

# Long-Term Mortality in Nationwide Cohorts of Childhood-Onset Type 1 Diabetes in Japan and Finland

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**OBJECTIVE** — This study compares mortality from type 1 diabetes in Japan and Finland and examines the effects of sex, age at diagnosis, and calendar time period of diagnosis on mortality.

**RESEARCH DESIGN AND METHODS** — Patients with type 1 diabetes from Japan ( $n = 1,408$ ) and Finland ( $n = 5,126$ ), diagnosed from 1965 through 1979, at age  $<18$  years, were followed until 1994. Mortality was estimated with and without adjustment for that of the general population to assess absolute and relative mortality using Cox proportional hazard models.

**RESULTS** — Overall mortality rates in Japan and Finland were 607 (95% CI 510–718) and 352 (315–393), respectively, per 100,000 person-years; standardized mortality ratios were 12.9 (10.8–15.3) and 3.7 (3.3–4.1), respectively. Absolute mortality was higher for men than for women in Finland, but relative mortality was higher for women than for men in both cohorts. Absolute mortality was higher in both cohorts among those whose diabetes was diagnosed during puberty, but relative mortality did not show any significant difference by age at diagnosis in either cohort. In Japan, both absolute and relative mortality were higher among those whose diagnosis was in the 1960s rather than the 1970s.

**CONCLUSIONS** — Mortality from type 1 diabetes was higher in Japan compared with Finland. The increased risk of death from type 1 diabetes seems to vary by sex, age at diagnosis, and calendar time period of diagnosis. Further investigation, especially on cause-specific mortality, is warranted in the two countries.

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**M**ortality from childhood-onset type 1 diabetes differs greatly from country to country (1–4). The Diabetes Epidemiology Research In-

ternational (DERI) Mortality Study Group has previously shown that Japanese patients with type 1 diabetes diagnosed from 1965 through 1979 had higher mor-

tality rates than patients in three other countries: Israel, Finland, and the U.S. (5,6). The greater risk of diabetic renal disease in Japan is one reason for the higher mortality rate (7).

We conducted a follow-up study through 1994 of the Japanese and Finnish cohorts of the original DERI study (5,6) to observe how mortality patterns from type 1 diabetes might have changed with the age of the subjects and longer duration of diabetes. Because some of the subjects had reached their forties, the increasing risk of death unrelated to diabetes could not be ignored. Likewise, with follow-up lasting 25 years, mortality in each country's general population might have changed significantly and have affected the mortality from type 1 diabetes. Therefore, we needed to examine both the absolute and relative mortality of type 1 diabetes. The aims of this extended comparative study were, thus, to compare the mortality of patients with type 1 diabetes in Japan and Finland and to examine the effects of sex, age at diagnosis, and calendar time period of diagnosis on mortality.

## RESEARCH DESIGN AND METHODS

### Subjects

Inclusion criteria are described in detail elsewhere (5,6). In short, patients were eligible if they 1) had received a diagnosis of diabetes before the age of 18 years, 2) had started insulin treatment within 1 month after diagnosis, and 3) had received a diagnosis of diabetes from 1965 through 1969 and were alive as of 1 January 1970, or had received a diagnosis from 1970 through 1979 and were alive as of 1 January 1980. Patients with Down's syndrome and other congenital diseases commonly associated with diabetes were excluded.

In Japan, patients with type 1 diabetes were identified from nationwide surveys in 1970 (8) and 1981 (9). That cohort consisted of 1,408 patients, 20 fewer than the previously published number, owing

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**Abbreviations:** DERI, Diabetes Epidemiology Research International.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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to a correction for misclassification and violations of the inclusion criteria discovered during follow-up. In Finland, patients were identified through the National Social Insurance Institution, which registers all people receiving free-of-charge insulin for diabetes (10). The Finnish cohort consisted of 5,126 patients, 22 fewer than the number previously reported because they were found to have Down's syndrome.

### Methods of follow-up

The vital statistics of the Japanese patients as of 31 December 1994 were obtained mainly from attending doctors, residence registry, or family registry with the permission of the Ministry of Justice of Japan. The vital statistics of the Finnish patients, also up to 31 December 1994, were obtained by record linkage with the National Death Registry. Since the early 1960s, every Finnish resident has had a personal identification number, which can be found in all formal contacts regarding any issues where personal identification is needed. Vital statuses were obtained for 1,390 patients in Japan (99.7%) and for 5,126 patients in Finland (100%). Mean follow-up periods were  $16.3 \pm 3.8$  (mean  $\pm$  SD) and  $17.8 \pm 4.5$  patient-years for the Japanese and Finnish cohorts, respectively.

### Statistical analyses

Because the Japanese cohort was established from two earlier cross-sectional studies, patients in both cohorts who had received a diagnosis of type 1 diabetes from 1965 through 1969 entered the follow-up study in 1970, and those who had received a diagnosis from 1970 through 1979 entered the follow-up in 1980. Mean duration of diabetes before beginning follow-up was  $3.5 \pm 2.6$  years (mean  $\pm$  SD) for the Japanese cohort and  $4.2 \pm 2.8$  years for the Finnish cohort. Age at diagnosis was dichotomized—prepubertal age <11 years for girls and <12 years for boys, and pubertal age for older than these ages—as in our previous report (11).

Overall and stratified mortality rates were calculated by deaths per 100,000 person-years. Standardized mortality ratios were also calculated with use of the population mortality statistics for both countries published by the World Health Organization. To calculate the expected number of deaths, the serial mortality

rates of the general population specific for countries, 5-year attained age-groups, sex, and 5-year calendar time periods were applied to similarly defined arrays of observed person-years at risk. The 95% CIs for the mortality rates and the standardized mortality ratios were derived with the assumption that deaths occurred with Byar's approximation for a Poisson distribution (12).

Multivariate Cox proportional hazard models were built to evaluate the effects of sex, age at diagnosis, and calendar time period of diagnosis, with adjustments for disease duration before the start of follow-up. Both hazard ratios were calculated without adjustment for the mortality rates of the general population (13). The hazard ratios without adjustment assessed absolute mortality, while those with adjustment assessed relative mortality. The counting process style of input by age and calendar time, both in 5-year segments, was used to include a natural log of the similarly arrayed mortality rate of the general population as a time-dependent offset variable (14). Cumulative survival probability curves were drawn for the stratified cohorts based on the Cox proportional hazard models without adjustment of mortality in general populations.

Statistical modeling and estimations of the parameters were performed with SAS computer software (SAS Institute, Cary, NC). The SAS program used for the Cox proportional hazard model with adjustment for mortality in the general population can be obtained upon request from the corresponding author.

**RESULTS**— There were 137 deaths (9.7%) in the Japanese cohort and 319 deaths (6.2%) in the Finnish cohort. The overall mortality rate was 607 (95% CI 510–718) per 100,000 person-years for the Japanese patients and 352 (315–393) for the Finnish patients (Table 1). The overall standardized mortality ratio in Japan was 12.9 (10.8–15.3), whereas in Finland it was much lower, at 3.7 (3.3–4.1). Among the Japanese patients, no sex difference was observed, but in the Finnish cohort, the absolute mortality rate was higher in men than in women. After adjustment for mortality in the general population, women had a lower risk of death in both countries, in contrast to the results for absolute mortality. In both Japan and Finland, absolute mortality was about twice as high among patients whose

diabetes was diagnosed in pubertal age rather than in prepubertal age. After adjustment for the mortality rates of the general population, however, this difference remained significant only in the Japanese cohort. Patients in Japan whose diabetes was diagnosed from 1965 through 1969 had a poorer prognosis than those diagnosed from 1975 through 1979. This effect was unchanged in the calculation of the standardized mortality ratio. No calendar time period effect for the time of diagnosis in mortality was observed in the Finnish cohort (Table 1, Fig. 1).

Multivariate Cox proportional hazards models showed that in Japan the risk of death was 1.94 times higher in patients with diabetes diagnosed in pubertal age than in those with diagnoses in prepubertal age. It also showed that the risk was 3.12 times higher for those with diagnoses in the 1960s than for those with diagnoses in the 1970s. In Finland, the risk of death was 1.93 times higher in men than in women, and 1.62 times higher for patients with diabetes diagnosed in pubertal age than for those diagnosed in prepubertal age. After adjustment for mortality rates in the general population, the effect of diagnosis during the earlier calendar time period remained significant in the Japanese cohort (hazards ratio 2.25). In addition, the effect of sex appeared. The mortality rate in men was lower than that in women (hazards ratio 0.52). For the Finnish cohort, the effect of sex was inverted after adjustment for the mortality rates of the general population: namely, men had lower mortality rates than women (hazards ratio 0.63). The effect of diagnosis in pubertal age was no longer significant after adjustment for mortality in the general population in both cohorts (Table 2).

**CONCLUSIONS**— Our study evaluated absolute and relative mortality of type 1 diabetes and compared the effects of sex, age at diagnosis, and calendar time period of diagnosis in Japan and Finland, countries with very different incidences of type 1 diabetes. The study cohorts were a nationwide series, and the study itself was the longest follow-up of an unselected cohort of patients with type 1 diabetes. The duration of follow-up was 15–29 years. Absolute mortality in type 1 diabetes in Japan was almost twice that in Finland. Adjustment to the mortality rates of the populations only emphasized the differ-

Table 1—Overall and stratified mortality rates and standardized mortality ratios

Outcomes	n	Mortality rate (per 100,000 person-years)*	Standardized mortality ratio*
Japan			
Overall	1,408	607 (510–718)	12.9 (10.8–15.3)
Sex			
Men	566	617 (466–801)	9.0 (6.8–11.7)
Women	842	601 (477–747)	18.5 (14.7–23.0)
Age at diagnosis†			
Prepubertal	965	456 (356–576)	10.8 (8.4–13.6)
Pubertal	443	941 (728–1197)	16.4 (12.7–20.9)
Calendar time period of diagnosis			
1965–1969‡	285	869 (605–1208)	15.7 (10.9–21.8)
1975–1979‡	769	267 (180–381)	6.9 (4.6–9.8)
Finland			
Overall	5,126	352 (315–393)	3.7 (3.3–4.1)
Sex			
Men	2,817	448 (391–511)	3.2 (2.8–3.7)
Women	2,309	238 (193–290)	5.2 (4.2–6.3)
Age at diagnosis (years)†			
Prepubertal age	2,835	278 (234–328)	3.6 (3.1–4.3)
Pubertal age	2,291	446 (383–516)	3.7 (3.2–4.3)
Calendar time period of diagnosis			
1965–1969‡	1,582	243 (184–315)	2.9 (2.2–3.8)
1975–1979‡	1,793	225 (172–290)	3.1 (2.4–4.0)

\*Values in the parentheses are 95% CIs. †Prepubertal age <11 years old for women and <12 years old for men; pubertal age ≥11 years old for women and ≥12 years old for men. ‡Follow-up period was limited to 15 years to make the values comparable. Mortality rate and standardized mortality ratios for those with diabetes diagnosed in 1970–1974 are not shown in this comparison, but these patients are included in other analyses shown in this table.

ence: mortality in the cohort with type 1 diabetes was 3.7 times higher than that in the general population in Finland and almost 13 times higher in Japan.

In the Japanese cohort, sex did not affect absolute mortality, but women had

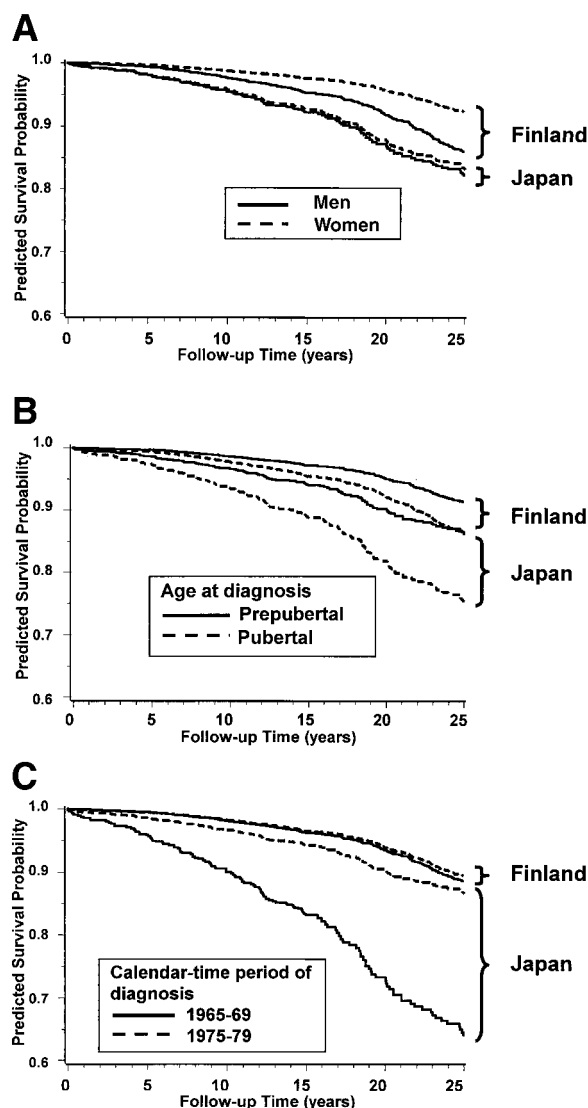
a higher relative mortality. In the Finnish cohort, men had a higher absolute mortality but women had a higher relative mortality. Overall, the relative effect of diabetes was greater in women than in men in both countries. In the background

population of this generation in both countries, women have lower mortality rates than men. These observations suggest possible mechanisms protecting women that diminish if they develop diabetes. Several studies (15–20) have sug-

Table 2—Multivariate Cox proportional hazard models\*

Independent variables	Hazard ratio (95% CI)	
	Model without adjustment for the mortality rates of the general population	Model with adjustment for the mortality rates of the general population
Japan		
Sex (men vs. women)	1.12 (0.79–1.57)	0.52 (0.37–0.73)
Age at diagnosis (pubertal vs. prepubertal age) (years)†	1.94 (1.38–2.71)	1.33 (0.94–1.86)
Calendar time period of diagnosis		
1965–1969 vs. 1975–1979	3.12 (1.91–5.08)	2.25 (1.38–3.68)
1970–1974 vs. 1975–1979	0.82 (0.38–1.76)	0.83 (0.38–1.79)
Finland		
Sex (men vs. women)	1.93 (1.52–2.45)	0.63 (0.49–0.79)
Age at diagnosis (pubertal vs. prepubertal age)†	1.62 (1.30–2.02)	1.02 (0.82–1.27)
Calendar time period of diagnosis		
1965–1969 vs. 1975–1979	1.09 (0.76–1.56)	0.99 (0.69–1.42)
1970–1974 vs. 1975–1979	0.91 (0.55–1.51)	0.91 (0.55–1.50)

\*Number of years of having diabetes upon entering follow-up was adjusted in both models. †Prepubertal age <11 years old for women and <12 years old for men; pubertal age ≥11 years old for women and ≥12 years old for men.



**Figure 1**—A–C: Stratified cumulative-predicted survival probabilities in the Japanese and Finnish cohorts. The predicted survival probabilities were calculated with the Cox hazard models and stratified by sex, age at diagnosis, and calendar time period of diagnosis in each cohort. A: Stratified cumulative-predicted survival probabilities by sex. B: Stratified cumulative-predicted survival probabilities by age at diagnosis (prepubertal age versus pubertal age:  $\geq 11$  years old for women and  $\geq 12$  years old for men). C: Stratified cumulative-predicted survival probabilities by calendar time period of diagnosis. The survival curves for those with diabetes diagnosed in 1970–1974 are not shown in C because they had a longer duration of diabetes before starting follow-up than did those with diabetes diagnosed in 1965–1969 and 1975–1979. To draw the predicted survival curves, the proportions of sex, age at diagnosis (prepubertal age versus pubertal age), and calendar time period of diagnosis (1965–1969, 1970–1974, and 1975–1979), as well as the mean years before entering the follow-up in the combined sample of the two cohorts, were applied as covariates of the models.

gested that diabetes is a greater risk factor for atherosclerosis in women than in men. In addition, several reports show a higher frequency of albuminuria in women with diabetes than in men (21,22). The risk factors for coronary artery disease, but not its incidence rates, may differ between men and women with type 1 diabetes

(23). Diabetic neuropathy, thought to be related to increased mortality (24–26), might develop more often in women (27,28). However, the finding of a greater relative mortality among women compared with men needs to be evaluated, especially for cause-specific mortality, since sex differences in the mortality of

patients with type 1 diabetes have been inconsistent in previous studies (29–34).

Patients in both Japan and Finland with diagnoses during pubertal age had higher absolute mortality than patients diagnosed in prepubertal age. However, the effect of age at diagnosis on the risk of death did not remain significant after being adjusted for mortality in the general population in both cohorts. Possible explanations for the adverse effects of diagnosis in pubertal age include the heterogeneity of the etiology of diabetes (35–37) and psychosocial problems during pubertal age. However, recent studies have shown the importance of prepubertal, as well as pubertal and postpubertal, duration of diabetes for diabetic nephropathy and retinopathy (21,22,38). Our results suggest that the diagnosis of type 1 diabetes in pubertal age might be a risk factor for mortality, but that the risk can be partly explained by higher age attained, which, in general, means higher mortality during the long follow-up.

In Japan, patients with diabetes diagnosed in the 1960s had higher absolute and relative mortality than patients diagnosed in the 1970s. The lower hazard ratio for those in Japan diagnosed in 1970–1974 than that for those diagnosed in 1975–1979 might be an underestimation due to a possible low detection of early deceased cases. Absolute and relative mortality can be decreased by improved care for diabetes and a more supportive socioeconomic environment. Much emphasis has been placed on the diabetes care system in Finland because of its very high incidence of type 1 diabetes (39). Finland has had a nationally organized diabetes care system since the 1960s, free-of-charge insulin since 1965, and the first national management guidelines for diabetes were published in 1975. In contrast, the health care system for type 1 diabetes in Japan was poorly developed before the 1980s (40), at least partially because Japan has an extremely low incidence of type 1 diabetes (39). Improved glycemic and blood pressure controls, as well as improved treatment of acute complications, might have effectively reduced mortality in Japan (41,42). Although Japanese patients with diabetes diagnosed in the 1960s should also have benefited from these recent advances in diabetes care in Japan, absolute and relative mortality in type 1 diabetes diagnosed in the 1960s was significantly higher than that



diagnosed in the 1970s. It is possible that the adverse effects of poor diabetes control in the early stages of the disease might affect mortality over a long period. Studies in several other countries have shown a reduction of absolute and relative mortality over time (2,4,15,18).

In conclusion, mortality from type 1 diabetes was higher in Japan compared with Finland. This effect seems to vary by sex, age at diagnosis, and calendar time period of diagnosis. From clinical and public health points of view, mortality of the general population should be taken into account when determining both the magnitude of the risk of death related to diabetes and the reasons for the increased risk. To answer these questions, we will continue our international comparative study. Cause-specific mortality in the two countries is still under investigation.

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Data for the national mortality in Japan and Finland were obtained from the World Health Organization, World Health Statistics Annual 1972, 1979, 1981, 1984, 1985, 1988, 1989, and 1993.

## APPENDIX

**DERI Mortality Study Group.** Japan: N. Tajima, N. Fukushima, S. Harada, T. Toyota, S. Konda, T. Urakami, Y. Uchigata, N. Hotta, G. Isshiki, A. Takeda, Y. Kaino, Y. Nakamura, T. Jinnouchi, M. Matsushima, R. Nishimura, T. Kawamura, and K. Asao. Finland: J. Tuomilehto, C. Sarti, T. Forsen, V. Hytti-nen, and A. Reunanen.

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