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ORIGINAL ARTICLE

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Premature death and risk of cardiovascular disease in young-onset diabetes: a 23-year follow-up of the Da Qing Diabetes Study

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Abstract

Objective This study aimed to investigate premature mortality and the risk of cardiovascular disease (CVD) in Chinese adults with diabetes diagnosed before the age of 45 years.

Methods A total of 519 participants with normal glucose tolerance (NGT) and 630 with newly diagnosed diabetes mellitus (DM) were recruited in 1986 in the Da Qing Diabetes Study. In 2009, the participants were followed up to assess mortality and CVD events. The subjects were stratified into four subgroups according to age and diabetes status: age <45 years with NGT ($NGT_{<45y}$), age <45 years with DM ($DM_{<45y}$), age ≥45 years with NGT ($NGT_{\geq 45y}$), and age ≥45 years with DM ($DM_{\geq 45y}$). The risk of death and CVD events in patients with young-onset DM and elder subjects with NGT were compared to show the extent of premature death and CVD in the DM participants.

Results During the 23-year follow-up, 26 (10.40%) participants in $NGT_{<45y}$, 72 (34.12%) in $DM_{<45y}$, 74 (30.58%) in $NGT_{\geq 45y}$, and 266 (68.73%) in $DM_{\geq 45y}$ died, including 13 (5.20%), 36 (17.06%), 24 (9.92%), and 128 (33.07%) death attributed to CVD. The corresponding rates of CVD events were 56 (22.40%), 90 (42.65%), 89 (36.78), and 213 (55.04%). It also showed that the risk of all-cause death (HR 1.23, 95% CI 0.88–1.71) or CVD events (HR 1.25, 95% CI 0.93–1.69) did not differ significantly between the $DM_{<45y}$ and $NGT_{\geq 45y}$ groups after adjusting for sex, smoking, body mass index, systolic blood pressure, total cholesterol and previous history of CVD. Of note, participants in the $DM_{<45y}$ group had an higher risk of CVD mortality compared with that in the $NGT_{\geq 45y}$ group (HR 1.76, 95% CI 1.04–2.98), although the mean age in the former group was 12 years lesser than that in the latter group (39.01 ± 5.00 vs 51.45 ± 5.14).

Conclusions Young-onset diabetes is a risk factor for the premature death and cardiovascular disease. Early prevention and intensive treatment are warrented in patients with young-onset diabetes.

Keywords Young-onset diabetes · Cardiovascular disease · Premature death · Follow-up

Introduction

The prevalence of diabetes has increased and the age of onset has decreased in the Chinese population in recent decades [1, 2]. In China, a particular alarming observation was that an increased prevalence of diabetes was found in the middle-aged group (35–45 years) since 1994 [3]. The definition of young-onset diabetes remains inconsistence worldwide. According to The American Diabetes Association recommendation [4], participants with diabetes diagnosed before the age of 45 years were classified as young-onset diabetes in the present analysis.

It was reported that for those with young-onset diabetes, the increased lifetime exposure to hyperglycemia predicts a high risk of complications [5]. However, the death and cardiovascular outcome in young-onset diabetes is not

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accurate due to the limited follow-up data. A higher risk of death and cardiovascular disease (CVD) in young-onset diabetes has been reported, but only through a mean of 3-year follow up [6]. Another study indicated that 50-year-old diabetes patients without history of vascular disease was about 6 years younger at the time of death compared with counterparts without diabetes [7]. CVD is associated with diabetes resulting in morbidity and mortality which particularly due to myocardial infarction, congestive heart failure, and stroke [8]. A Markov modeling approach used by Rhodes et al. has predicted that patients with type 2 diabetes diagnosed between 15 and 24 years would lose 15-year life expectancy, and some will develop severe chronic complications in their fifth decade [9].

In Chinese population, long-term population-based cohort studies of the natural history of young-onset diabetes are thus required to implement more effective and efficient health care strategies to manage this vulnerable population. The China Da Qing Diabetes Study was the first of the large-scale trials and examined the survival of the diabetes patients and the effect of different lifestyle interventions in a group setting among Chinese people with impaired glucose tolerance [10]. The present study used the data from the Da Qing Diabetes Study to investigate the risk of mortality and CVD during a 23-year period among young adults with newly diagnosed diabetes aged < 45 years.

Populations and methods

Research design

In 1986, 281,589 residents in Da Qing, China, aged 25–74 years, received health care in designated clinics located throughout the city. Half of these clinics, which served 126,715 people, were selected for diabetes screening. Plasma glucose concentration 2 h after a standard breakfast (a 100-g steamed bread bun containing 80-g carbohydrate) was measured in 110,660 participants (87.3% of the target population; 55,391 men and 55,269 women). Further, 3956 participants (94.0%) without previously diagnosed diabetes or with 2 h plasma glucose ≥6.7 mmol/L after a standard meal were given a 75-g oral glucose tolerance test (OGTT), which included measurement of fasting and 2 h post-load plasma glucose concentration. Based on the OGTT results, classified by 1985 World Health Organization (WHO) criteria, 630 participants (300 men and 330 women) were identified as newly diagnosed diabetes mellitus (DM; defined as 2 h plasma glucose concentration ≥11.1 mmol/L) and 519 (282 men and 237 women) were identified as normal glucose tolerance (NGT; defined as 2 h plasma glucose concentration <6.7 mmol/L).

A baseline clinical examination, including measurements of blood pressure, body mass index (BMI), and a 12-lead electrocardiogram (ECG), was collected in each participant as described previously [11]. The participants with diabetes were informed of the diagnosis and referred to their local clinics for continuing medical care. Most of them were treated with oral antihyperglycemic agents or insulin. In this analysis, all participants were stratified into four subgroups according to baseline age and diabetes status to investigate the risk of premature death and CVD in Chinese adults: age < 45 years with NGT ($NGT_{<45y}$), age < 45 years with DM ($DM_{<45y}$), age ≥ 45 years with NGT ($NGT_{\geq 45y}$), and age ≥ 45 years with DM ($DM_{\geq 45y}$). In 2009, a follow-up study was conducted to determine CVD incidence and mortality.

The study was approved by institutional review boards at the WHO and the China–Japan Friendship Hospital. Written informed consent was given by all living participants and the proxies who provided information about deceased participants.

Data collection

In 2009, each participant was contacted to determine their vital status. Follow-up data for living participants were obtained by personal interview, clinical examination, and medical chart review to determine CVD status and date of diagnosis of the events. Data for deceased participants were collected by proxy interview and medical chart reviews. The proxy interview was carried out to determine the date, place, and circumstances of death among the participants. The proxies were also asked to provide information on hospitals where the participant had received medical care around the time of death. The death certificates, medical records, and proxy interviews were reviewed independently by two physicians to establish the underlying cause of death. Differences were resolved by a third senior physician as previously described [12, 13].

Outcome classification

Mortality was counted based on the death, including all-cause death and CVD death, caused by myocardial infarction, sudden death, congestive heart failure, and stroke. CVD events were defined as the first nonfatal or fatal cardiovascular events, including myocardial infarction, sudden death, and stroke. The diagnosis of myocardial infarction was made on the basis of clinical manifestations, evidence of ECG, and enzyme assays. Stroke was defined as rapidly developing clinical signs of brain dysfunction lasting more than 24 h or leading to death, without apparent cause other than blood vessel origin. The transient ischemic attacks were not included in the population.

Statistical analyses

The incidence for each outcome was calculated as the number of events divided by the number of person-years at risk, with censoring at the time of diagnosis, death, loss to follow-up, or 31 December 2009. The statistical significance of differences between groups was assessed using the *t* test for continuous and the Chi-square test for categorical variables. Confidence intervals for incidence density were calculated using Poisson distribution estimates. Hazard ratios (HR) adjusted for sex, smoking, BMI, SBP, total cholesterol, and previous history of CVD were obtained from the Cox proportional hazards analyses. All the statistical tests were two sided, and significance was accepted when *P* value was <0.05. All statistical analyses were conducted using the SAS version 9.4 (SAS Institute, NC, USA).

Results

A total of 598 (94.9%) participants with diabetes and 492 (94.8%) with NGT completed the clinical reports. Table 1 shows the clinical characteristics of the participants based upon age and diabetic status. Participants with DM in the <45 years or ≥45 years age groups, were older and had higher BMI, blood pressure and total cholesterol compared with the corresponding age group of NGT. Compared with the $NGT_{\geq 45y}$ group, participants in the $DM_{<45y}$ group, who were 12 years younger than those in the $NGT_{\geq 45y}$ group, had a significantly higher BMI (25.37 ± 3.36 vs. 23.79 ± 3.63 kg/m^2, $P < 0.0001$) and cholesterol (5.12 ± 1.57 vs. 4.82 ± 1.04 mmol/L, $P = 0.021$), more males and fewer smokers ($P < 0.0001$). No differences in systolic blood pressure ($P = 0.75$) and diastolic blood pressure ($P = 0.84$) were found between $NGT_{\geq 45y}$ group and $DM_{<45y}$ group.

Age-specific incidence of mortality and CVD events in different groups are shown in Table 2. In each corresponding age group, the DM group had a significantly high incidence of all-cause mortality, CVD mortality, and CVD events compared with the NGT group. The comparison of $DM_{<45y}$ and $NGT_{\geq 45y}$ groups, despite the 12-year discrepancy in age, showed no significant differences in the all-cause mortality (16.31/1000 vs. 14.70/1000 person-years, $P = 0.52$) and CVD events (22.74 vs. 19.60/1000 person-years, $P = 0.28$). Even worse, the incidence of CVD death was about twice as high in $DM_{<45y}$ as in $NGT_{\geq 45y}$ (8.16 vs. 4.77/1000 person-years, $P = 0.04$). The number of deaths before the age of 60 years accounted for 12.16% (9/74) and 65.28% (47/72) of the total number of deaths in the $NGT_{\geq 45y}$ group and $DM_{<45y}$ group, respectively. In the $DM_{<45y}$ group, all deaths occurred before the age of 70 years, whereas in the $NGT_{\geq 45y}$ group, 55.41% (41/74) deaths occurred after this age. The number of CVD events before the age of 60 years accounted for 75.56% (68/90) and 14.61% (13/89) in the $DM_{<45y}$ group and $NGT_{\geq 45y}$ group, respectively. No CVD event, over the 23-year follow-up period, occurred before the age of 50 years in the $NGT_{\geq 45y}$ group, but 15.56% (14/90) CVD events occurred before this age in the $DM_{<45y}$ group. The cumulative incidence of all-cause death, CVD death, and CVD events are presented in Fig. 1a–c. The Cox proportional hazard analysis showed that, after adjusting for sex, smoking, BMI at baseline, SBP, total cholesterol and previous history of CVD, the CVD mortality in the $DM_{<45y}$ group was significantly higher than that in the $NGT_{\geq 45y}$ group (HR 1.76; 95% CI 1.04–2.98). A nonsignificant increase in the risk of deaths (HR 1.23; 95% CI 0.88–1.71) and CVD events (HR

Table 1 Baseline characteristics of the participants according to age and diabetic status

	<45 years ($n = 461$)			≥45 years ($n = 629$)			
	$NGT_{<45y}$ ($n = 250$)	$DM_{<45y}$ ($n = 211$)	*P* value	$NGT_{\geq 45y}$ ($n = 242$)	$DM_{\geq 45y}$ ($n = 387$)	*P* value	*P* value for $DM_{<45y}$ vs $NGT_{\geq 45y}$
Age (year)	36.79 ± 5.08	39.01 ± 5.00	<0.0001	51.45 ± 5.14	53.29 ± 6.15	<0.0001	<0.0001
Male (%)	53.20	60.66	0.11	35.95	46.51	0.0091	<0.0001
Smokers (%)	42.00	29.38	0.005	49.17	38.24	0.007	<0.0001
BMI (kg/m^2)	23.52 ± 3.10	25.37 ± 3.36	<0.0001	23.79 ± 3.63	25.63 ± 3.76	<0.0001	<0.0001
Fasting plasma glucose (mmol/L)	4.72 ± 0.78	8.59 ± 2.78	<0.0001	4.81 ± 0.53	8.62 ± 3.15	<0.0001	<0.0001
2-h plasma glucose (mmol/L)[a]	4.96 ± 1.38	14.86 ± 3.24	<0.0001	5.06 ± 0.88	15.6 ± 3.8	<0.0001	<0.0001
Systolic blood pressure (mm Hg)	117.92 ± 18.00	126.66 ± 20.17	<0.0001	127.31 ± 23.37	140.23 ± 24.31	<0.0001	0.75
Diastolic blood pressure (mmHg)	79.09 ± 11.90	84.59 ± 13.53	<0.0001	84.86 ± 15.22	89.96 ± 14.55	<0.0001	0.84
Total cholesterol (mmol/L)	4.80 ± 1.25	5.12 ± 1.57	0.015	4.82 ± 1.04	5.44 ± 1.61	<0.0001	0.021

Data are mean ± standard deviation or % in each group

[a]Venous plasma glucose concentration 2 h after 75 g oral glucose load

Table 2 Incidence of mortality and CVD events among participants according to baseline age and diabetic status

	<45 years ($n = 461$)			≥45 years ($n = 629$)			
	$NGT_{<45y}$ ($n = 250$)	$DM_{<45y}$ ($n = 211$)	*P* value	$NGT_{\geq 45y}$ ($n = 242$)	$DM_{\geq 45y}$ ($n = 387$)	*P* value	*P* value for $DM_{<45y}$ vs. $NGT_{\geq 45y}$
All-cause death							
No. of cases	26	72		74	266		
Person-years	5585	4414		5035	6281		
Incidence per 1000 person-years (95% CI)	4.66 (2.87–6.44)	16.31 (12.54–20.08)	<0.0001	14.70 (11.35–18.04)	42.35 (37.26–47.44)	<0.0001	0.52
CVD death							
No. of cases	13	36		24	128		
Person-years	5585	4414		5035	6281		
Incidence per 1000 person-years (95% CI)	2.33 (1.06–3.59)	8.16 (5.49–10.82)	<0.0001	4.77 (2.86–6.67)	20.38 (16.85–23.90)	<0.0001	0.04
CVD events							
No. of cases	56	90		89	213		
Person-years	5235	3958		4540	5353		
Incidence per 1000 person-years (95% CI)	10.70 (7.89–13.50)	22.74 (18.04–27.44)	<0.0001	19.60 (15.53–23.68)	39.79 (34.44–45.13)	<0.0001	0.28

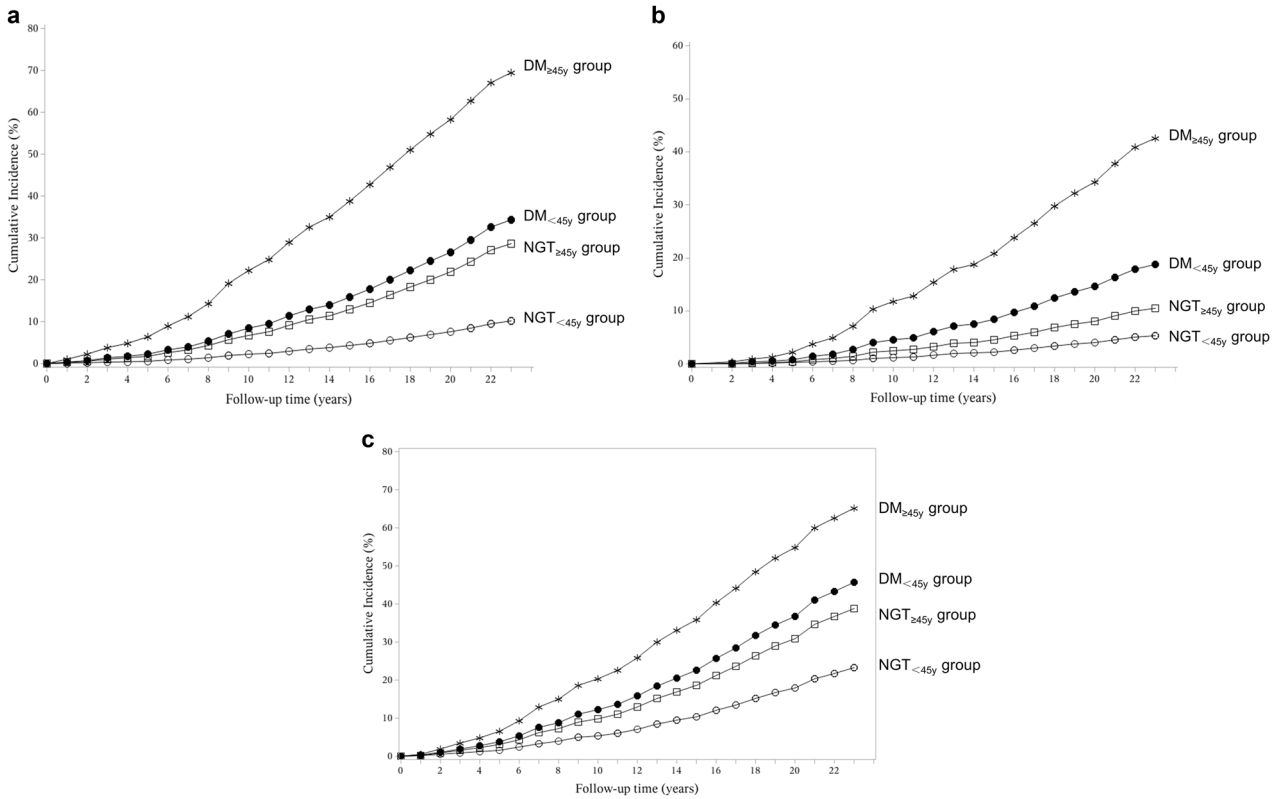

Fig. 1 **a** The cumulative incidence of all-cause death during the 23-year follow-up in the $DM_{\geq 45y}$ group (black stars), $DM_{<45y}$ group (black circles), $NGT_{\geq 45y}$ group (white squares), and $NGT_{<45y}$ group (white circles). **b** The cumulative incidence of CVD death during the 23-year follow-up in the $DM_{\geq 45y}$ group (black stars), $DM_{<45y}$ group (black circles), $NGT_{\geq 45y}$ group (white squares), and $NGT_{<45y}$ group (white circles). **c** The cumulative incidence of CVD events during the 23-year follow-up in the $DM_{\geq 45y}$ group (black stars), $DM_{<45y}$ group (black circles), $NGT_{\geq 45y}$ group (white squares), and $NGT_{<45y}$ group (white circles)

1.25; 95% CI 0.923–1.69) in the $DM_{<45y}$ group was also found (Table 3).

When both DM and NGT participants were stratified into <40, 40–49, and ≥50 years age groups, a higher incidence of deaths, CVD events, and CVD mortality were found in the DM group than those in the corresponding NGT group ($P < 0.0001$). Of note, the risk of death and CVD events in the DM group was equal to or even higher than that in the NGT group who was 10 years older. The incidence of all-cause mortality per 1000 person-years was 14.08 for the $DM_{<40y}$ group and 8.34 for the $NGT_{40–49y}$ group ($P = 0.03$). The corresponding CVD mortality was 4.69 versus 2.34/1000 person-years ($P = 0.12$), and the incidence of CVD events was 15.91 versus 18.23/1000 person-years ($P = 0.59$). The $DM_{40–49y}$ group had a significantly higher incidence of CVD events compared with that in the $NGT_{≥50y}$ group (28.86 vs. 20.90/1000 person-years, $P = 0.04$). Between the two groups, the incidence of all-cause death was 22.08 versus 19.61/1000 person-years ($P = 0.44$), and CVD mortality was 11.81 versus 7.84/1000 person-years ($P = 0.09$) (Supplemental Fig. 1).

Discussion

Type 2 diabetes has long been regarded as a disease that mostly affects older people [14]. Since 2004, the epidemic of diabetes in younger adults and the increase of vascular outcomes caused by diabetes have attracted much attention in many countries across the world [15–18]. In a Swedish study, with an average follow-up time of 8.5 years, 58% of the death in young-onset type 2 diabetes was attributable to the circulatory disease [19]. An Australia-based study indicated that 50% of patients with young-onset type 2 diabetes died of CVD after a median observation of 21.4 years [20]. However, few population-based studies investigated the risk of death and CVD in people with newly diagnosed diabetes who were followed up for several decades. In recognition of the paucity of data on survival in young-onset diabetes, Rhodes et al. used a Markov modeling approach to project survival outcomes, predicting that patients with type 2 diabetes diagnoses between 15 and 24 years would lose 15-year life expectancy [9]. In China, the increased prevalence of diabetes in the middle-aged group (35–45 years) was reported since 1994 [21]. The prevalence of prediabetes was reported recently to be as high as 28% among younger Chinese adults, which may translate into a greater epidemic of type 2 diabetes in the near future [1]. In the Da Qing Diabetes Study, participants were followed up for 23 years; nearly half of patients with young-onset diabetes developed CVD events and more than one third of them died over the follow-up period, providing an estimate of mortality and morbidity in Chinese population.

In the present study, we reported a higher risk of death and CVD in young-onset diabetes in Chinese population. The present data showed that the risk of death and CVD events, including the first fatal and nonfatal myocardial infarction and stroke, was more than twice as high in participants with newly diagnosed diabetes than those with NGT of similar age. Despite a baseline age of 12 years younger, the rates of all-cause mortality and CVD events in younger patients with diabetes were equal to those in the elder participants with NGT. Even worse, the CVD mortality was significantly higher compared with the latter. These data implicated that patients with young-onset diabetes were died or experienced CVD events 12 years earlier than those with NGT. The results also showed that majority of deaths appeared to be caused by CVD in the young-onset type 2 diabetes population. These findings reinforced the notion that young patients with diabetes were not impervious to the life-threatening manifestations of atherosclerosis at an earlier average age [6, 7].

The present study also showed that among patients with young-onset diabetes, CVD accounted for half of all deaths. However, in the elder NGT subjects, only one third of the deaths were related to CVD. Compared with elder participants with NGT, the younger patients with diabetes had an 76% higher risk of CVD mortality during the 23-year follow-up period, confirming a significantly high risk of CVD in young-onset diabetes at an earlier age. The increased risk of CVD associated with young-onset type 2 diabetes was due to long-standing diabetes and then metabolic profiles [22]. In our study, the baseline data of the patients with young-onset diabetes had similar blood pressure, but higher BMI, total cholesterol and blood glucose compared with elder participants with NGT. During the 23-year follow-up, patients with young-onset diabetes

Table 3 HRs for all-cause death, CVD death and CVD events in $DM_{<45y}$ compared with $NGT_{≥45y}$ with adjustment for conventional cardiovascular risk factors

Variable adjusted	HR	95%CI	*P*
All-cause death			
Unadjusted	1.11	0.81–1.54	0.52
Sex, smoking, BMI, SBP, cholesterol, and previous CVD	1.23	0.88–1.71	0.22
CVD death			
Unadjusted	1.71	1.02–2.87	0.04
Sex, smoking, BMI, SBP, cholesterol, and previous CVD	1.76	1.04–2.98	0.03
CVD events			
Unadjusted	1.17	0.88–1.57	0.28
Sex, smoking, BMI, SBP, cholesterol, and previous CVD	1.25	0.93–1.69	0.14

had a similar or even greater risk of premature death and CVD compared with elder patients with NGT after adjusting for sex, smoking, BMI, SBP, total cholesterol and previous history of CVD. These results implicated that the improvement in glycemic control was a key step to prevent or delay the diabetes-related macro- and microvascular complications [12, 23].

Diabetes is a major risk factor for morbidity and mortality worldwide [24]. The findings of the present study indicated that diagnosis of diabetes before the age of 45 years had an important impact on patients' mortality. The increased premature death and CVD events in young patients with diabetes present a threating to the human life, a great loss of productivity, and an unaffordable increased demand for medical expenditure. Randomized clinical trials have shown that interventions involving diet and exercise could reduce the risk of type 2 diabetes [25, 26]. Therefore, efforts focused on preventing the onset of diabetes at a younger age may help to reduce the risk of premature death and CVD events. Furthermore, active management targeted at a strict control of hypertension, dyslipidemia and hyperglycemia in young-onset diabetes must be implemented because the United Kingdom Prospective Study showed that the intensive management of newly diagnosed type 2 diabetes reduced the development of long-term CVD [27]. In view of the fact that currently more than one third of Chinese adults aged less than 40 years have either diabetes or prediabetes [1], the prevention, early detection and effective management of diabetes are crucial in the young adult Chinese population.

This present study had several advantages. Firstly, this population-based study could avoid potential selective biases seen in hospital-based studies. Secondly, DM or NGT status of the participants was confirmed by a standard OGTT at the entry of the study, and all people with DM in this study had never been diagnosed before. In addition, a 23-year follow-up of the study was enough to confirm the natural history of young-onset diabetes. However, this study also had some limitations. Firstly, it did not systematically evaluate the impacts of clinical treatment and changes of other risk factors in the CVD events. Secondly, participants were not reexamined at defined intervals throughout the follow-up.

Conclusions

Nearly half of participants with young-onset diabetes had experienced at least one fatal or nonfatal CVD events, and more than one third of them died during the 23-year follow-up period. It indicates that the young-onset diabetes had substantial higher risk of premature mortality and cardiovascular disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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