue transglutaminase and antithyroid autoantibodies in children with Down syndrome and celiac disease. J Pediatr Gastroenterol Nutr 40(2): 170–4; discussion 125–7.

Harigai S (1994) Longitudinal studies in hearing-impaired children with Down's syndrome. Nippon Jibiinkoka Gakkai Kaiho 97(12): 2208–2218.

Hasle H, Clemmensen IH & Mikkelsen M (2000) Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 355(9199): 165–169.

Haveman MJ, Maaskant MA, van Schrojenstein Lantman HM, Urlings HF & Kessels AG (1994) Mental health problems in elderly people with and without Down's syndrome. J Intellect Disabil Res 38 (Pt 3)(Pt 3): 341–355.

Hayes C, Johnson Z, Thornton L, Fogarty J, Lyons R, O'Connor M, Delany V & Buckley K (1997) Ten-year survival of Down syndrome births. Int J Epidemiol 26(4): 822–829.

Heikura U, Linna SL, Olsen P, Hartikainen AL, Taanila A & Jarvelin MR (2005) Etiological survey on intellectual disability in the northern Finland birth cohort 1986. Am J Ment Retard 110(3): 171–180.

Heller JH, Spiridigliozzi GA, Crissman BG, Sullivan JA, Eells RL, Li JS, Doraiswamy PM, Krishnan KR & Kishnani PS (2006) Safety and efficacy of rivastigmine in adolescents with Down syndrome: a preliminary 20-week, open-label study. J Child Adolesc Psychopharmacol 16(6): 755–765.

Heller JH, Spiridigliozzi GA, Sullivan JA, Doraiswamy PM, Krishnan RR & Kishnani PS (2003) Donepezil for the treatment of language deficits in adults with Down syndrome: a preliminary 24-week open trial. Am J Med Genet A 116A(2): 111–116.

Henderson A, Lynch SA, Wilkinson S & Hunter M (2007) Adults with Down's syndrome: the prevalence of complications and health care in the community. Br J Gen Pract 57(534): 50–55.

Hijii T, Fukushige J, Igarashi H, Takahashi N & Ueda K (1997) Life expectancy and social adaptation in individuals with Down syndrome with and without surgery for congenital heart disease. Clin Pediatr (Phila) 36(6): 327–332.

Hildmann A, Hildmann H & Kessler A (2002) Hearing disorders in children with Down's syndrome. Laryngorhinootologie 81(1): 3–7.

Hill DA, Gridley G, Cnattingius S, Mellemkjaer L, Linet M, Adami HO, Olsen JH, Nyren O & Fraumeni JF,Jr (2003) Mortality and cancer incidence among individuals with Down syndrome. Arch Intern Med 163(6): 705–711.

Holland AJ, Hon J, Huppert FA & Stevens F (2000) Incidence and course of dementia in people with Down's syndrome: findings from a population-based study. J Intellect Disabil Res 44(Pt 2): 138–146.

Holland AJ, Hon J, Huppert FA, Stevens F & Watson P (1998) Population-based study of the prevalence and presentation of dementia in adults with Down's syndrome. Br J Psychiatry 172: 493–498.

Iacono T, Torr J & Wong HY (2010) Relationships amongst age, language and related skills in adults with Down syndrome. Res Dev Disabil 31(2): 568–576.

Janicki MP & Dalton AJ (2000) Prevalence of dementia and impact on intellectual disability services. Ment Retard 38(3): 276–288.

Janicki MP, Dalton AJ, Henderson CM & Davidson PW (1999) Mortality and morbidity among older adults with intellectual disability: health services considerations. Disabil Rehabil 21(5–6): 284–294.

Jansson U & Johansson C (1995) Down syndrome and celiac disease. J Pediatr Gastroenterol Nutr 21(4): 443–445.

Jea A, Smith ER, Robertson R & Scott RM (2005) Moyamoya syndrome associated with Down syndrome: outcome after surgical revascularization. Pediatrics 116(5): e694–701.

Johannsen P, Christensen JE & Mai J (1996) The prevalence of dementia in Down syndrome. Dementia 7(4): 221–225.

Johnson N, Fahey C, Chicoine B, Chong G & Gitelman D (2003) Effects of donepezil on cognitive functioning in Down syndrome. Am J Ment Retard 108(6): 367–372.

Jonelid B, Anneren G & Holmstrom G (2002) Children and adolescents with Down syndrome. Continuous ophthalmological monitoring crucial! Lakartidningen 99(1–2): 29–32.

Johns Hopkins University (2011) Down syndrome. URI: http://omim.org/entry/190685. Cited 2011/09/23.

Juj H & Emery H (2009) The arthropathy of Down syndrome: an underdiagnosed and under-recognized condition. J Pediatr 154(2): 234–238.

Kaski M, Aaltonen S, Heiskala H, Hyvarinen L, Komulainen J, Maatta T, Noponen AL, Verkasalo M, Wilska M, Ala-Mello S, Hiiri A & Sakki A (2011) Update on current care guidelines: appropriate treatment of medical problems associated with Down's syndrome. Duodecim 127(4): 364–365.

Kaski M, Autti-Ramo I, Heiskanen K, Huovinen K, Hyvarinen L, Koivikko M, Maki OA, Noponen AL, Patja K, Pirttila T, Raitasuo S, Rytsola E, Verkasalo M & Wilska M (2005) Update on current care guidelines. Proper care of medical problems connected to Down Syndrome. Duodecim 121(19): 2118–2119.

Kaye PL, Fiske J, Bower EJ, Newton JT & Fenlon M (2005) Views and experiences of parents and siblings of adults with Down Syndrome regarding oral healthcare: a qualitative and quantitative study. Br Dent J 198(9): 571–8, discussion 559.

Kerins G, Petrovic K, Bruder MB & Gruman C (2008) Medical conditions and medication use in adults with Down syndrome: a descriptive analysis. Downs Syndr Res Pract 12(2): 141–147.

Kim JH, Hwang JM, Kim HJ & Yu YS (2002) Characteristic ocular findings in Asian children with Down syndrome. Eye 16(6): 710–714.

Kishnani PS, Heller JH, Spiridigliozzi GA, Lott I, Escobar L, Richardson S, Zhang R & McRae T (2010) Donepezil for treatment of cognitive dysfunction in children with Down syndrome aged 10–17. Am J Med Genet A 152A(12): 3028–3035.

Kishnani PS, Sommer BR, Handen BL, Seltzer B, Capone GT, Spiridigliozzi GA, Heller JH, Richardson S & McRae T (2009) The efficacy, safety, and tolerability of donepezil for the treatment of young adults with Down syndrome. Am J Med Genet A 149A(8): 1641–1654.

Kondoh T, Kanno A, Itoh H, Nakashima M, Honda R, Kojima M, Noguchi M, Nakane H, Nozaki H, Sasaki H, Nagai T, Kosaki R, Kakee N, Okuyama T, Fukuda M, Ikeda M, Shibata Y & Moriuchi H (2011) Donepezil significantly improves abilities in daily lives of female Down syndrome patients with severe cognitive impairment: a 24-week randomized, double-blind, placebo-controlled trial. Int J Psychiatry Med 41(1): 71–89.

Kortteisto T, Kaila M, Komulainen J, Mantyranta T & Rissanen P (2010) Healthcare professionals' intentions to use clinical guidelines: a survey using the theory of planned behaviour. Implement Sci 5: 51.

Krahn GL, Hammond L & Turner A (2006) A cascade of disparities: health and health care access for people with intellectual disabilities. Ment Retard Dev Disabil Res Rev 12(1): 70–82.

Kusters MA, Verstegen RH, Gemen EF & de Vries E (2009) Intrinsic defect of the immune system in children with Down syndrome: a review. Clin Exp Immunol 156(2): 189–193.

Lakshmi KT, Surekha RH, Srikanth B & Jyothy A (2008) Serum cholinesterases in Down syndrome children before and after nutritional supplementation. Singapore Med J 49(7): 561–564.

Lanfranchi S, Jerman O, Dal Pont E, Alberti A & Vianello R (2010) Executive function in adolescents with Down Syndrome. J Intellect Disabil Res 54(4): 308–319.

Lange R, Guenther T, Busch R, Hess J & Schreiber C (2007) The presence of Down syndrome is not a risk factor in complete atrioventricular septal defect repair. J Thorac Cardiovasc Surg 134(2): 304–310.

Laws G (2004) Contributions of phonological memory, language comprehension and hearing to the expressive language of adolescents and young adults with Down syndrome. J Child Psychol Psychiatry 45(6): 1085–1095.

Lee JH, Chulikavit M, Pang D, Zigman WB, Silverman W & Schupf N (2007) Association between genetic variants in sortilin-related receptor 1 (SORL1) and Alzheimer's disease in adults with Down syndrome. Neurosci Lett 425(2): 105–109.

Lennox N, Bain C, Rey-Conde T, Purdie D, Bush R & Pandeya N (2007) Effects of a comprehensive health assessment programme for Australian adults with intellectual disability: a cluster randomized trial. Int J Epidemiol 36(1): 139–146.

Leonard S, Bower C, Petterson B & Leonard H (2000) Survival of infants born with Down's syndrome: 1980–96. Paediatr Perinat Epidemiol 14(2): 163–171.

Libb JW, Dahle A, Smith K, McCollister FP & McLain C (1985) Hearing disorder and cognitive function of individuals with Down syndrome. Am J Ment Defic 90(3): 353–356.

Little JA, Woodhouse JM, Lauritzen JS & Saunders KJ (2009) Vernier acuity in Down syndrome. Invest Ophthalmol Vis Sci 50(2): 567–572.

Liza-Sharmini AT, Azlan ZN & Zilfalil BA (2006) Ocular findings in Malaysian children with Down syndrome. Singapore Med J 47(1): 14–19.

Lobaugh NJ, Karaskov V, Rombough V, Rovet J, Bryson S, Greenbaum R, Haslam RH & Koren G (2001) Piracetam therapy does not enhance cognitive functioning in children with down syndrome. Arch Pediatr Adolesc Med 155(4): 442–448.

Lott IT & Dierssen M (2010) Cognitive deficits and associated neurological complications in individuals with Down's syndrome. Lancet Neurol 9(6): 623–633.

Lowenthal R, Paula CS, Schwartzman JS, Brunoni D & Mercadante MT (2007) Prevalence of pervasive developmental disorder in Down's syndrome. J Autism Dev Disord 37(7): 1394–1395.

Malinge S, Izraeli S & Crispino JD (2009) Insights into the manifestations, outcomes, and mechanisms of leukemogenesis in Down syndrome. Blood 113(12): 2619–2628.

Mantry D, Cooper SA, Smiley E, Morrison J, Allan L, Williamson A, Finlayson J & Jackson A (2008) The prevalence and incidence of mental ill-health in adults with Down syndrome. J Intellect Disabil Res 52(Pt 2): 141–155.

Marcell MM & Cohen S (1992) Hearing abilities of Down syndrome and other mentally handicapped adolescents. Res Dev Disabil 13(6): 533–551.

Marcell MM, Ridgeway MM, Sewell DH & Whelan ML (1995) Sentence imitation by adolescents and young adults with Down's syndrome and other intellectual disabilities. J Intellect Disabil Res 39 (Pt 3)(Pt 3): 215–232.

Margallo-Lana M, Morris CM, Gibson AM, Tan AL, Kay DW, Tyrer SP, Moore BP & Ballard CG (2004) Influence of the amyloid precursor protein locus on dementia in Down syndrome. Neurology 62(11): 1996–1998.

Margallo-Lana ML, Moore PB, Kay DW, Perry RH, Reid BE, Berney TP & Tyrer SP (2007) Fifteen-year follow-up of 92 hospitalized adults with Down's syndrome: incidence of cognitive decline, its relationship to age and neuropathology. J Intellect Disabil Res 51(Pt. 6): 463–477.

Matsunaga S, Imakiire T, Koga H, Ishidou Y, Sasaki H, Taketomi E, Higo M, Tanaka H & Komiya S (2007) Occult spinal canal stenosis due to C-1 hypoplasia in children with Down syndrome. J Neurosurg 107(6 Suppl): 457–459.

McCarron M, Gill M, McCallion P & Begley C (2005) Health co-morbidities in ageing persons with Down syndrome and Alzheimer's dementia. J Intellect Disabil Res 49(Pt 7): 560–566.

McCarthy J (2008) Behaviour problems and adults with Down syndrome: childhood risk factors. J Intellect Disabil Res 52(10): 877–882.

McCarthy J & Boyd J (2001) Psychopathology and young people with Down's syndrome: childhood predictors and adult outcome of disorder. J Intellect Disabil Res 45(Pt 2): 99–105.

McDermott AL, Williams J, Kuo MJ, Reid AP & Proops DW (2008) The role of bone anchored hearing aids in children with Down syndrome. Int J Pediatr Otorhinolaryngol 72(6): 751–757.

McIntyre LL, Blacher J & Baker BL (2002) Behaviour/mental health problems in young adults with intellectual disability: the impact on families. J Intellect Disabil Res 46(Pt 3): 239–249.

Menendez M (2005) Down syndrome, Alzheimer's disease and seizures. Brain Dev 27(4): 246–252.

Mercer ES, Broecker B, Smith EA, Kirsch AJ, Scherz HC & A Massad C (2004) Urological manifestations of Down syndrome. J Urol 171(3): 1250–1253.

Merrick J (2000) Incidence and mortality of Down syndrome. Isr Med Assoc J 2(1): 25–26.

Meuwese-Jongejeugd A, van Splunder J, Vink M, Stilma JS, van Zanten B, Verschuure H, Bernsen R & Evenhuis H (2008) Combined sensory impairment (deaf-blindness) in five percent of adults with intellectual disabilities. Am J Ment Retard 113(4): 254–262.

Meuwese-Jongejeugd A, Vink M, van Zanten B, Verschuure H, Eichhorn E, Koopman D, Bernsen R & Evenhuis H (2006) Prevalence of hearing loss in 1598 adults with an intellectual disability: cross-sectional population based study. Int J Audiol 45(11): 660–669.

Morgan J (2007) Why is periodontal disease more prevalent and more severe in people with Down syndrome? Spec Care Dentist 27(5): 196–201.

Moss J & Howlin P (2009) Autism spectrum disorders in genetic syndromes: implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. J Intellect Disabil Res 53(10): 852–873.

Murphy J, Hoey HM, Philip M, Roche EF, Macken S, Mayne P, Duff D, O'Keefe M, McShane D, Fogarty E & O'Regan M (2005) Guidelines for the medical management of Irish children and adolescents with Down syndrome. Ir Med J 98(2): 48–52.

Murphy J, Philip M, Macken S, Meehan J, Roche E, Mayne PD, O'Regan M & Hoey HM (2008) Thyroid dysfunction in Down's syndrome and screening for hypothyroidism in children and adolescents using capillary TSH measurement. J Pediatr Endocrinol Metab 21(2): 155–163.

Myers BA & Pueschel SM (1995) Major depression in a small group of adults with Down syndrome. Res Dev Disabil 16(4): 285–299.

Naess KA, Lyster SA, Hulme C & Melby-Lervag M (2011) Language and verbal short-term memory skills in children with Down syndrome: A meta-analytic review. Res Dev Disabil 32(6): 2225–2234.

Nandakumar K & Leat SJ (2010) Bifocals in children with Down syndrome (BiDS) – visual acuity, accommodation and early literacy skills. Acta Ophthalmol 88(6): e196–204.

National Institute for Health and Welfare & Official Statistics of Finland (2011) Congenital anomalies 1993–2008 URI: http://www.stakes.fi/tilastot/tilastotiedotteet/2011/Tr07_11.pdf. Cited 2011/11/1.

Nelson L, Johnson JK, Freedman M, Lott I, Groot J, Chang M, Milgram NW & Head E (2005) Learning and memory as a function of age in Down syndrome: a study using animal-based tasks. Prog Neuropsychopharmacol Biol Psychiatry 29(3): 443–453.

Nelson LD, Orme D, Osann K & Lott IT (2001) Neurological changes and emotional functioning in adults with Down Syndrome. J Intellect Disabil Res 45(Pt 5): 450–456.

Nelson LD, Scheibel KE, Ringman JM & Sayre JW (2007) An experimental approach to detecting dementia in Down syndrome: a paradigm for Alzheimer's disease. Brain Cogn 64(1): 92–103.

Nicham R, Weitzdorfer R, Hauser E, Freidl M, Schubert M, Wurst E, Lubec G & Seidl R (2003) Spectrum of cognitive, behavioural and emotional problems in children and young adults with Down syndrome. J Neural Transm Suppl (67): 173–191.

Nieuwenhuis-Mark RE (2009) Diagnosing Alzheimer's dementia in Down syndrome: problems and possible solutions. Res Dev Disabil 30(5): 827–838.

Nihira K, Leland H & Lambert N (1993) AAMR Adaptive Behavior Scales, Residential and Community Edition. 2nd ed. TX:Pro-Ed.

Nisihara RM, Kotze LM, Utiyama SR, Oliveira NP, Fiedler PT & Messias-Reason IT (2005) Celiac disease in children and adolescents with Down syndrome. J Pediatr (Rio J) 81(5): 373–376.

Numminen H, Service E, Ahonen T & Ruoppila I (2001) Working memory and everyday cognition in adults with Down's syndrome. J Intellect Disabil Res 45(Pt 2): 157–168.

Olsen CL, Cross PK & Gensburg LJ (2003) Down syndrome: interaction between culture, demography, and biology in determining the prevalence of a genetic trait. Hum Biol 75(4): 503–520.

Park J, Oh Y & Chung KC (2009) Two key genes closely implicated with the neuropathological characteristics in Down syndrome: DYRK1A and RCAN1. BMB Rep 42(1): 6–15.

Patel A, Rees SD, Kelly MA, Bain SC, Barnett AH, Thalitaya D & Prasher VP (2011) Association of variants within APOE, SORL1, RUNX1, BACE1 and ALDH18A1 with dementia in Alzheimer's disease in subjects with Down syndrome. Neurosci Lett 487(2):144–148.

Patja K, Pukkala E, Sund R, Iivanainen M & Kaski M (2006) Cancer incidence of persons with Down syndrome in Finland: a population-based study. Int J Cancer 118(7): 1769–1772.

Pekkonen E, Osipova D, Sauna-Aho O & Arvio M (2007) Delayed auditory processing underlying stimulus detection in Down syndrome. Neuroimage 35(4): 1547–1550

Prasher V & Gomez G (2007) Natural history of thyroid function in adults with Down syndrome–10-year follow-up study. J Intellect Disabil Res 51(Pt 4): 312–317.

Prasher VP & Chung MC (1996) Causes of age-related decline in adaptive behavior of adults with Down syndrome: differential diagnoses of dementia. Am J Ment Retard 101(2): 175–183.

Prasher VP, Chung MC & Haque MS (1998) Longitudinal changes in adaptive behavior in adults with Down syndrome: interim findings from a longitudinal study. Am J Ment Retard 103(1): 40–46.

Prasher VP, Huxley A, Haque MS & Down syndrome Ageing Study Group (2002) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Down syndrome and Alzheimer's disease–pilot study. Int J Geriatr Psychiatry 17(3): 270–278.

Prasher VP, Sajith SG, Rees SD, Patel A, Tewari S, Schupf N & Zigman WB (2008) Significant effect of APOE epsilon 4 genotype on the risk of dementia in Alzheimer's disease and mortality in persons with Down syndrome. Int J Geriatr Psychiatry 23(11): 1134–1140.

Pueschel SM, Romano C, Failla P, Barone C, Pettinato R, Castellano Chiodo A & Plumari DL (1999) A prevalence study of celiac disease in persons with Down syndrome residing in the United States of America. Acta Paediatr 88(9): 953–956.

Puri BK & Singh I (2007) Prevalence of cataract in adult Down's syndrome patients aged 28 to 83 years. Clin Pract Epidemol Ment Health 3: 26.

Rabin KR & Whitlock JA (2009) Malignancy in children with trisomy 21. Oncologist 14(2): 164–173.

Rachidi M & Lopes C (2010) Molecular and cellular mechanisms elucidating neurocognitive basis of functional impairments associated with intellectual disability in Down syndrome. Am J Intellect Dev Disabil 115(2): 83–112.

Ram G & Chinen J (2011) Infections and immunodeficiency in Down syndrome. Clin Exp Immunol 164(1): 9–16.

Rantakallio P & von Wendt L (1986) Mental retardation and subnormality in a birth cohort of 12,000 children in Northern Finland. Am J Ment Defic 90(4): 380–387.

Rasmussen DE & Sobsey D (1994) Age, adaptive behavior, and Alzheimer disease in Down syndrome: cross-sectional and longitudinal analyses. Am J Ment Retard 99(2): 151–165.

Rasmussen SA, Whitehead N, Collier SA & Frias JL (2008) Setting a public health research agenda for Down syndrome: Summary of a meeting sponsored by the Centers for Disease Control and Prevention and the National Down Syndrome Society. Am J Med Genet A 146A(23):2998–3010.

Rasmussen SA, Wong LY, Correa A, Gambrell D & Friedman JM (2006) Survival in infants with Down syndrome, Metropolitan Atlanta, 1979–1998. J Pediatr 148(6): 806–812.

Roubertoux PL & Carlier M (2010) Mouse models of cognitive disabilities in trisomy 21 (Down syndrome). Am J Med Genet C Semin Med Genet 154C(4): 400–416.

Roizen NJ & Patterson D (2003) Down's syndrome. Lancet 361(9365): 1281–1289.

Roizen NJ, Wolters C, Nicol T & Blondis TA (1993) Hearing loss in children with Down syndrome. J Pediatr 123(1): S9–12.

Romeo R, Knapp M, Morrison J, Melville C, Allan L, Finlayson J & Cooper SA (2009) Cost estimation of a health-check intervention for adults with intellectual disabilities in the UK. J Intellect Disabil Res 53(5):426–439.

Rumbo M, Chirdo FG, Ben R, Saldungaray I & Villalobos R (2002) Evaluation of coeliac disease serological markers in Down syndrome patients. Dig Liver Dis 34(2): 116–121.

Schalock RL, Borthwick-Duffy SA, Bradley VJ, Buntinx WH, Coulter DL, Craig EM *et al.* (2010) Intellectual Disability: Definition, classification, and systems of supports. Washington DC: American Association on Intellectual and Developmental Disabilities.

Schieve LA, Boulet SL, Boyle C, Rasmussen SA & Schendel D (2009) Health of children 3 to 17 years of age with Down syndrome in the 1997–2005 national health interview survey. Pediatrics 123(2): e253–60.

Schliebs R & Arendt T (2011) The cholinergic system in aging and neuronal degeneration. Behav Brain Res 221(2): 555–563.

Schupf N, Lee JH, Wei M, Pang D, Chace C, Cheng R, Zigman WB, Tycko B & Silverman W (2008) Estrogen receptor-alpha variants increase risk of Alzheimer's disease in women with Down syndrome. Dement Geriatr Cogn Disord 25(5): 476–482.

Schupf N, Patel B, Pang D, Zigman WB, Silverman W, Mehta PD & Mayeux R (2007) Elevated plasma beta-amyloid peptide Abeta(42) levels, incident dementia, and mortality in Down syndrome. Arch Neurol 64(7): 1007–1013.

Schupf N, Winsten S, Patel B, Pang D, Ferin M, Zigman WB, Silverman W & Mayeux R (2006) Bioavailable estradiol and age at onset of Alzheimer's disease in postmenopausal women with Down syndrome. Neurosci Lett 406(3): 298–302.

Sciberras C, Vella C & Grech V (2004) The prevalence of coeliac disease in Down's syndrome in Malta. Ann Trop Paediatr 24(1): 81–83.

Shamaly H, Hartman C, Pollack S, Hujerat M, Katz R, Gideoni O & Shamir R (2007) Tissue transglutaminase antibodies are a useful serological marker for the diagnosis of celiac disease in patients with Down syndrome. J Pediatr Gastroenterol Nutr 44(5): 583–586.

Sheehan PZ & Hans PS (2006) UK and Ireland experience of bone anchored hearing aids (BAHA) in individuals with Down syndrome. Int J Pediatr Otorhinolaryngol 70(6): 981–986.

Shepperdson B (1995) Two longitudinal studies of the abilities of people with Down's syndrome. J Intellect Disabil Res 39 (Pt 5): 419–431.

Shott SR, Amin R, Chini B, Heubi C, Hotze S & Akers R (2006) Obstructive sleep apnea: Should all children with Down syndrome be tested? Arch Otolaryngol Head Neck Surg 132(4): 432–436.

Shott SR, Joseph A & Heithaus D (2001) Hearing loss in children with Down syndrome. Int J Pediatr Otorhinolaryngol 61(3): 199–205.

Silverman W (2007) Down syndrome: cognitive phenotype. Ment Retard Dev Disabil Res Rev 13(3): 228–236.

Spiridigliozzi GA, Heller JH, Crissman BG, Sullivan-Saarela JA, Eells R, Dawson D, Li J & Kishnani PS (2007) Preliminary study of the safety and efficacy of donepezil hydrochloride in children with Down syndrome: a clinical report series. Am J Med Genet A 143A(13): 1408–1413.

Steffelaar JW & Evenhuis HM (1989) Epidemiologic study of the estimated number of older patients with Down's syndrome in 1990–2025. Ned Tijdschr Geneeskd 133(22): 1121–1125.

Stephen E, Dickson J, Kindley AD, Scott CC & Charleton PM (2007) Surveillance of vision and ocular disorders in children with Down syndrome. Dev Med Child Neurol 49(7): 513–515.

Stewart RE, Margaret Woodhouse J & Trojanowska LD (2005) In focus: the use of bifocal spectacles with children with Down's syndrome. Ophthalmic Physiol Opt 25(6): 514–522.

Stewart RE, Woodhouse JM, Cregg M & Pakeman VH (2007) Association between accommodative accuracy, hypermetropia, and strabismus in children with Down's syndrome. Optom Vis Sci 84(2): 149–155.

Strydom A, Livingston G, King M & Hassiotis A (2007) Prevalence of dementia in intellectual disability using different diagnostic criteria. Br J Psychiatry 191: 150–157.

Suttle CM & Turner AM (2004) Transient pattern visual evoked potentials in children with Down's syndrome. Ophthalmic Physiol Opt 24(2): 91–99.

Swigonski NL, Kuhlenschmidt HL, Bull MJ, Corkins MR & Downs SM (2006) Screening for celiac disease in asymptomatic children with Down syndrome: cost-effectiveness of preventing lymphoma. Pediatrics 118(2): 594–602.

Teipel SJ & Hampel H (2006) Neuroanatomy of Down syndrome in vivo: a model of preclinical Alzheimer's disease. Behav Genet 36(3): 405–415.

Teipel SJ, Schapiro MB, Alexander GE, Krasuski JS, Horwitz B, Hoehne C, Moller HJ, Rapoport SI & Hampel H (2003) Relation of corpus callosum and hippocampal size to age in nondemented adults with Down's syndrome. Am J Psychiatry 160(10): 1870–1878.

Torr J, Strydom A, Patti P, Jokinen N (2010) Aging in Down syndrome: Morbidity and Mortality. J Policy Practice Intellect Disabil 7(1): 70–81.

Toscano E, Trivellini V & Andria G (2001) Cholelithiasis in Down's syndrome. Arch Dis Child 85(3): 242–243.

Tsao R & Kindelberger C (2009) Variability of cognitive development in children with Down syndrome: relevance of good reasons for using the cluster procedure. Res Dev Disabil 30(3): 426–432.

Turner S, Alborz A & Gayle V (2008) Predictors of academic attainments of young people with Down's syndrome. J Intellect Disabil Res 52(Pt 5): 380–392.

Tyrrell J, Cosgrave M, McCarron M, McPherson J, Calvert J, Kelly A, McLaughlin M, Gill M & Lawlor BA (2001) Dementia in people with Down's syndrome. Int J Geriatr Psychiatry 16(12): 1168–1174.

Uibo O, Teesalu K, Metskula K, Reimand T, Saat R, Sillat T, Reimand K, Talvik T & Uibo R (2006) Screening for celiac disease in Down's syndrome patients revealed cases of subtotal villous atrophy without typical for celiac disease HLA-DQ and tissue transglutaminase antibodies. World J Gastroenterol 12(9): 1430–1434.

Unachak K, Tanpaiboon P, Pongprot Y, Sittivangkul R, Silvilairat S, Dejkhamron P & Sudasna J (2008) Thyroid functions in children with Down's syndrome. J Med Assoc Thai 91(1): 56–61.

Urv TK, Zigman WB & Silverman W (2008) Maladaptive behaviors related to dementia status in adults with Down syndrome. Am J Ment Retard 113(2): 73–86.

Urv TK, Zigman WB & Silverman W (2010) Psychiatric symptoms in adults with Down syndrome and Alzheimer's disease. Am J Intellect Dev Disabil 115(4): 265–276.

Vachon L, Fareau GE, Wilson MG & Chan LS (2006) Testicular microlithiasis in patients with Down syndrome. J Pediatr 149(2): 233–236.

Van Cleve SN & Cohen WI (2006) Part I: clinical practice guidelines for children with Down syndrome from birth to 12 years. J Pediatr Health Care 20(1): 47–54.

van Duijn G, Dijkxhoorn Y, Scholte EM & van Berckelaer-Onnes IA (2010) The development of adaptive skills in young people with Down syndrome. J Intellect Disabil Res 54(11): 943–953.

van Gameren-Oosterom HB, Fekkes M, Buitendijk SE, Mohangoo AD, Bruil J & Van Wouwe JP (2011) Development, problem behavior, and quality of life in a population based sample of eight-year-old children with Down syndrome. PLoS One 6(7): e21879.

van Schrojenstein Lantman-de Valk HM, Haveman MJ, Maaskant MA, Kessels AG, Urlings HF & Sturmans F (1994) The need for assessment of sensory functioning in ageing people with mental handicap. J Intellect Disabil Res 38 (Pt 3): 289–298.

van Splunder J, Stilma JS, Bernsen RM & Evenhuis HM (2006) Prevalence of visual impairment in adults with intellectual disabilities in the Netherlands: cross-sectional study. Eye 20(9): 1004–1010.

van Trotsenburg AS, Heymans HS, Tijssen JG, de Vijlder JJ & Vulsma T (2006a) Comorbidity, hospitalization, and medication use and their influence on mental and motor development of young infants with Down syndrome. Pediatrics 118(4): 1633–1639.

van Trotsenburg AS, Kempers MJ, Endert E, Tijssen JG, de Vijlder JJ & Vulsma T (2006b) Trisomy 21 causes persistent congenital hypothyroidism presumably of thyroidal origin. Thyroid 16(7): 671–680.

van Trotsenburg AS, Vulsma T, van Rozenburg-Marres SL, van Baar AL, Ridder JC, Heymans HS, Tijssen JG & de Vijlder JJ (2005) The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old Down syndrome children: a randomized clinical trial. J Clin Endocrinol Metab 90(6): 3304–3311.

Virji-Babul N, Eichmann A, Kisly D, Down J & Haslam RH (2007) Use of health care guidelines in patients with Down syndrome by family physicians across Canada. Paediatr Child Health 12(3): 179–183.

Vis JC, de Bruin-Bon RH, Bouma BJ, Huisman SA, Imschoot L, van den Brink K & Mulder BJ (2010) Congenital heart defects are under-recognised in adult patients with Down's syndrome. Heart 96(18): 1480–1484.

Vis JC, Duffels MG, Winter MM, Weijerman ME, Cobben JM, Huisman SA & Mulder BJ (2009) Down syndrome: a cardiovascular perspective. J Intellect Disabil Res 53(5): 419–425.

Webb D, Roberts I & Vyas P (2007) Haematology of Down syndrome. Arch Dis Child Fetal Neonatal Ed 92(6): F503–7.

Weijerman ME, van Furth AM, Vonk Noordegraaf A, van Wouwe JP, Broers CJ & Gemke RJ (2008) Prevalence, neonatal characteristics, and first-year mortality of Down syndrome: a national study. J Pediatr 152(1): 15–19.

Weijerman ME & de Winter JP (2010) Clinical practice. The care of children with Down syndrome. Eur J Pediatr 169(12): 1445–1452.

Westerinen H, Kaski M, Virta L, Almqvist F & Iivanainen M (2007) Prevalence of intellectual disability: a comprehensive study based on national registers. J Intellect Disabil Res 51(Pt 9): 715–725.

Westerinen H (2004), unpublished information.

Wexler ID, Abu-Libdeh A, Kastiel Y, Nimrodi A, Kerem E & Tenenbaum A (2009) Optimizing health care for individuals with Down syndrome in Israel. Isr Med Assoc J 11(11): 655–659.

Wiseman FK, Alford KA, Tybulewicz VL & Fisher EM (2009) Down syndrome–recent progress and future prospects. Hum Mol Genet 18(R1): R75–83.

Wisniewski KE, Dalton AJ, McLachlan C, Wen GY & Wisniewski HM (1985) Alzheimer's disease in Down's syndrome: clinicopathologic studies. Neurology 35(7): 957–961.

Woodhouse JM, Cregg M, Gunter HL, Sanders DP, Saunders KJ, Pakeman VH, Parker M, Fraser WI & Sastry P (2000) The effect of age, size of target, and cognitive factors on accommodative responses of children with Down syndrome. Invest Ophthalmol Vis Sci 41(9): 2479–2485.

World Health Organization (2001) The International Classification of Functioning, Disability and Health URI: http://www.who.int/classifications/icf/en/. Cited 2011/09/23.

World Health Organization (2006) International Statistical Classification of Diseases and Related Health Problems, 10th Revision Version for 2007 URI: http://apps.who.int/classifications/apps/icd/icd10online/. Cited 2011/09/23.

Wouters J, Weijerman ME, van Furth AM, Schreurs MW, Crusius JB, von Blomberg BM, de Baaij LR, Broers CJ & Gemke RJ (2009) Prospective human leukocyte antigen, endomysium immunoglobulin A antibodies, and transglutaminase antibodies testing for celiac disease in children with Down syndrome. J Pediatr 154(2): 239–242.

Yam WK, Tse PW, Yu CM, Chow CB, But WM, Li KY, Lee LP, Fung EL, Mak PP & Lau JT (2008) Medical issues among children and teenagers with Down syndrome in Hong Kong. Downs Syndr Res Pract 12(2): 138–140.

Yang Q, Rasmussen SA & Friedman JM (2002) Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet 359(9311): 1019–1025.

Zachor DA, Mroczek-Musulman E & Brown P (2000) Prevalence of celiac disease in Down syndrome in the United States. J Pediatr Gastroenterol Nutr 31(3): 275–279.

Zigman WB & Lott IT (2007) Alzheimer's disease in Down syndrome: neurobiology and risk. Ment Retard Dev Disabil Res Rev 13(3): 237–246.

Zigman WB, Schupf N, Devenny DA, Miezejeski C, Ryan R, Urv TK, Schubert R & Silverman W (2004) Incidence and prevalence of dementia in elderly adults with mental retardation without down syndrome. Am J Ment Retard 109(2): 126–141.

Zigman WB, Schupf N, Jenkins EC, Urv TK, Tycko B & Silverman W (2007) Cholesterol level, statin use and Alzheimer's disease in adults with Down syndrome. Neurosci Lett 416(3): 279–284.

Zigman WB, Schupf N, Sersen E & Silverman W (1996) Prevalence of dementia in adults with and without Down syndrome. Am J Ment Retard 100(4): 403–412.

Zigman WB, Schupf N, Urv T, Zigman A & Silverman W (2002) Incidence and temporal patterns of adaptive behavior change in adults with mental retardation. Am J Ment Retard 107(3): 161–174.

Zubillaga P, Vitoria JC, Arrieta A, Echaniz P & Garcia-Masdevall MD (1993) Down's syndrome and celiac disease. J Pediatr Gastroenterol Nutr 16(2): 168–171.

Zwaan MC, Reinhardt D, Hitzler J & Vyas P (2008) Acute leukemias in children with Down syndrome. Pediatr Clin North Am 55(1): 53–70.

Original publications

I Määttä T, Kaski M, Taanila A, Keinänen-Kiukaanniemi S & Iivanainen M (2006) Sensory impairments and health concerns related to the degree of intellectual disability in people with Down syndrome. Downs Syndr Res Pract 11(2): 78–83.

II Määttä T, Määttä J, Tervo-Määttä T, Taanila A, Kaski M & Iivanainen M (2011) Healthcare and guidelines: A population-based survey of recorded medical problems and health surveillance for people with Down syndrome. J Intellect Dev Disabil. 36(2): 118–26.

III Määttä T, Tervo-Määttä T, Taanila A, Kaski M & Iivanainen M (2006) Mental health, behaviour and intellectual abilities of people with Down syndrome. Downs Syndr Res Pract 11(1): 37–43.

IV Määttä T, Tervo-Määttä T, Taanila A, Kaski M & Iivanainen M (2011) Adaptive behaviour change in adults with Down syndrome, a prospective clinical follow-up study. Manuscript.

Original publications are not included in the electronic version of the dissertation.

1129. Moilanen, Kristiina (2011) Diagnostics and determinants of schizophrenia : The Northern Finland 1966 Birth Cohort Study

1130. Haapsamo, Mervi (2011) Low-dose aspirin therapy in IVF and ICSI patients

1131. Hyttinen, Laura (2011) Long-term effects of the cholesterol level and its drug treatment

1132. Hannula, Samuli (2011) Hearing among older adults–an epidemiological study

1133. Paananen, Markus (2011) Multi-site musculoskeletal pain in adolescence: occurrence, determinants, and consequences

1134. Kaustinen, Teija (2011) Oulu-hoitoisuusluokitus ja hoitohenkilökunnan ajankäyttö hoitotyön laatuvaatimusten näkökulmasta

1135. Liukkonen, Timo (2011) Low-grade inflammation in depression, anxiety and sleep disturbances

1136. Tölli, Hanna (2011) Reindeer-derived bone protein extract in the healing of bone defects : Evaluation of various carrier materials and delivery systems

1137. Tourula, Marjo (2011) The childcare practice of children's daytime sleeping outdoors in the context of Northern Finnish winter

1138. Mäkelä, Jussi (2011) Bone marrow-derived stem cell therapy in acute myocardial infarction : An experimental porcine model

1139. Törmänen, Outi (2011) Malli kunnallisten terveyspalveluiden arvokeskustelusta : Pehmeä systeemianalyysi kolmen kunnan yhteistoiminta-alueella

1140. Kangas, Maarit (2011) Development of accelerometry-based fall detection : from laboratory environment to real life

1141. Määttä, Tuomo (2011) Down syndrome, health and disability : A population-based case record and follow-up study

1142. Leskelä, Tarja (2011) Human δ opioid receptor Phe27 and Cys27 variants : The role of heteromerization and pharmacological chaperones in receptor processing and trafficking

1143. Karjalainen, Minna (2011) Genetic predisposition to spontaneous preterm birth : Approaches to identify susceptibility genes

1144. Saaristo, Timo (2011) Assessment of risk and prevention of type 2 diabetes in primary health care

Book orders:
Granum: Virtual book store
http://granum.uta.fi/granum/

UNIVERSITY OF OULU P.O.B. 7500 FI-90014 UNIVERSITY OF OULU FINLAND

ACTA UNIVERSITATIS OULUENSIS

ISBN 978-951-42-9708-3 (Paperback)
ISBN 978-951-42-9709-0 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)

UNIVERSITY of OULU
OULUN YLIOPISTO