Health and disease in adults with Down syndrome

BACKGROUND The increasing life expectancy of persons with Down syndrome calls for a knowledge of conditions that frequently occur in adults with the syndrome and of which health personnel should be particularly aware.

METHOD The article is based on a literature search in PubMed and the authors' clinical experience with the patient group.

RESULTS Altered immune system function, muscular hypotonia, dysmorphic otolaryngologic features and premature ageing contribute to health problems. The group is susceptible to infections, particularly of the respiratory and the gastrointestinal tract. Congenital heart defects may give rise to symptoms, also in adults. Many also develop mitral valve disease, including those without congenital heart defects. Hypothyroidism develops in up to half, and coeliac disease in one of five. Obstructive sleep apnoea syndrome occurs in approximately half. Sensorineural hearing loss and cataract may occur before the age of 30. Atlantoaxial instability occurs, and radiological examination of the neck must take place before intervention under general anaesthesia. Behavioural changes with loss of skills, withdrawal, psychomotoric retardation and mutism occur frequently from the age of 30 and may be symptoms of mental illness or the onset of Alzheimer's dementia.

INTERPRETATION Adults with Down syndrome need to undergo regular medical examinations, and we recommend an annual check-up with the primary doctor. Screening for hearing loss and cataract is also recommended every three and five years, respectively. In the event of concomitant symptoms, particularly related to neurological and psychiatric conditions, the patient can be referred to the habilitation service.

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MAIN POINTS

The life expectancy of persons with Down syndrome has increased in recent years and is now about 60

The syndrome is associated with specific diseases and accelerated ageing processes

A number of diseases occur more frequently or earlier in persons with Down syndrome

Regular clinical check-ups should be carried out by the primary doctor

Down syndrome is the most frequently occurring chromosomal abnormality in humans, and in 2010 there were 69 live births of infants with Down syndrome in Norway (1.1 of 1 000 live births) (1). The syndrome is due to trisomy of the whole or part of chromosome 21 in all or some cells of the body and is associated with mental retardation, congenital heart defects, gastrointestinal anomalies, reduced neuromuscular tone, dysmorphic features of the head, neck and airways, characteristic facial and physical features, audiovestibular and visual impairment and a higher incidence of other clinical disorders (2, 3).

Thanks to medical progress, particularly in cardiovascular surgery and cancer therapy, the life expectancy of persons with Down syndrome has increased from an average of 35 in 1982 to about 60 today (4, 5). As a result, the health service more frequently encounters adults with Down syndrome and with typical health challenges. This paper provides a brief overview of conditions that doctors should be aware of in this patient group.

Method

The article is based on literature identified through search in the PubMed database with the subject search term «Down syndrome» and the text word «adult» combined with each of the terms «ageing», «Alzheimer's disease», «autoimmune diseases», «cognitive impairment», «dementia», «dermatitis», «endocrine system diseases», «epilepsy», «eye diseases», «gastrointestinal diseases», «health», «hearing loss», «heart», «immune system diseases», «mental disorders», «musculoskeletal diseases», «neoplasms», «nervous system diseases», «obesity», «otolaryngologic diseases», «periodontal diseases», «seizures», «sleep apnoea syndromes» and «thyroid gland». The search was limited to the period 2000–2012 and the cut-off was April 2012. The search did not include constraints on study design or type of article. We first conducted a search based on conditions that we know from our own clinical experience frequently occur in adults with Down syndrome. The search was refined and repeated with a number of search terms after we had read articles indicating that more conditions should be included. We identified 486 articles, and these were assessed on the basis of the abstract. Empirical articles and reviews dealing with clinical disorders in adults with Down syndrome were read in full text (n = 142). The search identified no meta-analyses. The articles regarded as of most relevance to our subject were included. Searches in the Cochrane Library and Best Practice databases did not identify any further relevant articles. The article is also based on the authors' own clinical experience with the patient group.

Results

A number of clinical conditions occur more frequently in adults with Down syndrome than in the rest of the adult population (Table 1) (6–24). Some conditions are associated with specific dysmorphic features, while others are assumed to be due to accelerated ageing processes (15, 25). Anomalous prevalence figures are quoted for some conditions. This is primarily because the evidence base consists of a few, small studies using dissimilar methods.

Table 1 Frequently occurring disorders in adults with Down syndrome. Estimated prevalence in per cent. Articles from which the estimates originate in right-hand column. Anomalous prevalence figures are due to few, small studies using dissimilar methods

Medical condition	Estimated prevalence (%)	Reference
Higher infection tendency	100	(6, 7)
Gastrointestinal disorders	> 70	(8)
Mitral valve prolapse	57	(9, 10)
Alzheimer's disease	50–70 (at age 60)	(5, 9, 11)
Obstructive sleep apnoea syndrome	30–50	(9, 12)
Cataract	17–29	(13)
Mitral valve regurgitation	17	(9, 10)
Atlantoaxial instability	14	(9)
Hearing loss	12–72	(14, 15)
Epilepsy	12–46	(14, 16)
Mental disorders	11–30	(17, 18)
Keratoconus	8–10	(19)
Hypothyroidism	7–50	(10)
Coeliac disease	2–18	(20, 21)
Type 1 diabetes	4	(22, 23)
Hyperthyroidism	1–3	(24)
Atlantoaxial subluxation	1–2	(9)

Cognition

Persons with Down syndrome are on average mildly to moderately mentally retarded, equivalent to a mental age of 8–9 years, but there are wide individual variations (26). Neuropsychological tests show that many have a cognitive profile with special weakness in verbal memory and strength in solving visuospatial problems (27). The ability to plan and change strategies is often weaker than their mental age would imply (28). Visual aids are more important to learning than frequent repetition.

Fertility

Women are usually fertile, and guidance on contraception is necessary (15). Conversely, men with Down syndrome are usually sterile. Mentally retarded persons are generally at greater risk of being sexually exploited, and counselling on behaviour and boundary-setting may help to prevent this (29).

Cardiovascular disease

Almost half of children with Down syndrome have a congenital heart defect, and atrioventricular and ventricular septum defects constitute 80 % of these (10). Some will require cardiological monitoring as adults – for example for mitral insufficiency, mitral stenosis, outflow stenoses, residual shunt through septum, AV block, pulmonary hypertension and development of heart failure (30, 31). Many also develop mitral valve disease, including those without congenital heart defects (9).

Arteriosclerosis

The prevalence of obesity in adults with Down syndrome has been reported to be 31–47 %, and it is common to find lipid metabolic disorders such as elevated LDL cholesterol and triglycerides and low HDL cholesterol (10, 32). Despite this, the prevalence of arteriosclerosis is lower than among the normal population (10).

Immune-related diseases

The prevalence of immune-related diseases is higher in Down syndrome than in the general population (20).

Infections

Low cellular and humoral immunity results in a high incidence of infections in persons with Down syndrome of all ages (6, 7, 33). Infections of the middle ear, respiratory system and gastrointestinal tract are seen particularly frequently (7). Pneumonia and influenza contribute to excess mortality in persons with Down syndrome, and infection-related excess mortality increases with age (34).

Thyroid disease

Down syndrome is associated with several autoimmune diseases, and the thyroid is often affected. The prevalence of thyroid disorders with Down syndrome varies in the different studies (7–50 %) depending on the population and diagnostic criteria (10). There is much to indicate that the risk increases with age, and there do not appear to be gender-related differences. Hypothyroidism is the most prevalent, but the prevalence of hyperthyroidism is also slightly high (24). We would recommend that thyroid function be checked annually in all persons with Down syndrome (Table 2) (14, 35).

Coeliac disease

The prevalence of coeliac disease in the general population is 0.3–0.5 %, while the prevalence in persons with Down syndrome is 2.5–18.6 % depending on patient selection and screening method (20, 21, 36).

Diabetes

The prevalence of type 1 diabetes has been found to be over four times higher in persons with Down syndrome than in the general population (22).

Table 2 Recommended routine medical follow-up of adults with Down syndrome. The recommendations have been drawn up by the authors, but are based largely on the booklet *Diagnosing and treating persons with retardation and dementia* (Norwegian text) (35) from the South-Eastern Norway Regional Health Authority (Helse Sør-Øst). The booklet contains a Norwegian adaptation of recommendations from the International Association for the Scientific Study of Intellectual Disability (IASSID), WHO and the Ageing and Health, Norwegian Centre for Research, Education and Service Development

Time interval[1]	Medical assessment	Comment
Every six months	Dental health	
Annual	Behavioural change	
	Nutrition	Recording of weight and weight change
	Gastrointestinal symptoms	
	Cardiopulmonary symptoms	Auscultation Assess need for ECG, echocardiography and referral to cardiologist Cardiological monitoring of congenital heart defect
	Hearing	Annual clinical assessment Audiological examination every three years
	Testicular cancer	Palpation annually
	Metabolism	Check TSH and T_4-values annually
	Vision	Annual clinical assessment Specialist examination every 5 years
	Other supplementary tests	Test fasting glucose, haematology, SR, CRP, liver and kidney function tests, B_{12}, folic acid, serum iron, ferritin, lipid status, calcium/phosphate, vitamin D
Other	Atlantoaxial instability	X-ray of neck before general anaesthesia
	Osteoporosis	Measurement of bone density early in menopause
	General screening tests	Adhere to common national guidelines

[1] In the event of abnormal findings, check-ups must be more frequent and scheduled individually

Dermatological diseases
Atopic dermatitis, vitiligo, alopecia areata, fungal infections of the skin and nails, seborrhoeic eczema and dry skin are more prevalent in persons with Down syndrome than in the general population (15, 21).

Hearing loss
Persons with Down syndrome have narrow auditory canals, and accumulation of wax in the external auditory canal may result is hearing loss. Age-related sensorineural hearing loss associated with Down syndrome occurs 30–40 years earlier than in the general population and is estimated to occur in 12–72 %, depending on the survey method (14, 15). Regular screening every three years is recommended by several authors (9, 35).

Visual impairment and eye diseases
Visual impairment and eye diseases such as astigmatism, impaired accommodation, strabismus, cataract and keratoconus are common (19). The first three conditions tend to manifest themselves during childhood. Keratoconus occurs in 8–10 % and is often discovered in the teens or early twenties. Age-related cataract may develop in the twenties or thirties. It is recommended that adults with Down syndrome be examined by an eye specialist every five years, more frequently in the event that disorders are found (13, 19).

Musculoskeletal diseases
Adults with Down syndrome often develop musculoskeletal diseases such as arthritis at a relatively early age (4).

Atlantoaxial instability
Radiological tests show signs of atlantoaxial instability in up to 14 % of persons with Down syndrome, and 1–2 % have subluxation symptoms (9). X-rays of the thoracic spine in neutral, flexed and extended positions are indicated if patients have symptoms that may point to this (9). Prior to intervention under general anaesthesia, X-ray scans of the neck of patients with Down syndrome should always be taken as standard procedure.

Osteoporosis
Down syndrome appears to be a specific vulnerability factor for the development of osteoporosis, and both general and compression fractures of the spine occur frequently (4). Contributory factors may be low muscle tone and strength, limited physical activity and autoimmune conditions. Solberg et al. recommend bone density measurement for women early in the menopause (35).

Obstructive sleep apnoea
Persons with Down syndrome have many risk factors that make them prone to obstructive sleep apnoea syndrome, such as abnormalities in the head, throat and respiratory system, overweight and hypothyroidism (12). One small clinical study found a higher incidence of severe obstructive sleep apnoea with hypoxaemia, hypoventilation and fragmented sleep in adult patients with Down syndrome than in subjects without the syndrome (37).

Gastrointestinal diseases
Abnormal developments in the enteric nervous system are associated with Down syndrome and gastrointestinal complications can be found in over 70 % (8). In adults, gastrointestinal reflux, dysphagia, obstipation, diarrhoea, gallstones, achalasia and pathological liver function tests occur most frequently. The prevalence of Hirschsprung's disease is elevated, and is found in 2–15 %, compared to about 0.15 % in the general population.

Periodontal disease
Gingivitis and periodontitis, often immune-conditioned, are more common in persons with Down syndrome, and we recommend biannual dental check-ups (9, 35).

Neoplasms
The incidence of cancer in persons with Down syndrome has a distinctive profile with a strongly elevated risk of certain types of leukaemia in young children (38). There is also an elevated risk of testicular cancer in men with Down syndrome, and a number of authors recommend annual palpation of the testicles (20, 35). However, persons of all ages with Down syndrome have been found to have a lower risk of solid tumours (34, 38). The mechanisms behind this have not yet been fully determined.

Central nervous system disorders
Epilepsy The incidence of epilepsy increases from an estimated 2–6 % in childhood to 12–46 % in those aged over 50 (37). The onset of seizures appears to have a triphasic distribution, with frequent onset in early childhood, the third decade and after the age of 50 (16). About half of the epilepsy cases are partial and half are generalised. Senile myoclonic epilepsy is the most common type in adults (39). Late-onset seizures are attributed to neuropathological changes as

with Alzheimer's disease. The choice of treatment depends on the type of seizure and epilepsy syndrome and is a task for specialists.

Mental disorders

Since Langdon Down (1828–96) described the syndrome in 1866, there has been a common perception that persons with Down syndrome have a friendly, amiable personality (40). Studies confirm good general social skills with social understanding commensurate with mental age and a special ability to imitate gestures and mimic (41, 42). Persons with Down syndrome appear to develop behavioural and emotional problems less frequently in their childhood and adolescence than persons with other causes of intellectual disability. From the age of 20–30 however, a growing incidence of anxiety and depression is found, with symptoms such as withdrawal, mutism, psychomotoric retardation, subdued moods, passivity, loss of appetite and sleeping disorders (11). Hallucinations associated with serious depressions are not unusual. Obsessive-compulsive disorders with retarded movement, tics and freeze responses occur relatively frequently, particularly in women. Bipolar disorders and schizophrenia, on the other hand, appear to occur relatively seldom in persons with Down syndrome. However, there is a relatively high incidence, in women in particular, of unspecified psychoses characterised by a low level of aggression, but a high level of visual and auditory hallucinations (40). At the same time, persons with Down syndrome often have a strong imagination which makes it difficult to distinguish fantasies from hallucinations (43). Other signs of psychosis in patients with Down syndrome are withdrawal, mutism and retarded movement, a symptomatology similar to that of depression.

Because of their greater susceptibility to disease and generally shorter life expectancy, persons with Down syndrome often experience that close friends and fellow members of collectives die. An intense fear that their parents will die is not uncommon either. Complicated grieving processes may ensue, followed by prolonged helplessness, anxiety and depression. Good psychological preparation and support are important for preventing this.

Alzheimer's disease

Studies have shown that almost all persons with Down syndrome have developed neuropathological changes with amyloid plaque and neurofibrillary tangles by the age of 35–40 (5). The changes are most pronounced in the frontal lobes and medially in the temporal lobes. This can most likely explain changes in spatial orientation, language, speech and social interaction which are frequently seen in persons over the age of 30 with Down syndrome. The first signs of incipient dementia with Down syndrome are often a change in behaviour, as opposed to the normal population, where reduced short-term memory is the most common initial symptom (44).

Women with Down syndrome undergo menopause earlier than women in the normal population, and menopause is found to be correlated with age at the onset of Alzheimer's disease (45, 46). A number of drugs are used to delay the development of Alzheimer-type dementia in the normal population, but there are few controlled studies of the effect on persons with Down syndrome. In a recently published study in which 21 persons with Down syndrome and severe cognitive impairment were randomised to either treatment with donepezil for 24 weeks or a placebo, a significant improvement in general and mental function was found in the intervention group (47). However, in a study with a similar design and 52 weeks of treatment with memantine, no effect could be identified (48).

Concluding remarks

Primary care doctors and other health personnel who meet adult persons with Down syndrome must be aware of the special health problems that this group is prone to. We believe there is a need for regular examinations with the most common disorders in mind (Table 2), (9, 14, 35). Persons with Down syndrome are followed up and treated in the ordinary primary and specialist health service. Those needing long-term, coordinated services have a right to take part in the scheme with an individual plan to ensure integrated, coordinated and individually tailored services. Patients with extensive and complex needs can be referred to the habilitation service. This applies particularly when a change in performance and behaviour gives rise to suspicion of a central nervous system disease.

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References

1. Medisinsk fødselsregister. Medfødte misdannelser, 2010. http://mfr-nesstar.uib.no/mfr/ (15.6.2012).
2. Van Cleve SN, Cohen WI. Part I: Clinical practice guidelines for children with Down syndrome from birth to 12 years. J Pediatr Health Care 2006; 20: 47–54.
3. Van Cleve SN, Cannon S, Cohen WI. Part II: Clinical practice guidelines for adolescents and young adults with Down syndrome: 12 to 21 Years. J Pediatr Health Care 2006; 20: 198–205.
4. Barnhart RC, Connolly B. Ageing and Down syndrome: implications for physical therapy. Phys Ther 2007; 87: 1399–406.
5. Zigman WB, Lott IT. Alzheimer's disease in Down syndrome: neurobiology and risk. Ment Retard Dev Disabil Res Rev 2007; 13: 237–46.
6. Hill DA, Gridley G, Cnattingius S et al. Mortality and cancer incidence among individuals with Down syndrome. Arch Intern Med 2003; 163: 705–11.
7. Chaushu S, Yefenof E, Becker A et al. Severe impairment of secretory Ig production in parotid saliva of Down Syndrome individuals. J Dent Res 2002; 81: 308–12.
8. Moore SW. Down syndrome and the enteric nervous system. Pediatr Surg Int 2008; 24: 873–83.
9. Smith DS. Health care management of adults with Down syndrome. Am Fam Physician 2001; 64: 1031–8.
10. Vis JC, Duffels MG, Winter MM et al. Down syndrome: a cardiovascular perspective. J Intellect Disabil Res 2009; 53: 419–25.

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11. Dykens EM. Psychiatric and behavioral disorders in persons with Down syndrome. Ment Retard Dev Disabil Res Rev 2007; 13: 272–8.
12. Finesilver C. A new age for childhood diseases. Down syndrome. RN 2002; 65: 43–8, quiz 49.
13. Puri BK, Singh I. Prevalence of cataract in adult Down's syndrome patients aged 28 to 83 years. Clin Pract Epidemol Ment Health 2007; 3: 26.
14. Määttä T, Määttä J, Tervo-Määttä T et al. Healthcare and guidelines: a population-based survey of recorded medical problems and health surveillance for people with Down syndrome. J Intellect Dev Disabil 2011; 36: 118–26.
15. Esbensen AJ. Health conditions associated with ageing and end of life of adults with Down syndrome. Int Rev Res Ment Retard 2010; 39 (C): 107–26.
16. Smigielska-Kuzia J, Sobaniec W, Kulak W et al. Clinical and EEG features of epilepsy in children and adolescents in Down syndrome. J Child Neurol 2009; 24: 416–20.
17. Cooper SA, van der Speck R. Epidemiology of mental ill health in adults with intellectual disabilities. Curr Opin Psychiatry 2009; 22: 431–6.
18. Mantry D, Cooper SA, Smiley E et al. The prevalence and incidence of mental ill-health in adults with Down syndrome. J Intellect Disabil Res 2008; 52: 141–55.
19. Haugen OH, Høvding G, Riise R. Øyeforandringer ved Downs syndrom. Tidsskr Nor Lægeforen 2004; 124: 186–8.
20. Goldacre MJ, Wotton CJ, Seagroatt V et al. Cancers and immune related diseases associated with Down's syndrome: a record linkage study. Arch Dis Child 2004; 89: 1014–7.
21. Roizen NJ, Patterson D. Down's syndrome. Lancet 2003; 361: 1281–9.
22. Bergholdt R, Eising S, Nerup J et al. Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: A nationwide population-based study. Diabetologia 2006; 49: 1179–82.
23. Eaton WW, Pedersen MG, Atladóttir HO et al. The prevalence of 30 ICD-10 autoimmune diseases in Denmark. Immunol Res 2010; 47: 228–31.
24. Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA et al. Hyperthyroidism in a population with Down syndrome (DS). Clin Endocrinol (Oxf) 2009; 71: 110–4.
25. Devenny DA, Silverman WP, Hill AL et al. Normal ageing in adults with Down's syndrome: a longitudinal study. J Intellect Disabil Res 1996; 40: 208–21.
26. Rachidi M, Lopes C. Molecular and cellular mechanisms elucidating neurocognitive basis of functional impairments associated with intellectual disability in Down syndrome. Am J Intellect Dev Disabil 2010; 115: 83–112.
27. Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. Lancet Neurol 2010; 9: 623–33.
28. Lanfranchi S, Jerman O, Dal Pont E et al. Executive function in adolescents with Down Syndrome. J Intellect Disabil Res 2010; 54: 308–19.
29. Eastgate G, Scheermeyer E, van Driel ML et al. Intellectual disability, sexuality and sexual abuse prevention – a study of family members and support workers. Aust Fam Physician 2012; 41: 135–9.
30. Martínez-Quintana E, Rodríguez-González F, Medina-Gil JM et al. Clinical outcome in Down syndrome patients with congenital heart disease. Cir Cir 2010; 78: 245–50.
31. Hayek E, Gring CN, Griffin BP. Mitral valve prolapse. Lancet 2005; 365: 507–18.
32. Nagyová A, Sustrová M, Raslová K. Serum lipid resistance to oxidation and uric acid levels in subjects with Down's syndrome. Physiol Res 2000; 49: 227–31.
33. Costa V, Sommese L, Casamassimi A et al. Impairment of circulating endothelial progenitors in Down syndrome. BMC Med Genomics 2010; 3: 40.
34. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet 2002; 359: 1019–25.
35. Solberg KO, Davidsen EM, Lybæk KA et al. Diagnostisering og behandling av personer med utviklingshemming og demens. Ottestad: Habiliteringstjenestene i Helse Øst, 2006. http://ebookbrowse.com/gdoc.php?id=407221037&url=973c78eb5745269d32e3573217d2bdfa (15.6.2012).
36. Lundin KE, Farstad IN, Sollid LM. Cøliaki – nye kliniske erkjennelser og diagnostiske hjelpemidler. Tidsskr Nor Lægeforen 2003; 123: 3226–9.
37. Trois MS, Capone GT, Lutz JA et al. Obstructive sleep apnea in adults with Down syndrome. J Clin Sleep Med 2009; 5: 317–23.
38. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 2000; 355: 165–9.
39. De Simone R, Puig XS, Gélisse P et al. Senile myoclonic epilepsy: delineation of a common condition associated with Alzheimer's disease in Down syndrome. Seizure 2010; 19: 383–9.
40. Down JLH. Observations on an ethnic classification of idiots. London Hospital Reports 1866; 3: 259–62.
41. Hippolyte L, Iglesias K, Van der Linden M et al. Social reasoning skills in adults with Down syndrome: the role of language, executive functions and socio-emotional behaviour. J Intellect Disabil Res 2010; 54: 714–26.
42. Vanvuchelen M, Feys H, De Weerdt W. Is the good-imitator-poor-talker profile syndrome-specific in Down syndrome?: evidence from standardised imitation and language measures. Res Dev Disabil 2011; 32: 148–57.
43. Capone G, Goyal P, Ares W et al. Neurobehavioral disorders in children, adolescents, and young adults with Down syndrome. Am J Med Genet C Semin Med Genet 2006; 142C: 158–72.
44. Zigman WB, Schupf N, Urv T et al. Incidence and temporal patterns of adaptive behavior change in adults with mental retardation. Am J Ment Retard 2002; 107: 161–74.
45. Schupf N, Pang D, Patel BN et al. Onset of dementia is associated with age at menopause in women with Down's syndrome. Ann Neurol 2003; 54: 433–8.
46. Lee JH, Gurney S, Pang D et al. Polymorphisms in HSD17B1: Early onset and increased risk of Alzheimer's disease in women with Down syndrome. Curr Gerontol Geriatr Res 2012; 2012: 361218.
47. Kondoh T, Kanno A, Itoh H et al. 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 2011; 41: 71–89.
48. Hanney M, Prasher V, Williams N, et al. Memantine for dementia in adults older than 40 years with Down's syndrome (MEADOWS): a randomised, double-blind, placebo-controlled trial. Lancet 2012; 379: 528–36.

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