

University of Groningen

Sex and gender differences in diabetes care

Hendriks, Steven

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Hendriks, S. (2017). *Sex and gender differences in diabetes care*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Chapter 3

Sex differences in survival of patients with type 2 diabetes in primary care (ZODIAC-50)

Submitted as:
Hendriks SH, van Hateren KJJ, Groenier KH, Landman GWD, Maas AHEM, Bilo HJG, Kleeftstra N. Sex differences in survival of patients with type 2 diabetes in primary care (ZODIAC-50).

Abstract

Objective

To investigate sex differences in survival of primary care treated patients with type 2 diabetes in the Netherlands.

Research design and Methods

Patients with type 2 diabetes treated in primary care participating in a prospective observational cohort study (ZODIAC) were included. Inclusion took place in 1998, 1999 and 2001. Vital status was assessed in 2013. Survival was calculated using relative survival analysis. Relative survival was expressed as the ratio of observed survival of patients divided by the survival of the general population in the Netherlands with comparable age.

Results

A total of 1815 patients, mean age 67 (SD 12) years, was included of which 56% was female. After 14 years, 888 (49%) patients had died. The relative survival rate was 0.88 (0.81 – 0.94) for men and 0.82 (0.76 – 0.87) for women with type 2 diabetes after 14 years (p-value for difference between sexes = 0.169). In patients without a history of cardiovascular diseases the relative survival was 0.99 (0.94 – 1.05) in men and 0.92 (0.87 – 0.97) in women (p-value for difference between sexes = 0.046).

Conclusions

The survival of men and women with type 2 diabetes was 12% and 18% lower, respectively, after 14 years of follow-up compared to men and women in the general population. This corresponds to a decrease in median survival of 2.2 and 3.5 years in men and women respectively. In our study, a significantly higher impact of type 2 diabetes in women compared to men was only found in patients without a history of cardiovascular diseases.

Introduction

Mortality rates in patients with type 2 diabetes (T2D) are higher compared to the general population, which is predominantly caused by a higher occurrence of cardiovascular diseases in patients with T2D (1–3). This excess mortality rate is described to be more pronounced in women compared to men with T2D (2–5). In a recent meta-analysis, the relative risk for mortality of incident coronary heart disease was 2.8 in women and 2.0 in men compared to men and women without diabetes, respectively (2).

Current knowledge on sex differences in mortality is mostly based on older cohort studies. Whether these results are still reflecting current practice is less clear, as the care for patients with T2D has significantly improved over the last years (6). In the Netherlands, most patients with T2D receive protocol-based treatment exclusively in primary care. The mortality in this population is low, which is probably the result of a general improvement in quality of diabetes care over the last years (7). It is less well established whether sex differences in mortality also exist in well-controlled primary care patients. Only a few studies have been recently conducted in countries with a comparable care system to the Netherlands (8–10). A study from Norway also described a more pronounced excess mortality rate in women with T2D, however this study also included secondary care treated patients (10). A retrospective study from the U.K in primary care found only a slightly higher hazard ratio for all-cause mortality in women than in men with T2D, when compared with non-diabetics (8).

The aim of the present study was to investigate the survival of prospectively followed men and women with T2D, treated in primary care, compared to men and women in the general population.

Methods

Study population and design

The study population consisted of patients who were included in the Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC) study. This study was initiated in 1998, in the Zwolle region of the Netherlands. The design and details of this study have been published previously (11). In this study, general practitioners were assisted by hospital-based diabetes specialist nurses in their care of patients with T2D. In the first year, 1,143 patients with T2D were included in this prospective cohort study. Another 127 and 545 patients with T2D entered this study in 1999 and 2001 respectively, resulting in a combined cohort of 1,815 patients. All patients with T2D were selected from general practices in Zwolle region of the Netherlands. Patients with a very short life expectancy

or insufficient cognitive capabilities were excluded from participation as the care for these patients has not been delegated to diabetes specialist nurses. Whether the life expectancy was long enough to be included in the ZODIAC study was based on the judgement of the general practitioners.

The survival of this cohort was compared with the expected survival of men and women with the same age from the general population in the Netherlands. These expected survival rates were derived from data provided by Statistics Netherlands. This organization provides survival rates for men and women of every age in the Netherlands (12).

Data collection and measurements

Before participating in the ZODIAC study, T2D was already diagnosed in all individuals by their general practitioners based on the guidelines of the Dutch College of General Practitioners (2 times a fasting plasma glucose level ≥ 7 mmol/l or one time a non-fasting plasma glucose level ≥ 11.1 mmol/l accompanied by symptoms of hyperglycemia) (13). Information on cardiovascular diseases, smoking and medication use was collected during the check-up of the patient by the general practitioner or practice nurse at baseline of the study. Patients were considered to have a history of CVD if a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or a transient ischemic attack was documented in the patient record of the general practice. Data on heart failure was not collected as it was not properly documented at baseline. Smoking was included in the analyses as a categorical variable (yes/no). Laboratory and physical assessment data were collected at baseline during the annual check-up of the patients by their general practitioner and practice nurse and included non-fasting lipid profile, glycated hemoglobin (HbA1c), serum creatinine (SCr), urinary albumin-to-creatinine ratio (ACR), blood pressure and information about neuropathy and diabetic retinopathy. ACR was measured using immunonephelometry (Behring Nephelometer; Mannheim, Germany), and blood pressure was measured twice with a Welch Allyn sphygmomanometer in the supine position after at least 5 minutes of rest. Foot sensibility was tested with 5.07 Semmes-Weinstein monofilaments. Neuropathy was defined as two or more errors in a test of three, at least at one foot. Diabetic retinopathy (DRP) was investigated with a retinal camera and the fundus photos were judged by an ophthalmologist. Microalbuminuria was defined as an albumin-to-creatinine ratio between 3.5 and 35 mg/mmol for women and between 2.5 and 25 mg/mmol for men. Macroalbuminuria was defined as an albumin-to-creatinine ratio > 35 mg/mmol for women and > 25 mg/mmol for men. The same methods were used in each baseline year to measure the laboratory and physical assessment data.

Clinical endpoints

The primary end-point was the relative survival rate of men and women with T2D compared with the general population in the Netherlands. Secondary end-points were the relative survival rates of patients with T2D in different subgroups, and the median survival of men and women. Subgroups for the relative survival analyses were defined for: age (<60, 60-75 and >75 years), Body Mass Index (BMI) (<25, 25-30 and >30 kg/m²), smoking, history of CVD, albuminuria (normo-, micro- and macroalbuminuria), microvascular complications (defined as the presence of albuminuria, neuropathy or DRP) and for patients with a low CVD risk (defined as non-smoking patients without a history of CVD and microvascular complications). In 2013, vital status and cause of death of T2D patients were retrieved from records maintained by the hospital and the general practitioners or from the nationwide Municipal Personal Records Database. Causes of death were coded according to the International Classification of Diseases, 9th revision (ICD-9). Cardiovascular death was defined as death in which the principal cause of death was cardiovascular in nature, using ICD-9 codes 390-459.

Statistical analyses

Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and Stata 14 (StataCorp, College Station, Texas, USA). Baseline results are expressed as mean with standard deviation (SD) or median with interquartile range (IQR) for normally distributed and non-normally distributed data, respectively. Categorical variables are described in numbers and percentages. Differences were considered to be significant at a p-value of <0.05. Survival was calculated using relative survival analysis (14). The relative survival rate was calculated by measuring the ratio of survival of patients observed in our ZODIAC cohort in comparison to the survival of men and women with corresponding age in the same baseline year in the general population in the Netherlands. First, interval-specific and cumulative survival rates were measured for both the study population and the general population, using the Hakulinen method (15). The interval-specific observed survival rate for each follow-up year of the study population was calculated based on the number of patients at risk, the number of deaths and the number of patients lost to follow-up in each year. The interval-specific expected survival rate for the general population was calculated using yearly-specific survival data of the general population (12). Consequently, the cumulative survival rate was measured for both the study group and the general population. Finally, the relative cumulative survival rate was calculated. The relative cumulative survival rate for the total study population is described for each of the 14 follow-up years for men and women separately. To investigate whether the relative survival was significant different between sexes, the p-value was calculated at 14 years of follow-up. For the

subgroup analyses, the relative cumulative survival rate is only described after 10 years of follow-up. Cumulative survival rates after 10 years are described due to the fact that 14 years survival data were only available for patients who were included in 1998. The relative cumulative survival rates after 10 years are therefore more reliable. P-values for the differences between sexes were calculated at 10 years of follow-up for the subgroup analyses. An estimation of the median survival of the study population was calculated using linear interpolation. For the general population, linear extrapolation with the average difference between the cumulative survivals of the general population was conducted first, before using linear interpolation to estimate the median survival.

Ethical approval

This study was approved by the local ethical committee of Isala, Zwolle, the Netherlands. All patients gave written informed consent.

Results

Baseline results of the study population are described in table 1. Fifty-six percent of the patients were female. Mean age was 65.0 (11.8) years in men and 68.6 (11.6) years in women. The median diabetes duration was 4.0 (1.8-9.0) and 5.0 (2.0-10.0) years in men and women, respectively. Men smoked more frequently and had also more often albuminuria and a previous history of CVD compared to women. Women had a higher systolic blood pressure, a higher BMI, and more often diabetic retinopathy than men. Men were more often on diet treatment only while women were more often on insulin. Lipid lowering drugs and antiplatelet drugs were more often used in men.

Relative survival analyses

The incidence rate for all-cause mortality was 7.4 (6.7 – 8.2) and 7.2 (6.5 – 7.8) per 100 person years in men and women with T2D, respectively. The incidence rate for CVD mortality was 3.1 (2.7 - 3.6) and 3.0 (2.6 - 3.4) per 100 person years in men and women with T2D, respectively. The comparison between the survival of the patients with T2D and the general population is presented in table 2 and figure 1 for men and women separately. After 14 years, the relative survival rate was 0.88 (95%CI: 0.81 - 0.94) for men and 0.82 (95%CI: 0.76 – 0.87) for women with T2D (p-value for difference between sexes = 0.169). The estimated median survival of men (mean age: 65.0) and women (mean age: 68.8) in the study population was 13.8 and 13.0 years, respectively. In the general population, the estimated median survival of men and women was 16.0 and 16.5 year respectively.

Table 1. Baseline characteristics of the study population.

	Total (n = 1815)	Men (n = 800)	Women (n = 1015)	p-value
Age (years)	67.0 (\pm 11.8)	65.0 (\pm 11.8)	68.6 (\pm 11.6)	<0.001
Diabetes duration (years)	4.0 (2.0-9.0)	4.0 (1.8-9.0)	5.0 (2.0-10.0)	0.017
History of CVD	605 (33.3)	307 (38.4)	298 (29.4)	<0.001
Smoking	342 (19.0)	206 (26.0)	136 (13.5)	<0.001
BMI (kg/m ²)	29.1 (\pm 4.8)	28.2 (\pm 4.1)	29.9 (\pm 5.2)	<0.001
SBP (mmHg)	151.5 (\pm 24.4)	147.2 (\pm 23.4)	155.0 (\pm 24.5)	<0.001
HbA1c (mmol/mol)	7.0 (6.3-8.1)	6.9 (6.2-8.1)	7.1 (6.4-8.1)	0.131
Creatinine (μ mol/L)	92.0 (82.0-104.0)	98.0 (89.0-109.0)	86.0 (77.0-97.0)	<0.001
Chol-HDL ratio	4.8 (3.9-5.9)	4.9 (4.0-6.0)	4.7 (3.8-5.8)	0.001
Retinopathy	190 (10.9)	70 (9.1)	120 (12.3)	0.030
Microalbuminuria	544 (30.8)	267 (34.0)	277 (28.3)	0.011
Macroalbuminuria	114 (6.5)	68 (8.7)	46 (4.7)	0.001
Neuropathy	477 (26.6)	212 (26.7)	265 (26.6)	0.931
Microvascular complications [#]	1012 (57.7)	466 (59.7)	546 (56.1)	0.120
Low CVD risk [*]	424 (23.4)	154 (19.3)	270 (26.6)	<0.001
DM treatment				
Diet	318 (17.5)	158 (19.8)	160 (15.8)	0.026
Oral only	1230 (67.8)	540 (67.6)	690 (68.0)	0.834
Insulin	262 (14.5)	99 (12.4)	163 (16.1)	0.028
ACEi/ARB	433 (27.1)	179 (25.1)	254 (28.7)	0.108
Lipid lowering drugs	278 (15.6)	139 (17.7)	139 (13.9)	0.030
Antiplatelet drugs	279 (15.6)	139 (17.6)	140 (14.0)	0.035
Death	888 (48.9)	381 (47.6)	507 (50.0)	0.325
CVD death	374 (20.6)	161 (20.1)	213 (21.0)	0.653

Values are depicted as n (%), mean (\pm SD), or median (IQR). [#] Defined as the presence of albuminuria, neuropathy or DRP. ^{*} defined as non-smoking patients without a history of CVD and microvascular complications. Abbreviations: CVD: cardiovascular disease; BMI: body mass index; SBP: systolic blood pressure; Chol-HDL: cholesterol-HDL; DM: diabetes mellitus; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

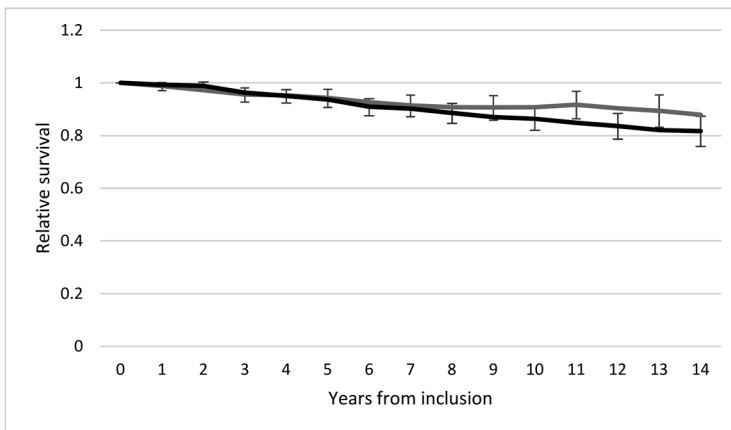


Figure 1. Relative survival with 95% CI for men and women with T2D. Men: grey line, Women: black line.

Table 2. Relative survival for men and women with T2D compared with men and women with the same age from the general population.

Follow-up	Men					Women						
	N	Death	Lost to follow-up	COS	CES	Relative cumulative survival	N	Death	Lost to follow-up	COS	CES	Relative cumulative survival
0-1	800	36	1	0.96	0.97	0.99 (0.97 - 1.00)	1015	35	2	0.97	0.97	0.99 (0.98 - 1.00)
1-2	763	38	0	0.91	0.93	0.97 (0.95 - 0.99)	978	32	0	0.93	0.94	0.99 (0.97 - 1.00)
2-3	725	38	0	0.86	0.90	0.96 (0.93 - 0.98)	946	53	0	0.88	0.92	0.96 (0.94 - 0.98)
3-4	687	28	1	0.82	0.87	0.95 (0.92 - 0.98)	893	40	2	0.84	0.89	0.95 (0.92 - 0.97)
4-5	658	31	0	0.79	0.83	0.94 (0.91 - 0.98)	851	41	0	0.80	0.86	0.94 (0.91 - 0.96)
5-6	627	35	1	0.74	0.80	0.93 (0.89 - 0.96)	810	52	4	0.75	0.83	0.91 (0.88 - 0.94)
6-7	591	30	3	0.70	0.77	0.91 (0.87 - 0.95)	754	53	6	0.72	0.79	0.90 (0.87 - 0.94)
7-8	558	26	1	0.67	0.74	0.91 (0.86 - 0.95)	715	40	0	0.68	0.76	0.89 (0.85 - 0.92)
8-9	531	22	0	0.64	0.71	0.91 (0.86 - 0.95)	675	38	3	0.64	0.73	0.87 (0.83 - 0.91)
9-10	509	20	0	0.62	0.68	0.91 (0.86 - 0.96)	634	30	0	0.61	0.70	0.86 (0.82 - 0.91)
10-11	489	15	58	0.60	0.65	0.92 (0.86 - 0.97)	604	35	62	0.57	0.67	0.85 (0.80 - 0.89)
11-12	416	22	101	0.56	0.62	0.90 (0.85 - 0.96)	507	28	93	0.54	0.64	0.84 (0.79 - 0.88)
12-13	293	17	3	0.53	0.59	0.89 (0.83 - 0.95)	386	26	4	0.50	0.61	0.82 (0.77 - 0.88)
13-14	273	16	60	0.49	0.56	0.88 (0.81 - 0.94)	356	18	97	0.47	0.58	0.82 (0.76 - 0.87)

Abbreviations: N: number of patients at risk; COS: cumulative observed survival; CES: cumulative expected survival.

Subgroup analyses

The relative survival rate after 10 years for different subgroups is described in table 3 and figure 2 for men and women separately. In the subgroup of T2D patients without microvascular complications, the relative survival rate of men and women with T2D was 1.01 (95%CI: 0.95 – 1.07) and 0.98 (95%CI: 0.93 – 1.03), respectively ($p = 0.488$). In patients with microvascular complications, the relative survival rate decreased to 0.82 (95%CI: 0.74 – 0.89) for men and 0.77 (95%CI: 0.71 – 0.84) for women with T2D ($p = 0.395$). In men and women with low CVD risk (defined as non-smoking patients without a history of CVD and microvascular complications) the relative survival rate was 1.08 (95%CI: 1.00 – 1.14) and 1.01 (0.94 – 1.07), respectively ($p = 0.106$). The relative survival rates of men <60 years, of men with a BMI between 25 and 30 kg/m², of men without a history of CVD, and of men without albuminuria were not significantly different from men in the general population. The relative survival rate in women in all these categories was significantly lower compared to women in the general population. For patients without a history of CVD, the relative survival was significantly lower in women with T2D compared to men ($p = 0.046$).

Table 3. Relative survival after 10 years for different subgroups.

Category	Men		Women		p-value [‡]
	N	Relative survival (95% CI)	N	Relative survival (95% CI)	
Age < 60	276	0.98 (0.94 – 1.01)	224	0.93 (0.87 – 0.96)	0.052
Age ≥ 60 and < 75	337	0.89 (0.81 – 0.96)	448	0.89 (0.84 – 0.95)	0.870
Age ≥ 75	187	0.59 (0.42 – 0.80)	343	0.68 (0.56 – 0.79)	0.909
Diabetes duration <2 years	206	0.99 (0.92 – 1.06)	232	0.97 (0.90 – 1.03)	0.626
BMI < 25	174	0.79 (0.66 – 0.92)	169	0.80 (0.67 – 0.91)	0.914
BMI 25-30	392	0.94 (0.87 – 1.01)	377	0.87 (0.79 – 0.94)	0.126
BMI > 30	232	0.91 (0.83 – 0.99)	465	0.89 (0.83 – 0.94)	0.616
Non-smokers	583	0.93 (0.87 – 0.99)	869	0.86 (0.82 – 0.92)	0.121
Smokers	206	0.84 (0.75 – 0.92)	136	0.84 (0.73 – 0.92)	0.931
No history of CVD	492	0.99 (0.94 – 1.05)	717	0.92 (0.87 – 0.97)	0.046
History of CVD	306	0.73 (0.63 – 0.82)	298	0.70 (0.61 – 0.79)	0.648
Normoalbuminuria	450	1.00 (0.94 – 1.05)	655	0.95 (0.90 – 1.00)	0.214
Microalbuminuria	266	0.81 (0.71 – 0.90)	277	0.75 (0.66 – 0.84)	0.444
Macroalbuminuria	168	0.59 (0.40 – 0.78)	46	0.54 (0.34 – 0.73)	0.886
No microvascular complications	314	1.01 (0.95 – 1.07)	428	0.98 (0.93 – 1.03)	0.488
Microvascular complications*	464	0.82 (0.74 – 0.89)	546	0.77 (0.71 – 0.84)	0.395
Low risk profile†	154	1.08 (1.00 – 1.14)	270	1.01 (0.94 – 1.07)	0.106

Difference between men and women. * Defined as the presence of albuminuria, neuropathy or DRP. † defined as non-smoking patients without a history of CVD and microvascular complications. Abbreviations: BMI: body mass index; CVD: cardiovascular disease.

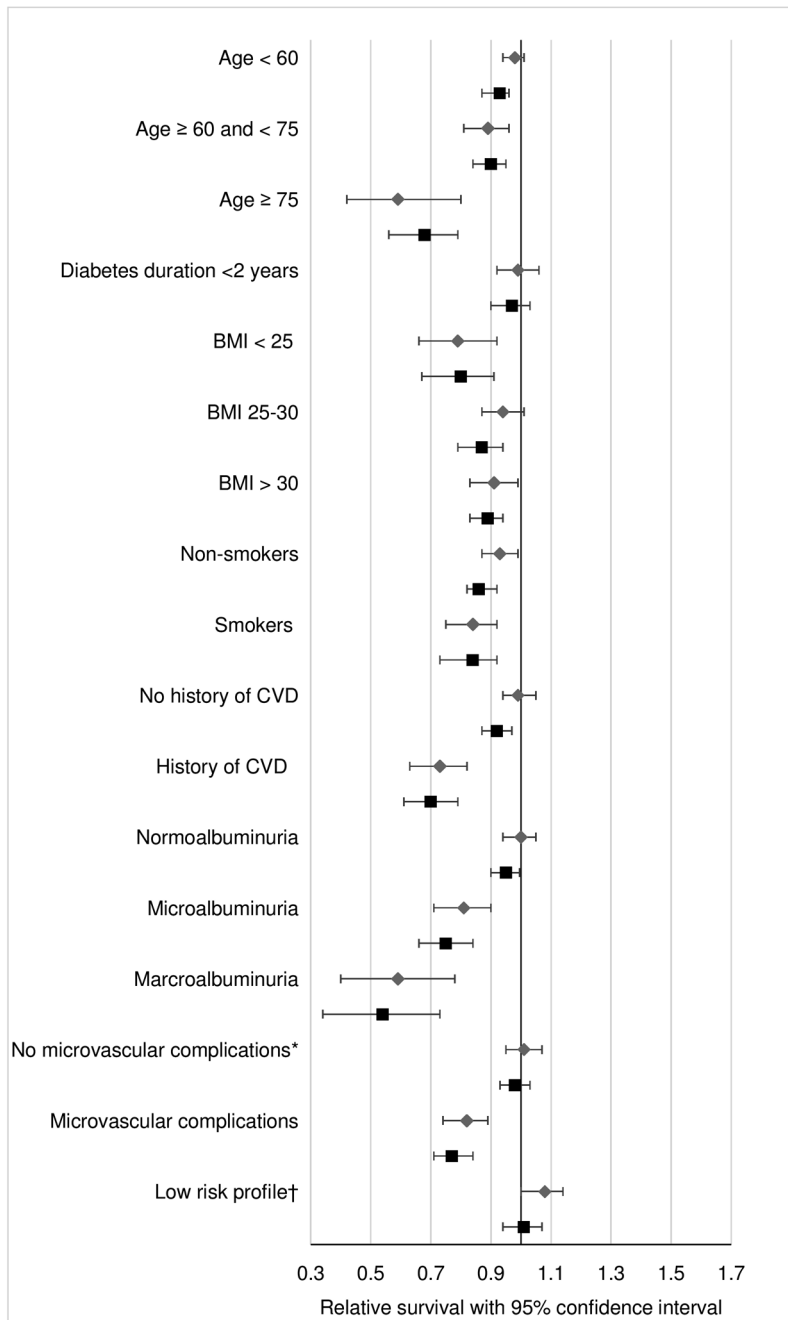


Figure 2. Relative survival with 95% CI for men and women with T2D after 10 years in different subgroups. Men: grey diamonds, women: black squares.

* Defined as the presence of albuminuria, neuropathy or DRP; † defined as non-smoking patients without a history of CVD and microvascular complications.

Discussion

In primary care treated T2D patients, the relative survival of men and women was 12% and 18% lower after 14 years of follow-up compared to age-matched men and women in the general population, respectively. This translates into an overall decrease in median survival of 2.2 years in men and 3.5 years in women with T2D compared to men and women in the general population. Although the relative survival of women with T2D seems to be lower than in male counterparts, no significant difference between sexes was found in the total study population. The survival rate in certain subgroups of men with T2D (young age, no albuminuria, no history of CVD, BMI 25-30) was comparable to the survival rate of men in the general population. In women in these subgroups the relative survival was significantly lower compared to women without T2D. Only for T2D patients without a history of CVD a significantly lower relative survival in women compared to men with T2D was found.

Many studies have described a higher excess mortality rate in women than in men with T2D (4,5,16). In our study, a higher impact of T2D in women was only found in the subgroup of patients without a history of CVD. In subgroups of patients < 60 year of age, without albuminuria and with a BMI between 25-30 kg/m² the relative survival of women with T2D was lower compared to women in the general population but not lower compared to the relative survival of men with T2D. The comparable survival of men with T2D without a history of CVD to men in the general population has partly been described before by Kalyani et al. (17). In a population without ischemic heart disease, they found an increased risk for the combined outcome of ischemic heart disease and mortality in women with diabetes compared to women without diabetes whereas they found no differences in men.

The decrease in median survival which is found in our study seems to be smaller than those seen in previous studies. Results from the Framingham Heart Study showed that men and women with diabetes lived on average 7.5 (95CI: 5.5 to 9.5) and 8.2 (95CI: 6.1 to 10.4) years less compared to men and women without diabetes. However, this cohort started between 1948 and 1951 when treatment options for T2D were limited. In a more recent study from Canada, for both men and women at the age of 55 on average a 5.0 (95CI: 4.9 to 5.1) and 6.0 (95CI: 5.9 to 6.1) years lower life expectancy was estimated compared to men and women without diabetes (18). Although patient characteristics differ between studies and various methods were used to measure survival, it may indicate that the loss of life years due to diabetes is decreasing in both men and women.

Although different theories have been described which may explain the observed sex difference in the impact of diabetes on survival, it is still not completely understood. Undertreatment of women with T2D is mentioned as a possible explaining factor. A lower prescription percentage for aspirin and lipid lowering drugs was found in women compared to men with T2D (19). However, in a recent study in primary care we did not find significant sex differences in these prescribed medications (20). The sex difference in survival may also be explained by a greater excess in cardiovascular risk factors between women with and without T2D compared to their male counterparts (4,21). This greater excess in risk factors is probably the result of a more favorable risk factor profile and a lower insulin resistance in women without diabetes compared to men (21,22). Although the relatively higher risk for women with T2D for fatal ischemic heart disease remained significant in various meta-analyses after adjustment for other cardiovascular risk factors, it may still be an explanation as only traditional risk factors were taken into account (2,4). The lower relative survival could also be a result of a higher prevalence of obesity in women with T2D. In the Netherlands, the prevalence of obesity is described to be 25 to 50% higher in women compared to men with T2D, whereas the prevalence of overweight is 20 to 35% higher in men compared to women in different age categories (20). Knowing that overweight is associated with a lower mortality risk and obesity with a higher mortality risk compared to patient with a normal weight, this could possibly be one of the explaining factors for the higher relative mortality rate in women with T2D (23). Finally, the relative higher mortality in women with T2D may be a result of underdiagnosis of ischemic heart disease in women. Women with T2D have less obstructive coronary disease compared to men, with higher rates of microvascular coronary dysfunction that may be more difficult to diagnose and treat (24). Also, a higher prevalence of undiagnosed heart failure with preserved ejection fraction (HFpEF) is described in women compared to men with T2D (25). When focusing on the common symptoms and diagnostic criteria for ischemic heart disease and HFpEF, these diagnoses could be easily missed in women. This may lead to undertreatment of women, resulting in a higher mortality when having T2D.

Some limitations should be mentioned. According to Hakulinen, relative survival is the ratio of the observed survival in a group of patients compared with the expected survival in a group of individuals in the general population, who are comparable with the patients concerning all possible factors affecting survival, except for the disease of interest (15). Our choice to compare survival of patients with T2D to the general population can therefore be criticized. However, the underlying assumption by the use of the expected survivals of the general population is that the deaths directly due to T2D are a negligible proportion of all deaths in the general population. Furthermore, no data

were known concerning clinical variables in the general population, as we did not use a specific control group but expected survival rates which were derived from mortality rates of the entire nation. Therefore the results of the subgroups should be interpreted with caution. The study population consisted only of patients with T2D who are treated in primary care. Patients in secondary care often have worse manifestations of T2D and more often macrovascular disease and will probably have a lower survival. Furthermore, patients with a very short life expectancy or insufficient cognitive capabilities were also excluded from participation. Although these limitations imply that the generalizability of our results is limited to primary care, it is still representative for a large part of the T2D population due to the fact that the majority (>85%) of the patients with T2D is treated in primary care in the Netherlands (26).

In conclusion, the relative survival in men and women with T2D compared to the general population was 12% and 18% lower. The results of this study further show that survival in subgroups of men (i.e. younger men, no albuminuria, no history CVD, BMI between 25 and 30) is comparable to men in the general population, while the survival in women in these subgroups is still lower compared to women in the general population. Only in women with T2D without a history of CVD the impact of diabetes on survival is higher compared to men with T2D.

References

1. Barnett KN, Ogston SA, McMurdo MET, Morris AD, Evans JMM. A 12-year follow-up study of all-cause and cardiovascular mortality among 10,532 people newly diagnosed with Type 2 diabetes in Tayside, Scotland. *Diabet Med J Br Diabet Assoc.* 2010 Oct;27(10):1124–9.
2. Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia.* 2014 Aug;57(8):1542–51.
3. Roche MM, Wang PP. Sex differences in all-cause and cardiovascular mortality, hospitalization for individuals with and without diabetes, and patients with diabetes diagnosed early and late. *Diabetes Care.* 2013 Sep;36(9):2582–90.
4. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ.* 2006 Jan 14;332(7533):73–8.
5. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care.* 2000 Jul;23(7):962–8.
6. van Hateren KJJ, Drion I, Kleefstra N, Groenier KH, Houweling ST, van der Meer K, et al. A prospective observational study of quality of diabetes care in a shared care setting: trends and age differences (ZODIAC-19). *BMJ Open.* 2012;2(4).
7. Lutgers HL, Gerrits EG, Sluiter WJ, Ubink-Veltmaat LJ, Landman GWD, Links TP, et al. Life expectancy in a large cohort of type 2 diabetes patients treated in primary care (ZODIAC-10). *PLoS One.* 2009;4(8):e6817.
8. Liang H, Vallarino C, Joseph G, Manne S, Perez A, Zhang S. Increased risk of subsequent myocardial infarction in patients with type 2 diabetes: a retrospective cohort study using the U.K. General Practice Research Database. *Diabetes Care.* 2014;37(5):1329–37.
9. Hyvärinen M, Tuomilehto J, Laatikainen T, Söderberg S, Eliasson M, Nilsson P, et al. The impact of diabetes on coronary heart disease differs from that on ischaemic stroke with regard to the gender. *Cardiovasc Diabetol.* 2009;8:17.
10. Madssen E, Vatten L, Nilsen TI, Midthjell K, Wiseth R, Dale AC. Abnormal glucose regulation and gender-specific risk of fatal coronary artery disease in the HUNT 1 study. *Scand Cardiovasc J SCJ.* 2012 Aug;46(4):219–25.
11. Ubink-Veltmaat LJ, Bilo HJG, Groenier KH, Rischen RO, Meyboom-de Jong B. Shared care with task delegation to nurses for type 2 diabetes: prospective observational study. *Neth J Med.* 2005 Mar;63(3):103–10.
12. Data published by Statistics Netherlands. In Dutch: “‘Centraal Bureau voor de Statistiek’”. [Internet]. Available from: <http://statline.cbs.nl/Statweb/selection/?DM=SLNL&PA=70701NED&VW=T>
13. Rutten GEHM, Verhoeven S, Heine RJ, de Grauw WJC, Cromme PVM, Reenders K, et al. NHG-Standaard Diabetes Mellitus Type 2. Eerste herziening. *Huisarts Wet.* 1999;42(2):67–84.
14. Hockey R, Tooth L, Dobson A. Relative survival: a useful tool to assess generalisability in longitudinal studies of health in older persons. *Emerg Themes Epidemiol.* 2011;8(1):3.
15. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. *Biometrics.* 1982 Dec;38(4):933–42.
16. Kanaya AM, Grady D, Barrett-Connor E. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med.* 2002 Aug 12;162(15):1737–45.
17. Kalyani RR, Lazo M, Ouyang P, Turkbey E, Chevalier K, Brancati F, et al. Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults. *Diabetes Care.* 2014;37(3):830–8.
18. Loukine L, Waters C, Choi BC, Ellison J. Impact of diabetes mellitus on life expectancy and health-adjusted life expectancy in Canada. *Popul Health Metr.* 2012;10(1):7.

19. Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. *Diabetes Care*. 2005 Mar;28(3):514–20.
20. Hendriks SH, van Hateren KJJ, Groenier KH, Houweling ST, Maas AHEM, Kleefstra N, et al. Sex Differences in the Quality of Diabetes Care in the Netherlands (ZODIAC-45). *PloS One*. 2015;10(12):e0145907.
21. Wannamethee SG, Papacosta O, Lawlor DA, Whincup PH, Lowe GD, Ebrahim S, et al. Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. *Diabetologia*. 2012 Jan;55(1):80–7.
22. Orchard TJ, Becker DJ, Kuller LH, Wagener DK, LaPorte RE, Drash AL. Age and sex variations in glucose tolerance and insulin responses: parallels with cardiovascular risk. *J Chronic Dis*. 1982 Feb;35(2):123–32.
23. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013 Jan 2;309(1):71–82.
24. Tamis-Holland JE, Lu J, Korytkowski M, Magee M, Rogers WJ, Lopes N, et al. Sex differences in presentation and outcome among patients with type 2 diabetes and coronary artery disease treated with contemporary medical therapy with or without prompt revascularization: a report from the BARI 2D Trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes). *J Am Coll Cardiol*. 2013 Apr 30;61(17):1767–76.
25. Boonman-de Winter LJM, Rutten FH, Cramer MJM, Landman MJ, Liem AH, Rutten GEHM, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia*. 2012 Aug;55(8):2154–62.
26. InEen. In Dutch: Transparante ketenzorg diabetes mellitus, COPD en VRM rapportage zorggroepen over 2013. 2014 Jun.

