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Diabetes and number of years of life lost with and without cardiovascular disease: a multi-state homogeneous semi-Markov model

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Abstract

Aims We quantified the impact of type 2 diabetes on incidence of non-fatal cardiovascular disease (CVD) and mortality, considering CVD as a continuum from occurrence of diabetes to the end point, and estimated the 15-year life expectancy with and without CVD.

Methods A total of 7239 Iranian adults (3246 men), aged ≥ 30 years, were followed from 1999 to 2014. We applied a multi-state semi-Markov model with three transitions including CVD-free to non-fatal CVD, CVD-free to death and non-fatal CVD to death, and studied the influence of diabetes on each transition rate, stratifying by sex and adjusting for confounders.

Results Diabetes was significantly associated with increased risk of non-fatal CVD in men [hazard ratio, 1.70 (1.36–3.53)] and women [2.19 (1.74–2.77)], and of all-cause death [2.72 (2.03–3.63) and 1.92 (1.37–2.67) in men and women, respectively]. An increased risk of mortality was found only among diabetic men, when non-fatal CVD was occurred [2.19 (1.36–3.53)]. Men with diabetes experienced first non-fatal CVD and death without CVD 1.7 and 1.4 years, respectively, earlier than those without diabetes; the corresponding values were 1.4 and 0.7 years for women. Moreover, diabetic men lived 1.3 years less than non-diabetic counterparts when non-fatal CVD was occurred.

Conclusions Diabetes increased the risk of non-fatal CVD events and all-cause mortality and consequently decreased the number of years lived without CVD. A decrease in LE was found only among diabetic men compared to non-diabetics after non-fatal CVD occurred.

Keywords Diabetes · Cardiovascular disease · Mortality · Multi-state · Markov model

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Introduction

Diabetes is a major and fast-growing health problem worldwide [1–3], increasing the risk of early mortality and both macrovascular and microvascular complications [4]. Current studies indicate that long-term glycemic control is an important predictor not only of microvascular disease, but also macrovascular complications [5]. Excess mortality in diabetes is multi-factorial, but the major cause of death remains cardiovascular disease (CVD) [6, 7]. Among patients with diabetes, the impact of CVD on mortality has previously been evaluated after acute myocardial infarction (MI) [8–10]. On the other hand, increased risk of all-cause death among diabetic patients has been evaluated without considering CVD as a continuum from occurrence of diabetes to the end point [1, 5, 11–13]; these studies considered the transition from the initial state to a one primary endpoint. However, more than one endpoint may exist in the path

between the initial and final point. In fact, separate analyses are usually conducted for each of the endpoints which are not completely satisfying, since they fail to demonstrate the relations between different types of events.

Recently, multi-state methods have been developed in which a number of states are defined and the focus is on the process of going from one state to another [14, 15]. Multi-state models have widely been studied and clinical applications becoming more common in medical research [16, 17], because they can provide a detailed insight into effects of exposures on each state. Additionally, during the course of the disease, predictions for outcome can be adjusted when additional information, e.g., the occurrence of intermediate events is available [18].

In the present study, we used multi-state model to (1) ascertain how diabetes were associated with all-cause mortality with and without CVD, (2) estimate the 15-year life expectancy (LE) of a large population in different states and to compare it among the populations with and without diabetes, and (3) estimate the number of years of life lost due to diabetes with and without CVD.

Methods

Data sources and population

We used data from the Tehran lipid and glucose study (TLGS), a large prospective cohort of Iranian population. The study has been described in detail elsewhere [19]. For the present analysis, we selected all subjects aged ≥ 30 yr from the first (1999–2001) and second (2002–2005) phases as baseline population ($n = 9553$) and excluded 602 participants with prevalent CVD at baseline, 385 individuals without information on diabetes status, and 747 individuals without any follow-up data until end of the study (March 20, 2014). We also, excluded 580 individuals with missing data on potential confounders. Thus, the final sample included 7239 participants (3246 men and 3993 women) (Online Resource 1). This study was approved by the ethics committee of the Research Institute for Endocrine Sciences of the Shahid Beheshti University of Medical Sciences according to the principles of the Declaration of Helsinki. All participants were informed of the study protocol, and their written informed consents were obtained before inclusion.

Data collection

At baseline, information on age, sex, education, history of CVD, medication use, smoking habits and anthropometric measures including weight and height was obtained [19]. BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured

twice, and the mean of two consecutive measurements was documented. Fasting plasma glucose (FPG) and serum total cholesterol (TC) were measured using standard laboratory techniques [19]. In first phase, physical activity level (PAL) was assessed by the lipid research clinic questionnaire [19]. It was replaced by the Modifiable Activity Questionnaire from the second phase, for obtaining the quantitative measure of PAL [20].

Definition of diabetes

At baseline, diabetes was defined as FPG ≥ 7 mmol/L or 2 h post-challenge plasma glucose (2 h-PCPG) ≥ 11.1 mmol/L or taking anti-diabetic medications.

Definition of confounders

We considered multiple potential confounders at the design stage of study and based on both our previous studies [13, 21] and other literature available [1, 22]; these included: age, TC, systolic BP (SBP) and BMI as continuous variables, and the others as categorical, including sex, education (< 9, 9–11 and ≥ 12 years of education), smoking status (current, former, or never) and family history of CVD (FH-CVD). Active participants were identified as those who participated in a vigorous physical activity at least 3 days per week or achieving a minimum of at least 600 MET (metabolic equivalent task)-minutes per week [23].

Assessment of outcomes

Details of the collection of outcomes in TLGS have been published elsewhere [19]. In brief, participants were followed annually for any medical conditions from the date of the baseline examination until the date of first documented outcome; data collected were then evaluated by an outcome committee to code the events according to the International Classification of Diseases, 10th edition. The main outcome measures were incident non-fatal CVD and all-cause mortality. Non-fatal CVD was defined as definite MI, probable MI, unstable angina pectoris, angiographic proven CHD, heart failure and stroke. All-cause mortality was determined as death from all causes including CVD and non-CVD death. Details are presented in Online Resource 2.

Statistical analysis

Continuous and categorical variables at baseline were compared using the independent sample t tests and χ^2 test, respectively. To minimize type I error related to multiple comparisons, we considered the Bonferroni correction; accordingly, two-tailed P values < 0.006 were considered statistically significant. Incidence density rate of events and

respective 95% confidence intervals (CI) were calculated by dividing the number of events by the person-years at risk.

Multi-state model

We defined a three-state model for our data analysis: CVD-free (state 1), non-fatal CVD (state 2) and all-cause death (state 3 or absorbing state); in Fig. 1, boxes represent the states and arrows symbolize the possible transitions. All individuals start free of CVD in state 1 at time t, and move to either a non-fatal CVD event in state 2 or death of any cause at state 3. Participants are not allowed to move back from state 2 to state 1, and only the first entry into a state is considered [15]. We used the time homogeneous semi-Markov model for our analysis [14, 15]. Cox's proportional hazards model (Cox PH) was applied for estimation of each transition hazard. Analyses were performed separately in the total population, men and women. Model 1 was adjusted for age/sex, and Model 2 was adjusted for age/sex, smoking status, PAL, education level, FH-CVD, TC, SBP and BMI. Details are presented in Online Resource 2.

Mean survival time

To estimate the mean survival years in 15 years of follow-up in each transition, we used restricted mean survival time (RMST) which is defined as the area under the curve of the survival function up to a truncation time point (a pre-specified time horizon):

$$\mu_t = \int_0^\tau S(t)\,dt$$

where $S(t)$ is the survival function for the time t. Interpreting this quantity is straightforward; for example, if t is equal to 15 years, then, μ is interpreted as 15-year LE, i.e., "what is the LE for the next 15 years" [24, 25] (details are shown in Online Resource 2).

Results were presented in the following ways: (1) RMST for diabetic and non-diabetic individuals, (2) differences between diabetic patients' RMST and the RMST of the

non-diabetic population which is interpreted as the number of years of life lost due to the diabetes [24–26], (3) restricted mean time lost (RMTL) is defined as the average survival time lost during the follow-up time, and (4) the ratio of RMTL of diabetic and non-diabetic participants.

All analysis was performed in R (https://CRAN.R-project.org) and completed in 2017. We estimated unadjusted RMST and RMTL using survRM2 package. To obtain adjusted estimation for RMST, we used the pseudo-package [27]. The multi-state Markov model and the PH Cox model were fitted using the mstate [28] and survival packages, respectively. Two-tailed P values < 0.05 were considered statistically significant.

Results

Baseline characteristics and incidence of outcomes

The study sample included 3246 men and 3993 women, aged ≥ 30 yr with mean (SD) ages of 47.5 (12.9) and 45.9 (11.3) yr, respectively. Among both genders, diabetic individuals, had higher mean TC, SBP and BMI ($P < 0.001$), and were less educated compared with non-diabetic counterparts ($P < 0.001$) (Table 1). During the study period, 7239 individuals were at risk of transition from the state 1 to states 2 and 3. Of these, 812 (469 men and 343 women) experienced a transition to the state 2, and 398 (234 men and 164 women) to state 3. Of 812 individuals who experienced first non-fatal CVD, 124 (81 men and 43 women) died of all causes (Table 2). Overall 522 cases of all-cause mortality were documented, 398 cases from transition 2 and 124 from transition 3.

Incidence density rate of non-fatal CVD was 12.4 (95% CI: 11.3–13.6) and 6.9 (6.2–7.7) per 1000 persons years in men and women, respectively. Incidence density rate of mortality was 6.2 (5.4–7.0) and 3.3 (2.8–3.8) in transition 2, and 3.1 (2.5–3.9) and 2.4 (1.8–3.2) in transition 3 in men and women, respectively.

Diabetes and risk of CVD and mortality

Results of the multi-state model are summarized in Table 3. Among diabetic patients in the total population and in males, increased risk of developing non-fatal CVD, of mortality among those with non-fatal CVD, and of mortality among those free of CVD was observed compared to their non-diabetic counterparts (Table 3). However, diabetic women had increased risk of developing non-fatal CVD and of mortality among those free of CVD compared to their non-diabetic counterparts. Figure 2 illustrates the estimated cumulative hazards for the three transitions. In all transitions, the cumulative hazards were higher for diabetic participants. Online
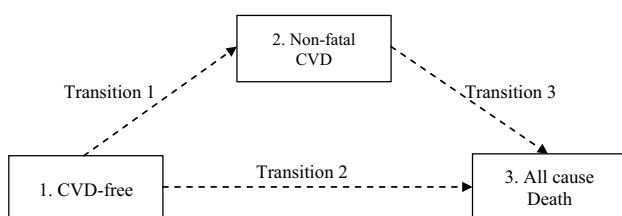
Fig. 1 A graphical representation of the multi-state model; *CVD* cardiovascular disease

Table 1 Characteristics of study population at baseline by the presence of diabetes mellitus; Tehran Lipid and Glucose Study (1999–2014)

	Men				Women				Total population			
	Diabetes n = 388	No diabetes n = 2858	Total men n = 3246	P value	Diabetes n = 567	No diabetes n = 3426	Total women n = 3993	P value	Diabetes n = 955	No diabetes n = 6284	Total n = 7239	P value
Mean (SD)												
Age	55.9 (11.5)	46.4 (12.7)	47.5 (12.9)	< 0.001	53.4 (10.2)	44.7 (11.1)	45.9 (11.3)	< 0.001	54.5 (10.1)	45.5 (11.9)	46.7 (12.1)	< 0.001
TC	5.6 (1.2)	5.3 (1.1)	5.4 (1.1)	< 0.001	6.2 (1.2)	5.5 (1.1)	5.6 (1.2)	< 0.001	6.0 (1.3)	5.5 (1.1)	5.5 (1.2)	< 0.001
SBP	132.8 (22.2)	119.0 (17.8)	121.4 (18.9)	< 0.001	135.3 (22.6)	118 (18.8)	121.3 (20.2)	< 0.001	134.4 (22.5)	119.4 (18.4)	121.4 (19.6)	< 0.001
BMI	27.7 (3.9)	26.1 (3.9)	26.2 (3.9)	< 0.001	29.8 (4.8)	28.3 (4.6)	28.5 (4.7)	< 0.001	29.0 (4.6)	27.3 (4.5)	27.5 (4.5)	< 0.001
N (%)												
Smoking status												
Current	93 (24.0)	911 (31.9)	1004 (30.9)	< 0.001	26 (4.6)	156 (4.6)	182 (4.6)	0.001	119 (12.5)	1067 (17.0)	1186 (16.4)	0.002
Never	214 (55.2)	1514 (53.0)	1728 (53.2)		516 (91.0)	3201 (93.4)	3717 (93.1)		730 (76.4)	4715 (75.0)	5445 (75.2)	
Past	81 (20.9)	433 (15.2)	514 (15.8)		25 (4.4)	69 (2.0)	94 (2.4)		106 (11.1)	502 (8.0)	608 (8.4)	
Education level												
< 9 years	177 (45.6)	835 (29.2)	1012 (31.2)	< 0.001	414 (73.0)	1525 (44.5)	1939 (48.6)	< 0.001	591 (61.9)	2360 (37.6)	2951 (40.8)	< 0.001
9–12 years	158 (40.7)	1485 (52.0)	1643 (50.6)		142 (25.0)	1618 (47.2)	1760 (44.1)		300 (31.4)	3103 (49.4)	3403 (47.0)	
> 12 years	53 (13.7)	538 (18.8)	591 (18.2)		11 (1.9)	283 (8.3)	294 (7.4)		64 (6.7)	821 (13.1)	885 (12.2)	
PAL												
*Active	106 (27.3)	794 (27.8)	900 (27.7)	0.904	155 (27.3)	1025 (29.9)	1180 (29.6)	0.233	261 (27.3)	1819 (28.9)	2080 (28.7)	0.318
FH-CVD												
Yes	49 (12.6)	406 (14.2)	455 (14.0)	0.436	136 (24.0)	584 (17.0)	720 (18.0)	< 0.001	185 (19.4)	990 (15.8)	1175 (16.2)	0.005

TC total cholesterol, SBP systolic blood pressure, BMI body mass index, FH-CVD family history of cardiovascular disease

* Doing exercise or labor more than three times a week or performing activities achieving ≥ 600 metabolic equivalent of task (MET)

Table 2 Numbers and percentages of population in the 3-state model; Tehran Lipid and Glucose Study (1999-2014)

Origin states	Total entering	Destination states		
		1: CVD-free	2: Non-fatal CVD	3: All-cause death
1: CVD-free	7239	6029 (83.3%)	812 (11.2%)	398 (5.5%)
2: Non-fatal CVD	812	–	688 (84.8%)	124 (15.2%)
3: All-cause death	522	–	–	522 (100%)

CVD cardiovascular diseases

Resource 3 shows stacked probability transition curves for participants.

Fifteen-year RMST

In transition 1, from the initial state, non-diabetic men had an RMST of 13.9 years over the next 15 years for experiencing the non-fatal CVD, while RMST of men with diabetes was 12.2 years (Table 4). Therefore, non-fatal CVD-free LE was 1.7 years lower for diabetic compared to non-diabetic men on average ($P < 0.001$). Diabetic women had 1.4 years lower non-fatal CVD-free LE compared to non-diabetic women (13.1 vs. 14.5) ($P < 0.001$). In transition 2, for both men and women, diabetes was associated with fewer years lived (1.4 and 0.7 years for men and women, respectively). In transition 3, differences in number of years lived with CVD between non-diabetic and diabetic men were 1.3 years ($P < 0.05$), not however, significant for women.

Years of life lost

The average years of life lost (RMTL) of diabetic men and women without CVD (transition 2), were 3.9 and 4.1 times higher, respectively, compared to their non-diabetic counterparts ($P < 0.001$); however, the RMTL with non-fatal CVD (transition 3) was 1.8 times higher in diabetic compared to non-diabetic men ($P < 0.05$) (Table 4). The RMTL ratio of diabetic and non-diabetic women with non-fatal CVD was not significant. Online Resource 4 shows the results of adjusted RMST; diabetic individuals had the shorter RMST, namely 0.83, 0.83 and 1.07 years in transitions 1, 2 and 3, respectively, than their non-diabetic counterparts.

Discussion

In this study, we found that among the total population, having diabetes at age ≥ 30 years was associated with higher risk of developing non-fatal CVD and mortality with and without CVD. Individuals with diabetes in total population experienced first non-fatal CVD 1.5 years earlier than those without diabetes. Also, LE with and without CVD was decreased by about 11 months in diabetic compared to non-diabetic participants.

Although diabetes mellitus has been known as an established risk factor for CVD [29, 30], there is uncertainty concerning the extent of its associated with CVD [31, 32]. In 2009, a systematic review reported that predictive role of FPG for CHD was inconsistent even in good quality cohort studies [33]. Then, a meta-analysis of 102 prospective studies found that diabetes conferred about a twofold excess risk of CHD, major stroke subtypes, and deaths attributed to other vascular causes [32].

We found that diabetic men and women had 1.92 and 2.19 times higher risk of developing non-fatal CVD, respectively, compared to their non-diabetic counterparts.

Current evidence shows that heart diseases death rates among adults with diabetes are 2–4 times higher than the rates for those without diabetes [34]. Furthermore, in a collaborative meta-analysis from 97 prospective studies, diabetes was associated with a 80% higher risk of all-cause mortality [35]. In line with current evidence, we found that the risk of all-cause mortality was 2.72 and 1.92 times higher in CVD-free diabetic men and women, respectively, than for their non-diabetic counterparts.

A number of studies have also investigated the impact of diabetes on mortality in patients with CVD [9, 10]. A recently published study reported that among those with non-fatal MI at baseline, there was a 48% increased risk of death in those with diabetes compared to those without it [9]; however, we could not find any study to estimate the impact of diabetes on the CVD and mortality simultaneously in a multi-state Markov model. In 2006, Franco et al. [22] built a multi-state life tables to estimate the associations of diabetes with total LE and total life years with and without CVD at the age of 50 years using data from the Framingham Heart Study (the 1950s to the 1980s). They showed that diabetic men and women, compared with their non-diabetic counterparts, had more than double the risk of developing CVD and a 1.7 and 2.22 times higher risk of death, respectively, once CVD was present. A similar result was found in our study for men, although we found no significant difference in risk of mortality between diabetic and non-diabetic women once CVD had occurred. The contradictory results found in our study might be attributable to the relatively small numbers of events among women and consequently inadequate power to reach statistical significance. Lower occurrence of events observed among women in our study might

Table 3 Hazard ratios for non-fatal CVD and death; Tehran Lipid and Glucose Study (1999–2014)

| Transitions	Number of participants entered/number of events	Model 1 HR (95% CI)[a]	Model 2 HR (95% CI)[b]
Men			
State 1 → State 2			
Total	3246/469		
Non-diabetic	2858/358	Reference	Reference
Diabetic	388/111	2.02 (1.62–2.51)	1.70 (1.36–3.53)
State 1 → State 3			
Total	3246/234		
Non-diabetic	2858/161	Reference	Reference
Diabetic	388/73	2.48 (1.87–3.28)	2.72 (2.03–3.63)
State 2 → state 3			
Total	469/81		
Non-diabetic	358/50	Reference	Reference
Diabetic	111/31	2.11 (1.34–3.31)	2.19 (1.36–3.53)
Women			
State 1 → State 2			
Total	3993/343		
Non-diabetic	3426/216	Reference	Reference
Diabetic	567/127	2.64 (2.10–3.32)	2.19 (1.74–2.77)
State 1 → State 3			
Total	3993/164		
Non-diabetic	3426/104	Reference	Reference
Diabetic	567/60	2.04 (1.48–2.82)	1.92 (1.37–2.67)
State 2 → state 3			
Total	343/43		
Non-diabetic	216/21	Reference	Reference
Diabetic	127/22	1.54 (0.85–2.81)	1.62 (0.85–3.06)
Total population			
State 1 → State 2			
Total	7239/812		
Non-diabetic	6284/574	Reference	Reference
Diabetic	955/238	2.32 (1.98–2.71)	1.92 (1.64–2.25)
State 1 → State 3			
Total	7239/398		
Non-diabetic	6284/265	Reference	Reference
Diabetic	955/133	2.31 (1.87-2.86)	2.33 (1.87-2.90)
State 2→ state 3			
Total	812/124		
Non-diabetic	574/71	Reference	Reference
Diabetic	238/53	1.87 (1.30–2.69)	1.98 (1.35–2.89)

State 1 → State 2: CVD-free to non-fatal CVD

State 1 → State 3: CVD-free to all-cause death

State 2 → State 3: Non-fatal CVD to all-cause death

[a] Adjusted for age and sex in total population and for age in men and women

[b] Adjusted for age, sex, smoking, education level, physical activity level, TC, SBP, BMI and FH-CVD in total population; for men and women, adjustment were done for all confounders except for sex

TC total cholesterol, *SBP* systolic blood pressure, *BMI* body mass index, *FH-CVD* family history of cardiovascular disease
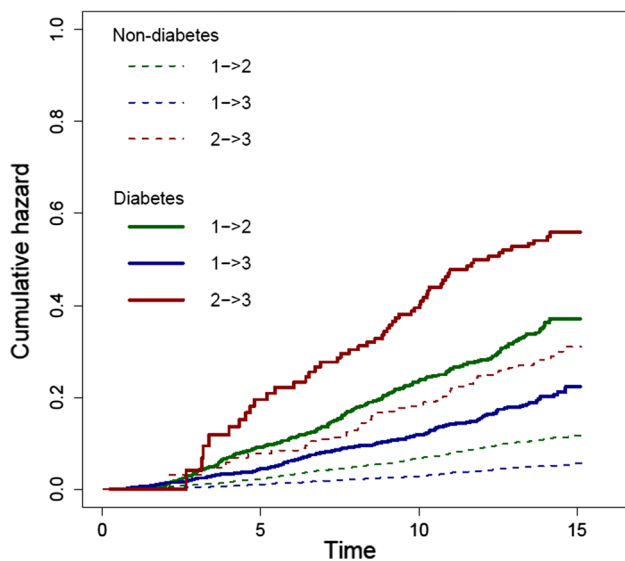
Fig. 2 Estimated baseline cumulative hazards, diabetes vs. non-diabetes, Tehran lipid and glucose study (1999–2014). 1 → 2: CVD-free to non-fatal CVD, 1 → 3: CVD-free to all-cause death, 2 → 3: Non-fatal CVD to all-cause death

be due to increased medication adherence among women living with heart disease, compared to men in our country. Non-adherence to cardiovascular medications is a global threat which is associated with adverse health outcomes [36]. According to a meta-analysis, approximately 50% of patients with CVD had poor adherence to their prescribed medications [37]. Moreover, the contradictory results are most likely due to the sex differences in the occurrence of various manifestations of CVD among diabetic individuals. Among individuals with diabetes, a range of 17–59% have been reported for prevalence of myocardial ischemia, and 46% for carotid arterial disease [38]. Current evidence also shows that women with diabetes have the highest mortality after MI [39]. Women in our study had a lower incidence of definite non-fatal MI (8.5 vs. 18.5%) than men; hence, sex differences in mortality risk after non-fatal CVD may be due to the lower incidence of MI among women, compared to men. Additionally, in the present study we included participants aged ≥ 30 years, whereas Franco et al. [22] investigated a population aged ≥ 50 years. It has been reported that MI imposes higher risk of coronary artery disease and worse outcomes only after menopause in diabetic women than men [40]. Further studies are needed to clarify the sex difference in risk of mortality after CVD events among individuals with diabetes.

We found that over 15 years follow-up, potential lifetimes were about 11 and 17 months less among CVD-free diabetic individuals in total population and males, respectively, compared to their non-diabetic participants. Gu et al. [41] previously showed that median LE was 8 years

lower for diabetic individuals aged 55–64 years compared to their non-diabetic counterparts. Using cross-sectional data, Narayan et al. [42] estimated loss of 8 years in LE among 50-year-old non-Hispanic men with diabetes. However, the above studies did not assess the association of diabetes with LE. Using the multi-state life table, Franco et al. [22] showed that at age ≥ 50 years, women and men with diabetes were expected to live 8.4 and 7.8 years less, free of CVD, respectively. However, they found no significant difference between the years spent with CVD between diabetic and non-diabetic populations. Unlike their study, we found significant difference between LE of diabetic and non-diabetic men once a non-fatal CVD event had occurred. Some of the differences in conclusions regarding differences in LE with CVD are most likely due to the methodology we used to calculate LE, i.e., we estimated LE over 15 years of follow-up using RMST, whereas, Franco et al. [22] estimated total lifetime expectancy using life table analysis. Secondly, this difference could be due to date of study; Franco et al. [22] analyzed data from the 1950s to the 1980s, whereas we selected participants starting from 1999 and followed them until 2014, when there had been significant improvement in healthy life expectancy worldwide [43] compared to 1950–1980.

Interestingly, we did not find any significant differences in the years spent with CVD between diabetic and non-diabetic women, unlike men; the gender difference in LE with CVD is most likely due to the lower incidence of non-fatal MI among women compared to men, as previously mentioned. On the other hand, we included participants aged ≥ 30 years. Evidence shows that at younger ages, men have a higher risk of CHD than women [44]; this gender difference could also be explained by the higher LE of females than males in Iran. In 2010, global healthy life expectancy at birth was 59.0 and 63.2 years for Iranian males and females, respectively [43].

The strengths of the present study include use of data from a prospective cohort with a relatively long-term follow-up. We used a combination of glycemia tests (FPG and 2 h-PCPG) and pharmacological treatment of diabetes rather than self-reported diabetes status for diagnosis of diabetes. We estimated associations between diabetes and LE with and without CVD using the multi-state Markov model which is an ideal method for establishing life expectancies [45]. Our study has some limitations. First, as inherent to any prospective study, the level of some confounders such as smoking at the baseline examination might change during the follow-up. Second, we conducted our investigation among Persian ethnicities with relatively high incidence of diabetes and CVD events [3, 13]; therefore, results of our study are not expected to be similar across the populations with different incidence rates of CVD.

Table 4 RMST according to transitions and diabetic status of participants; Tehran Lipid and Glucose Study (1999–2014)

Transitions	Diabetic status	RMST (CI)	RMST (Diabetic)–RMST (Non-diabetic) (CI)	RMTL (CI)	RMTL (Diabetic)/ RMTL (Non-diabetic) (CI)
Men					
State 1 → State 2	Non-diabetic	13.9 (13.8–14.1)	− 1.7(− 2.1 to − 1.2)**	1.0 (0.95-1.1)	2.7 (2.1–3.2)**
	Diabetic	12.2 (11.8–12.7)		2.7 (2.2–3.1)	
State 1 → State 3	Non-diabetic	14.5(14.4–14.6)	− 1.4(− 1.8 to − 0.9)**	0.46 (0.3–0.6)	3.9 (3.0–5.2)**
	Diabetic	13.1(12.7–13.5)		1.80 (1.4–2.2)	
State 2 → state 3	Non-diabetic	10.2 (9.8–10.7)	− 1.3 (− 2.4 to − 0.3)*	1.7 (1.2–2.1)	1.8 (1.2–2.6)*
	Diabetic	8.9 (7.9–9.8)		3.1 (2.1–4.0)	
Women					
State 1 → State 2	Non-diabetic	14.5(14.4–14.6)	− 1.4 (− 1.7 to − 1.1)**	0.46 (0.3–0.5)	4.1(3.2–5.1)**
	Diabetic	13.1(12.8–13.4)		1.90 (1.5–2.1)	
State 1 → State 3	Non-diabetic	14.8(14.7–14.8)	− 0.7(− 0.9 to − 0.4)**	0.22 (0.1–0.2)	4.1(2.9–5.7)**
	Diabetic	14.1(13.8–14.3)		0.90 (0.6–1.1)	
State 2 → state 3	Non-diabetic	10.6 (10.1–11.2)	− 0.7(− 1.6 to 0.1)	1.3 (0.7–1.8)	1.5 (0.9–2.6)
	Diabetic	9.9 (9.2–10.7)		2.0 (1.2–2.7)	
Total population					
State 1 → State 2	Non-diabetic	14.3 (14.2–14.4)	− 1.5(− 1.7 to − 1.2)**	0.7 (0.6–0.8)	3.1 (2.6–3.6)**
	Diabetic	12.8 (12.5–13.1)		2.2 (1.9–2.4)	
State 1 → State 3	Non-diabetic	14.7 (14.6–14.7)	− 0.9(− 1.1 to − 0.7)**	0.33 (0.2–0.4)	3.9 (3.1–4.8)**
	Diabetic	13.8 (13.5–13.9)		1.30 (1.1–1.5)	
State 2 → state 3	Non-diabetic	10.4 (10.1–10.7)	− 0.9(− 1.6 to − 0.3)**	1.5 (1.2–1.8)	1.6 (1.1–2.1)*
	Diabetic	9.5 (8.9–10.1)		2.5 (1.9–3.1)	

State 1 → State 2: CVD-free to non-fatal CVD

State 1 → State 3: CVD-free to all-cause death

State 2 → state 3: Non-fatal CVD to all-cause death

RMST restricted mean survival time, *RMTL* restricted mean time lost, *CI* confidence interval

* *P* value < 0.01, ** *P* value < 0.001

Conclusions

We found that diabetes was associated with higher risk of CVD and all-cause mortality which can be translated to a 1.5 years early onset of CVD among diabetic subjects. Furthermore, about 11 months decrease was shown in lifetime years spent with and without CVD among diabetic compared to non-diabetic patients. However, this decrease was influenced mainly by CVD events among diabetic men.

Compliance with ethical standards

Conflicts of interest None.

Ethical approval This study was approved by the ethics committee of the Research Institute for Endocrine Sciences of the Shahid Beheshti University of Medical Sciences according to the principles of the Declaration of Helsinki.

Informed consent All participants were informed of the study protocol, and their written informed consents were obtained before inclusion.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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