Survival in Elderly Persons with Down Syndrome

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The longer life expectancy now experienced by persons with Down syndrome (DS) makes it necessary to know the factors influencing survival in older persons with this syndrome. In a prospective longitudinal cohort study of dementia and mortality, 506 persons with DS aged 45 and older were followed for a mean of 4.5 years (range 0.0–7.6 years). Cognitive and social functioning were tested at baseline and annual follow-up. The diagnosis of dementia was determined according to a standardized protocol. Cox proportional hazards modeling was used for survival analysis.

Relative preservation of cognitive and functional ability is associated with better survival in this study population. Clinically, the most important disorders in persons with DS that are related to mortality are dementia, mobility restrictions, visual impairment, and epilepsy but not cardiovascular diseases. Also, level of intellectual disability and institutionalization are associated with mortality. **J Am Geriatr Soc 56:2311–2316, 2008.**

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In recent decades there has been a distinct trend toward longer survival in persons with Down syndrome (DS),[1] increasing from 9 years in 1929 to 12 in 1949 and 49 in 1997.[2] In developed countries, recent estimates indicate a mean age of death of older than 50.[3–7] The change in mortality pattern raises the question of what the most important determinants of mortality are.

Despite major progress, persons with DS still show greater mortality rates early in life, as well as in later stages of life,[2] suggesting that there still may be differences from the general population.

Knowledge of factors influencing survival in older persons with DS is limited.

Nearly 20% of persons with DS aged 45 and older suffer from dementia,[8] and several studies have shown a greater risk of mortality for persons with DS and dementia or cognitive decline.[9–11] Cognitive decline has been shown to be associated with mortality in elderly people with and without dementia with and without DS.[12,13] In addition to age, other factors that have been suggested might influence mortality risk in DS are the gene encoding for apolipoprotein E (APOE)[12,14,15] and comorbidity.[3]

The objective of this study was to assess the effect of cognitive and functional decline and physical comorbidity on mortality risk over time in a population-based cohort of persons with DS aged 45 and older.

METHODS

Study Population

The design of this study, a prospective longitudinal study on dementia and mortality in persons with DS, has been described in detail elsewhere.[16] Briefly, 506 persons with DS aged 45 and older were enrolled in the study from December 1, 1999, to December 1, 2003. All participants were monitored annually until they died (n = 109) or their representatives withdrew them from the study (n = 7) up to the reference date of January 1, 2007. At the time of study entry, each person received a complete assessment including interviews with relatives, caregivers, and their general practitioner. The medical records were reviewed to examine past or present disorders (e.g., cardiovascular risk factors, epilepsy, and depression), mobility, and the possible use of drugs. All persons obtained a general physical and neurological examination and, if compliant, a venapuncture. The same questionnaires and interviews were used annually from 1999 to 2007.

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Premorbid severity of intellectual disability, obtained from the medical records, was classified using the *International Classification of Diseases, Tenth Revision* (ICD-10).[17] According to these criteria, 192 (38.5%) of the participants had a severe to profound level of intellectual disability, and 250 (50.1%) had a moderate to mild level of intellectual disability. The severity of intellectual disability was not known for 57 (11.4%) participants.

The diagnosis of dementia was based on the ICD-10 Symptom Checklist for Mental Disorders, in particular, dementia and Alzheimer's disease,[17] and according to the guidelines produced by an international consensus panel established under the auspices of the Ageing Special Interest Group of the International Association for the Scientific Study of Intellectual Disabilities.[18] Vital status was obtained using follow-up interviews and written correspondence. Information on causes of death was obtained from relatives or the primary caregivers of the deceased and was augmented with information from medical reports or autopsy records.

The medical ethical committee of the Erasmus Medical Center and the ethical committees of the local organizations approved the study protocol. Written informed consent to participate and to provide blood samples was obtained from legal representatives. Written consent was also obtained from persons with DS who had the mental capacity to consent.

Diagnosis of Dementia

Baseline

At baseline, the first-line relative, the primary caregiver, and the general practitioner were asked to answer the question: "Has this patient been suffering from dementia for at least 6 months?" The research physician (AMWC) confirmed the diagnosis according to a standardized protocol, including a medical checklist and a physical examination. Participants fulfilling the criteria were included in the group of persons with dementia at baseline as prevalent cases.

Follow-Up

Participants who did not have dementia at baseline were screened annually. Those who fulfilled the dementia criteria at baseline or during follow-up were followed more intensively at 6-month intervals. The diagnosis of dementia was supported using two observer-rated questionnaires, the Dementia Questionnaire for persons with an Intellectual Disability (DMR)[19,20] and the Social Competence Rating Scale for persons with an Intellectual Disability (SRZ).[21] The DMR is a 50-item questionnaire with two types of scores: those related to cognitive function (DMR/SCS; score range 0–44) and those related to social scores (DMR/SOS; score range 0–56). Higher DMR scores represent a higher frequency of behaviors that are considered to be indicative of dementia. The SRZ is a 31-item questionnaire (score range 0–124) that covers aspects such as social skills, daily living skills, and effective use of language. Higher SRZ scores indicate better functioning. Diagnoses of dementia were based on a clinical examination by the research physician (AMWC). Diagnostic examination was performed in patients who had a worsening of 7 points or more on the DMR/SCS scale, a worsening of 5 points or more on the DMR/SOS scale, or a 10% decrease in SRZ score.

All new diagnoses were discussed in a panel consisting of members of the reference group with expertise in the field of intellectual disability (AMWC, G-JV, FEV, and HME). A final diagnosis was based on consensus of the panel.

Clinical Assessments

The history of past or current disorders was ascertained using medical record review. Body mass index (BMI) was computed as weight in kilograms divided by height in square meters (kg/m^2). Visual impairment was assessed using a picture-graded test (the Teller acuity card) and hearing ability using a simple speech and whisper test. Screening for mobility restrictions took place during the personal physical examinations using a standardized protocol.[16]

Apolipoprotein E

Blood samples for determination of APOE were collected from participants who provided consent (n = 425). APOE genotypes were determined using Taqman allelic discrimination technology. APOE genotyping was obtained blind to all clinical information and coded dichotomously for analysis. Participants had one or two APOEε4 alleles or no APOEε4 alleles. APOE allele frequencies were comparable with the general Dutch population.[15]

Statistics

The risk of mortality according to participant characteristics and clinical diagnoses was investigated using Cox proportional hazards models adjusting for age at baseline as a covariate. Follow-up time was defined according to date at entry and date at death or January 1, 2007. The risks of mortality between groups were compared by estimating hazard ratios in the Cox models. Survival analyses were performed in persons for whom complete data were available (75.8%).

The relationship between rate of decline in DMR and SRZ and risk of mortality was investigated in persons without dementia using a mixed-model repeated-measures procedure.[22] This procedure takes into account that the same individual contributes information at different time points and allows the inclusion of persons with incomplete follow-up. Decline in functioning was investigated in patients with at least 5 years of follow-up (n = 483), totaling five measurements of cognitive, functional, and social ability. Participants were categorized into three groups according to their DMR and SRZ scores at baseline. Mean DMR and SRZ scores were compared between tertiles and between survivors and decedents.

To further investigate the effect of age and birth cohort effects, the study population was divided into two birth cohorts based on the participant's age at the reference date. The birth cohorts distinguished patients who were aged 60 and older (born before 1947; n = 118) and those who were younger than 60 (born after 1947; n = 381). There were more persons with a profound or severe intellectual disability in those born before 1947 (31.3% vs 17.6%, $P = .01$). The cohorts did not differ according to sex or living situation. Follow-up time was defined according to date

at entry into the study and date at death or January 1, 2007, as exit.

To establish whether there was a relationship between the presence of an APOEε4 allele and survival, the Cox models were additionally adjusted for sex, premorbid severity of intellectual disability, and living situation. To investigate whether the relationship between APOEε4 and survival was related to dementia status or birth cohort, the Cox analyses were repeated in subgroups stratified according to dementia status and in subgroups stratified according to birth cohort. In persons without dementia, the time to event variable was time since entry into the study until incidence of dementia, death, or the reference date. Also in persons with dementia, the time to event variable was time since entry into the study, although in the incident persons with dementia, it was the time since onset of dementia until death or the reference date.

Finally, the Cox analysis was repeated including all covariates found to be related to mortality risk. To exclude that inclusion of patients in the final stages of dementia explained the relationship between poorer mobility and mortality, the analysis was repeated without persons known to be in the terminal phase of dementia.[23]

RESULTS

A total of 506 persons with DS were studied, of whom 304 were men (60.1%). At baseline, mean age was 51.9 for men (range 45–70) and 52.0 for women (range 45–77). Seven persons, or their relatives, refused to participate in the study during the follow-up time, leaving 499 participants. The mean follow-up time was 4.5 years (range 0.0–7.6 years). At January 1, 2007, 78.2% of the original study population were alive. One hundred nine persons had died, yielding a mortality rate of 4.8 per 100 person-years.

There was no significant difference between men and women in mean age at death (57.7 vs 58.4; $P = .61$), and there was no significant sex difference in survival (chi-square = 0.11; $P = .73$). Mean age at death for persons without dementia (n = 29) was 56.6 and did not differ significantly ($P = .12$) from that of persons with dementia (58.5, n = 80).

Patients died of respiratory disease (n = 38), cardiac failure (n = 8), cerebrovascular disease (n = 9), carcinoma (n = 7), epilepsy (n = 2), and other diseases (frequency n = 1). The frequencies of causes of death were significantly different between persons with DS with and without dementia ($P < .01$). Physical health conditions and special respiratory problems were most frequently a cause of death in persons with dementia, and cardiac failure was the most frequent cause of death in persons without dementia. Cause of death was not known in one-third of those who had died.

The risks of mortality according to patient characteristics and different health conditions are described in Tables 1 and 2. Older persons at baseline, those with physical handicaps, those living in institutions, and those with a severe to profound level of intellectual disability were more likely to have died during follow-up (Table 1). Mortality risk was significantly related to morbidity (Table 2), except for depression and cardiovascular conditions and risk factors. The presence of a cardiovascular condition or risk factor was not associated with greater mortality risk.

A decrease in function over the annual assessment periods was observed in the DMR and SRZ scores in patients without dementia (Figure 1). Participants who had died after 5 years of follow-up showed significantly greater decline in functioning than those who survived at all levels of performance ($P < .001$).

In persons with DS younger than 60, persons with dementia had a 6 times greater mortality risk than those without (hazard rate (HR) = 6.11, 95% confidence interval (CI) = 3.34–11.17). In persons aged 60 and older, the risk was 2.79 times as great (95% CI = 1.49–5.26), although

Table 1. Vital Status at Follow-Up and Risk of Mortality According to Baseline Characteristics

Characteristic	Survivors	Decedents	Hazard Rate (95% Confidence Interval)	*P*-Value
All, n (%)	390 (78.2)	109 (21.8)		
Sex, n (%)				
Women	154 (39.5)	45 (41.3)		
Men	236 (60.5)	64 (58.7)	1.10 (0.75–1.63)*	.62
Age start, years, mean ± standard deviation	51.0 ± 4.5	55.4 ± 6.2	1.15 (1.12–1.19)	<.001
Birth cohort				
Born before 1947	64 (16.4)	54 (49.5)		
Born after 1947	326 (83.6)	55 (50.5)	0.24 (0.16–0.35)	<.001
Level of intellectual disability, n (%)				
Moderate to mild	209 (60.6)	41 (42.3)		
Severe to profound	136 (39.4)	56 (57.7)	1.84 (1.22–2.77)*	.003
Living situation, n (%)				
Community living	154 (39.5)	29 (26.6)		
Institutionalized	236 (60.5)	80 (73.4)	1.67 (1.08–2.57)*	.02
Apolipoprotein Eε4 allele, n (%)				
Absent	254 (74.3)	55 (66.3)		
Present	88 (25.7)	28 (33.7)	1.58 (1.00–2.50)*	.05

* Adjusted for age.

Table 2. Vital Status at Follow-Up and Risk of Mortality According to Morbidity at Baseline

Characteristic	Survivors n (%)	Decedents n (%)	Hazard Rate (95% Confidence Interval)	*P*-Value
Epilepsy	69 (20.6)	40 (44.4)	2.29 (1.50–3.48)	<.001
Depression	84 (25.7)	32 (36.8)	1.41 (0.91–2.19)	.12
Presence of dementia at baseline	45 (11.5)	40 (44.4)	2.91 (1.94–4.36)	<.001
Incidence of dementia during follow-up	57 (14.6)	38 (34.9)	1.97 (1.32–2.94)	<.001
Vision <30% at baseline	135 (37.3)	62 (63.9)	2.33 (1.54–3.55)	<.001
Hearing impairment at baseline	136 (46.5)	45 (61.6)	1.55 (0.94–2.56)	.08
Mobility restriction	72 (19.5)	55 (51.9)	2.76 (1.85–4.13)	<.001
Cardiovascular risk factors*	77 (19.7)	20 (18.5)	0.96 (0.59–1.57)	.88

* Cardiovascular conditions and risk factors were rare, so diabetes mellitus (n = 6), hypertension (n = 8), cerebrovascular disease (n = 12), known myocardial infarction (n = 2), and smoking (n = 72) were combined. Ninety-seven participants had more than one condition/risk factor.

the difference in HR between the two birth cohorts was not statistically significant ($P = .46$).

A significant 1.64 times greater risk of mortality (95% CI = 1.01–2.64; $P = .04$) was found for APOEε4 carriers. The presence of at least one APOEε4 allele was associated with greater mortality risk in persons with and without dementia, but these associations were not statistically significant (HR = 1.07, 95% CI = 0.58–1.95, and HR = 1.64, 95% CI = 0.88–3.01, respectively).

The association between APOEε4 and survival did not differ between the two birth cohorts.

Finally, age at baseline, severity of intellectual disability, living situation, dementia status, epilepsy, mobility, visual impairment. and APOEε4 carrier status were studied in

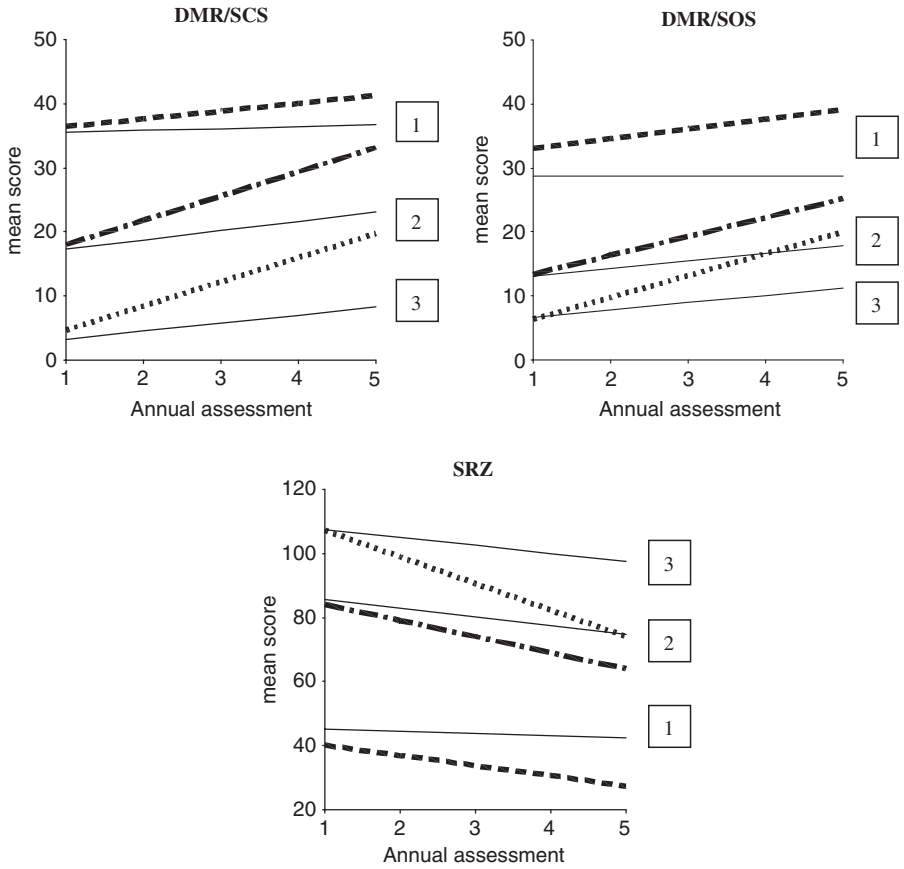

Figure 1. Mean scores of functioning in persons without dementia after 5 years of follow-up. _____ Mean predicted values in those who are alive at the reference date (n = 345). All broken lines(--;-·-;···) Mean predicted values in those who died after 5 years of follow-up before the reference date (n = 69). Reference date: January 1, 2007. 1 = lowest tertile in performance at baseline; 2 = second tertile in performance at baseline; 3 = highest tertile in performance at baseline. DMR/SCS = Dementia Questionnaire for persons with an Intellectual Disability, Sum of the Cognitive Scores. DMR/SOS = Dementia Questionnaire for persons with an Intellectual Disability, Sum of the Social Scores; SRZ = Social Competence Rating Scale for persons with an intellectual disability.

a multivariate survival analysis. Only dementia (HR 4.03, 95% CI = 2.16–7.49; $P < .001$), age at baseline (HR 1.11, 95% CI = 1.05–1.16; $P < .001$), and restricted mobility (HR 1.92, 95% CI = 1.06–3.46; $P = .03$) remained significantly associated with mortality risk. Excluding patients in the terminal phase of dementia did not alter the results.

DISCUSSION

Age, presence of dementia, and mobility restrictions are the most important predictors of mortality in this study cohort of almost 500 people with DS aged 45 and older. In contrast to the general population, impaired mobility, severity of intellectual disability, the presence of epilepsy and visual impairment, not cardiovascular risk factors or sex, predicted survival. From a population perspective, one of the most remarkable findings was that sex did not predict mortality. It is most likely that the fact that mortality from cardiovascular disease is not an important cause of death in this population (neither in absolute numbers nor as predictors of mortality) explains this.

Before interpreting the results of this study, three methodological issues need to be addressed. First, the study focused on elderly persons with DS and included persons aged 45 and older. No information was available on persons who died before the age of 45. This means that several of the findings remain unexplained, such as the lower percentage of women in the study population. Second, some of the data were collected retrospectively from the medical records, which implies that the accuracy of the assessments such as premorbid level of intellectual disability could not be controlled, yet these assessments are relatively standard or part of usual care. Third, DMR and SRZ were informant-based questionnaires, completed by caregivers. Participants may have had different caregivers during follow-up, and their living situation may have changed. Reference standards may have differed and affected the observed performance of the participant; observation bias cannot be excluded. Nevertheless, all participants were followed longitudinally for clinical signs of dementia. A final diagnosis of dementia was based on consensus of a panel consisting of members of the reference group.

A gradual decrease in function in the participants without dementia in this study was documented (Figure 1). Although they never met the criteria for dementia, these persons showed a decline in cognitive and functional skills during follow-up. More-extensive longitudinal studies are required to identify whether it was likely that this decline was the result of the preclinical onset of Alzheimer's or of normal aging in DS. One of the clinical challenges will be to discriminate between persons with faster and slower decline.

Even in participants not suffering from clinically manifest dementia, more-rapid decline was associated with a greater risk of mortality. This finding is consistent with those of others, in subjects with and without DS,[12,13,24,25] although the current study is the largest in persons with DS, with all participants examined in person and a clinical follow-up. The results of this study, using different screening instruments, show a decline in participants without dementia, irrespective of previous level of performance. Although it is difficult to detect a decline in those with the lowest level of performance, this decline, monitored using screenings tests, was related to mortality even in this group. In addition, other studies[7,26–28] have shown a significant negative association between severity of intellectual disability and survival, although this relationship did not remain significant in the multivariate analyses including all predictors.

This study found an effect of the APOEε4 allele on mortality. Persons with one or two APOEε4 alleles have a 1.64 times greater mortality risk (95% CI = 1.01–2.64). However, this greater risk did not remain significant after adjusting for dementia, although in persons with dementia and in particular in persons with DS without dementia, the risk remained greater (HR = 1.64, 95% CI = 0.88–3.01). This estimate is lower than that found in a previous study.[14] which found that persons with at least one APOEε4 allele were approximately 5 times as likely to die (4 out of 27 APOEε4 carriers) in a 5- to 7-year follow-up study of persons with DS without dementia. In addition, cognitive decline in persons without dementia is a predictor of mortality. Taken together with the findings of APOEε4, these findings suggest that early pathology that does not express clinically as dementia is associated with mortality in persons with DS.

Because of the longer life expectancy, and their living in the community, persons with DS come to the attention of general practitioners and clinicians specializing in the care of elderly people. An important clinical implication of the data presented in this study is that these clinicians should focus not on cardiovascular risk factors but on impaired mobility and respiratory complications. Diseases of the respiratory system seem to be the most important cause of death in persons with DS with dementia.

In one-third of those who died, the cause of death could not be determined. This finding indicates the need for further clinical and pathological research. The limitation will be whether clinicians are willing to ask for autopsies.

Age and dementia have long been recognized as major predictors of mortality. This study demonstrates that other factors, such as underlying and associated disorders, mobility, morbidity, and social and functional skills also contribute to survival.

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