



Age at menopause and mortality in Taiwan: A cohort analysis

Te-Yi Shen, Carol Strong, Tsung Yu*

Department of Public Health, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

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ABSTRACT

Objective: Previous research suggested age at menopause may predict risk of all-cause, cardiovascular disease (CVD), cancer and diabetes mortality; however, findings were inconsistent across populations. We aimed to investigate this association in Taiwanese postmenopausal women.

Study design: We used data from the MJ Health Database in Taiwan and included 36,931 postmenopausal women who entered health check-up programs during 1999–2016. Information on age at menopause and covariates were collected from health surveys and medical examinations at baseline. Age at menopause was categorized into < 40–44, 45–49, 50–54 (reference) and 55–60 years. We used Cox proportional hazards regression for analysis.

Main outcome measures: Causes of death (obtained from the National Register of Death as of July 2018).

Results: Mean age (SD) at menopause was 50.2 (4.0) years and there were 5316 deaths over an average follow-up time of 14.6 years. After adjustment for birth cohort, education, smoking, BMI and comorbidities, results showed women aged < 40–44 years at menopause compared with the reference category had higher diabetes mortality (hazard ratio [HR] = 1.44; 95 % CI: 1.03, 2.02). Women aged 45–49 years at menopause had higher all-cause mortality (HR = 1.07, 1.01, 1.14), and these women were also associated with increased CVD mortality (HR = 1.22; 1.07, 1.40).

Conclusions: In Taiwanese women, early age (< 40–44) at menopause is associated with higher diabetes mortality, and earlier age (45–49) at menopause is associated with higher all-cause and CVD mortality. Age at menopause could be deemed an important cardio-metabolic disease marker for women at midlife that indicates future longevity.

1. Introduction

Menopause is the cessation of ovulation and marks the declining of sex hormones (e.g., estrogen) produced by the ovaries. A decline in estrogen in the body affects many organs and systems including cardiovascular and bone systems and increases disease risks, such as for metabolic syndrome [1], diabetes [2], cardiovascular diseases [3], osteoporosis and fractures [4–7]. The association between menopause and health can also be explained by the “iron hypothesis” proposed by Sullivan [8]. According to the iron hypothesis, after menopause the body is exposed to high iron levels because of the dramatic alteration in iron metabolism. High blood iron may increase oxidative stress and be responsible for the development of, for example, cardiovascular disease [9].

Timing of onset of menopause matters to women’s health as well. Age at menopause is not only a biological marker of starting reproductive aging but also indicates somatic aging. In epidemiological

studies, early onset of menopause was found to be associated with more chronic diseases and death [10]. Findings from meta-analysis suggested that premature menopause (menopause under age 40) or early menopause (menopause between age 40 and 45) is linked to a higher risk of all-cause, cardiovascular disease and coronary heart disease mortality [11]. Furthermore, some studies showed that there is also a higher risk of diabetes associated with early onset of menopause [12,13].

Research findings regarding age at menopause and cancer mortality, however, are less consistent. Because late onset of menopause indicates longer lifetime exposure to sex hormones, late menopause (after age 55) is associated with more breast, uterine, and ovarian cancers [14–16]. Earlier studies such as Mondul et al. found that cancer mortality rates were lower in American women who experienced menopause at a younger age [14]. Recently, Roman Lay and colleagues from Brazil showed that women having menopause at 41–44 or 45–49 had twice the risk of cancer death than women having menopause at 50–54, and they did not find an increased risk in women having menopause after

* Corresponding author at: Department of Public Health, College of Medicine, National Cheng Kung University, Address: No.1, University Road, Tainan City, 701, Taiwan.

E-mail address: tsungyu@mail.ncku.edu.tw (T. Yu).

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55 [17]. Given the heterogeneous study results, research communities are still unsure about the association of age at menopause and cancer mortality.

To our best knowledge, there have been no published studies examining the association of age at menopause and cause-specific mortality in Taiwanese women. Women in Taiwan, as those in other East Asian countries, may have different reproductive patterns and lifestyles than Caucasian women or women in other parts of the world. Racial and ethnic differences in reproductive health are important to study since they represent some underlying determinants of health, such as environmental, sociocultural and genetic factors [18]. Besides, the increasing life expectancy in Taiwanese women [19] has made research into the risk factors for cardiovascular diseases, diabetes and cancers more and more important. We therefore carried out a cohort analysis to investigate the relation between age at menopause and risk of all-cause death, death from cardiovascular disease, death from cancers and death from diabetes among Taiwanese women.

2. Methods

2.1. Data source

We obtained participant data for the current analysis from the MJ Health Database built by the MJ Health Management Institution (<http://www.mjhrf.org/main/index/en>). In brief, the MJ Health Management Institution is a private healthcare facility in Taipei, Taiwan, that provides health examination services and has been collecting the health survey and medical examination data since 1994. The health survey questionnaire asked participants questions regarding sociodemographics, lifestyles, medical history, and reproductive history, etc. The health examination included physical exams, blood analyses, urine analyses, and image tests, etc. During health examinations, participants were queried about the use of their data for research purposes; the MJ Health Database included only those who gave proper consent. Many participants had multiple visits for health examinations over the years; the database has included over 1.5 million participant visits. Researchers in Taiwan and across the world have used this database and published many important epidemiological studies [20].

Questions on menopausal status were added into the questionnaire in 1999; hence, we included female participants who came to MJ Health Examination Centers from 1999 up to 2016. We further restricted our inclusion criteria to women who had reached menopause and who were 49 years of age or older when receiving their health examination. When a woman had multiple visits in the database, we only kept data from their first visit after menopause. As a result, we set up a study cohort consisting of 36,931 postmenopausal women who, on average, were 61 years of age at baseline. The protocol for this study was approved by the Ethics Committee at the National Cheng Kung University in Taiwan.

2.2. Study outcome: mortality

The main outcome of the study was death from all causes, death from cardiovascular diseases, death from diabetes and death from all cancers identified from January 1999 through July 2018. We linked our participant data to the data file of the National Register of Death using a unique citizen identifying number. The underlying cause of death was classified by International Classification of Diseases, 9th or 10th Revision (ICD-9-CM or ICD-10-CM). Death from cardiovascular diseases included death from coronary heart disease (ICD-9 = 410–414 and 420–429; ICD-10 = I20–I25), stroke (ICD-9 = 430–438; ICD-10 = I60–I69) and other circulatory diseases (ICD-9 = 390–392, 393–398, 401–405 and 440; ICD-10 = I10–I15, I01–I02.0, I05–I09, I27, I30–I52, I70 and I71). For cancer deaths, we used codes of ICD-9 = 140–208 or ICD-10 = C00–C97. We determined the death from diabetes with ICD-9 = 250 or ICD-10 = E10–E14.

2.3. Study exposure: age at menopause

Age at menopause was obtained from participants' responses to the health survey questionnaire. We asked participants "Have you reached menopause (having gone 12 months in a row without a period)? If yes, what was your age at menopause?" Age at menopause was further categorized into < 40–44, 45–49, 50–54, and 55–60 years. Other gynecology-related questions included (1) "Have you been using hormone therapy (HT)?", (2) "Have you been taking contraceptive pills?" and (3) "Have you had any gynecological surgery?"

2.4. Covariates

Covariates were derived based on information gained from the health survey or medical examination at baseline. Sociodemographic variables included birth year (categorized into five groups: ≤ 1930, 1931–1935, 1936–1940, 1941–1945, and 1946–1950), age at time of survey, educational level attained (illiterate, elementary school, junior high school, senior high school, and college or above), and marital status (married, never married, divorced and widowed). Lifestyle variables included smoking (current or former smoker vs. non-smoker) and drinking (current or former drinker vs. non-drinker). Clinical variables included history of diabetes mellitus, hypertension and hyperlipidemia, and body mass index (BMI) in kg/m².

2.5. Data analysis

We compared baseline characteristics across categories of age at menopause by χ^2 test or analysis of variance. We used survival analysis (Cox proportional hazards model) to investigate the association between age at menopause and mortality. We defined the time origin as date of birth; age in years was used as the time scale. We computed the follow-up time in years (from age at entry to the event of interest, e.g., all-cause death or cardiovascular death). To adjust for the age differences at baseline, our survival model allowed for delayed entry [21]. The participants were at risk after they entered our study, for example, at age 50 or 60 years, depending on their age at first health check-up survey.

We further constructed multivariable Cox regression models that adjusted for potential confounders for the association of age at menopause with mortality, including birth year, education, smoking, BMI and comorbidities. These covariates were chosen according to our previous research [22]. Moreover, we stratified the analysis by the attained age (< 80 years and ≥ 80 years) of our participants. Missing data on covariates were imputed through multiple imputations when doing the analysis [23].

We conducted two sensitivity analyses. Given that hysterectomy, oophorectomy, and use of HT and contraceptive pills can mask the true age at natural menopause of our participants, we excluded those who had any gynecological surgery or had been using HT or contraceptive pills. Besides, we tried excluding participants who were followed-up for less than three years to minimize the problem of reverse causality. To graphically display the association of age at menopause and mortality, we computed the hazard ratios using the restricted cubic splines model and plotted the estimates and 95 % confidence intervals. All analyses were conducted using the Stata software version 15 (Stata Corp, College Station, TX); the restricted cubic splines plots were generated using the R software 3.5.3 (codes provided by Woodward et al.) [24].

3. Results

Our analysis included 36,931 Taiwanese women. Table 1 shows the baseline characteristics across four categories of age at menopause. The mean age at menopause of all participants is 50.2 (standard deviation 4.0) years and the distribution of birth cohort varied across women with different ages at menopause ($p < 0.001$). The mean age at survey

Table 1
Baseline characteristics stratified by age at menopause (N = 36,931).

Characteristics	Age at menopause (years)					P-value
	Total n = 36,931	< 40–44 n = 3384	45–49n = 9155	50–54n = 19,265	55–60n = 5127	
Age at baseline in years, mean ± SD	61.2 ± 6.9	61.1 ± 7.1	61.1 ± 7.2	61.0 ± 6.9	62.3 ± 6.2	< 0.001
Birth cohort, %						< 0.001
1930 or before	7.8	7.6	8.6	7.7	7.2	
1931–1935	10.8	10.6	11.3	10.5	11.2	
1936–1940	20.3	18.9	20.7	19.7	23.2	
1941–1945	27.0	27.0	25.5	27.0	29.9	
1946–1950	34.0	35.9	34.0	35.2	28.5	
Marital status, %						0.071
Never married	0.7	0.8	0.9	0.7	0.5	
Married	70.8	69.3	70.6	71.1	71.5	
Divorced	2.9	3.4	3.4	2.8	2.7	
Widowed	25.5	26.5	25.5	25.4	25.3	
Education, %						< 0.001
Illiterate	21.9	22.3	24.0	20.7	22.1	
Elementary	44.2	43.0	43.2	44.4	45.9	
Junior high	11.9	11.8	11.1	12.2	12.2	
Senior high	12.2	12.2	11.6	12.7	11.3	
College or above	9.9	10.7	10.1	10.0	8.6	
Body mass index (kg/m ²), mean ± SD	24.3 ± 3.5	24.4 ± 3.6	24.3 ± 3.5	24.2 ± 3.4	24.6 ± 3.4	< 0.001
Hypertension, % ^a						< 0.001
Yes	46.9	45.7	45.8	46.5	51.5	
No	53.1	54.3	54.2	53.5	48.5	
Diabetes, % ^b						< 0.001
Yes	14.1	15.9	14.2	13.3	15.9	
No	85.9	84.1	85.8	86.7	84.1	
High blood cholesterol, % ^c						0.303
Yes	25.8	24.9	26.1	25.6	26.5	
No	74.2	75.1	74.0	74.4	73.5	
Smoking, %						0.016
Current or former smoker	9.7	10.6	10.3	9.3	9.8	
Never smoker	90.3	89.4	89.7	90.8	90.2	
Drinking, %						0.402
Current or former drinker	6.0	6.0	5.9	5.9	6.6	
Never drinker	94.0	94.0	94.1	94.1	93.4	

Abbreviation: SD = standard deviation.

^a Hypertension was defined as using antihypertensives, self-reported having hypertension or that systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure was ≥ 90 mmHg.

^b Diabetes was defined as using diabetes medications, self-reported having diabetes or that fasting blood glucose was ≥ 126 mg/dl.

^c High blood cholesterol was defined as using cholesterol-lowering medications or that total cholesterol was ≥ 240 mg/dl.

was 61.2 ± 6.9 years and the baseline age was older (62.3 ± 6.2) in women who were 55–60 years old at menopause. There were also significant between-category differences in educational level, BMI, smoking status and history of hypertension and diabetes. There were no significant differences in marital status, history of hyperlipidemia or drinking status among women in different categories of age at menopause.

The total follow-up time for all participants in this study was 538,459 person-years. There were 5316 deaths identified during the follow-up period: 1141 (21 %) were due to cardiovascular diseases; 2011 (38 %) were due to cancers; 355 (7 %) deaths were due to diabetes (see Table 2). The unadjusted results showed there is a 52 % higher risk (hazard ratio [HR] = 1.52, 95 % CI: 1.09, 2.13) of diabetes mortality in women with early menopause (< 40–44 years), relative to the reference group (women who had menopause at 50–54 years). Also, there is a higher risk of all-cause death in women with early menopause (HR = 1.10, 95 % CI: 1.00, 1.21) and earlier menopause (45–49 years; HR = 1.08, 95 % CI: 1.01, 1.15) than the reference group.

Table 2 also shows that women who had menopause at 45–49 years had a 21 % higher risk (HR = 1.21, 95 % CI: 1.06–1.39) of cardiovascular death relative to the reference group. Women who were 55–60 years old at menopause had a lower risk of cardiovascular death than the reference group, but the effect was not significant (HR = 0.88, 95 % CI: 0.73, 1.06). The association between age at menopause and

cancer mortality did not reach statistical significance, but higher risks were noted in women who had menopause at < 40–44, 45–49 and 55–60 years compared to the reference group.

Results from the multivariable models—with adjustment for birth cohort, educational attainment, smoking status, BMI and comorbidities (history of hypertension, diabetes and hyperlipidemia)—can be found in Table 2 as well. These effects (HRs) did not change much from the effects in the unadjusted models. For instance, result of the association between early age at menopause and diabetes mortality was attenuated after adjustment for risk factors, but it remained significant (HR = 1.44, 95 % CI: 1.03, 2.02).

Results of the first sensitivity analysis (n = 21,621), where we excluded those who had any gynecological surgery or had been using HT or contraceptive pills, can be found in the Supplementary Table 1. Supplementary Table 2 shows the result of the second sensitivity analysis (36,421) that excluded women with follow-up time less than three years. Although the effect estimates (HRs) for mortalities were slightly different from our main analysis findings (Table 2), the overall pattern for both sensitivity analyses seemed to be similar.

The Fig. 1 graphed the adjusted hazard ratios from the restricted cubic splines models for the association of age at menopause and mortalities, with 50 years as the reference age. We found that the shape of the curve was smooth for all-cause death, with lowest risk of all-cause mortality at around 52 years of age at menopause. For cardiovascular death, we observed a curve with inverted U shape. Women

Table 2
Hazard ratios of age at menopause and mortality.

Age at menopause	Person-years	No. of deaths	Unadjusted		Adjusted ^a	
			Hazard ratio	95 % CI	Hazard ratio	95 % CI
<i>All-causes</i>						
< 40–44	48853	498	1.10	1.00–1.21	1.09	0.99–1.20
45–49	135469	1424	1.08 ^b	1.01–1.15	1.07 ^b	1.01–1.14
50–54	282783	2667	1.00	–	1.00	–
55–60	71354	727	1.00	0.92–1.09	0.98	0.90–1.06
<i>Cardiovascular diseases (ICD9 = 390-392, 393-398, 401-405, 410-414, 420-429, 430-438, 440; ICD10 = I10-I15, I01-I02.0, I05-I09, I20-I25, I27, I30-I52, I60-I69, I70, I71)</i>						
< 40–44	48853	101	1.06	0.85–1.31	1.05	0.85–1.30
45–49	135469	342	1.21 ^b	1.06–1.39	1.22 ^b	1.07–1.40
50–54	282783	563	1.00	–	1.00	–
55–60	71354	135	0.88	0.73-1.06	0.84	0.70-1.02
<i>All cancers (ICD9 = 140-208; ICD10 = C00-C97)</i>						
< 40–44	48853	182	1.07	0.92–1.26	1.07	0.91–1.25
45–49	135469	534	1.10	0.99–1.23	1.10	0.99–1.22
50–54	282783	991	1.00	–	1.00	–
55–60	71354	304	1.13	0.99–1.29	1.12	0.99–1.28
<i>Diabetes mellitus (ICD9 = 250; ICD10 = E10-E14)</i>						
< 40–44	48853	43	1.52 ^b	1.09–2.13	1.44 ^b	1.03–2.02
45–49	135469	99	1.20	0.94–1.54	1.19	0.93–1.53
50–54	282783	166	1.00	–	1.00	–
55–60	71354	47	1.03	0.74–1.42	0.91	0.66–1.26

Abbreviations: CI = Confidence Interval; ICD = International Classification of Diseases.

^a Adjusted for birth cohort, education, smoking status, body mass index, hypertension, diabetes, and high blood cholesterol.

^b $p < 0.05$.

who had menopause at around 45 years had the highest risk of cardiovascular mortality and the risk was decreasing for women who had menopause at a later age. For all-cancer mortality, the risk was slightly higher at an earlier age at menopause, but the risk started increasing again for women who had a later age at menopause. For diabetes mortality, the risk got decreased with increasing menopausal age.

We stratified the association of age at menopause with risk of mortality by attained age (< 80 years and ≥ 80 years). The results can be found in Table 3. When comparing the results from women with attained age < 80 years versus ≥ 80 years, we observed that some effect estimates were attenuated in women with attained age ≥ 80 years. For example, women with attained age < 80 years and who had menopause at < 40–44 years had 1.73 (adjusted HR, 95 % CI: 1.14–2.61) and 1.15 (adjusted HR, 95 % CI: 1.02–1.30) times risk of diabetes and all-cause mortality, respectively, compared to the reference group; the effect was 1.14 (95 % CI: 0.63–2.07) and 1.09 (95 % CI: 0.93–1.28) in women with attained age ≥ 80 years. Women with attained age < 80 years and who had menopause at 55–60 years had 0.76 (adjusted HR, 95 % CI: 0.58–1.00) times risk of cardiovascular mortality than the reference group; the effect was 0.95 (95 % CI: 0.73–1.24) in women with attained age ≥ 80 years.

3.1. Discussion

Based on a large cohort of postmenopausal women in Taiwan, we found that early (40–44) and earlier (45–49) age at menopause were associated with higher risk of all-cause mortality. In further cause-specific analysis, we revealed that women with early (40–44) menopause were at a much higher risk of diabetes mortality. In addition, we showed that an earlier age at menopause (45–49) was significantly associated with higher risk of CVD mortality while later (55–60) age at menopause was associated with lower risk. The results on cancer mortality were not statistically significant, but the risk may be higher both in women having earlier menopause and in women having later menopause.

The results suggested a 22 % increase in the risk of CVD mortality in women having menopause at 45–49 years and a 16 % decrease in risk in women having menopause at 55–60 years, compared to women having menopause at 50–54 years. Sex hormones such as estrogen is known to have cardioprotective effects. For example, estrogen reduces fibrosis and oxidative stress, stimulates angiogenesis and vasodilation, and improves mitochondrial function [25]. Less lifetime exposure to estrogen, using earlier age at menopause as a surrogate, is therefore likely to increase the risk of CVD and CVD mortality. Others suggested that the effect of menopause on risk of chronic diseases is explained by the “iron hypothesis”. Higher exposure to elevated iron levels in the body after menopause [9] and enhanced inflammatory responses may be one potential mechanism linking early onset of menopause with cardiovascular diseases. Still others suggested that genetics may play a role. It has been speculated that there is an association between DNA damage repair response and early menopause, which can lead to increased risk of CVD and diabetes [26,27]. Future studies are needed to explore these biological mechanisms.

Our study highlights the impact of early menopause on diabetes mortality, which is in line with recent findings [12,13]. The mechanisms linking age at menopause with diabetes are still unclear. One possible explanation is that the association is due to polycystic ovary syndrome (PCOS). Women with polycystic ovary syndrome (PCOS) have a higher risk of diabetes and are often diagnosed with diabetes at an earlier age [28], which can result in increased diabetes mortality. It is also of note that in our adjusted analysis for both diabetes and CVD mortality, the association did not change substantially after adjustment for traditional risk factors, which may suggest that the effect of age at menopause on mortality is independent of traditional cardiovascular risk factors and requires further exploration.

We noted in our study, however, that women who had their menopause the earliest (< 40–44 years) did not have a significantly higher risk of CVD death, which may be due to the following reasons. For one thing, women with early menopause or premature menopause may die of causes other than CVD. The impact of hormone deficiency is universal and involves multiple organs and systems. Some studies have shown that in women with early menopause the causes of death may be a consequence of osteoporosis or fractures [6]. Mondul and colleagues [14] reported that women who had earlier menopause had higher risk of mortality that can be attributed to respiratory disease, genitourinary disease and external causes, which reflected the complications of fractures. For another, our sample of women were surveyed at a relatively old age (mean: 61.2 years). The women who had premature menopause or early menopause would have a lower chance of entering our sample because they might be more likely to die prematurely. This leads to the issue of left truncation in survival analysis [29]; we tried to address it by computing the survival time that adjusted for delayed entry.

As for cancer mortality, their relationship with age at menopause is less clear given that we noted slightly higher cancer deaths in women having earlier menopause and also later menopause, but the results were not statistically significant. Because we were not able to differentiate different types of cancer in our study, the type of cancer associated with earlier menopause may be different from the type of cancer associated with later menopause. For instance, research has shown that women exposed to longer time of sex hormones have an increased risk for breast cancer and ovarian cancer [16,30–32]. At the same time, we also learned from clinical trials that the use of HT was associated with a lower risk for colorectal cancer, stomach cancer, or lung cancer [33–36]. The relationship between age at menopause and cancer incidence or cancer mortality is rather complicated since the effects may vary greatly depending on the type of cancer. Hence, we think that systematic research synthesis may be needed in order to examine these associations carefully and identify the current evidence gap.

In the analysis that was stratified by attained age (< 80 vs. ≥ 80 years), there were differences in the associations between age at menopause and cause-specific mortality. The magnitude of effect for all-

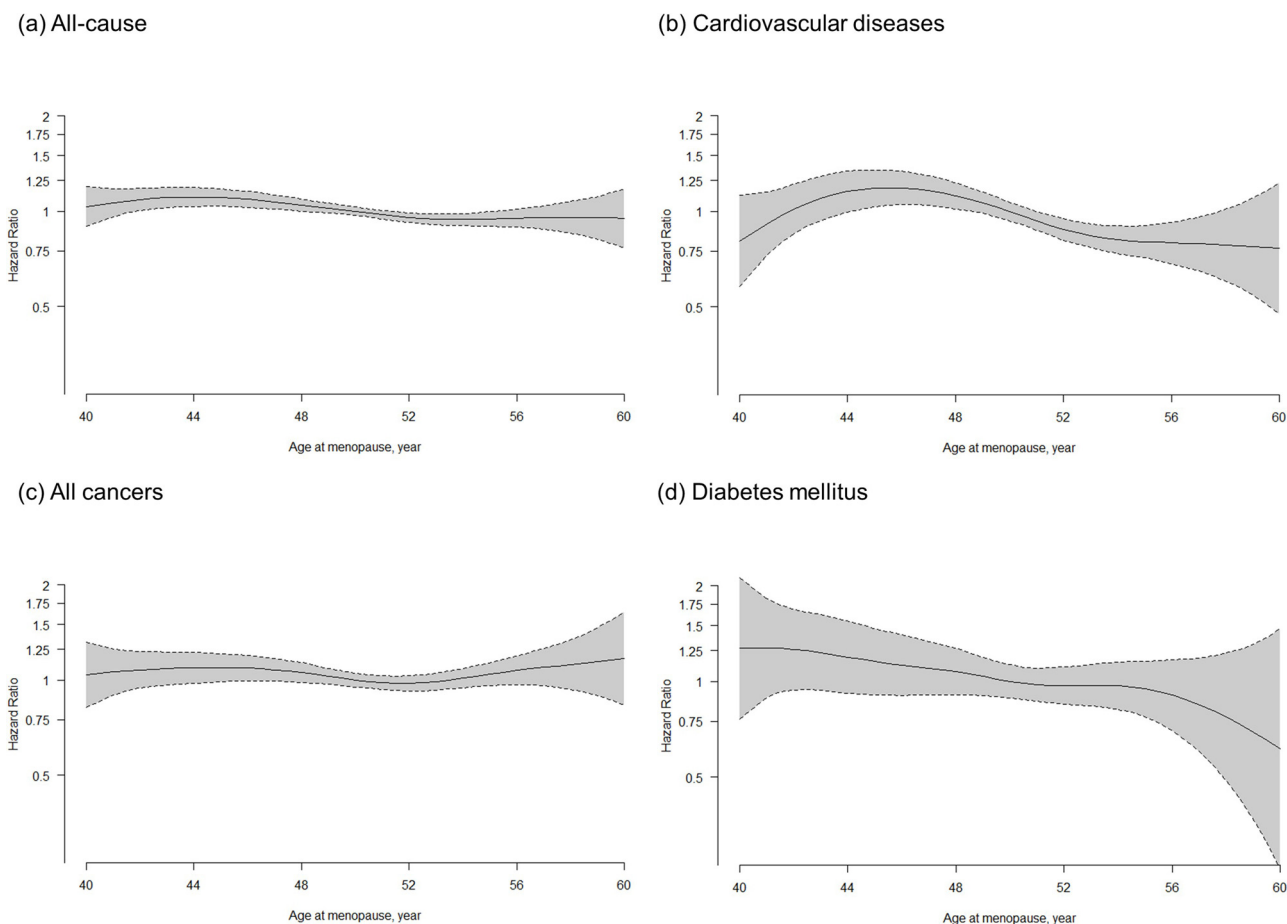


Fig. 1. Restricted cubic spline plots with adjusted hazard ratios (95 % CI) for all-cause (a), cardiovascular diseases (b), all cancers (c) and diabetes (d) mortality associated with women’s age at menopause. We adjusted for birth cohort, education, smoking status, BMI, hypertension, diabetes and high blood cholesterol in analysis.

Table 3
Hazard ratios of age at menopause and mortality by attained age.

Age at menopause	Attained age < 80					Attained age ≥ 80				
	No. of Deaths	Unadjusted		Adjusted ^a		No. of Deaths	Unadjusted		Adjusted ^a	
		Hazard ratio	95 % CI	Hazard ratio	95 % CI		Hazard ratio	95 % CI	Hazard ratio	95 % CI
<i>All-causes</i>										
< 40–44	316	1.11	0.99–1.25	1.15 ^b	1.02–1.30	182	1.09	0.93–1.28	1.09	0.93–1.28
45–49	904	1.11 ^b	1.02–1.20	1.06	0.98–1.15	520	1.01	0.91–1.12	1.02	0.92–1.13
50–54	1675	1.00	–	1.00	–	992	1.00	–	1.00	–
55–60	448	0.94	0.84–1.04	0.95	0.86–1.06	279	1.06	0.93–1.21	1.05	0.92–1.20
<i>Cardiovascular diseases (ICD9 = 390-392, 393-398, 401-405, 410-414, 420-429, 430-438, 440; ICD10= I10-I15, I01-I02.0, I05-I09, I20-I25, I27, I30-I52, I60-I69, I70, I71)</i>										
< 40–44	56	1.11	0.83–1.47	1.15	0.86–1.53	45	1.01	0.74–1.39	1.01	0.73–1.38
45–49	183	1.23 ^b	1.02–1.48	1.18	0.98–1.42	159	1.16	0.95–1.41	1.17	0.96–1.43
50–54	299	1.00	–	1.00	–	264	1.00	–	1.00	–
55–60	67	0.76 ^b	0.58–0.99	0.76 ^b	0.58–1.00	68	0.97	0.74–1.27	0.95	0.73–1.24
<i>All cancers (ICD9 = 140–208; ICD10= C00-C97)</i>										
< 40–44	135	1.03	0.86–1.23	1.07	0.89–1.28	47	1.25	0.91–1.72	1.25	0.91–1.72
45–49	413	1.12	0.99–1.26	1.08	0.96–1.22	121	1.06	0.85–1.32	1.06	0.85–1.32
50–54	772	1.00	–	1.00	–	219	1.00	–	1.00	–
55–60	233	1.08	0.93–1.25	1.10	0.95–1.28	71	1.22	0.93–1.59	1.23	0.94–1.61
<i>Diabetes mellitus (ICD9 = 250; ICD10= E10-E14)</i>										
< 40–44	30	1.80 ^b	1.20–2.71	1.73 ^b	1.14–2.61	13	1.15	0.63–2.08	1.14	0.63–2.07
45–49	64	1.32	0.97–1.81	1.18	0.86–1.61	35	1.01	0.67–1.52	1.07	0.71–1.61
50–54	99	1.00	–	1.00	–	67	1.00	–	1.00	–
55–60	26	0.89	0.58–1.38	0.89	0.57–1.37	21	1.18	0.72–1.93	1.09	0.66–1.78

Abbreviations: CI = Confidence Interval; ICD = International Classification of Diseases.

^a Adjusted for birth cohort, education, smoking status, body mass index, hypertension, diabetes, and high blood cholesterol.

^b *p* < 0.05.

cause mortality and CVD mortality seemed to be stronger in women with an attained age < 80, while the effect for cancer mortality seemed to be stronger in women with an attained age ≥ 80 . We do not fully understand the reasons; perhaps some of the conditions related to early menopause such as CVD and stroke may develop and progress rather quickly in the women's life course. In contrast, the development and progression of some breast cancer may be relatively slow. But due to the small proportion of deaths and potentially a lack of power after we made the stratification, we cannot really conclude with the current data.

The present study is not free from limitations. In the questionnaire, these women were not asked if they had received a hysterectomy or bilateral oophorectomy, which leads to surgical menopause prior to natural menopause. The only relevant question we could use was whether they had received gynecological surgery, so in the sensitivity analysis we excluded those women who had received any gynecological surgery from our sample. Also, in the sensitivity analysis, we excluded women who reported having used HT and oral contraceptives to minimize the confounding influences, and the results overall were not so different from the primary analysis. Moreover, there were concerns regarding the misclassification of age at menopause, since age at reaching menopause was based on women's recall, and some of them were surveyed at relatively old age. But research has shown that recall of age at menopause is oftentimes reliable [37], so we did not expect that misclassification of age at menopause would seriously bias the true association.

The major strength of this study is the large sample size ($n = 36,931$) of postmenopausal women and the prospective long-term follow-up (up to almost 20 years). Through linking our health examination data and the National Register of Death in Taiwan, we were able to track the vital status of our study participants. Besides, because we had data on the categories of causes of death, analysis of the cause-specific mortality was hence made possible.

To conclude, our study demonstrated the association between women's age at menopause and risk of all-cause, CVD, cancer and diabetes mortality in an East Asian population. Our findings suggest that age at menopause is an important disease marker for midlife women that is indicative of future longevity. Our results may inform clinicians about future development of management strategies or interventions. More research is needed to examine physiological mechanism of menopause-related adverse effects on cardio-metabolic health.

Contributors

Te-Yi Shen was responsible for study design, analysis, interpretation of data and drafting the article.

Carol Strong was responsible for interpretation of data.

Tsung Yu was responsible for acquisition of data, study design, analysis, interpretation of data and drafting the article.

All authors contributed to revising the article and approved the final manuscript. We are grateful to the Health Data Science Center, Ministry of Health and Welfare in Taiwan for assistance in data linkage.

Conflict of interest

The authors declare that they have no conflict of interest.

Provenance and peer review

This article has undergone peer review.

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Ethical approval

The protocol for this study was approved by the Ethics Committee at the National Cheng Kung University in Taiwan (A-ER-107-351).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.maturitas.2020.04.008>.

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