ORIGINAL ARTICLE

Excess Mortality among Persons with Type 2 Diabetes

Mauro Tancredi, M.D., Annika Rosengren, M.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D., Aldina Pivodic, M.Sc., Soffia Gudbjörnsdottir, M.D., Ph.D., Hans Wedel, Ph.D., Mark Clements, M.D., Ph.D., Sofia Dahlqvist, and Marcus Lind, M.D., Ph.D.

ABSTRACT

BACKGROUND

The excess risks of death from any cause and death from cardiovascular causes among persons with type 2 diabetes and various levels of glycemic control and renal complications are unknown. In this registry-based study, we assessed these risks according to glycemic control and renal complications among persons with type 2 diabetes.

METHODS

We included patients with type 2 diabetes who were registered in the Swedish National Diabetes Register on or after January 1, 1998. For each patient, five controls were randomly selected from the general population and matched according to age, sex, and county. All the participants were followed until December 31, 2011, in the Swedish Registry for Cause-Specific Mortality.

RESULTS

The mean follow-up was 4.6 years in the diabetes group and 4.8 years in the control group. Overall, 77,117 of 435,369 patients with diabetes (17.7%) died, as compared with 306,097 of 2,117,483 controls (14.5%) (adjusted hazard ratio, 1.15; 95% confidence interval [CI], 1.14 to 1.16). The rate of cardiovascular death was 7.9% among patients versus 6.1% among controls (adjusted hazard ratio, 1.14; 95% CI, 1.13 to 1.15). The excess risks of death from any cause and cardiovascular death increased with younger age, worse glycemic control, and greater severity of renal complications. As compared with controls, the hazard ratio for death from any cause among patients younger than 55 years of age who had a glycated hemoglobin level of 6.9% or less (≤52 mmol per mole of nonglycated hemoglobin) was 1.92 (95% CI, 1.75 to 2.11); the corresponding hazard ratio among patients 75 years of age or older was 0.95 (95% CI, 0.94 to 0.96). Among patients with normoalbuminuria, the hazard ratio for death among those younger than 55 years of age with a glycated hemoglobin level of 6.9% or less, as compared with controls, was 1.60 (95% CI, 1.40 to 1.82); the corresponding hazard ratio among patients 75 years of age or older was 0.76 (95% CI, 0.75 to 0.78), and patients 65 to 74 years of age also had a significantly lower risk of death (hazard ratio, 0.87; 95% CI, 0.84 to 0.91).

CONCLUSIONS

Mortality among persons with type 2 diabetes, as compared with that in the general population, varied greatly, from substantial excess risks in large patient groups to lower risks of death depending on age, glycemic control, and renal complications. (Funded by the Swedish government and others.)

From the Department of Molecular and Clinical Medicine, University of Gothenburg (M.T., A.R., S.G., M.L.), Center of Registers in Region Västra Götaland (A.-M.S.), Statistiska Konsultgruppen (A.P.), and Nordic School of Public Health (H.W.), Gothenburg, and the Department of Medicine, NU Hospital Group, Trollhättan and Uddevalla (M.T., S.D., M.L.) — all in Sweden; Saint Luke's Mid America Heart Institute (M.K.) and Children's Mercy Hospital (M.C.), University of Missouri–Kansas City School of Medicine, Kansas City; and the University of Kansas School of Medicine, Kansas City (M.C.). Address reprint requests to Dr. Lind at the Department of Medicine, Uddevalla Hospital, 451 80 Uddevalla, Sweden, or at lind.marcus@telia.com.

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The global burden of diabetes has risen dramatically over the past two decades and is expected to affect more than 500 million adults by 2030, with most having type 2 diabetes.[1] Myocardial infarction is the most common cause of death in these patients.[2,3] Although factors that are known to reduce the risk of myocardial infarction,[2,4,5] including the use of lipid-lowering and antihypertensive medications and better glycemic control over time,[6-8] have been noted in persons with type 2 diabetes, an excess risk of death still exists.[9]

Population-based studies have generally not evaluated the excess risks of death from any cause and of death from cardiovascular causes among persons with type 2 diabetes and various levels of risk-factor control.[9-18] We recently found that all-cause mortality and cardiovascular mortality increased markedly with worsening glycemic control among patients with type 1 diabetes[19]; however, even patients with at-goal glycated hemoglobin levels (≤6.9% [≤52 mmol per mole of nonglycated hemoglobin]) had a risk of death that was twice that in the general population. The present study evaluated the excess risk of death among patients with type 2 diabetes, as compared with controls, according to glycemic control and renal complications among persons who had data included in the Swedish National Diabetes Register.

Methods

Study Oversight

The study was designed by three of the authors and was approved by the ethics committee of the University of Gothenburg, Sweden. The first and last authors wrote the first draft of the manuscript. All the authors analyzed the data and reviewed, edited, and approved the final manuscript. The fifth and last authors vouch for the accuracy and integrity of the data and analyses. The study had no commercial sponsorship.

Study Design

The National Diabetes Register, initiated in 1996, has been described previously[19,20]; it includes information on risk factors, complications of diabetes, and medications in patients 18 years of age or older. Each patient provides informed consent (verbal or written) for inclusion in the register, and more than 90% of all persons with type 2 diabetes in Sweden are included. As in previous National Diabetes Register studies,[20] persons were considered to have type 2 diabetes if they were receiving treatment with diet with or without the use of oral hypoglycemic agents or treatment with insulin with or without the use of oral hypoglycemic agents. The latter category applied only to patients who were 40 years of age or older at the time of diabetes diagnosis.

Patients with at least one entry in the National Diabetes Register from January 1, 1998, until December 31, 2011, were included in the study. For each patient, five controls were randomly selected from the general population in Sweden and matched for age, sex, and county.[19]

Information on coexisting conditions and cause of death was retrieved by linking numbers personally identifying patients and controls to the Swedish Inpatient Register and the Swedish Registry for Cause-Specific Mortality. Information on educational level and country of birth was retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies.[19,21] Educational level was categorized as low (compulsory only), intermediate, or high (university level or similar). Country of birth was categorized as Sweden or other. Data regarding prescription and overall drug use were retrieved from the Swedish Prescribed Drug Register, which includes information for the entire Swedish population from July 2005 onward.[22]

Patients and controls were followed from baseline until death or December 31, 2011, whichever came first. In total, 0.07% of patients with type 2 diabetes (291 of 435,660 patients) and 1.3% of matched controls (27,084 of 2,144,567 controls) were excluded from the study because of inconsistent data on vital status, leaving 435,369 patients and 2,117,483 controls.

The Inpatient Register includes nationwide coverage of all inpatient admissions from 1987 onward. Codes from the *International Classification of Diseases, Tenth Revision* (ICD), were used to define acute myocardial infarction, coronary heart disease, hospitalization for heart failure, atrial fibrillation, stroke, cancer diagnoses, renal dialysis, and transplantation from 1987 onward. (For ICD codes, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) Dates and diagnoses for death from cardiovascular causes, death from cancer, diabetes-related death, and external and all other causes of death were retrieved from the cause-of-death register.

Microalbuminuria was defined by two positive results on three urine samples obtained within 1 year, with positivity defined by an albumin:creatinine ratio of 3 to 30 mg per millimole (approximately 30 to 300 mg per gram) or a urinary albumin clearance of 20 to 200 μg per minute [20 to 300 mg per liter]). Macroalbuminuria was defined by an albumin:creatinine ratio of more than 30 mg per millimole (approximately >300 mg per gram) or a urinary albumin clearance of more than 200 μg per minute (>300 mg per liter). The estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease equation.[23] Stage 5 chronic kidney disease was defined by the need for dialysis or renal transplantation or by an eGFR of less than 15 ml per minute.

All-cause mortality and cardiovascular mortality were assessed across categories of time-updated mean glycated hemoglobin level[24] to compare mortality among patients with type 2 diabetes with that among matched controls, according to levels of glycemic control. (The time-updated mean is the mean value calculated at a certain time [e.g., if three values exist for glycated hemoglobin level until that point, then the time-updated mean is the mean level of those values].) Corresponding analyses of mortality were performed for two renal variables, with the first categorized as normoalbuminuria, microalbuminuria, macroalbuminuria, or stage 5 chronic kidney disease and the second categorized as an eGFR of 15 to 30 ml per minute, more than 30 to 45 ml per minute, more than 45 to 60 ml per minute, more than 60 to 90 ml per minute, or more than 90 ml per minute or stage 5 chronic kidney disease.

STATISTICAL ANALYSIS

Crude mortality rates were described as events per 1000 person-years, with 95% exact Poisson confidence intervals. Survival analyses were performed with the use of Cox regression, with adjustment in model 1 for sex and time-updated (i.e., the value recorded closest to the time preceding each event) age categories (<55 years, 55 to 64 years, 65 to 74 years, or ≥75 years). In model 2, the analysis was additionally stratified in the type 2 diabetes group and the matched control group according to diabetes duration in the diabetes group (0 to 1 years, >1 to 5 years, >5 to 10 years, >10 to 20 years, or >20 years); the controls were assigned to the same stratification category as the patients in the diabetes group with whom they were matched. In model 3, the analysis was further adjusted for educational level (low, intermediate, or high), country of birth (Sweden or other), and status at baseline with regard to a history of coexisting conditions (acute myocardial infarction, coronary heart disease, atrial fibrillation, heart failure, stroke, or cancer) according to records in the Inpatient Register.

Model 3, which included an interaction term between age categories and glycated hemoglobin levels, was used to evaluate the association of categories of time-updated mean glycated hemoglobin among patients with type 2 diabetes with outcomes as compared with controls. Interactions for diabetes with sex and with prespecified years (<2005 vs. ≥2005) were also investigated. Mortality analyses according to status with respect to renal disease were performed with methods similar to those for the time-updated mean glycated hemoglobin level. The proportional-hazards assumption was fulfilled.

A Cox regression model was used to evaluate the effect of additional risk factors on the relationship between glycated hemoglobin, renal disease, and outcomes in the diabetes group (see the Supplementary Appendix). All the tests were two-tailed and conducted at a significance level of 0.05. All the analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION AND FOLLOW-UP

The baseline characteristics of the two study groups are shown in Table 1, and in Table S1 in the Supplementary Appendix. Among 435,369 patients with type 2 diabetes and 2,117,483 controls, the proportion of women and the distribution according to age were similar. However, as compared with controls, fewer patients with diabetes were born in Sweden and fewer had a university education or higher. All cardiovascular coexisting conditions were more common among patients with diabetes than among controls. In the diabetes group, the mean glycated hemoglobin level at baseline was 7.1% (54.3 mmol per mole) and the mean duration of diabetes was 5.7 years. The mean follow-up of patients with type 2 diabetes was 4.6 years, and the mean follow-up of controls was 4.8 years.

Table 1. Baseline Characteristics of Patients with Type 2 Diabetes and Matched Controls from the General Population.*

Characteristic	Patients with Type 2 Diabetes (N = 435,369)	Controls (N = 2,117,483)
Age — yr	65.8±12.6	65.5±12.5
Women — no. (%)	193,540 (44.5)	953,960 (45.1)
Born in Sweden — no. (%)	360,856 (82.9)	1,855,675 (87.6)
Educational level — no./total no. (%)		
Low	189,808/425,706 (44.6)	781,319/2,080,022 (37.6)
Intermediate	169,159/425,706 (39.7)	812,340/2,080,022 (39.1)
High	66,739/425,706 (15.7)	486,363/2,080,022 (23.4)
Information from National Diabetes Register		
Glycated hemoglobin		
No. of persons with data	388,643	—
Mean — mmol/mole of nonglycated hemoglobin	54.3±14.5	—
Diabetes treatment — no. (%)		
Diet	165,144 (37.9)	—
Tablets	184,002 (42.3)	—
Insulin	46,037 (10.6)	—
Insulin and tablets	40,186 (9.2)	—
Diabetes duration		
No. of persons with data	386,621	—
Mean — yr	5.66±7.07	—
Body-mass index		
No. of persons with data	326,586	—
Mean	29.6±5.3	—
Low-density lipoprotein cholesterol		
No. of persons with data	210,262	—
Mean — mmol/liter	2.94±0.95	—
Blood pressure		
No. of persons with data	375,133	—
Systolic — mm Hg	140.4±18.4	—
Diastolic — mm Hg	78.5±9.9	—
Smoking — no./total no. (%)	53,796/351,842 (15.3)	—
Blood-pressure–lowering medication — no./total no. (%)	265,846/409,442 (64.9)	—
Lipid-lowering medication — no./total no. (%)	163,431/407,357 (40.1)	—
Registration in the In-Patient Register before baseline — no. (%)†		
Acute myocardial infarction	39,115 (9.0)	90,933 (4.3)
Coronary heart disease	68,945 (15.8)	168,292 (7.9)
Atrial fibrillation	38,164 (8.8)	117,844 (5.6)
Heart failure	30,249 (6.9)	69,844 (3.3)
Stroke	27,293 (6.3)	81,976 (3.9)
Cancer	45,907 (10.5)	209,394 (9.9)

* Plus–minus values are means ±SD. Educational level was categorized as low (compulsory only), intermediate, or high (university level or similar). Percentages for the glycated hemoglobin level were based on values from the National Glycohemoglobin Standardization Program, and concentrations were based on values from the International Federation of Clinical Chemistry. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† The following codes from the *International Classification of Diseases, 10th Revision*, were used: I21 for acute myocardial infarction; I20 through I25 for coronary heart disease; I48 for atrial fibrillation; I50 for heart failure; I61, I62.9, I63, I64, and I67.9 for stroke; and C00 through C97 for cancer.

MORTALITY

Table 2 shows the unadjusted rates of death from any cause and death from cardiovascular causes stratified according to baseline age. The overall rate of death per 1000 person-years was 38.64 among persons with type 2 diabetes (77,117 deaths among 435,369 patients [17.7%]), as compared with 30.30 among controls (306,097 deaths among 2,117,483 controls [14.5%]). For cardiovascular mortality, the rate per 1000 person-years was 17.15 among patients with type 2 diabetes, as compared with 12.86 among controls.

Table 2 also shows the unadjusted rates of death from cancer, death from external causes, and death from diabetes-related causes, stratified according to baseline age. As compared with controls, the rate ratios were higher among younger persons than among older persons for all-cause mortality and for cardiovascular mortality. Patients with diabetes had higher rates of diabetes-related death and cancer-related death than did controls, whereas deaths due to other causes were more common among controls than among patients.

In Cox regression analyses, hazard ratios for death from any cause among persons with type 2 diabetes versus controls were 1.27 (95% confidence interval [CI], 1.26 to 1.28) with adjustment for sex and time-updated age, 1.28 (95% CI, 1.27 to 1.29) with additional adjustment for diabetes duration, and 1.15 (95% CI, 1.14 to 1.16) with additional adjustment for country of birth, educational level, and history of coexisting conditions at baseline. The corresponding hazard ratios for death from cardiovascular causes were 1.33 (95% CI, 1.31 to 1.34), 1.33 (95% CI, 1.32 to 1.35), and 1.14 (95% CI, 1.13 to 1.15). We found an interaction between diabetes and age for the analyses of all-cause mortality and cardiovascular mortality ($P<0.001$ for both comparisons), but no interaction was observed between diabetes and sex for the analysis of all-cause mortality ($P=0.21$) or cardiovascular mortality ($P=0.67$).

There was also a time interaction, in which the adjusted hazard ratios for death from any cause among patients with diabetes as compared with controls were significantly lower during the last 7 years of follow-up (2005 or later) than during the initial 7 years of follow-up (before 2005) (hazard ratio in the last 7 years of follow-up, 1.13 [95% CI, 1.12 to 1.14]; hazard ratio in the initial 7 years of follow-up, 1.17 [95% CI, 1.15 to 1.19]; $P=0.004$ for interaction). Similar results were observed for cardiovascular mortality (hazard ratio in the last 7 years of follow-up, 1.11 [95% CI, 1.09 to 1.12]; hazard ratio in the initial 7 years of follow-up, 1.19 [95% CI, 1.16 to 1.22]; $P<0.001$ for interaction). Hazard ratios according to age group during the initial 7 years of follow-up and the last 7 years of follow-up for death from any cause and for cardiovascular death are shown in Figure 1.

RISK OF DEATH IN RELATION TO GLYCEMIC CONTROL AND RENAL COMPLICATIONS

The excess risk of death increased monotonically with higher levels of time-updated mean glycated hemoglobin in all age categories (Table 3 for model 3, and Table S2 in the Supplementary Appendix for models 1 and 2). Among persons with type 2 diabetes with a time-updated mean glycated hemoglobin level of 6.9% or less (≤52 mmol per mole) and an age of less than 55 years, the excess risks of death were approximately twice as high as the risks among controls (hazard ratio for death from any cause, 1.92; 95% CI, 1.75 to 2.11; hazard ratio for cardiovascular death, 2.18; 95% CI, 1.81 to 2.64) (Table 3). However, patients 75 years of age or older had lower risks of death than controls (hazard ratio for death from any cause, 0.95; 95% CI, 0.94 to 0.96; hazard ratio for cardiovascular death, 0.92; 95% CI, 0.90 to 0.94).

Among patients in the highest category of glycated hemoglobin level (≥9.7% [≥83 mmol per mole]) who were younger than 55 years of age, the hazard ratio for death from any cause, as compared with controls, was 4.23 (95% CI, 3.56 to 5.02) and the hazard ratio for cardiovascular death was 5.38 (95% CI, 3.89 to 7.43). Among patients 75 years of age or older in this glycated-hemoglobin category, the corresponding hazard ratio for death from any cause was 1.55 (95% CI, 1.47 to 1.63) and the hazard ratio for cardiovascular death was 1.42 (95% CI, 1.32 to 1.53).

The mean number of glycated hemoglobin measurements per year was 1.4 (interquartile range, 1.0 to 1.5). In analyses in the diabetes group, the risks of death from any cause and cardiovascular death increased incrementally with higher time-updated mean glycated hemoglobin level (Table S3 in the Supplementary Appendix) but were stable when the analysis was additionally adjusted. The average increase in risk

Table 2. Mortality, According to Cause of Death, among Patients with Type 2 Diabetes and Matched Controls from the General Population, According to Age at Baseline.*

Cause of Death	Patients (N=435,369)	Controls (N=2,117,483)	<55 Yr		55–64 Yr		65–74 Yr		≥75 Yr	
			Patients (N=78,086)	Controls (N=389,657)	Patients (N=115,451)	Controls (N=574,492)	Patients (N=126,530)	Controls (N=619,517)	Patients (N=115,302)	Controls (N=533,817)
Any cause										
No. of persons (%)	77,117 (17.7)	306,097 (14.5)	2603 (3.3)	5691 (1.5)	9203 (8.0)	27,302 (4.8)	20,647 (16.3)	74,594 (12.0)	44,664 (38.7)	198,510 (37.2)
No. of deaths per 1000 person-yr (95% CI)	38.64 (38.37–38.91)	30.30 (30.19–30.41)	6.89 (6.63–7.16)	2.97 (2.90–3.05)	16.20 (15.87–16.54)	9.42 (9.31–9.54)	35.19 (34.71–35.67)	24.79 (24.61–24.97)	96.41 (95.52–97.31)	87.00 (86.62–87.39)
Cardiovascular cause										
No. of persons (%)	34,238 (7.9)	129,917 (6.1)	831 (1.1)	1374 (0.4)	3254 (2.8)	7,653 (1.3)	8,287 (6.5)	26,579 (4.3)	21,866 (19.0)	94,311 (17.7)
No. of deaths per 1000 person-yr (95% CI)	17.15 (16.97–17.34)	12.86 (12.79–12.93)	2.20 (2.05–2.35)	0.72 (0.68–0.76)	5.73 (5.53–5.93)	2.64 (2.58–2.70)	14.12 (13.82–14.43)	8.83 (8.73–8.94)	47.20 (46.58–47.83)	41.33 (41.07–41.60)
Cancer										
No. of persons (%)	16,873 (3.9)	77,149 (3.6)	622 (0.8)	2098 (0.5)	2921 (2.5)	11,759 (2.0)	5,735 (4.5)	26,742 (4.3)	7,595 (6.6)	36,550 (6.8)
No. of deaths per 1000 person-yr (95% CI)	8.45 (8.33–8.58)	7.64 (7.58–7.69)	1.65 (1.52–1.78)	1.10 (1.05–1.14)	5.14 (4.96–5.33)	4.06 (3.99–4.13)	9.77 (9.52–10.03)	8.89 (8.78–9.00)	16.39 (16.03–16.77)	16.02 (15.86–16.18)
Diabetes-related cause										
No. of persons (%)	8,024 (1.8)	3,893 (0.2)	273 (0.3)	89 (<0.1)	884 (0.8)	357 (0.1)	2,127 (1.7)	931 (0.2)	4,740 (4.1)	2,516 (0.5)
No. of deaths per 1000 person-yr (95% CI)	4.02 (3.93–4.11)	0.39 (0.37–0.40)	0.72 (0.64–0.81)	0.05 (0.04–0.06)	1.56 (1.46–1.66)	0.12 (0.11–0.14)	3.62 (3.47–3.78)	0.31 (0.29–0.33)	10.23 (9.94–10.53)	1.10 (1.06–1.15)
External cause										
No. of persons (%)	2,462 (0.6)	11,088 (0.5)	287 (0.4)	883 (0.2)	390 (0.3)	1,696 (0.3)	568 (0.4)	2,379 (0.4)	1,217 (1.1)	6,130 (1.1)
No. of deaths per 1000 person-yr (95% CI)	1.23 (1.19–1.28)	1.10 (1.08–1.12)	0.76 (0.67–0.85)	0.46 (0.43–0.49)	0.69 (0.62–0.76)	0.59 (0.56–0.61)	0.97 (0.89–1.05)	0.79 (0.76–0.82)	2.63 (2.48–2.78)	2.69 (2.62–2.75)
Other										
No. of persons (%)	15,520 (3.6)	84,050 (4.0)	590 (0.8)	1247 (0.3)	1754 (1.5)	5,837 (1.0)	3,930 (3.1)	17,963 (2.9)	9,246 (8.0)	59,003 (11.1)
No. of deaths per 1000 person-yr (95% CI)	7.78 (7.65–7.90)	8.32 (8.26–8.38)	1.56 (1.44–1.69)	0.65 (0.62–0.69)	3.09 (2.95–3.24)	2.01 (1.96–2.07)	6.70 (6.49–6.91)	5.97 (5.88–6.06)	19.96 (19.55–20.37)	25.86 (25.65–26.07)

* CI denotes confidence interval.

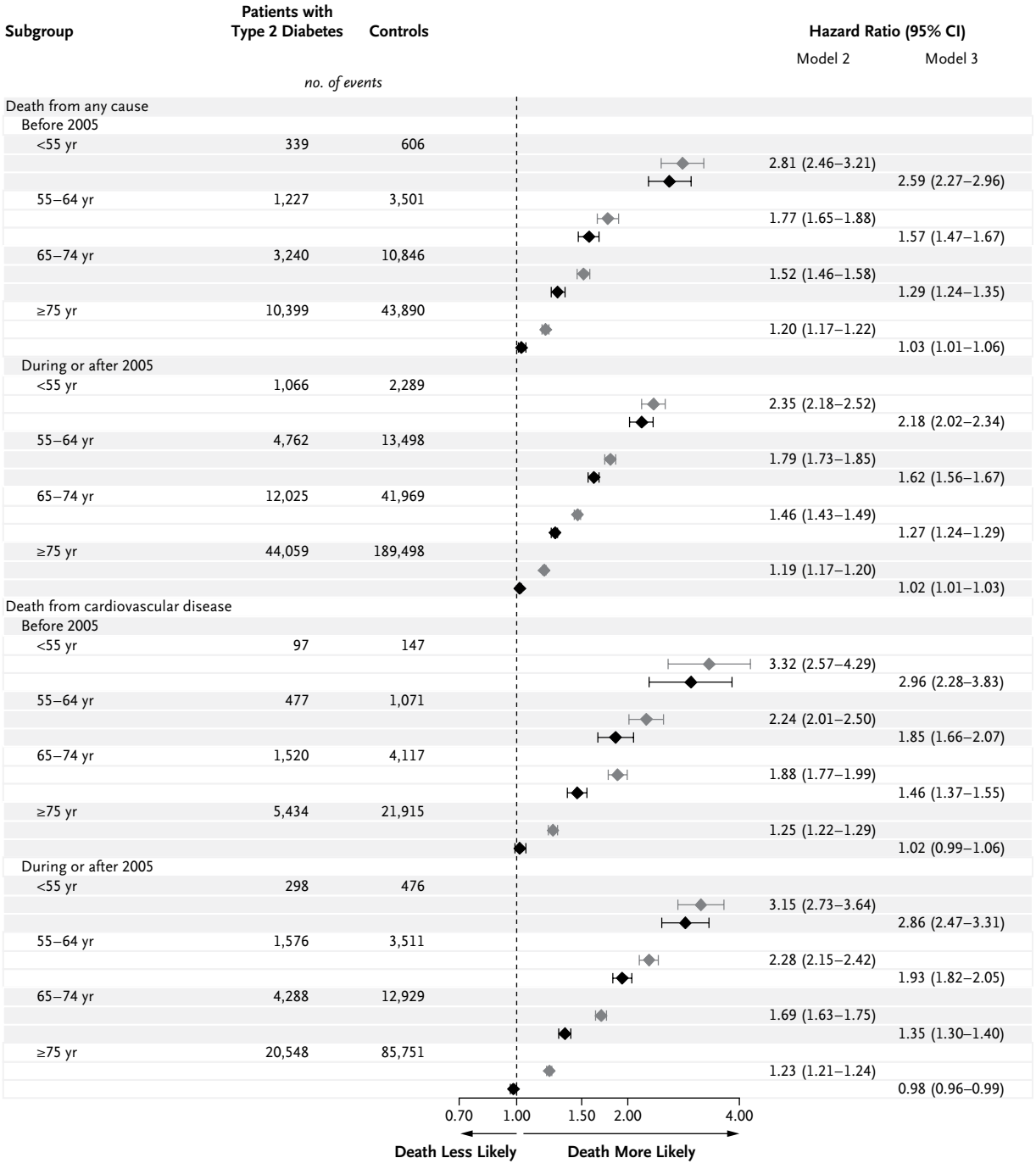

Figure 1. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes, According to Year Range and Age Category, in Models 2 and 3.

The analysis, which was based on Cox regression, was adjusted for time-updated age and sex and was stratified according to duration of diabetes in the diabetes group (0 to 1 years, >1 to 5 years, >5 to 10 years, >10 to 20 years, or >20 years) in model 2; controls were assigned to the same stratification category as the patients in the diabetes group with whom they were matched. In model 3, the analysis was additionally adjusted for country of birth (Sweden or other), educational level (low [compulsory only], intermediate, or high [university level or similar]), and status with respect to history of coexisting conditions at baseline.

Table 3. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 2 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level or Renal Disease Status and Time-Updated Age Category in Model 3.*

Variable	Death from Any Cause				Death from Cardiovascular Causes			
	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr
Time-updated mean glycated hemoglobin level†								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
≤6.9%	1.92 (1.75–2.11)	1.40 (1.34–1.46)	1.11 (1.08–1.14)	0.95 (0.94–0.96)	2.18 (1.81–2.64)	1.57 (1.46–1.70)	1.13 (1.08–1.18)	0.92 (0.90–0.94)
7.0–7.8%	2.00 (1.77–2.27)	1.55 (1.47–1.63)	1.25 (1.21–1.29)	1.03 (1.02–1.05)	2.59 (2.04–3.28)	1.92 (1.75–2.10)	1.34 (1.27–1.41)	1.02 (0.99 –1.04)
7.9–8.7%	2.50 (2.17–2.87)	1.71 (1.60–1.83)	1.56 (1.49–1.62)	1.20 (1.18–1.23)	3.76 (2.93–4.82)	2.16 (1.93–2.41)	1.86 (1.75–1.98)	1.15 (1.11–1.19)
8.8–9.6%	2.92 (2.44–3.49)	2.31 (2.13–2.52)	1.84 (1.74–1.95)	1.34 (1.29–1.39)	4.06 (2.94–5.61)	2.96 (2.58–3.40)	2.22 (2.03–2.43)	1.29 (1.23–1.36)
≥9.7%	4.23 (3.56–5.02)	2.77 (2.51–3.05)	2.48 (2.31–2.67)	1.55 (1.47–1.63)	5.38 (3.89–7.43)	3.51 (2.99–4.11)	3.10 (2.78–3.45)	1.42 (1.32–1.53)
Time-updated renal disease								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Normoalbuminuria	1.87 (1.70–2.04)	1.27 (1.22–1.32)	0.96 (0.94–0.99)	0.83 (0.82–0.84)	2.19 (1.82–2.62)	1.43 (1.33–1.55)	0.95 (0.91–1.00)	0.79 (0.78–0.81)
Microalbuminuria	2.61 (2.19–3.10)	1.88 (1.75–2.02)	1.44 (1.38–1.50)	1.04 (1.02–1.07)	4.26 (3.19–5.70)	2.38 (2.11–2.69)	1.55 (1.44–1.66)	1.01 (0.97–1.04)
Macroalbuminuria	3.78 (3.03–4.71)	2.88 (2.65–3.13)	2.14 (2.04–2.24)	1.40 (1.37–1.44)	5.58 (3.79–8.20)	3.81 (3.33–4.35)	2.62 (2.44–2.81)	1.37 (1.32–1.42)
Stage 5 chronic kidney disease	14.63 (9.53–22.48)	7.19 (5.75–8.98)	5.97 (5.29–6.73)	3.31 (3.02–3.62)	30.03 (16.08–56.10)	9.22 (6.40–13.29)	5.45 (4.43–6.70)	2.45 (2.11–2.86)
Time-updated eGFR and stage 5 chronic kidney disease								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
>90 ml/min	2.07 (1.90–2.26)	1.47 (1.41–1.54)	1.17 (1.13–1.21)	0.88 (0.86–0.91)	2.47 (2.08–2.94)	1.56 (1.43–1.69)	1.02 (0.96–1.09)	0.72 (0.69–0.76)
>60–90 ml/min	1.92 (1.69–2.17)	1.30 (1.24–1.36)	0.96 (0.93–0.99)	0.81 (0.80–0.82)	2.59 (2.05–3.27)	1.60 (1.47–1.74)	1.04 (1.00–1.10)	0.77 (0.75–0.78)
>45–60 ml/min	3.84 (2.68–5.50)	2.60 (2.35–2.88)	1.48 (1.41–1.55)	1.02 (1.00–1.04)	5.56 (2.98–10.38)	3.83 (3.29–4.45)	1.75 (1.63–1.89)	1.02 (1.00–1.05)
>30–45 ml/min	5.52 (3.05–9.97)	4.00 (3.44–4.64)	2.42 (2.26–2.58)	1.37 (1.34–1.41)	8.59 (3.21–22.97)	4.72 (3.69–6.04)	2.94 (2.68–3.24)	1.39 (1.35–1.44)
15–30 ml/min	18.79 (11.50–30.72)	6.98 (5.75–8.48)	4.21 (3.84–4.62)	2.21 (2.12–2.30)	35.03 (16.63–73.79)	8.96 (6.59–12.19)	4.58 (3.97–5.28)	2.13 (2.01–2.25)
Stage 5 chronic kidney disease	14.70 (9.57–22.59)	7.23 (5.79–9.04)	6.09 (5.40–6.87)	3.33 (3.04–3.64)	30.26 (16.20–56.52)	9.30 (6.45–13.40)	5.57 (4.53–6.86)	2.48 (2.13–2.89)

* The analysis, based on Cox regression, was adjusted for time-updated age, sex, country of birth (Sweden or other), educational level, and status with respect to a history of coexisting conditions at baseline and was stratified according to duration of diabetes in the diabetes group (0 to 1 years, >1 to 5 years, >5 to 10 years, >10 to 20 years, or >20 years), with controls assigned to the same stratification category as the patients in the diabetes group with whom they were matched, in accordance with model 3 of the survival analysis (see the Supplementary Appendix). The term "time-updated" refers to the value recorded closest to the time of each event. Numbers in parentheses are 95% confidence intervals. P values for the interaction term between time-updated mean glycated hemoglobin or renal disease status and time-updated age categories were less than 0.001 in all models. The term eGFR denotes estimated glomerular filtration rate.

† Molar equivalents for the glycated hemoglobin levels are as follows: 6.9% or lower, 52 mmol per mole or lower; 7.0 to 7.8%, 53 to 62 mmol per mole; 7.9 to 8.7%, 63 to 72 mmol per mole; 8.8 to 9.6%, 73 to 82 mmol per mole; and 9.7% or higher, 83 mmol per mole or higher.

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for each increase of 1 percentage point (10 mmol per mole) in the glycated hemoglobin level was 12% in the analysis of all-cause mortality and 14% in the analysis of cardiovascular mortality.

Among patients with type 2 diabetes who had normoalbuminuria, the adjusted risks of death from any cause and cardiovascular death were twice as high among patients younger than 55 years of age than among controls (hazard ratio for death from any cause, 1.87 [95% CI, 1.70 to 2.04]; hazard ratio for cardiovascular death, 2.19 [95% CI, 1.82 to 2.62]) (Table 3 for model 3, and Table S4 in the Supplementary Appendix for models 1 and 2). However, patients with normoalbuminuria who were 65 to 74 years of age or who were 75 years of age or older had a lower risk than controls with respect to death from any cause and cardiovascular death. Across the different age categories, the hazard ratios for death from any cause ranged from 2.61 to 1.04 among patients with microalbuminuria, from 3.78 to 1.40 among those with macroalbuminuria, and from 14.63 to 3.31 among those with stage 5 chronic kidney disease.

When eGFR was considered, the excess risks of death from any cause and cardiovascular death decreased with increasing age (Table 3). Among patients younger than 55 years of age, at an eGFR of 60 to 90 ml per minute or more than 90 ml per minute, the excess risk of death from any cause was twice as high and the excess risk of cardiovascular death was 2.5 times as high as the risks among controls. Among patients in this age category with an eGFR of 15 to 30 ml per minute, the risk of death from any cause was approximately 20 times as high as that among controls, and the risk of cardiovascular death was 35 times as high; among those with stage 5 chronic kidney disease, these risks were, respectively, approximately 15 times as high and 30 times as high. The relationship between renal complications and mortality remained stable when the analysis was additionally adjusted for other risk factors (Table S5 in the Supplementary Appendix).

Tables S6A through S8B in the Supplementary Appendix show the excess risks of death from any cause and cardiovascular death with regard to glycated hemoglobin level, renal complications, and eGFR separately for men and women. Similar hazard ratios were generally found among men and women, but some differences were observed in certain groups, such as younger patients with advanced renal complications.

When we evaluated the interaction of normoalbuminuria and level of glycemic control, the hazard ratio among patients with a glycated hemoglobin level of 6.9% or less, as compared with controls, was 1.60 (95% CI, 1.40 to 1.82) among those younger than 55 years of age, but was lower among patients 65 years of age or older. After adjustment for history of coexisting conditions, patients who were 75 years of age or older with a glycated hemoglobin level of 7.8% or less also had a lower risk of death than controls (Table 4, and Table S9 in the Supplementary Appendix). Corresponding estimates for an eGFR of more than 60 ml per minute are shown in Table 4, and Table S9 in the Supplementary Appendix.

Of the total evaluated person-years in the study, 31.7% of the time belonged to patients with normoalbuminuria and coexisting glycated hemoglobin levels that are associated with lower mortality (as compared with controls), and 44.5% of the patients were in these categories at any time during follow-up. Regarding categories of an eGFR of more than 60 ml per minute and coexisting glycated hemoglobin levels associated with lower mortality, the corresponding proportions belonging to these categories were 31.6% of the total evaluated person-years and 51.2% of the patients. The excess risks of death were generally similar among men and women (Tables S10 and S11 in the Supplementary Appendix).

MEDICATIONS AND SMOKING

According to the Swedish Prescribed Drug Register, from July 2005 onward, a total of 63.4% of the patients with type 2 diabetes received prescriptions for lipid-lowering medications and 66.6% received prescriptions for renin–angiotensin–aldosterone system (RAAS) inhibitors, as compared with 24.8% and 30.7% of controls, respectively. The use of lipid-lowering medications and the use of RAAS inhibitors were more common among persons with type 2 diabetes than among controls in all age groups, with younger persons having a rate of use of lipid-lowering medications that was eight times as high and a rate of use of RAAS inhibitors that was five times as high as the respective rates among controls (Table S12 in the Supplementary Appendix).

Table 4. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 2 Diabetes and Normoalbuminuria or an eGFR of More than 60 ml per Minute, as Compared with Controls, According to Time-Updated Mean Glycated Hemoglobin Level and Age Category in Model 3.*

Variable	Death from Any Cause				Death from Cardiovascular Causes			
	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr
Normoalbuminuria								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
≤6.9%	1.60 (1.40–1.82)	1.15 (1.08–1.22)	0.87 (0.84–0.91)	0.76 (0.75–0.78)	1.94 (1.51–2.50)	1.25 (1.12–1.39)	0.81 (0.75–0.86)	0.73 (0.71–0.75)
7.0–7.8%	1.72 (1.44–2.05)	1.25 (1.15–1.35)	0.95 (0.91–1.00)	0.83 (0.81–0.85)	1.87 (1.31–2.69)	1.39 (1.21–1.60)	0.92 (0.85–1.01)	0.80 (0.77–0.83)
7.9–8.7%	2.23 (1.80–2.76)	1.38 (1.24–1.53)	1.17 (1.09–1.25)	1.01 (0.97–1.05)	2.75 (1.83–4.14)	1.63 (1.36–1.94)	1.32 (1.18–1.47)	0.96 (0.91–1.02)
8.8–9.6%	2.29 (1.68–3.12)	1.80 (1.56–2.09)	1.33 (1.18–1.49)	1.11 (1.03–1.20)	2.26 (1.17–4.36)	2.03 (1.57–2.62)	1.65 (1.38–1.97)	1.01 (0.91–1.13)
≥9.7%	4.23 (3.17–5.65)	2.26 (1.88–2.71)	1.65 (1.39–1.95)	1.37 (1.23–1.54)	5.59 (3.29–9.50)	3.06 (2.28–4.10)	2.01 (1.55–2.60)	1.27 (1.08–1.50)
eGFR >60 ml/min								
Reference	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
≤6.9%	1.73 (1.55–1.92)	1.21 (1.15–1.28)	0.93 (0.90–0.96)	0.77 (0.75–0.78)	1.96 (1.57–2.44)	1.29 (1.18–1.42)	0.86 (0.81–0.91)	0.70 (0.68–0.72)
7.0–7.8%	1.83 (1.58–2.11)	1.36 (1.28–1.45)	1.00 (0.96–1.05)	0.82 (0.80–0.84)	2.28 (1.73–3.02)	1.60 (1.43–1.78)	1.01 (0.94–1.08)	0.75 (0.72–0.78)
7.9–8.7%	2.32 (1.96–2.75)	1.51 (1.40–1.64)	1.28 (1.21–1.36)	1.00 (0.97–1.04)	3.62 (2.70–4.85)	1.77 (1.53–2.03)	1.44 (1.31–1.57)	0.93 (0.88–0.98)
8.8–9.6%	2.67 (2.13–3.34)	1.98 (1.77–2.21)	1.45 (1.33–1.59)	1.10 (1.03–1.18)	3.17 (2.05–4.90)	2.27 (1.88–2.75)	1.65 (1.44–1.90)	1.01 (0.91–1.11)
≥9.7%	4.43 (3.61–5.45)	2.58 (2.27–2.93)	2.03 (1.81–2.28)	1.33 (1.20–1.46)	5.08 (3.38–7.63)	3.44 (2.80–4.22)	2.38 (2.00–2.84)	1.07 (0.92–1.24)

* The analysis, based on Cox regression, was adjusted for time-updated age, sex, country of birth, educational level, and status with respect to a history of coexisting conditions at baseline, and was stratified according to duration of diabetes, in accordance with model 3 of the survival analysis (see the Supplementary Appendix for details). Numbers in parentheses are 95% confidence intervals. P values for the interaction term between time-updated mean glycated hemoglobin level and time-updated age categories were less than 0.001 in all models.

The results from the last assessment of risk factors in persons with type 2 diabetes according to age are shown in Table S13 in the Supplementary Appendix. The use of lipid-lowering medications was more common and the smoking frequency was lower among persons with type 2 diabetes who had their data censored at the end of the study than among those who had died; patients with censored data also had a lower mean systolic blood pressure than those who had died (Table S13 in the Supplementary Appendix). Smoking was more common and the body-mass index (the weight in kilograms divided by the square of the height in meters) was higher among younger persons with type 2 diabetes than in all other age groups of patients.

DISCUSSION

This nationwide study involving more than 400,000 persons with type 2 diabetes and more than 2 million matched controls in Sweden showed that excess mortality in type 2 diabetes was substantially higher with worsening glycemic control, severe renal complications, impaired renal function, and younger age. The excess risk of death also varied substantially in several large subgroups of patients with type 2 diabetes, with an excess risk in some and a lower risk in others.

When the analysis was adjusted for age and sex, the overall excess risk of death from any cause on a group level was low (27%) as compared with earlier reports[9]; the excess risk decreased to 15% when the analysis was further adjusted for coexisting diseases. The major contributors to the excess risk of death were cardiovascular disease and diabetes-related conditions, whereas cancer, although a significant contributor, had a relatively small effect. The relatively low mortality is probably due to aggressive treatment with statins and blood-pressure medications,[4,5] which were considerably more common in patients with diabetes than in controls, as well as improvements in glycemic control over time.[2]

The excess risk of death has previously been reported to decrease with older age.[9,17] In the current study, after the analysis was adjusted for history of coexisting conditions at baseline, persons with diabetes who were 75 years of age or older had a significantly attenuated risk of death, approaching that of the general population. However, the absolute risk of death among elderly patients varied substantially depending on glucose control and coexisting conditions. Specifically, when diabetes was accompanied by renal complications, the excess risk of death was increased in this age group, a finding that emphasizes the importance of reducing the risk and severity of diabetes-related complications in older persons.

In other age groups, the excess risk of death ranged from 30 to 40% among patients 65 to 74 years of age, as compared with controls in the same age group, whereas the excess mortality was 100% to 200% among those younger than 55 years of age, as compared with controls. However, patients 65 to 74 years of age with normoalbuminuria and a glycated hemoglobin level of 6.9% or less had a risk that was lower than that among controls. The risk was also lower among patients 75 years of age or older with a glycated hemoglobin level of 7.8% or less than among controls, but the risk was substantially higher among patients younger than 55 years of age than among controls, despite a glycated hemoglobin level in the target range and normoalbuminuria.

Despite higher mortality among younger persons with type 2 diabetes, it is noteworthy that blood pressure was generally well controlled and that these patients received statin medications eight times as often as controls. However, more patients with type 2 diabetes were smokers, including 38% of those who died and 24% of those with censored data, as compared with 18% in general population reports.[25] Furthermore, 56% of the patients with type 2 diabetes were obese, as compared with 14% of the general population.[25] However, the body-mass index was similar in patients with type 2 diabetes who died and those with censored data.

Therefore, in younger patients with type 2 diabetes, strict control of blood pressure, prescription of statins, targeting of good glycemic control, and avoidance of microalbuminuria are probably not enough to reduce excess mortality to the rate in the general population. Smoking cessation, increased physical activity, and the development of new cardiovascular-protective drugs, such as alternative lipid-lowering medications for persons who cannot take statins, may further improve outcomes in younger patients. Reducing the risk of renal complications in all

age groups is highly important; the excess mortality among younger patients with advanced chronic kidney disease was approximately 15 times as high as that among controls. Hyperglycemia is a prerequisite for the development of diabetic nephropathy[26]; therefore, early prevention of diabetes[27] and strict glucose control that begins at diagnosis[2,28] when long-term survival is expected may further reduce mortality.

Recent evaluations from Canada and the United Kingdom that included mainly patients with type 2 diabetes[9] showed a reduced excess risk of death over time. However, a study in which patients were followed from 1988 until 2006 and which defined diabetes according to the glycated hemoglobin level showed no mortality reductions over time,[29] in contrast to other U.S. studies.[16,30] Moreover, the overall mortality excess among patients with type 1 diabetes[19] from the same background population was much higher than that among patients with type 2 diabetes. However, the mean age of the patients with type 2 diabetes was much higher than that of patients with type 1 diabetes, and younger persons with type 2 diabetes who had a glycated hemoglobin level in the target range still had a risk of death that was twice as high as the risk among controls, which is a magnitude of risk that is similar to that among patients with type 1 diabetes.

The strengths of the present study are that it included more than 90% of all the patients with type 2 diabetes in Sweden and that most patients had at least one measurement of a glycated hemoglobin level (97%), grade of albuminuria (88%), or eGFR (91%). In contrast to earlier studies, comparisons were not made with general life tables, but information on coexisting diseases and psychosocial variables in controls were available over a period of at least 11 years before the start of follow-up, which is essential to estimations.

There are certain limitations in this study. Some variables that are possibly associated with mortality were not available on an individual level for controls. Owing to the observational nature of our study, we cannot definitively exclude possible residual confounding. The prevalence of obesity, diet, and diabetes care may differ among countries, so the evaluations may not be generalizable to other nations. Deaths that were attributed to diabetes made up an unknown proportion of deaths in which cardiovascular disease played an important part; hence, the calculated risks for diabetes-related death and cardiovascular death may be underestimated.

In conclusion, the overall excess risk of death among persons with type 2 diabetes has dropped to a historically low level of approximately 15%. However, mortality remains high in certain patient groups and remains substantially higher among patients younger than 55 years of age, as compared with controls, even among patients whose glycemic values are within the target range and who have normoalbuminuria.

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