Health-Related Quality of Life and Mortality in a General and Elderly Population of Patients With Type 2 Diabetes (ZODIAC-18)

OBJECTIVE — Diabetes negatively impacts the health-related quality of life (HRQOL) of patients with type 2 diabetes. An earlier analysis showed HRQOL to be associated with mortality, which suggests that measuring HRQOL could have clinical implications. We studied the association between HRQOL and total and cardiovascular mortality in patients with type 2 diabetes during long-term follow-up and specifically focused on old age and sex differences.

RESEARCH DESIGN AND METHODS — HRQOL was measured in a prospectively followed cohort of 1,353 patients with type 2 diabetes using the RAND-36. Cox proportional hazard models were used to measure the independent effect of baseline HRQOL on mortality.

RESULTS — During a mean follow-up of 9.6 years, 570 (42%) patients died, 280 of whom died of cardiovascular disease (49%). The Physical Component Score (PCS) and the Mental Component Score (MCS) were inversely associated with total mortality, with hazard ratios of 0.988 (95% CI 0.983–0.993) and 0.990 (95% CI 0.985–0.995), respectively. A 10-point-higher score on the PCS and MCS decreased the risk for total mortality by 11 and 10%, respectively. An inverse relationship with mortality was also seen for men, women, and for patients aged >75 years. Mental health was significantly related to mortality in men but not in women.

CONCLUSIONS — Lower physical and mental HRQOL was associated with a higher total mortality and cardiovascular mortality in patients with type 2 diabetes; this is also the case when studying men and women and the elderly separately. The dimension mental health, related to depression and anxiety, was only associated with mortality in men, not in women.

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RESEARCH DESIGN AND METHODS — In 1998, in the Zwolle region of the Netherlands, a large diabetes project was initiated. In the Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC), general practitioners were assisted by hospital-based diabetes specialist nurses in providing care for patients with type 2 diabetes. As part of this project, patients with type 2 diabetes in 32 primary-care practices con-
sulted (and still consult) these specialist nurses on an annual basis. Patients with a very short life expectancy (including patients with active cancer) and patients with insufficient cognitive abilities were excluded from the study. All patients with type 2 diabetes were identified during the first 2 years of the project. Any patients being treated by an internal medicine specialist (20%) were excluded, as they were no longer in the primary-care setting. Five percent of patients were excluded because of a short life expectancy or because they had insufficient cognitive abilities to complete the necessary questionnaires. A total of 1,353 (90%) patients agreed to participate in the study. The ZODIAC study was approved by the medical ethics committee, and all patients provided informed consent. The details of this study have been published previously (11).

Baseline data, collected in 1998 and 1999, included the RAND-36 questionnaires, a full medical history including the presence or absence of macrovascular complications, the use of medication, and tobacco consumption. Laboratory and physical assessment data were collected annually and included a lipid profile, A1C, serum creatinine, urinary albumin, urinary creatinine, blood pressure, weight, and height. Subsequently, life status and causes of death were retrieved from the records maintained by the hospital and the general practitioners. The causes of death were coded according to the ICD-9.

The RAND-36 is considered a generic measure as it is used to assess aspects of health that are relevant to any individual’s functional status and well being (12,13). The RAND-36 consists of 36 questions covering nine aspects of health status: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, mental health, and health change. The scores for questions relating to each scale are summed and rescaled to a 100-point scale, where 100 is the best possible score and 0 the worst. The nine scales in the RAND-36 can further be divided into two component summaries: a physical component summary (PCS) and a mental component summary (MCS) (12). Low PCS scores indicate substantial limitations in self-care, physical and social activities, severe bodily pain, or frequent tiredness. Low MCS scores indicate frequent psychological distress and substantial social and role limitations due to emotional problems.

To study mortality, standardized mortality ratios were calculated for total and cardiovascular mortality using general mortality reference rates from the Netherlands (http://statline.cbs.nl/statweb/). Cox proportional hazard modeling was used to assess the association between HRQOL and total mortality and cardiovascular mortality. The health dimensions and component scales all have a different mean value between countries. Comparing scales between countries is difficult; therefore, we transformed the scales. The transformation used is a linear T-score transformation with reference data from the Netherlands (14), which has the advantage of making the different dimensions of health easier to interpret without further reference to normative data (12,15). This results in scores for all the dimensions and the summary scores to have a mean (±SD) of 50 ± 10. The use of the same mean and SD for purposes of transforming scores has the advantage of permitting comparisons of mean scores for HRQOL across countries (16).

A model was constructed that included all possible confounders in the analysis (see below). Separate analyses were performed to study the effect of age and sex on mortality. For the age-specific analysis, patients were stratified into two age-groups, those aged >75 years and those aged ≤75 years. For the sex-specific analysis, we investigated whether significant interaction takes place between sex and HRQOL. Subsequently, we performed multivariate analyses stratified according to sex. The following variables as possible confounders were included (age, sex, smoking [yes/no], duration of diabetes, serum creatinine, BMI, systolic blood pressure, total-to-HDL cholesterol ratio, macrovascular complications [yes/no], use of statins [yes/no], insulin use [yes/no], and urinary albumin-to-creatinine ratio). The proportional hazards assumption was examined using log (−log) survival plots. The parallel lines in the plots indicate that the assumption was met. All tests were two sided, and analyses were performed with SPSS, version 15.0.1 (SPSS, Chicago, IL).

**RESULTS**—Patient characteristics at baseline are presented in Table 1. After a median follow-up period of 9.6 years, 570 of 1,353 patients had died (42%). Life status was not known for 20 patients (1%), and causes of death were unknown for 29 patients (5%). 238 deaths (42%) had cardiovascular causes and 122 deaths (21%) were due to cancer. HRQOL data were available and complete for 1,053 patients (78%). The standardized mortality ratios (95% CIs) for total mortality and cardiovascular mortality were 2.35 (95% CI 1.77–3.04) and 2.67 (2.36–3.05).

| Table 1—Baseline characteristics |
|----------------------------------|
| Characteristics                  | Total         | Deceased patients | Survived patients |
|----------------------------------|---------------|-------------------|-------------------|
| n                                | 1,353         | 570               | 783               |
| Age (years)                      | 67.8 ± 11.7   | 75.3 ± 8.6        | 62.4 ± 10.6†      |
| Female (%)                       | 57.6          | 57.2              | 57.9              |
| Diabetes duration (years)        | 6 (3–11)      | 7 (3–13)          | 5 (2–10)†         |
| Smoking (%)                      | 18.6          | 14.8              | 21.4              |
| BMI (kg/m²)                      | 28.9 ± 4.8    | 28.3 ± 4.7        | 29.4 ± 4.7†       |
| Systolic blood pressure (mmHg)   | 153 ± 25      | 156 ± 27          | 152 ± 24*         |
| A1C (%)                          | 7.5 ± 1.2     | 7.4 ± 1.3         | 7.5 ± 1.2         |
| Creatinine clearance (ml/min)    | 73.9 ± 28.1   | 60.3 ± 22.2       | 83.8 ± 27.9†      |
| Total-to-HDL ratio               | 5.2 ± 1.6     | 5.1 ± 1.6         | 5.2 ± 1.6         |
| Albumin-to-creatinine ratio      | 2.1 (1.0–7.2) | 3.9 (1.4–12.3)    | 1.0 (0.9–4.4)†    |
| Macrovascular complications (%)  | 32.7          | 46.1              | 23.0‡             |
| Age >75 years (%)                | 27.6          | 53.3              | 8.9†              |
| PCS score                        | 71.6 (48.7–86.7) | 61.3 (41.5–80.5) | 76.8 (55.8–89.2)† |
| MCS score                        | 76.8 (39.3–87.6) | 71.3 (52.3–84.1) | 79.8 (61.8–88.8)† |

Data are means ± SD for normally distributed data, median (interquartile range) for nonnormally distributed data, or percent. †p < 0.05; ‡p < 0.001.
Sex-related differences

We found a significant interaction between mental health and sex (P = 0.042) (Table 4). After adding the interaction term between sex and mental health to the model, the association between mental health and total mortality became more pronounced (HR 0.976 [95% CI 0.960–0.994]). The PCS and MCS were inversely associated with total mortality for both women and men. For female patients, the HRs were 0.988 (0.982–0.994) and 0.992 (0.985–0.989) for PCS and MCS, respectively. For male patients, the HRs for PCS and MCS were 0.988 (0.981–0.996) and 0.987 (0.979–0.995) for female patients, the HRs were 0.988 (0.984–0.991) and 0.994 (0.989–0.999) for PCS and MCS, respectively. For male patients, the HRs for PCS and MCS were 0.988 (0.981–0.996) and 0.987 (0.979–0.995).

A total of six of nine health dimensions were related to total mortality for women and five of nine for men. There were three differences: the health dimension role functioning (physical) was significantly related to mortality in women but not in men, and bodily pain was significantly related to women but not in men, although absolute HRs did not really differ. Mental health was significantly related to mortality in men but not in women, with notable differences also in HR (0.998 [95% CI 0.996–0.999]) vs. 0.998 (0.992–1.004). When looking at the individual five questions from which the mental health dimension is composed, all five relating to depression and anxiety, these five questions were related to mortality in men but none in women (data not shown).

Analyzing of the model with the variable “incomplete questionnaire” (instead of the RAND-36 scores), patients who did not complete the RAND-36 had an increased total mortality risk compared with patients who completed the questionnaire. When excluding the first 2 years of follow-up, the relationship between the two component summaries and total and cardiovascular mortality was still present and did not relevantly change (data not shown). Survival was also predicted by the factors age, sex, serum creatinine, and albumin-to-creatinine ratio. The proportional hazard assumptions were met for all analyses.

**CONCLUSIONS** — After a median follow-up period of almost 10 years, total and cardiovascular mortality was increased for type 2 diabetic patients who had a lower HRQOL at baseline. Both the PCS and MCS were related to total and cardiovascular mortality regardless of confounders such as age and sex. A 10-point-higher score, on a 100-point scale, on the PCS and MCS decreased the risk for mortality by 11 and 10%, respectively. A 1% decrease on the PCS and MCS decreased the risk for cardiovascular mortality regardless of confounders such as age and sex. A 1% decrease on the PCS and MCS decreased the risk for mortality by 11 and 10%, respectively. A 1% decrease in A1C (17). Our study supports the recommendations to include measurement and integration of health status in clinical practice (18, 19). As it is difficult to interpret the applicability of our results into

![Table 3—Relationship between HRQOL and total mortality stratified according to age](image-url)
Table 4—Relationship between HRQOL and total mortality stratified according to sex

| RAND-36 dimensions                              | HR (95%CI)* | HR (95%CI)* |
|------------------------------------------------|-------------|-------------|
| 1-point higher score                           | Male subjects | Female subjects |
| PCS                                            | 0.988 (0.981–0.996) | 0.988 (0.982–0.994) |
| MCS                                            | 0.987 (0.979–0.995) | 0.992 (0.985–0.998) |
| Physical functioning                           | 0.988 (0.983–0.994) | 0.988 (0.982–0.993) |
| Social functioning                             | 0.990 (0.984–0.996) | 0.993 (0.988–0.998) |
| Role functioning, physical                     | 0.997 (0.993–1.001) | 0.996 (0.993–0.999) |
| Role functioning, emotional                    | 0.996 (0.992–1.001) | 0.997 (0.994–1.000) |
| Mental health                                  | 0.984 (0.976–0.992) | 0.994 (0.989–0.999) |
| Bodily pain                                    | 0.994 (0.989–1.000) | 0.994 (0.989–0.999) |
| Vitality                                       | 0.993 (0.987–0.999) | 0.993 (0.988–0.999) |
| General health perception                      | 0.986 (0.976–0.996) | 0.983 (0.974–0.992) |
| Health change                                  | 0.998 (0.989–1.006) | 0.997 (0.989–1.004) |

*Corrected for age, smoking, duration of diabetes, serum creatinine, BMI, systolic blood pressure, total-to-HDL cholesterol ratio, macrovascular complications, use of statins, insulin use, and urinary albumin-to-creatinine ratio. Significant relationships are indicated in bold.

daily practice, we present an example: if a female patient has a score of 40 on the PCS, this means that her absolute score is 10 points lower than the mean (using the T-score transformation, the PCS has a mean of 50). Her HR for mortality would be 11.4% higher (0.988 to the power of 10).

In our previous study, which had a median follow-up period of 5.8 years, the only significant association we found was between the PCS score and total mortality, and two separate health dimensions: ‘physical functioning’ and ‘general health perception’ (6). The association between the MCS score and mortality was 1.008 (CI 0.994–1.022). In our present study, with almost 10 years of follow-up, the relationship is quite different, and MCS is now inversely associated with mortality. This may imply that low MCS scores can only predict mortality after a longer follow-up period. Furthermore, the relationships between the separate health dimensions and mortality have become more pronounced, with most dimensions being inversely related to mortality.

For the sex-specific analysis, an interesting interaction between mental health and sex existed. Such an interaction could mean that sex has an effect on the relationship between mental health and mortality. Stratification for sex revealed one relevant difference: mental health was related to mortality in men only. A 10-point-higher score on the dimension mental health decreased mortality risk with 15% in men. At baseline, women rated their mental health worse than men, with a median score of 79 vs. 71 in men (P = 0.001). Patients with decreased scores on the mental health dimension have symptoms related to depression and anxiety (20). This difference between men and women in our cohort could imply that poorer mental health, although less prevalent in man compared with women, has a greater effect on mortality in men. The individual questions from which the mental health dimension is composed are related to depression and anxiety, and there is some evidence in a non-diabetic population that depression effects mortality risk in men more than in women (21).

In the age-specific analysis, in which we stratified for age, many associations were not significant for patients aged >75 years. However, these differences do not seem to be clinically relevant and are probably caused by the reduction in sample size after stratification. According to the various subgroup analyses, the health dimensions physical functioning, social functioning, and general health were the most consistent predictors for mortality. Previous studies (22,23) have shown that a patient’s self-rated health status is consistently associated with mortality.

Due to this study’s observational design, it is not clear whether there is a true causal relationship between HRQOL and mortality. The question remains whether HRQOL is a modifiable risk factor or just a marker of disease burden. No randomized controlled trials have been performed in which an attempt was made to specifically improve HRQOL specifically. Whether HRQOL is a causal factor for mortality, we first would need to identify a possible treatment strategy to improve HRQOL. A recent meta-analysis could not identify psychosocial interventions with clinically relevant benefit with regard to physical and mental health in patients with diabetes (24). Developing such strategies remains an important challenge and could have implications for the understanding of interaction between physical and mental health. Patients with diabetes are also more prone to depression compared with patients without diabetes (25). The dimension mental health is correlated to depression (13), and depression is independently associated with a lower HRQOL and mortality (25); hence, one could hypothesize that treating depression, and indirectly HRQOL, may increase survival. Such a hypothesis needs to be investigated, however. Several trials have been performed in depressed patients following a myocardial infarction, but all interventions applied did not increase survival (26).

There are additional limitations to our study. Twenty-two percent of our patient population did not complete the RAND-36 questionnaire. As not completing the questionnaire was associated with an increased mortality, it is likely that the relationships between the HRQOL indexes and (cardiovascular) mortality are underestimated in this study. There may also be additional confounders, such as depression and social economic status, which we did not take into account and which may, therefore, have influenced the outcome (25). Furthermore, no adjustments were made for a history of diseases other than cardiovascular disease. However, after excluding the first 2 years of follow-up from the analysis, the relationship between HRQOL and (cardiovascular) mortality remained largely unchanged. Excluding the first 2 years of follow-up could correct for severe comorbidity or undiagnosed cancer at the start of the study, which could have influenced outcome.

Specific strengths of our study include the prospective nature of the design and a follow-up period of almost 10 years. The number of deaths after the 10-year period was sufficient to allow reliable estimates of associations with mortality. We also performed a T-score transformation, which has the advantage of permitting comparisons of mean scores for health in different countries (15).

Our study shows that a decrease in HRQOL is associated with an increase in (cardiovascular) mortality among young as well as elderly type 2 diabetic patients. HRQOL instruments may become an increasingly useful clinical tool to not only identify those patients with a low HRQOL...
but also to identify those patients with an associated increase in mortality risk. This study supports the clinical predictive use of HRQOL measures in combination with the well established risk factors for the assessment of mortality risk for patients type 2 diabetes.

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