

Reproductive factors predict risks of cardiovascular disease and premature death in postmenopausal women with type 2 diabetes: the Fukuoka Diabetes Registry

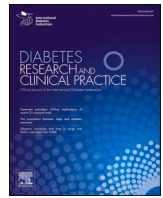
大城, 彩香

<https://hdl.handle.net/2324/7363666>

出版情報 : Kyushu University, 2024, 博士 (医学), 課程博士
バージョン :

権利関係 : © 2024 Elsevier B.V. All rights are reserved, including those for text and data mining, AI training, and similar technologies.





Reproductive factors predict risks of cardiovascular disease and premature death in postmenopausal women with type 2 diabetes: The Fukuoka Diabetes Registry

Ayaka Oshiro^a, Toshiaki Ohkuma^{a,*}, Masanori Iwase^b, Taiki Higashi^a, Masahito Yoshinari^a, Takanari Kitazono^a

^a Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

^b Diabetes Center, Hakujyuj Hospital, Fukuoka, Japan

ARTICLE INFO

Keywords:

Cardiovascular disease
Type 2 diabetes
Reproductive factors
Menarche
Menopause

ABSTRACT

Aims: Reproductive factors (reproductive period, age at menarche, and age at menopause) are associated with a risk of cardiovascular disease (CVD) and death in individuals without focusing on comorbid diabetes. However, it remains unclear whether this association also applies to individuals with diabetes. This study investigated the relationship between reproductive factors and the risk of CVD and death in postmenopausal Japanese women with type 2 diabetes.

Methods: 1,592 postmenopausal women with type 2 diabetes without pre-existing CVD were subclassified based on reproductive period (age at menopause minus age at menarche). The primary outcome was a composite of CVD incidence and all-cause death.

Results: The risk of the outcome decreased with a longer reproductive period. Compared with a reproductive period of ≤ 29 years, the multivariable-adjusted hazard ratios (95 % CI) were 0.80 (0.39–1.66), 0.73 (0.37–1.43), and 0.43 (0.19–0.99) for reproductive periods of 30–34, 35–39, and ≥ 40 years, respectively (p for trend = 0.046). Earlier age at menarche and later age at menopause were also associated with a decreased risk of the outcome.

Conclusions: Evaluating reproductive factors may help predict the risks of CVD and death in postmenopausal women with type 2 diabetes.

1. Introduction

Atherosclerotic cardiovascular diseases (CVDs), including coronary heart disease, cerebrovascular disease, and peripheral arterial disease, are the primary cause of morbidity and mortality in individuals with diabetes [1]. Recent large-scale meta-analyses have shown that the diabetes-related excess risk of CVD such as stroke [2], coronary heart disease [3], and heart failure [4] is greater in women than in men. The greater risk of CVD conferred by diabetes in women (i.e., the female disadvantage from diabetes) meant that the female advantage in CVD risk was diminished when women had diabetes [5], and highlights the importance of a sex-specific approach in diabetes management for preventing CVD [6].

Several possible mechanisms have been suggested to explain the sex

differences in CVD risk conferred by diabetes. Worse control of cardiovascular risk factors including glycemic level [7–10] and a longer exposure to hyperglycemia during prediabetes [11] in women compared with men may contribute to the sex differences. In addition, loss of protection after menopause may play a role in female disadvantage from diabetes [12]. Actually, female-specific reproductive factors have been associated with an increased risk of CVD; a shorter reproductive period, defined as the period from menarche to menopause, has been associated with an increased risk of CVD [13,14]. Both earlier and later age at menarche and later age at menopause have also been associated with the risk of CVD [13]. However, most previous studies have been conducted in Western countries, and scant evidence in Japan was available despite the existence of racial, ethnic, and regional variations in reproductive events [15] and the incidence of CVD [16]. In addition, although

* Corresponding author at: Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

E-mail address: okuma.toshiaki.704@m.kyushu-u.ac.jp (T. Ohkuma).

<https://doi.org/10.1016/j.diabres.2024.111907>

Received 28 March 2024; Received in revised form 20 October 2024; Accepted 27 October 2024

Available online 29 October 2024

0168-8227/© 2024 Elsevier B.V. All rights reserved, including those for text and data mining, AI training, and similar technologies.

diabetes is associated with reproductive dysfunction [17] and ovarian aging [18], few studies to date have examined the association of female reproductive factors with the long-term risk of CVD and death in individuals with diabetes who are at high risk of CVD.

The objective of this study was to investigate the association of female reproductive factors—such as reproductive period, age at menarche and menopause, and years after menopause—and the risk of CVD and premature death in Japanese postmenopausal women with type 2 diabetes.

2. Material and methods

2.1. Study design and population

The Fukuoka Diabetes Registry is a multicenter prospective study that was designed to evaluate the effects of modern treatments on the prognosis of individuals with diabetes who regularly visited 16 teaching hospitals or diabetes clinics certified by the Japan Diabetes Society in Fukuoka Prefecture, Japan (UMIN Clinical Trial Registry 000002627). A total of 5,131 individuals aged 20 years or more were registered between April 2008 and October 2010. Exclusion criteria were 1) individuals with drug-induced diabetes or taking corticosteroid therapy, 2) individuals under dialysis, 3) individuals with serious disease, such as advanced malignancies and decompensated liver cirrhosis, and 4) individuals unable to regularly visit a diabetologist. Among 5,131 participants included in the registry, 2,263 women were included in the present analyses. After excluding 130 individuals with type 1 diabetes, 165 premenopausal women, 364 individuals who had a prior history of ischemic heart disease or stroke, and 12 individuals whose follow-up information on CVD (i.e., myocardial infarction, stroke, or cardiovascular death) or death was not available, a total of 1,592 individuals were enrolled in the study. The study was approved by the Kyushu University Institutional Review Board, and written informed consent was obtained from all individuals.

2.2. Clinical evaluation at baseline

The participants completed a self-administered questionnaire that gathered information on age at menarche and menopause, duration of diabetes, smoking habits, alcohol intake, leisure time physical activity (LTPA), and exogenous female hormone use. Age at menarche was defined as age at the first menstrual period. The participants were regarded as postmenopausal when menstrual bleeding was not observed for a year or more and the reason for menopause (natural or surgical) was determined. The reproductive period was calculated by subtracting the age at menarche from the age at menopause. The study participants were classified by duration of reproductive period (≤ 29 , 30–34, 35–39, and ≥ 40 years), age at menarche (≤ 12 , 13–14, and ≥ 15 years), age at menopause (≤ 47 , 48–50, 51–53, and ≥ 54 years), and years after menopause (≤ 10 and > 10 years). Body mass index (BMI) was calculated using each participant's height and weight. Blood pressure was measured in the sitting position. Hypertension is defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive drugs.

2.3. Laboratory measurements

Blood samples were collected by venipuncture. Hemoglobin A_{1c} (HbA_{1c}) was determined using high-performance liquid chromatography (Tosoh Corp., Tokyo, Japan). Serum low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, creatinine, and urinary creatinine concentrations were measured using enzymatic methods. Elevated LDL-cholesterol was defined as LDL-cholesterol ≥ 3.1 mmol/L or current use of statin. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese Society of Nephrology equation [19]. Urinary albumin was measured

using the immunonephelometry method. The urinary albumin-creatinine ratio (UACR) was calculated by dividing the urinary albumin values by the urinary creatinine concentrations, based on a single urine sample.

2.4. Follow-up survey and assessment of outcome

The primary outcome of this study was a composite of the incidence of CVD (i.e., myocardial infarction, stroke, or cardiovascular death) and all-cause death. The secondary outcomes were each component of the primary outcome. Details of the follow-up and outcomes have been published previously [20–22]. In brief, the participants underwent an annual follow-up that consisted of interviews, a review of medical records, letters, telephone calls, and the municipal registration of residence. Information on death was collected based on medical records or death certificates and was coded in accordance with the International Classification of Diseases, 10th revision (ICD-10). Cardiovascular death was defined as death due to stroke, myocardial infarction, heart failure, and other cardiovascular causes (ICD-10: I00–I99) or death occurring less than 24 h from the onset of symptoms that were not otherwise explained (ICD-10: R96.1). The incidence of CVD was assessed using self-administered questionnaires, confirmed by contacting the participants' attending specialists and reviewing medical records, and subsequently assessed by the outcome adjudication committee. The follow-up period was the time from enrollment to the first diagnosis of CVD, death, or the planned study ending.

2.5. Statistical analysis

Continuous variables were presented as mean with standard deviation for variables that were approximately symmetrically distributed or median with interquartile range for variables with skewed distribution. Categorical variables were presented as numbers with percentages. Linear trends in the mean values or proportions of the variables across categories were tested using the Jonckheere–Terpstra or Cochran–Armitage tests, as appropriate. The incidence of the outcome was calculated by the person-year method. Cox proportional hazards models were used to estimate hazard ratios (HRs) and their 95% CIs for the association between the duration of the reproductive period and the risk of outcomes. Multivariable adjustments were made for age, BMI, diabetes duration, HbA_{1c}, LTPA, current smoking habits, current drinking habits, hypertension, elevated LDL-cholesterol, eGFR, log-transformed UACR, exogenous female hormone use, and reason for menopause. The associations of duration of reproductive period, age at menarche, and age at menopause as continuous variables with the primary outcome were also assessed by restricted cubic spline models. The heterogeneity in the association between the duration of the reproductive period and the primary outcome by baseline characteristics, such as age, BMI, duration of diabetes, HbA_{1c}, and ages at menarche and menopause, was investigated by adding interaction terms to the relevant models. The population attributable fraction (PAF) for the primary outcome due to risk factors included in the multivariable model was calculated as $PAF = PD (HR - 1) / HR$. PD represents the percentage of the exposed group among the participants who experienced the primary outcome, and HR is the multivariable-adjusted HR of each risk factor compared with that of the risk-free individuals [23]. All statistical analyses were conducted using Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata software (release 16.1, StataCorp, College Station, TX). P values < 0.05 were considered statistically significant in all analyses.

3. Results

The study participants' baseline characteristics by duration of reproductive period are shown in Table 1. The mean age and duration of diabetes decreased, whereas LDL-cholesterol increased with a longer

Table 1
Participants' clinical characteristics by duration of the reproductive period.

	Reproductive period (years)				p for trend
	≤ 29	30–34	35–39	≥ 40	
N	192	314	726	360	
Age at menarche (years)	14.5 ± 2.1	14.2 ± 1.9	13.7 ± 1.4	13.0 ± 1.5	<0.001
Age at menopause (years)	39.2 ± 4.8	46.5 ± 2.3	50.6 ± 1.7	54.9 ± 2.5	<0.001
Age (years)	68.8 ± 8.4	67.8 ± 8.2	66.9 ± 7.9	65.8 ± 7.7	<0.001
Duration of diabetes (years)	15.6 ± 10.2	14.4 ± 9.6	14.1 ± 9.2	12.8 ± 9.1	0.002
BMI (kg/m ²)	23.6 ± 4.0	23.7 ± 4.2	23.6 ± 4.1	24.1 ± 3.9	0.14
Current smoker (n, %)	8 (4.2)	21 (6.7)	48 (6.6)	19 (5.3)	0.79
Current drinker (n, %)	27 (14.1)	58 (18.5)	119 (16.4)	49 (13.6)	0.49
LTPA (METs h/week)	8.8 ± 11.1	10.1 ± 15.3	9.8 ± 12.7	9.9 ± 11.8	0.17
HbA _{1c} (%)	7.5 ± 0.9	7.5 ± 1.1	7.5 ± 1.0	7.5 ± 1.1	0.76
(mmol/mol)	58.1 ± 10.3	58.9 ± 12.0	58.7 ± 10.9	58.8 ± 11.9	
Insulin therapy (n, %)	52 (27.1)	100 (31.9)	206 (28.4)	83 (23.1)	0.10
Oral hypoglycemic agent use (n, %)	120 (62.5)	202 (64.3)	466 (64.2)	247 (68.6)	0.16
Systolic blood pressure (mmHg)	131 ± 17	132 ± 16	132 ± 18	131 ± 17	0.66
Diastolic blood pressure (mmHg)	73 ± 11	72 ± 10	73 ± 10	73 ± 10	0.51
Antihypertensive drug use (n, %)	105 (54.7)	175 (55.7)	384 (52.9)	181 (50.3)	0.18
Hypertension (n, %)	121 (63.0)	203 (64.7)	459 (63.2)	216 (60.0)	0.35
LDL-cholesterol (mmol/L)	3.0 ± 0.7	2.9 ± 0.6	3.0 ± 0.7	3.0 ± 0.7	0.04
HDL-cholesterol (mmol/L)	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	0.31
Statin use (n, %)	91 (47.4)	176 (56.1)	378 (52.1)	202 (56.1)	0.20
Elevated LDL-cholesterol (n, %)	137 (71.4)	249 (79.3)	581 (80.0)	294 (81.7)	0.01
eGFR (mL/min/1.73 m ²)	77.4 ± 22.2	75.9 ± 20.3	76.4 ± 19.5	78.9 ± 21.1	0.10
UACR (mg/gCr)	17.9 (9.5, 53.1)	19.8 (9.9, 48.8)	18.6 (9.3, 51.8)	20.9 (9.4, 51.2)	0.73
Menopause by surgery or medication (n, %)	116 (60.4)	77 (24.5)	53 (7.3)	17 (4.7)	<0.001
Exogenous female hormone use (n, %)	2 (1.0)	3 (1.0)	5 (0.7)	3 (0.8)	0.71

Values were presented as means ± standard deviation or number (percentages). The UACR is presented as a median (interquartile range).

Abbreviations: BMI, body mass index; LTPA, leisure-time physical activity; METs h/week, metabolic equivalent, hours per week; HbA_{1c}, hemoglobin A_{1c}; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rates; UACR, urinary albumin-creatinine ratio.

reproductive period. Individuals with longer reproductive periods experienced menarche at an earlier age and menopause at a later age compared with those with shorter reproductive periods. The proportion of individuals who experienced menopause caused by surgery or medication was higher in those with shorter reproductive periods. Exogenous female hormone use did not differ among groups.

During the follow-up period (median, 5.3 years; follow-up rate, 99.9%), 87 participants experienced the primary outcome of the composite of CVD and all-cause death. The outcome's incidence decreased with a longer reproductive period, with incidence rates of 13.9, 12.1, 10.8, and 6.3 per 1,000 person-years for those with reproductive periods of ≤29, 30–34, 35–39, and ≥40 years, respectively (Fig. 1). Compared with the participants with a reproductive period of ≤29 years,

multivariable-adjusted HRs (95% CIs) for the outcome were 0.80 (0.39–1.66), 0.73 (0.37–1.43), 0.43 (0.19–0.99) for those aged 30–34 years, 35–39 years, and ≥40 years, respectively (p for trend = 0.046). Similar findings were observed when CVD and all-cause death were analyzed separately. These trends remained unchanged after excluding the participants with a history of surgical menopause (Supplementary Fig. 1), after excluding exogenous female hormone use (Supplementary Fig. 2), or after including participants with a prior history of ischemic heart disease or stroke in addition to those without (Supplementary Fig. 3).

Subgroup analyses for the association between the reproductive period and the primary outcome by baseline characteristics are shown in Supplementary Figure 4. Overall, each 5-year increase in the reproductive period was associated with a 18% decreased risk of the primary outcome (HR 0.82; 95% CI 0.67–0.999). No evidence of heterogeneity was observed in the association between the reproductive period and the outcome across subgroups based on baseline age, BMI, duration of diabetes, HbA_{1c}, age at menarche, and age at menopause.

PAFs were calculated for the risk of the primary outcome by clinical risk factor (Supplementary Figure 5). The contribution of the duration of the reproductive period <35 years (PAF 12.2%) was smaller than that of age ≥65 years (37.3%), albuminuria (34.4%), decreased LTPA (19.6%) and elevated HbA_{1c} (18.4%), but was greater than that of other traditional risk factors such as decreased eGFR (11.2%), hypertension (10.4%), obesity (9.8%), current drinking habits (6.6%), current smoking habits (1.9%), and exogenous female hormone use (1.7%).

The association of age at menarche or menopause with the risk of outcomes was assessed (Fig. 2). Compared with women with age at menarche ≥15 years, those with an earlier age at menarche were at a lower risk of the primary outcome (p for trend = 0.09), although the difference did not reach statistical significance. In contrast, later age at menopause was associated with a lower risk of the primary outcome (p for trend = 0.10). Similar trends were observed for CVD and all-cause death. These trends remained unchanged when participants were divided based on age at menopause of <45, 45–49, 50–54, and ≥55 years (Supplementary Figure 6). The associations of duration of reproductive period, age at menarche, and age at menopause with the primary outcome were broadly similar, when the exposure variables were assessed as continuous variables (Supplementary Figure 7). More years after menopause were associated with an increased risk of the primary outcome (Fig. 3). Compared with women with a duration of ≤10 years after menopause, the HR for those with >10 years after menopause was 5.31 (95% CI 2.27–12.40). The association remained significant after an additional adjustment for age (2.57; 95% CI 1.01–6.56). Almost identical findings were found when CVD and all-cause death were analyzed individually; although they did not reach statistical significance, the point estimates of the association were broadly similar.

4. Discussion

In this prospective study of postmenopausal women with type 2 diabetes, a longer reproductive period was associated with a decreased risk of CVD and all-cause death, even after adjustments for potential confounders. In addition, when age at menarche and age at menopause were examined separately, younger age at menarche and older age at menopause were associated with a lower risk of the outcomes, which may support the main finding of an association between a longer reproductive period and the decreased risk of the outcome. The PAF of a reproductive period <35 years for the composite outcome of CVD and all-cause death was greater compared with other traditional risk factors, such as decreased kidney function, hypertension, overweight, current drinking, current smoking, and exogenous female hormone use. Moreover, the risk of the outcome increased as the years after menopause increased. To the best of our knowledge, this is the first study that shows a significant association between the duration of the female reproductive period and the risk of CVD and death in individuals with type 2

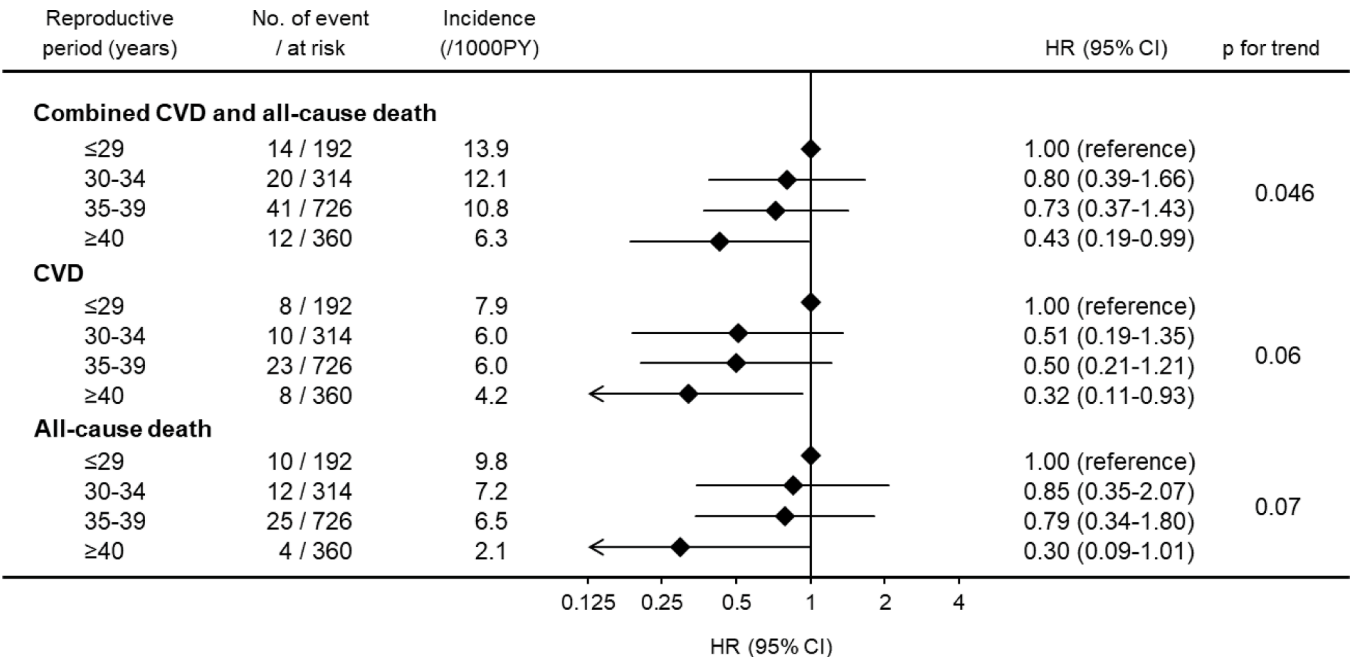


Fig. 1. Multivariable-adjusted hazard ratios and 95% CIs for combined CVD and all-cause death and its components by the duration of the reproductive period. Multivariable adjustments were conducted for age, body mass index, diabetes duration, hemoglobin A_{1c}, leisure-time physical activity, current smoking habits, current drinking habits, hypertension, elevated low-density lipoprotein-cholesterol, estimated glomerular filtration rates, log-transformed urinary albumin-creatinine ratio, exogenous female hormone use, and reason for menopause. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; PY, person-year; HR, hazard ratio.

diabetes. These findings may help clinicians identify individuals at high risk of CVD and death, allowing aggressive interventions to improve the long-term prognosis in postmenopausal women with type 2 diabetes.

Several previous studies have examined the association between the duration of the female reproductive period and the risk of CVD [13,14,24]. However, few studies have examined this issue among individuals with diabetes. A pooled analysis of 12 studies showed that a shorter reproductive life span was associated with a higher risk of incident CVD events [13]. Compared with women with a reproductive life span of 36–38 years, those with a reproductive lifespan of <30 years had a 71% increased risk and those with a reproductive period of ≥45 years had a 38% decreased risk of CVD [13]. The Nurses' Health Study also reported a decrease in the risk of CVD that was associated with an increase in the reproductive life span. The study showed a relative risk of 1.32 (95% CI 1.16–1.49) in women with a reproductive life span of <30 years compared with those with a reproductive period of ≥42 years [14]. This inverse association between the duration of the female reproductive period and the risk of CVD was also observed for the risk of death [25,26]. The Women's Health Initiative reported that the odds of longevity were 13% (3%–25%) higher in women with a reproductive life span ≥40 years compared with those with a reproductive period of <33 years [25]. Similarly, the risk of death was 18% higher in women with a reproductive period of ≤28 years compared with those with a reproductive life span of ≥35 years in a population-based study in Japan [26]. However, most previous studies have been conducted in the general population; therefore, whether these associations are observed in individuals with diabetes remains unclear. In our study of Japanese individuals with type 2 diabetes, a longer reproductive period was associated with a lower risk of CVD and death. Specifically, the HRs for CVD in women with a reproductive period of ≤29 years were 3.13 (1.08–9.09) compared with those in women with a reproductive period of ≥40 years (Fig. 1); the magnitudes of the relative risk differences were greater than in the previous studies, as mentioned above. The reasons for the observed differences in outcomes based on the duration of the reproductive period are unclear but may be due to diabetes-associated reproductive dysfunction [17] and ovarian aging [18], which may

enhance the adverse effects of a shorter reproductive period. This study extends previous findings in cohorts that have mainly consisted of the general population to individuals with diabetes who are at high risk of both reproductive dysfunction [17] and CVD [1]. In addition, we showed that the PAF for the composite outcome of CVD and death that is associated with a shorter reproductive period was comparable to or greater than that associated with traditional risk factors. These findings highlight the importance of considering the duration of the female reproductive period, in addition to known traditional risk factors, as a risk factor for CVD and death.

Age at menarche is also associated with a risk of CVD and death [13,14,26–29]. Most previous studies have shown the association between early age at menarche and the increased risk of CVD [14] and death [29]. Later age at menarche has also been associated with an elevated risk of outcomes [13,27,28]; a U-shaped association has been observed. In contrast, another population-based study in Japan [26] showed that earlier age at menarche was associated with a lower risk of premature death or CVD. Compared with women ≤13 years of age at menarche, HRs in those ≥16 years of age at menarche were 1.16 (95% CI 1.06–1.27) for death, 1.11 (95% CI 0.85–1.44) for heart disease, and 1.31 (95% CI 0.99–1.73) for cerebrovascular disease [26]; our results were consistent with these findings. The reasons for the inconsistency in results across studies are unclear, but regional and racial differences or differences in confounding factors across studies may be involved.

Earlier age at menopause has been consistently linked with a higher risk of long-term clinical outcomes, including CVD [13,14,24,30,31] and death [26]; our findings were consistent with these results. Although the associations of age at menopause, as well as age at menarche, with the risk of outcomes did not reach statistical significance and were marginally significant, it may be due to insufficient statistical power imposed by limited sample sizes. In addition to age at menopause, longer duration since the onset of menopause was associated with an increased risk of CVD in this and previous studies [24]. Furthermore, we observed that the elevated risk of outcomes that were associated with longer time since menopause persisted after additional adjustment for age, suggesting that years after menopause may be a risk that is independent of

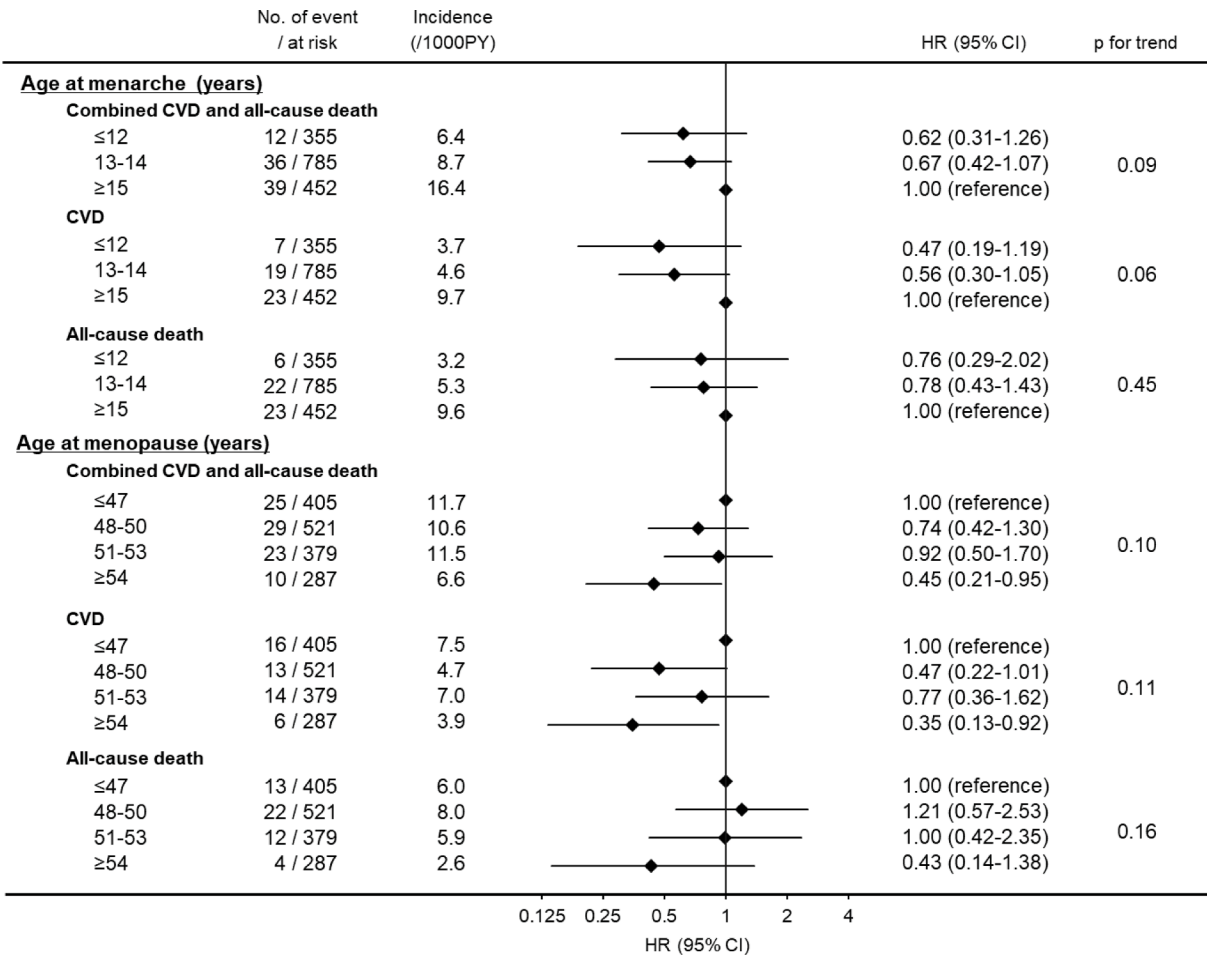


Fig. 2. Multivariable-adjusted hazard ratios and 95% CIs for combined CVD and all-cause death and its components by age at menarche and age at menopause. Multivariable adjustments were conducted for age, body mass index, diabetes duration, hemoglobin A_{1c}, leisure-time physical activity, current smoking habits, current drinking habits, hypertension, elevated low-density lipoprotein-cholesterol, estimated glomerular filtration rates, log-transformed urinary albumin-creatinine ratio, exogenous female hormone use, and reason for menopause. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; PY, person-year; HR, hazard ratio.

chronological aging.

Estrogen exposure is considered to underlie the association between a longer reproductive period and the decreased risk of CVD and death. Endogenous estrogen secretion increases during the reproductive lifespan and decreases after menopause [32]. Estrogen is considered to maintain endothelial homeostasis and enhance vasodilation by nitric oxide production, increased angiogenesis [33], and reduction in vasoconstriction after the inhibition of calcium currents and the activation of potassium channels [34]. Estrogen also improves lipoprotein metabolism by decreasing LDL-cholesterol and increasing HDL-C [35]. In addition, the lower risk of diabetes associated with a longer reproductive period [36] may be attributable to the association. Estrogen protects pancreatic β cells against apoptosis [37], increases insulin secretion, and subsequently maintains glucose homeostasis in animal models [38]. However, the significant association between a longer reproductive period and the lower risk of the outcomes in our study did not change after adjustment for HbA_{1c} and duration of diabetes. These findings suggest the direct beneficial effects of estrogen exposure on mortality and CVD even in a hyperglycemic milieu.

It is a study strength that this is the first investigation in individuals with diabetes to comprehensively evaluate the association of female reproductive factors, including total reproductive lifespan, age at menarche, age at menopause, and years after menopause with the long-term risk of CVD and death. No missing values were observed in the information on age at menarche and menopause, history of surgical

menopause, and exogenous female hormone use. Moreover, to mitigate potential confounding factors, we made multiple adjustments such as for diet and physical activity that were not adopted as covariates in previous studies. However, our study has several limitations. First, the ages at menarche and menopause were obtained using self-reported questionnaires; therefore, the possibility of recall bias cannot be ruled out. However, a small difference between the actual and memorized ages of menarche and menopause has been reported [39,40]. Second, information on the number of pregnancies, deliveries, and breastfeeding that may be related to estrogen exposure, CVD, and death was not available in this study. Third, our study was conducted in Japan, and thus the generalizability of the current findings to other ethnic populations may be limited. Notably, the incidence of CVD is considerably lower in Japan than in Western countries [16]. Fourth, socioeconomic status, which may be a possible confounding factor, was not evaluated in the present study. Finally, the possible existence of residual confounding factors that were not included in the analyses cannot be disregarded.

5. Conclusions

In conclusion, a longer reproductive period was associated with lower risks of CVD and death. Earlier age at menarche and later age at menopause were also associated with a lower risk of these outcomes. These findings suggest that evaluating female reproductive factors may help clinicians predict the risks of CVD and premature death in women

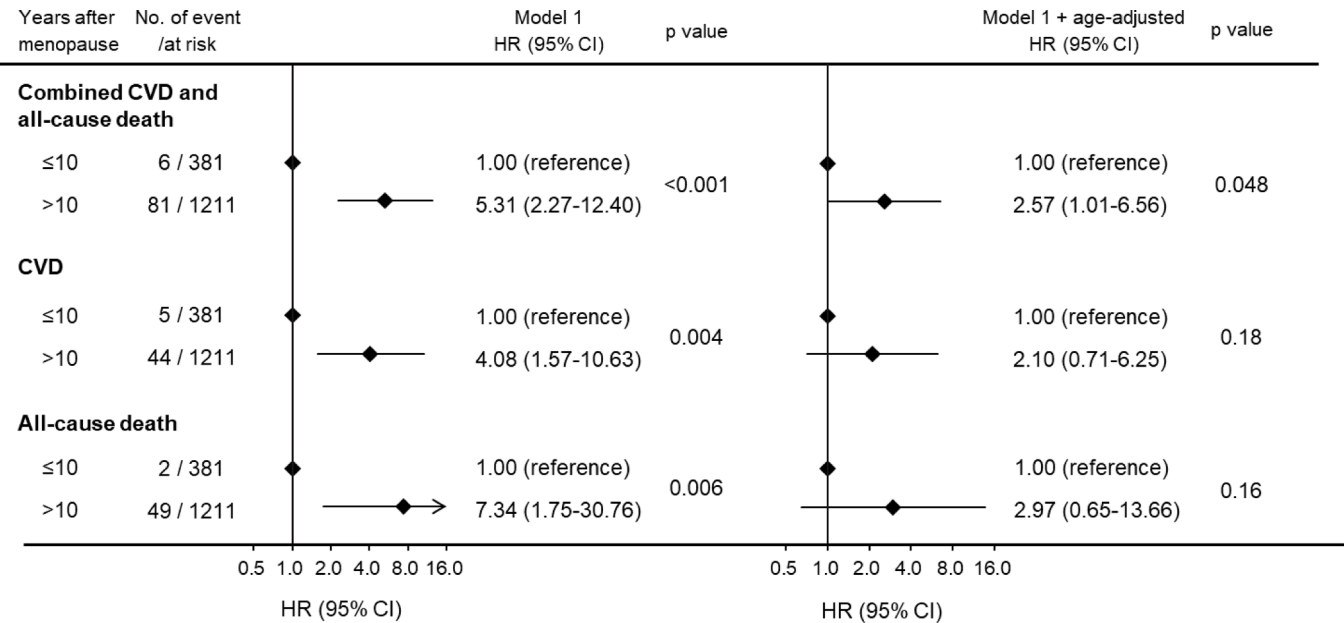


Fig. 3. Multivariable-adjusted hazard ratios and 95% CIs for combined CVD and all-cause death and its components by year after menopause. Multi-variable adjustments were conducted for body mass index, diabetes duration, hemoglobin A_{1c}, leisure-time physical activity, current smoking habits, current drinking habits, hypertension, elevated low-density lipoprotein-cholesterol, estimated glomerular filtration rates, log-transformed urinary albumin-creatinine ratio, exogenous female hormone use, and reason for menopause. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; PY, person-year; HR, hazard ratio.

with type 2 diabetes.

Funding

This work was supported in part by JSPS KAKENHI Grant Numbers JP23249037, JP23659353, JP16K00861, JP19K24229, and JP21K11700, a Junior Scientist Development Grant from the Japan Diabetes Society, Grants from Japan Association for Diabetes Education and Care, Grants for young researchers from Japan Association for Diabetes Education and Care, a Japan Diabetes Foundation, Novo Nordisk Pharma Ltd. Research Grant, and a grant from Daiwa Securities Foundation.

CRedit authorship contribution statement

Ayaka Oshiro: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Toshiaki Ohkuma:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Masanori Iwase:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Taiki Higashi:** Writing – review & editing, Investigation. **Masahito Yoshinari:** Writing – review & editing, Validation, Data curation. **Takanari Kitazono:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We acknowledge the late Hiroki Fujii for his critical contributions to the Fukuoka Diabetes Registry study. The authors thank Drs. Toshiharu Ninomiya, Dongchon Kang, Shuzo Kumagai, Yoichiro Hirakawa, Shinako Kaizu-Ogata, Akiko Sumi, Tamaki Jodai-Kitamura, Yuji Komorita, Ai Murao-Kimura, Yutaro Oku, Wakako Sakamoto, Mika Fujihira

(Kyushu University), Nobuhiro Sasaki, Hirofumi Imoto (Fukuoka Red Cross Hospital), Kiyohide Nunoi, Yuichi Sato, Yuji Uchizono, Kaori Itoh (St. Mary's Hospital), Udai Nakamura (Steel Memorial Yawata Hospital), Daisuke Gotoh (Kyushu Central Hospital), Sakae Nohara, Ayako Tsutsumi (Fukuoka Higashi Medical Centre), Yasuhiro Idewaki, Hitoshi Ide (Hakujyuu Hospital), Masae Minami (Clinic Minami Masae), Miya Wada (Wada Miya Naika Clinic), Yoshifumi Yokomizo (Yokomizo Naika Clinic), Masanori Kikuchi, Yohei Kikuchi (Kikuchi Naika Clinic), Riku Nomiya (Suzuki Naika Clinic), Shin Nakamura (Nakamura Naika Clinic), Kenji Tashiro (Oshima Eye Hospital), Mototaka Yoshinari, Masahito Yoshinari (Yoshinari Naika Clinic), Kojiro Ichikawa (Fukutsu Naika Clinic), and Yutaka Kiyohara (Hisayama Research Institute For Lifestyle Diseases). The authors also thank the clinical research coordinators, Chiho Ohba (Kyushu University), and those in the administration office, Tomoko Matake (Hisayama Research Institute For Lifestyle Diseases) and Mitsuko Kojima (Kyushu University). We thank Edanz Group (<https://jp.edanz.com/ac>) for editing a draft of this manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2024.111907>.

References

[1] American Diabetes Association. Standards of Medical Care in Diabetes-2023. *Diabetes Care* 2023;46(Suppl 1):S1–284.

[2] Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet* 2014;383:1973–80.

[3] Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia* 2014;57:1542–51.

[4] Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. *Diabetologia* 2019;62:1550–60.

[5] Millett ER, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. *BMJ* 2018;363:k4247.

- [6] Woodward M. Cardiovascular Disease and the Female Disadvantage. *Int J Environ Res Public Health* 2019;16.
- [7] Ohkuma T, Iwase M, Fujii H, Kitazono T. Sex differences in cardiovascular risk, lifestyle, and psychological factors in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *Biol Sex Differ* 2023;14:32.
- [8] Peters SAE, Woodward M. Sex Differences in the Burden and Complications of Diabetes. *Curr Diab Rep* 2018;18:33.
- [9] Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, et al. Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. *J Intern Med* 2013;274: 176–91.
- [10] Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. *Diabetes Care* 2005;28:514–20.
- [11] Bertram MY, Vos T. Quantifying the duration of pre-diabetes. *Aust N Z J Public Health* 2010;34:311–4.
- [12] Kautzky-Willer A, Leutner M, Harreiter J. Sex differences in type 2 diabetes. *Diabetologia* 2023;66:986–1002.
- [13] Mishra SR, Chung HF, Waller M, Dobson AJ, Greenwood DC, Cade JE, et al. Association Between Reproductive Life Span and Incident Nonfatal Cardiovascular Disease: A Pooled Analysis of Individual Patient Data From 12 Studies. *JAMA Cardiol* 2020;5:1410–8.
- [14] Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, et al. Duration of Reproductive Life Span, Age at Menarche, and Age at Menopause Are Associated With Risk of Cardiovascular Disease in Women. *J Am Heart Assoc* 2017;6.
- [15] Variations in reproductive events across life: a pooled analysis of data from 505 147 women across 10 countries. *Hum Reprod* 2019;34:881–93.
- [16] Cavender MA, Steg PG, Smith Jr SC, Eagle K, Ohman EM, Goto S, et al. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation* 2015;132:923–31.
- [17] Thong EP, Codner E, Laven JSE, Teede H. Diabetes: a metabolic and reproductive disorder in women. *Lancet Diabetes Endocrinol* 2020;8:134–49.
- [18] Wellons MF, Matthews JJ, Kim C. Ovarian aging in women with diabetes: An overview. *Maturitas* 2017;96:109–13.
- [19] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92.
- [20] Iwase M, Komorita Y, Ohkuma T, Fujii H, Ide H, Yoshinari M, et al. Incidence of stroke and its association with glycemic control and lifestyle in Japanese patients with type 2 diabetes mellitus: The Fukuoka diabetes registry. *Diabetes Res Clin Pract* 2021;172:108518.
- [21] Iwase M, Ohkuma T, Fujii H, Oku Y, Higashi T, Oshiro A, et al. Incidence and risks of coronary heart disease and heart failure in Japanese patients with type 2 diabetes mellitus: The Fukuoka diabetes registry. *Diabetes Res Clin Pract* 2023;201: 110732.
- [22] Komorita Y, Iwase M, Idewaki Y, Fujii H, Ohkuma T, Ide H, et al. Impact of hip fracture on all-cause mortality in Japanese patients with type 2 diabetes mellitus: The Fukuoka Diabetes Registry. *J Diabetes Investig* 2020;11:62–9.
- [23] Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998;88:15–9.
- [24] Yang L, Lin L, Kartsonaki C, Guo Y, Chen Y, Bian Z, et al. Menopause Characteristics, Total Reproductive Years, and Risk of Cardiovascular Disease Among Chinese Women. *Circ Cardiovasc Qual Outcomes* 2017;10:e004235.
- [25] Shadyab AH, Macera CA, Shaffer RA, Jain S, Gallo LC, Gass ML, et al. Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Women's Health Initiative. *Menopause* 2017;24:35–44.
- [26] Otsuki S, Saito E, Sawada N, Abe SK, Hidaka A, Yamaji T, et al. Female reproductive factors and risk of all-cause and cause-specific mortality among women: The Japan Public Health Center-based Prospective Study (JPHC study). *Ann Epidemiol* 2018;28:597–604.e6.
- [27] Lee JJ, Cook-Wiens G, Johnson BD, Braunstein GD, Berga SL, Stanczyk FZ, et al. Age at Menarche and Risk of Cardiovascular Disease Outcomes: Findings From the National Heart Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation. *J Am Heart Assoc* 2019;8:e012406.
- [28] Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, et al. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. *Circulation* 2015;131:237–44.
- [29] Jacobsen BK, Heuch I, Kvåle G. Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. *Am J Epidemiol* 2007;166:1431–7.
- [30] Yoshida Y, Chen Z, Baudier RL, Krousel-Wood M, Anderson AH, Fonseca VA, et al. Early Menopause and Cardiovascular Disease Risk in Women With or Without Type 2 Diabetes: A Pooled Analysis of 9,374 Postmenopausal Women. *Diabetes Care* 2021;44:2564–72.
- [31] Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health* 2019;4:e553–64.
- [32] Nappi RE, Chedraui P, Lambrinoudaki I, Simoncini T. Menopause: a cardiometabolic transition. *Lancet Diabetes Endocrinol* 2022;10:442–56.
- [33] Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biol Sex Differ* 2017;8:33.
- [34] Skafar DF, Xu R, Morales J, Ram J, Sowers JR. Clinical review 91: Female sex hormones and cardiovascular disease in women. *J Clin Endocrinol Metab* 1997;82: 3913–8.
- [35] Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;340:1801–11.
- [36] Mishra SR, Waller M, Chung HF, Mishra GD. Epidemiological studies of the association between reproductive lifespan characteristics and risk of Type 2 diabetes and hypertension: A systematic review. *Maturitas* 2022;155:14–23.
- [37] Le May C, Chu K, Hu M, Ortega CS, Simpson ER, Korach KS, et al. Estrogens protect pancreatic beta-cells from apoptosis and prevent insulin-deficient diabetes mellitus in mice. *Proc Natl Acad Sci U S A* 2006;103:9232–7.
- [38] Godsland IF. Oestrogens and insulin secretion. *Diabetologia* 2005;48:2213–20.
- [39] Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, et al. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol* 2002;155:672–9.
- [40] den Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. *Maturitas* 1997;27:117–23.