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

Short title: Sex differences in survival with type 2 diabetes

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Abstract

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

Setting: Primary care.

Participants: A total of 1815 patients who participated in a prospective observational cohort study (ZODIAC) was included of which 56% was female. Inclusion took place in 1998, 1999 and 2001. Vital status was assessed in 2013.

Main outcome measure: Relative survival of men and women with T2DM. The relative survival rate 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: 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. Only for T2D patients without a history of CVD a significantly lower relative survival in women compared to men with T2D was found.

Article summary: Strengths and limitations of this study

- This study provides insight in the current situation concerning the survival of men and women with type 2 diabetes who are treated in primary care in the Netherlands.
- This study used the technique of relative survival analysis, hereby a comparison between the survival of type 2 diabetes patients and the expected survival of whole general population could be made.
- The survival rates of men and women in the general population were derived from mortality rates of the entire nation.
- The generalizability is limited to primary care.
- No data were known concerning clinical variables in the general population and therefore the results of the subgroups should be interpreted with caution.

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.

Materials and 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 were expressed as mean with standard deviation (SD) or median with interquartile range [IQR] for normally distributed and non-normally distributed data, respectively. 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.

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 Fig. 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.

Subgroup analyses

The relative survival rate after 10 years for different subgroups is described in Table 3 and Fig. 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).

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 used 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.

Author Contributions: SHH, KJJH, KHG, HJGB and NK designed the study. SHH, KJJH and GWDL acquired the data. SHH, KJJH and KHG analysed the data. SHH, KJJH, KHG, GWDL, AHEMM, HJGB and NK interpreted the data. SHH and KJJH drafted the manuscript. KHG, GWDL, AHEMM, HJGB and NK reviewed and edited the manuscript. All authors read and approved the final manuscript.

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

Data sharing statement: No additional data are available.

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Tables and figures

Table 1. Baseline characteristics of the study population.

	Total (n = 1815)	Men (n = 800)	Women (n = 1015)	p-value
Age (years)	67.0 (±11.8)	65.0 (±11.8)	68.6 (±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 (±4.8)	28.2 (±4.1)	29.9 (±5.2)	<0.001
SBP (mmHg)	151.5 (±24.4)	147.2 (±23.4)	155.0 (±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 (µmol/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 (± SD), or median (IQR).

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.

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

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

Men							Women					
Follow-up	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.

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

	Men		Women		
Category	**N**	**Relative survival (95% CI)**	**N**	**Relative survival (95% CI)**	**p-value#**
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

Abbreviations**:** BMI: body mass index; CVD: cardiovascular disease.
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.

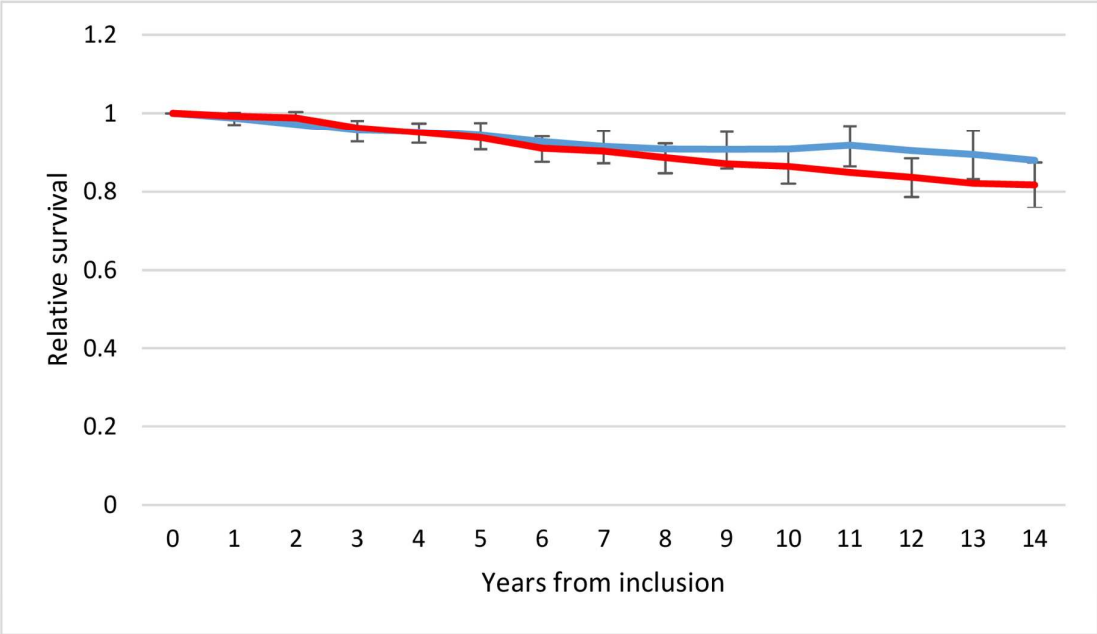

Fig. 1. Relative survival with 95% CI for men and women with T2D. Men: blue line, Women: red line.

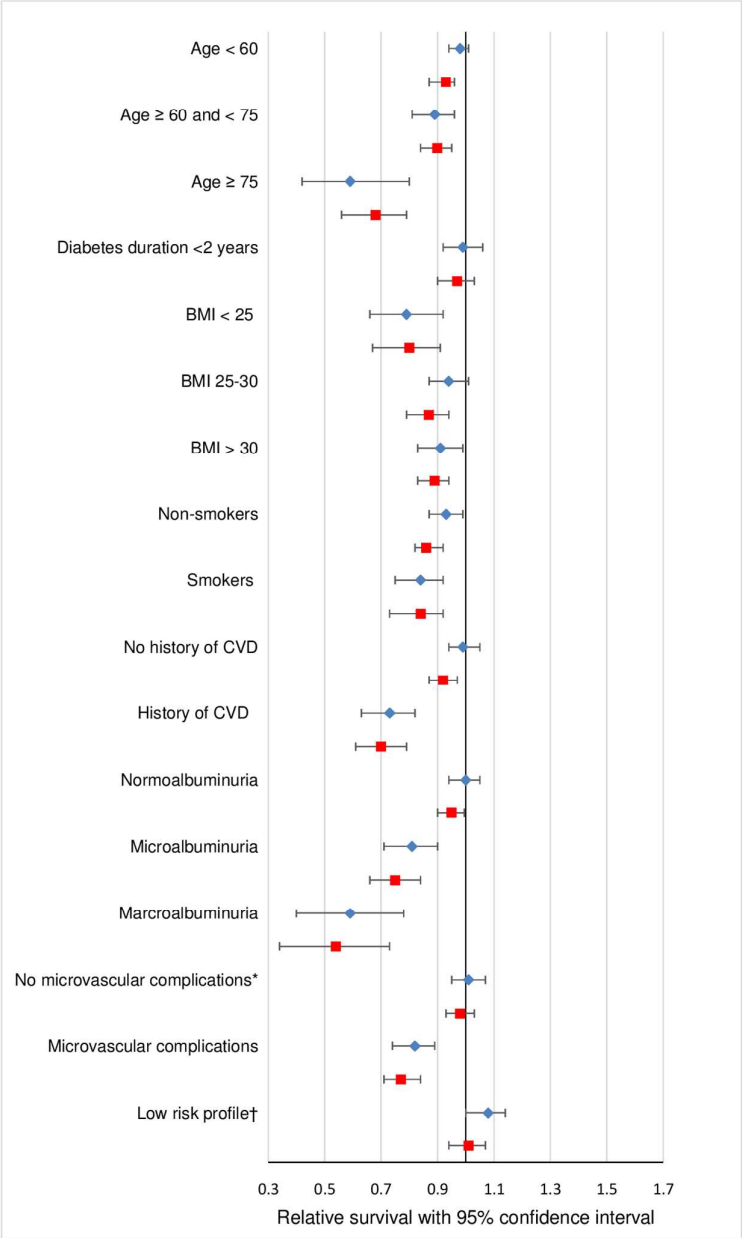

Fig. 2. Relative survival with 95% CI for men and women with T2D after 10 years in different subgroups. Men: blue, women: red.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	6,7,8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7,8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	18 (Table 2)
		(b) Give reasons for non-participation at each stage	18 (Table 2)
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8 and 17 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12,13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11,12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

Short title: Sex differences in survival with type 2 diabetes

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Abstract

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

Setting: Primary care.

Participants: A total of 1815 patients who participated in a prospective observational cohort study (ZODIAC) was included of which 56% was female. Inclusion took place in 1998, 1999 and 2001. Vital status was assessed in 2013.

Main outcome measure: Relative survival of men and women with T2DM. The relative survival rate 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: 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. Only for T2D patients without a history of CVD a significantly lower relative survival in women compared to men with T2D was found.

Article summary: Strengths and limitations of this study

- This study provides insight in the current situation concerning the survival of men and women with type 2 diabetes who are treated in primary care in the Netherlands.
- This study used the technique of relative survival analysis, hereby a comparison between the survival of type 2 diabetes patients and the expected survival of whole general population could be made.
- The survival rates of men and women in the general population were derived from mortality rates of the entire nation.
- The generalizability is limited to primary care.
- No data were known concerning clinical variables in the general population and therefore the results of the subgroups should be interpreted with caution.

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.

Materials and 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).

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

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 were expressed as mean with standard deviation (SD) or median with interquartile range [IQR] for normally distributed and non-normally distributed data, respectively. 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 (see supplementary file 1).

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 Fig. 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.

Subgroup analyses

The relative survival rate after 10 years for different subgroups is described in Table 3 and Fig. 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).

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.

The differences in relative survival between men and women in the total study population could possibly be explained by both the higher age and longer diabetes duration in women with T2D. Although women have a lower relative survival, it is not significantly lower compared to men. When women would have the same age and the same diabetes duration as men, the difference in relative survival would likely be smaller. This strengthens our conclusion that in the total population there is no significant difference in relative survival

between sexes. 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. First, 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 from the Zwolle region with 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. Second, although no specific indications exist which suggests that people in the Zwolle region are healthier or unhealthier compared to the whole population in the Netherlands, we do not now that for sure. It would have been better if we had used a control population from the Zwolle region, but unfortunately such a control population was not available. Third, no data were known concerning clinical variables in the general population, as we did not used 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. Fourth, the number of patients in subgroups was sometimes relatively low which has decreased the precision of the estimates. Fifth, selection bias has occurred in this study. 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 this group of patients with T2D, the

survival is only 2.2 years lower in men and 3.5 years lower in women compared to men and women the general population. In patients with T2D with no microvascular complication and in patients with a low risk profile, even no difference in survival compared to the general population was found.

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.

Author Contributions: SHH, KJJH, KHG, HJGB and NK designed the study. SHH, KJJH and GWDL acquired the data. SHH, KJJH and KHG analysed the data. SHH, KJJH, KHG, GWDL, AHEMM, HJGB and NK interpreted the data. SHH and KJJH drafted the manuscript. KHG, GWDL, AHEMM, HJGB and NK reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Data sharing statement: No additional data are available.

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Supplementary files

Supplementary file 1: estimation of the median survival

Tables and figures

Table 1. Baseline characteristics of the study population.

	Total (n = 1815)	Men (n = 800)	Women (n = 1015)	p-value
Age (years)	67.0 (±11.8)	65.0 (±11.8)	68.6 (±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 (±4.8)	28.2 (±4.1)	29.9 (±5.2)	<0.001
SBP (mmHg)	151.5 (±24.4)	147.2 (±23.4)	155.0 (±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 (µmol/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 (± SD), or median (IQR).

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.

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

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

Men							Women					
Follow-up	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	33	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.

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

	Men				Women				
Category	**N**	**Death**	**Lost to follow-up**	**Relative survival (95% CI)**	**N**	**Death**	**Lost to follow-up**	**Relative survival (95% CI)**	**p-value#**
Age < 60	276	24	3	0.98 (0.94 – 1.01)	224	26	4	0.93 (0.87 – 0.96)	0.052
Age ≥ 60 and < 75	337	126	3	0.89 (0.81 – 0.96)	448	123	5	0.89 (0.84 – 0.95)	0.870
Age ≥ 75	187	154	1	0.59 (0.42 – 0.80)	343	245	8	0.68 (0.56 – 0.79)	0.909
Diabetes duration <2 years	206	76	1	0.99 (0.92 – 1.06)	232	83	5	0.97 (0.90 – 1.03)	0.626
BMI < 25	174	96	1	0.79 (0.66 – 0.92)	169	83	4	0.80 (0.67 – 0.91)	0.914
BMI 25-30	392	135	4	0.94 (0.87 – 1.01)	377	153	6	0.87 (0.79 – 0.94)	0.126
BMI > 30	232	73	2	0.91 (0.83 – 0.99)	465	154	7	0.89 (0.83 – 0.94)	0.616
Non-smokers	583	226	5	0.93 (0.87 – 0.99)	869	349	14	0.86 (0.82 – 0.92)	0.121
Smokers	206	76	2	0.84 (0.75 – 0.92)	136	40	3	0.84 (0.73 – 0.92)	0.931
No history of CVD	492	132	3	0.99 (0.94 – 1.05)	717	228	11	0.92 (0.87 – 0.97)	0.046
History of CVD	306	172	4	0.73 (0.63 – 0.82)	298	166	6	0.70 (0.61 – 0.79)	0.648
Normoalbuminuria	450	116	3	1.00 (0.94 – 1.05)	655	198	11	0.95 (0.90 – 1.00)	0.214
Microalbuminuria	266	134	3	0.81 (0.71 – 0.90)	277	138	5	0.75 (0.66 – 0.84)	0.444
Macroalbuminuria	68	45	1	0.59 (0.40 – 0.78)	46	28	1	0.54 (0.34 – 0.73)	0.886
No microvascular complications	314	70	1	1.01 (0.95 – 1.07)	428	104	5	0.98 (0.93 – 1.03)	0.488
Microvascular complications*	464	227	5	0.82 (0.74 – 0.89)	546	263	10	0.77 (0.71 – 0.84)	0.395
Low risk profile†	154	21	1	1.08 (1.00 – 1.14)	270	58	4	1.01 (0.94 – 1.07)	0.106

Abbreviations**:** BMI: body mass index; CVD: cardiovascular disease. # 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.

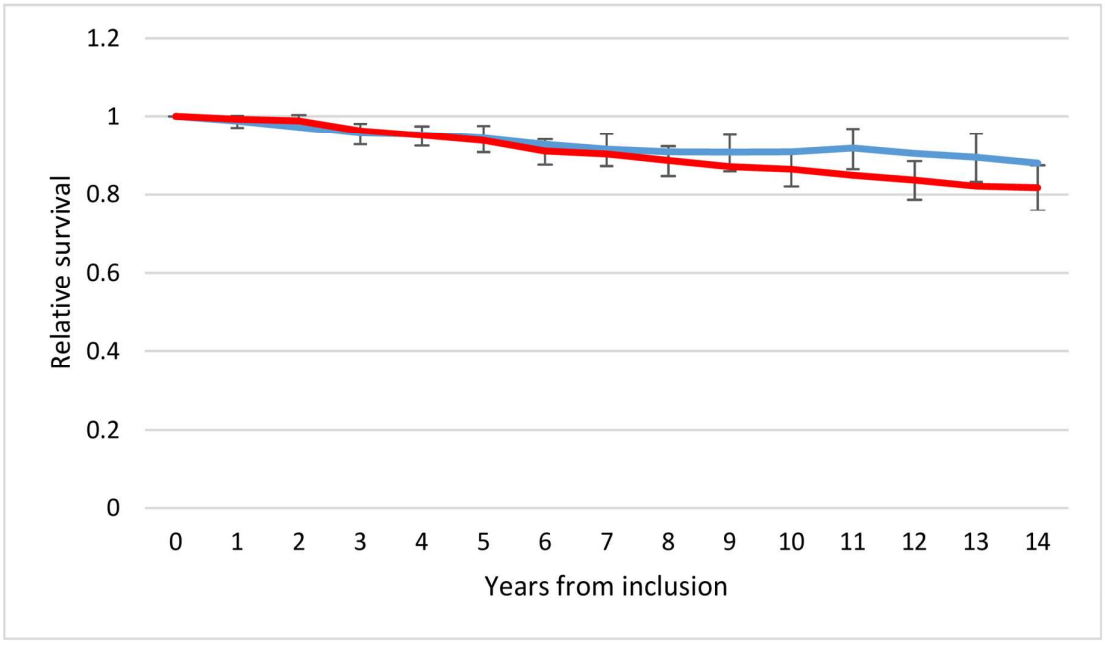

Fig. 1. Relative survival with 95% CI for men and women with T2D. Men: blue line, Women: red line.

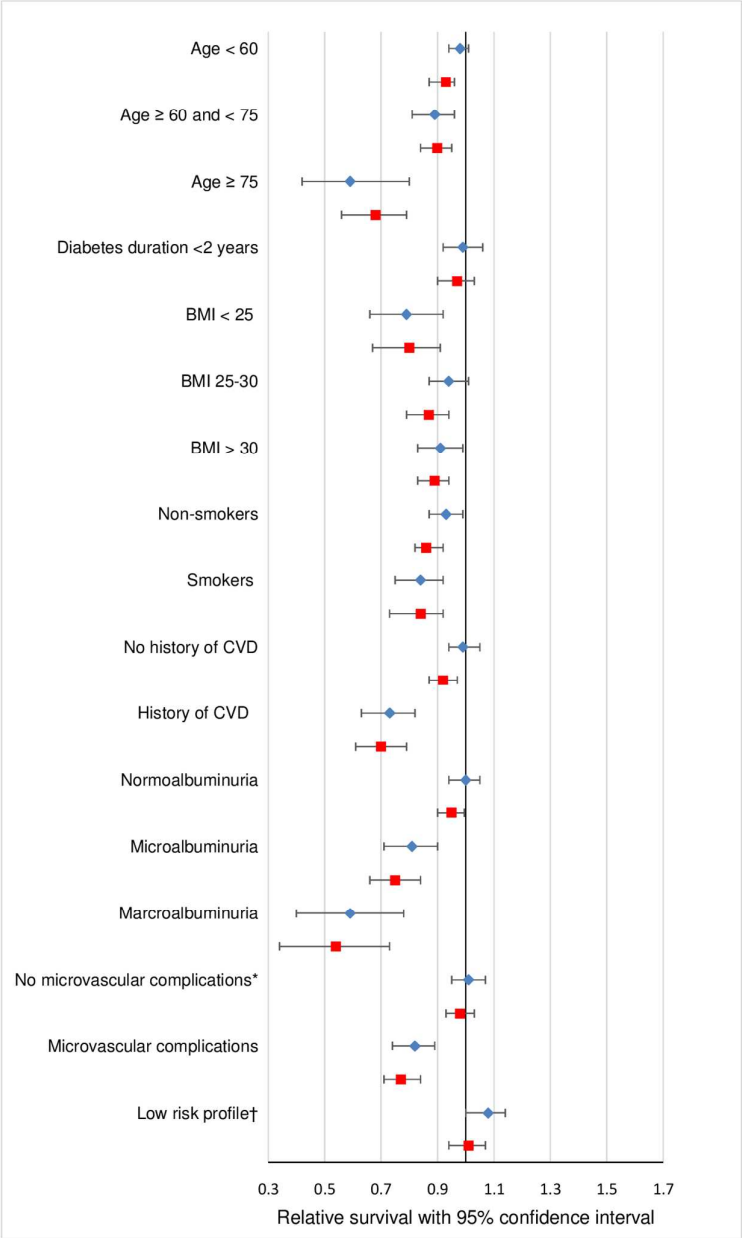

Fig. 2. Relative survival with 95% CI for men and women with T2D after 10 years in different subgroups. Men: blue, women: red.

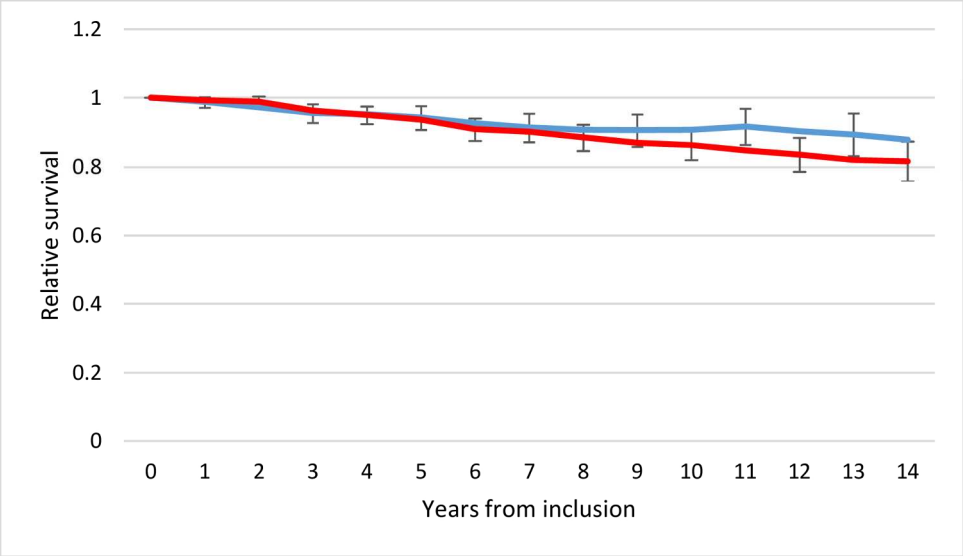

Fig. 1. Relative survival with 95% CI for men and women with T2D. Men: blue line, Women: red line.

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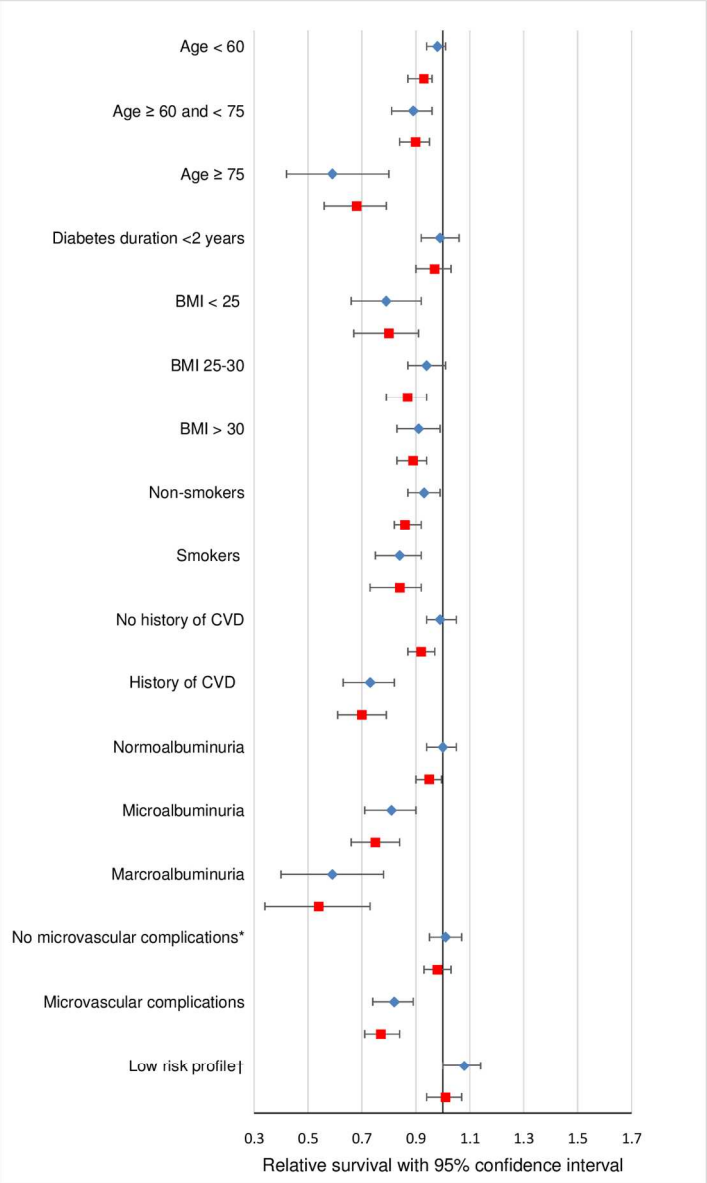

Fig. 2. Relative survival with 95% CI for men and women with T2D after 10 years in different subgroups. Men: blue, women: red.

109x176mm (300 x 300 DPI)

Supplementary file 1 Estimation of the median survival

We used the following formula to estimate the median survival:
X2 (median survival) = ((Y2 - Y1) (X3 - X1) / (Y3 - Y1)) + x1

Whereby (using men as an example):
X1 = the follow-up year in which more than 50% was still alive at the end (for men in our cohort, the 13th follow-up year
X3 = the follow-up year in which less than 50% was still alive at the end (for men in our cohort, the 14th follow-up year
Y1 = the cumulative survival at the end of X1 (for men cumulative survival 13th follow-p year = 0.5294 (rounded of 0.53)
Y2 = the median (= cumulative survival of 0.5)
Y3 = the cumulative survival at the end of X3 (for men cumulative survival 14th follow-p year = 0.4945)

Median survival of men with T2D = ((0.5 – 0.5294) (14 – 13) / (0.4945 – 0.5294)) + 13 = 13.8424 (rounded of 13.8).

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. We had to do that because after 14 years of follow-up, still more than 50% of the general population was alive (for men after 14 years the cumulative expected survival was 0.56).
For identifying X1, X3, Y1 and Y3 of the general population we used the following steps:

1. We calculated the average difference between the cumulative survivals of the 14 follow-up years (for men in our study population 0.031054)
2. We extrapolated the cumulative survival by extracting this average difference from the cumulative survival of the previous year (see table 1).
3. Finally we measured the median follow-up by using the estimated cumulative survival of the 16th and 17th follow-up year.

Table 1. Extrapolation for men in the general population.

Follow-up year	**Cumulative survival**	**Comment**
12 – 13	0.5922	Calculated
13 - 14	0.5628	Calculated
14 - 15	(0.5628 – 0.031054) = 0.531746	Estimated with extrapolation
15 – 16	(0.531746 – 0.031054) = 0.500692	Estimated with extrapolation
16 – 17	(0.500692 – 0.031054) = 0.469638	Estimated with extrapolation

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	6,7,8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7,8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	18 (Table 2)
		(b) Give reasons for non-participation at each stage	18 (Table 2)
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8 and 17 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12,13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11,12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.