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ORIGINAL ARTICLE

Risk and Age of Cardiovascular Event in Women with Metabolic Syndrome: Menopause Age in Focus

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Abstract

Background: There is still a controversy about the causal relationship between menopause status and cardiovascular disease (CVD). The present study aimed to evaluate whether premature menopause would predict higher risk and lower the age of CVD occurrence and how this differs in women with metabolic syndrome (MetS).
Methods: Using a population-based Isfahan Cohort Study (ICS), 1154 postmenopause women were followed up from 2001 to 2013 for any CVD occurrence. Cox proportional hazards regression analyses were used to estimate the association between menopause age of (≤45, 46–50, 51–55, ≥56 years) and CVD incidence. The menopause age group of 46–50 years was considered as reference group.
Results: During 12 years follow-up, 235 CV events were recorded. The mean age of menopause (±standard deviation) was 48.06 ± 5.48 years. The age at menopause was not predictive of total CV events, in women with and without MetS. In women without MetS, a trend with increasing incidence of stroke was observed at menopause age of ≤45 years (age adjusted hazard ratio: 4.84, 95% confidence interval: 0.99–23.5, $P = 0.05$). Women with menopause age of ≤45 years suffered from CV events, 5.7 years earlier than women with menopause age of ≥56 years ($P = 0.11$); this difference was 5.3 years in women with MetS ($P = 0.4$).
Conclusion: This study showed that younger age at menopause is not predictive of the occurrence of CV events. It also revealed that age at menopause is not associated with earlier CV events in postmenopause women, with and without MetS.

Keywords: women, cardiovascular disease, menopause, metabolic syndrome

Introduction

Estrogen has diverse effects on cardiovascular (CV) and coagulation system. Estrogen induces a prothrombotic state with an increase in procoagulant factors.[1] On the contrary, observational studies show that there is a 10-year delay in cardiovascular disease (CVD) occurrence in women, compared with men,[2] attributed to the protective effect of estrogen on the cardiovascular system, specifically structural and functional changes in arteries.[3] It is thus expected that an increase in CVD after menopause would occur, since endogenous estrogen level has decreased.[4]

There is still a controversy about the causal relationship between postmenopause status and CVD incidence. Studies that evaluated serum endogenous estrogen level failed to show any association with CVD in postmenopause women.[5,6] Some cohorts showed an increase in CVD events in postmenopause women.[4,7,8] but one meta-analysis demonstrated no association.[9] In contrast, there are frequent reports of positive association between age at menopause and incidence of ischemic heart

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disease (IHD)[10–13] and ischemic stroke (menopause age of ≤42 years).[14] A meta-analysis has shown that menopause age of ≤50 years increases CVD risk modestly (risk ratio: 1.25).[9]

MetS is a potent risk factor (RF) for CV events. It is estimated that 35% of Iranian women have MetS.[15] The Isfahan Cohort Study (ICS) revealed that the hazard ratio (HR) of MetS for IHD in women, living in three central cities in Iran was 2.49 [95% confidence interval (CI): 1.58–3.86, $P < 0.001$].[16] At the same time, some authors proposed that postmenopause women more often suffer from MetS, compared with premenopause women.[17,18]

There is actually a lack of validated data, regarding menopause status and the risk of CVD events in the Eastern Mediterranean region, and to the best of our knowledge, no previous study has been performed for evaluation of early menopause, as a RF for premature CV events in the presence of MetS. Therefore, the current study is aimed at investigating whether the MetS affects the association between age at menopause and age of CVD events and the associated risk in postmenopause women.

Materials and Methods

Subjects

ICS is a population-based longitudinal cohort study of 6504 adults, aged 35 years and older during enrollment, performed in 2001.[19] The participants in this ongoing study lived in both urban and rural areas of three provinces in the central Iran (Isfahan, Arak, and Najafabad). They participated in the Isfahan Healthy Heart Program (IHHP) study, which was a community trial for CVD prevention and control.[20] Exclusion criteria at baseline were as follows: having a history of CVD or a subject refusal to participate in the study. In addition, the Ethics Committee of Isfahan Cardiovascular Research Center (ICRC), a World Health Organization collaborating center, approved the study protocol, and informed written consent was obtained from all the participants.

Data collection

Recruitment was performed, from January to September 2001, through multistage random sampling and follow-up is ongoing since then. Details of IHHP, including its baseline survey and ICS methodology, have been reported previously.[19,20]

Women in postmenopause status in 2001 were selected for follow-up and analysis. A full medical interview, physical examination, and laboratory assays were performed by trained health providers, using a validated questionnaire, calibrated instruments, and standard protocol. Menopause was defined as menstrual cessation for at least 1 year. Age at menopause was defined as the age that the last menstruation had occurred. Natural menopause and surgical menopause were not differentiated. The age when the first menstruation had occurred to the woman was defined as age at menarche. The number of total pregnancies of a woman was considered as gravid number, and fetal losses before 24 weeks of pregnancy were defined as abortion. Data regarding the history and intake duration of oral contraceptive pills (OCP) before menopause and hormone replacement therapy (HRT) after menopause were collected. Paternal and maternal coronary artery disease (CAD) was described, if premature CV events occurred in the male parent before the age of 55 years and in the female parent before the age of 65 years.

Dyslipidemia was defined as if low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL, total cholesterol (TC) ≥200 mg/dL, triglycerides (TGs) ≥150 mg/dL, or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men or <50 mg/dL in women. Diabetes mellitus (DM) was defined as fasting blood glucose ≥126 mg/dL or if the patient was on antidiabetic agents. Patients with two readings of blood pressure (BP) ≥140/90 mmHg or antihypertensive drug takers were classified as hypertensive. Body mass index (BMI) was defined as body weight (kg) divided by square of body height (m^2). Participants who used at least one cigarette per day were considered as current smokers.

According to the updated Adult Treatment Panel (ATP) III guideline of the National Cholesterol Education Program (NCEP), MetS was defined as the presence of three or more of the following components: (1) serum TGs ≥150 mg/dL; (2) HDL-C <40 mg/dL for men and <50 mg/dL for women; (3) fasting glucose ≥100 mg/dL or on diabetic treatment; (4) BP ≥130/85 mmHg or antihypertensive medication user; and (5) waist circumference (WC) ≥102 cm in men and ≥88 cm in women.[21]

Follow-up

The follow-up of the participants was performed, biannually with telephone interviews for occurrence of first cardiovascular events, including IHD [fatal and nonfatal myocardial infarction (MI), unstable angina (UA), and sudden cardiac death (SCD)] and stroke.[19] In this study, the event data of 12th year of follow-up (2001–2013) were used. To confirm the events, two separate panels of specialists, consisting of four cardiologists and neurologists, blind to the subjects' RF profiles, reviewed all the documents, including death certificates, to make a final decision.

The diagnosis of acute MI was based on the presence of at least two out of the three following criteria: (1) typical chest pain lasting more than 30 min, (2) ST elevation ≥0.1 mV in at least two contiguous electrocardiogram leads (≥0.2mv in V2, V3), and (3) an increase in the serum level of cardiac biomarkers.[22] UA was defined as typical chest discomfort with a duration of more than 20 min within the last 24 hrs before admission, and representing a new onset angina or change in the usual pattern of angina or pain, occurring with a crescendo pattern, being severe and described as a frank pain. It could be accompanied by dynamic ST-segment or T-wave changes in at least two adjacent electrocardiogram leads.[23] SCD was described as death with cardiac etiology preceded by sudden loss of consciousness, within 1 hr of the onset of an acute change in cardiovascular status. In the cases of out of hospital death, a verbal autopsy was performed by trained nurses, interviewing the family members of the deceased. All cases of acute MI, UA, and SCD were categorized as IHD. For diagnosis of stroke, the WHO definition was used and defined as a rapid onset of focal neurological deficit, persisting at least 24 hrs with probable vascular etiology.[24] A combination of IHD and stroke was described as CVD events. Two separate panels of specialists, consisting of four cardiologists and neurologists, reviewed all relevant documents of every patient (primary questionnaires, registry records, medical records, secondary interviews, verbal autopsies, or death certificates) and made the final decision about all of the three main events (MI, stroke, and SCD).[19]

Statistical analysis

Data entry was carried out, using EPI info™. Data were analyzed by SPSS software, version 15 (SPSS, Inc., Chicago,

IL). For all analyses, statistical significance was assessed at a level of 0.05 (two-tailed). If variables had more than 3% of missing values, stochastic regression method was used to impute missing values.

Continuous variables are represented as mean ± standard deviation (SD), and compared by analysis of variance or Student *t*-test. Discrete variables were compared by chi-squared test. Strength of association was presented as HRs (95% CI), using cox model analysis, and were adjusted for age.

Postmenopause women were categorized, based on their age at menopause, into four groups: ≤45, 45–50, 51–55, and ≥56 years. The age group of 45–50 years was considered as the reference group because this category comprises the mean age at menopause, in our cohort and other studies in Iran. Initially, 1353 postmenopause women (784 with MetS) enrolled in the study, but after 12 years of follow-up, the event data of only 1154 women (674 with MetS) were statistically analyzed.

Results

During 12 years of follow-up [median (interquartile range): 11.08 (6.33–12.08)], 235 CV events were recorded, including 185 cases of IHD (UA: 119, MI: 42, SCD: 24) and 50 cases of stroke. The mean age of postmenopause women (±SD) at the time of enrollment in the study (2001) was 60 ± 9.3, while the mean age at menopause (±SD) was 48.06 ± 5.48. Majority of the women ($n = 832$, 61.5%) were within the range of 46–55 years of age at menopause.

Baseline characteristics, based on age category at menopause, are introduced in Table 1. Women at menopause age of ≤45 years were younger at the time of entry into the study, compared with the rest of the women ($P < 0.001$), and had lower total cholesterol (TC) and LDL-C, in comparison with the subjects at menopause age of 51–55 years ($P = 0.013$ and 0.019, respectively). Other RFs and drug usage were not significantly different between the age groups at menopause, except for BMI that was higher in the group of 51–55 years menopause age, compared with ≥56 years ($P = 0.011$).

Characteristics of postmenopause women with and without CV event are listed in Table 2. Women who developed CV events in 2013 were older at the start of the cohort (61.9 ± 9.29 vs. 59.6 ± 9.29, $P = 0.001$) and more often had metabolic syndrome (MetS), DM, and hypertension (HTN). They had higher indices of fasting blood sugar, TG, BP (systolic and diastolic), WC, and BMI. Values of TC and LDL-C were slightly higher in women with CV event ($P = 0.112$ and 0.204, respectively). Women without CV event had received aspirin and statin more prevalently ($P < 0.001$, 0.066, respectively). Smokers have been just 3.9% of the study population. Eighty-seven (40%) events occurred in women with menopause age of ≤45 years, but there was no significant association between the menopause age groups and the incidence of CV events ($P = 0.109$).

A large number of the study participants (674, 58.4%) had MetS. The means of age at menopause, in women with and without MetS (±SD) were 47.0 ± 5.44 and 47.11 ± 5.30, respectively ($P = 0.752$). CV events were identified in 24.2% of MetS women (69.4% of total events in postmenopause women) and in 15% of women without MetS. The frequency of each MetS component and the combinations of MetS are represented in Table 3. The 3 most common categories of MetS in our study (429 of 674 subjects) were

Table 1. Baseline Characteristic of Postmenopause Women in Age at Menopause Categories (Isfahan Cohort Study 2001)

	≤45	*46–50*	*51–55*	*≥56*	*Total*	
Age at menopause	N = *488*	N = *613*	N = *219*	N = *33*	N = *1353*	P
Age at entry	58.2 ± 10.0[a–c]	60.2 ± 8.69[d]	60.6 ± 7.64[d]	64.6 ± 6.89[d]	60.1 ± 9.14[d]	**<0.001**[e]
DM	84 (17.2)	105 (17.1)	36 (15.5)	8 (24.2)	233 (17.2)	0.744
HTN	258 (52.9)	291 (47.5)	114 (52.1)	20 (60.6)	583 (50.5)	0.179
Dyslipidemia	457 (93.6)	579 (94.5)	207 (94.5)	31 (93.9)	1274 (94.2)	0.944
Smoking	22 (4.5)	19 (3.1)	12 (5.5)	3 (9.1)	56 (4.1)	0.183
BMI	27.4 ± 4.80	27.5 ± 4.66	28.11 ± 4.58[d]	25.3 ± 3.68[c]	27.5 ± 4.69	**0.011**[e]
Systolic BP	131.6 ± 22.8	129.7 ± 21.3	131.8 ± 23.6	136.6 ± 28.4	130.9 ± 22.4	0.205
Diastolic BP	82.6 ± 12.4	81.7 ± 12.0	82.1 ± 11.7	84.1 ± 12.3	82.1 ± 12.1	0.498
TC	230.7 ± 53.2[c]	235.9 ± 56.1	245.2 ± 54.2[a]	240.0 ± 52.8	235.6 ± 54.8	**0.013**[e]
TG	201.9 ± 95.8	206.6 ± 105.5	214.1 ± 111.4	206.6 ± 95.1	206.1 ± 102.9	0.539
LDL-C	140.7 ± 44.2[c]	144.9 ± 46.0	152.2 ± 45.0[a]	148.8 ± 41.9	144.7 ± 45.2	**0.019**[e]
HDL-C	49.6 ± 10.7	49.7 ± 10.8	50.2 ± 10.6	49.8 ± 10.8	49.7 ± 10.8	0.921
Aspirin use	24 (8.5)	20 (5.5)	11 (9.2)	3 (14.3)	58 (7.4)	0.501
Statin use	60 (60.0)	79 (61.2)	40 (58.8)	6 (75.0)	185 (60.7)	0.456
Metabolic syndrome	284 (58.2)	361 (58.9)	119 (54.3)	21 (63.6)	784 (58.0)	0.689
TG+HDL+HTN+WC	66 (23.2)	93 (25.8)	31 (26.1)	6 (28.6)	196 (25.0)	0.913
TG+HDL+WC	55 (19.4)	72 (19.9)	18 (15.1)	2 (9.5)	147 (18.7)	
TG+HTN+WC	58 (20.4)	63 (17.5)	25 (21.0)	5 (23.8)	151 (19.2)	
Other	105 (36.1)	133 (36.8)	45 (37.8)	8 (38.1)	291 (37.1)	

Bolded P values are statistically significant.
[a]Shows significant difference with "age at menopause 46–50" group.
[b]Shows significant difference with "age at menopause 51–55" group.
[c]Shows significant difference with "age at menopause ≥56" group.
[d]Shows significant difference with "age at menopause ≤45" group.
[e]$P < 0.05$ considers statistically significant.
BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Table 2. Baseline Characteristics of Post Menopause Women With and Without Cardiovascular Disease Events in Isfahan Cohort Study: 2001–2013

	Without CVD	*With CVD*	*Total*	
	N = *919*	N = *235*	N = *1154*	P
Age at entry	59.6 ± 9.29	61.9 ± 9.29	60.0 ± 9.33	0.001[a]
Age at menopause, *n* (%)				0.109
≤45	292 (35.6)	87 (40.3)	379 (36.6)	
46–50	379 (46.2)	95 (44.0)	474 (45.8)	
51–55	137 (16.7)	27 (12.5)	164 (15.8)	
≥56	12 (1.5)	7 (3.2)	19 (1.8)	
Systolic BP	129.0 ± 21.8	138.9 ± 23.7	131.0 ± 22.5	<0.001[a]
Diastolic BP	81.2 ± 11.9	85.6 ± 13.1	82.1 ± 12.3	<0.001[a]
FBS	90.2 ± 32.2	105.5 ± 48.3	93.3 ± 36.6	<0.001[a]
TG	202.7 ± 99.7	218.0 ± 106.9	205.9 ± 101.3	0.039[a]
TC	234.6 ± 53.6	241.0 ± 57.9	235.9 ± 54.5	0.112
HDL-C	50.0 ± 10.8	49.1 ± 10.1	49.8 ± 10.6	0.220
LDL-C	144.0 ± 45.2	148.3 ± 47.3	144.9 ± 45.7	0.204
BMI	27.5 ± 4.64	28.2 ± 4.85	27.6 ± 4.69	0.024
Waist circumference	97.1 ± 12.7	99.6 ± 13.3	97.6 ± 12.9	0.007[a]
Current smoking, *n* (%)	31 (3.4)	14 (6.0)	45 (3.9)	0.086
DM, *n* (%)	113 (12.3)	66 (28.1)	179 (15.5)	<0.001[a]
HTN, *n* (%)	410 (44.6)	146 (62.1)	556 (48.2)	<0.001[a]
History of CVD, *n* (%)				0.261
Paternal	37 (4.0)	7 (3.0)	44 (3.8)	
Maternal	40 (4.4)	12 (5.1)	52 (4.5)	
Both	5 (0.5)	4 (1.7)	9 (0.8)	
None	837 (91.9)	212 (90.2)	1049 (90.9)	
Metabolic syndrome, *n* (%)	511 (55.6)	163 (69.4)	674 (58.4)	<0.001[a]
Aspirin use	43 (4.7)	31 (13.2)	74 (6.4)	<0.001[a]
Statin use	149 (57.1)	54 (60.0)	203 (57.8)	0.066

[a]$P < 0.05$ consider statistically significant.
CVD, cardiovascular disease; FBS, fasting blood sugar.

Table 3. Frequency of Metabolic Syndrome Factors and Combinations in Postmenopause Metabolic Syndrome Women With and Without Cardiovascular Disease Events in Isfahan Cohort Study: 2001–2013

Factors	*Without CVD,* N *(%)*	*With CVD,* N *(%)*	*Total,* N *(%)*
WC	490 (96.9)	152 (93.3)	642 (95.3)
TG	444 (86.9)	145 (88.9)	589 (87.4)
HTN	374 (73.2)	130 (79.8)	504 (74.8)
HDL	368 (72.0)	106 (65.0)	474 (70.3)
FBS	106 (20.7)	55 (33.7)	161 (23.9)
Combinations			
TG+HDL+HTN+WC	**136 (26.6)**	**38 (23.3)**	**174 (25.8)**
TG+HDL+WC	**108 (21.1)**	**20 (12.3)**	**128 (18.9)**
TG+HTN+WC	**98 (19.2)**	**29 (17.8)**	**127 (18.8)**
HDL+HTN+WC	50 (9.78)	12 (7.36)	62 (9.19)
TG+HDL+FBS+HTN+WC	34 (6.65)	20 (12.2)	54 (8.01)
TG+FBS+HTN+WC	25 (4.89)	15 (9.28)	40 (5.93)
TG+FBS+WC	14 (2.74)	9 (5.52)	23 (3.41)
TG+HDL+HTN	13 (2.54)	9 (5.52)	22 (3.26)
TG+HDL+FBS+WC	1 (2.35)	4 (2.45)	16 (2.37)
HDL+FBS+HTN+WC	7 (1.37)	2 (1.22)	9 (1.33)
FBS+HTN+WC	3 (0.59)	3 (1.84)	6 (0.89)
HDL+FBS+HTN	4 (0.78)	1 (0.61)	5 (0.74)
TG+FBS+HTN	3 (0.58)	1 (0.61)	4 (0.59)
HDL+FBS+WC	3 (0.59)	0 (0)	3 (0.44)
TG+HDL+FBS+HTN	1 (0.19)	0 (0)	1 (0.14)
Total	511	163	674

The *bolded* values are the three most common combinations of MetS.

Table 4. Hazard Ratios (95% Confidence Interval) of Reproductive Factors for Cardiovascular Events by Metabolic Syndrome in Postmenopause Women in Isfahan Cohort Study: 2001–2013

	Metabolic syndrome		*No metabolic syndrome*	
Reproductive factor	*Crude HR*	*Age adjusted HR*	*Crude HR*	*Age adjusted HR*
Type of menopause				
Natural	1		1	1
Artificial	0.97 (0.61–1.55)	1.15 (0.71–1.84)	0.92 (0.47–1.80)	1.06 (0.54–2.09)
Age at menarche (years)				
9–15	1	1	1	1
≥16	1.21 (0.72–2.06)	0.86 (0.36–1.75)	0.41 (0.12–1.33)	0.80 (0.36–1.75)
Gravid No.				
1–2	1	1	1	1
3–4	0.82 (0.28–2.38)	0.89 (0.31–2.59)	0.96 (0.18–4.99)	1.04 (0.20–5.40)
≥5	1.48 (0.65–3.35)	1.42 (0.63–3.23)	1.94 (0.47–7.94)	1.89 (0.46–7.75)
No. of abortion				
<3	1	1	1	1
≥3	1.16 (0.75–1.81)	1.12 (0.72–1.75)	1.89 (1.06–3.34)[a]	1.68 (0.94–2.99)[b]
History of OCP use	1.12 (0.81–1.56)	1.29 (0.91–1.81)	1.04 (0.63–1.71)	1.24 (0.74–2.07)
History of HRT	0.65 (0.32–1.31)	0.77 (0.37–1.59)	0.55 (0.17–1.74)	0.67 (0.20–2.16)

$P < 0.05$ consider statistically significant. Those without asterisk, P value >0.1.
[a]$P < 0.05$; [b]$P < 0.1$.
HR, hazard ratio; HRT, hormone replacement therapy; OCP, oral contraceptive pills.

"TG+HDL+HTN+WC, TG+HDL+WC, and TG+HTN+WC" combinations, with HR (95% CI, P value) for CV events: 1.58 (1.06–2.34, 0.023), 1.03 (0.63–1.69, 0.9), and 1.64 (1.07–2.53, 0.024), respectively.

The crude and age-adjusted HRs of reproductive factors, HRT and OCP use of CV events in postmenopause, and women with and without MetS are presented in Table 4. The only reproductive factor that predicts CV events was the history of multiple (≥3) abortions with HR: 1.89 (95% CI: 1.06–3.34, $P = 0.029$) in women without MetS, however, after adjustment for age, this association was not significant (HR: 1.68, 95% CI: 0.94–2.99, $P = 0.077$).

Table 5 introduces crude and age-adjusted HRs of four categories of age at menopause, for total CV events, IHD, and stroke incidence, based on the presence of MetS. As for the whole study population, age at menopause category was not predictive for CV events in women with MetS. In women without MetS, a trend with increasing incidence of stroke was observed in those with menopause age of ≤45 years (age-adjusted HR: 4.84, 95% CI: 0.99–23.5, $P = 0.05$).

In the current cohort study, younger age at menopause was not associated with lower age at occurrence of CV events (Table 6). Women with menopause age of ≤45 years suffered from CV events, 5.7 years earlier, compared with

Table 5. Hazard Ratios (95% Confidence Interval) for Cardiovascular Events by Age at Menopause and Metabolic Syndrome in Postmenopause Women in Isfahan Cohort Study: 2001–2013

	Metabolic syndrome		*No metabolic syndrome*	
CV event	*HR (95% CI)*	*Age-adjusted HR (95% CI)*	*HR (95% CI)*	*Age-adjusted HR (95% CI)*
Total CV event				
≤45	1.07 (0.76–1.51)	1.15 (0.82–1.62)	1.33 (0.81–2.20)	1.50 (0.90–2.49)
46–50	1	1	1	1
51–55	0.94 (0.59–1.51)	0.93 (0.58–1.48)	0.67 (0.31–1.46)	0.71 (0.33–1.56)
≥56	2.09 (0.91–4.80)	1.72 (0.74–3.98)	2.20 (0.67–7.21)	2.26 (0.69–7.42)
IHD				
≤45	1.05 (0.71–1.59)	1.12 (0.76–1.66)	1.08 (0.63–1.87)	1.22 (0.70–2.11)
46–50	1	1	1	1
51–55	1.01 (0.60–1.70)	0.98 (0.59–1.68)	0.53 (0.22–1.29)	0.57 (0.23–1.38)
≥56	2.29 (0.92–5.72)	1.93 (0.76–4.86)	0.79 (0.11–5.80)	0.81 (0.11–5.96)
Stroke				
≤45	1.11 (0.55–2.22)	1.19 (0.60–2.39)	4.39 (0.91–21.1)	4.84 (0.99–23.5)[a]
46–50	1	1	1	1
51–55	0.70 (0.24–2.08)	0.68 (0.23–2.04)	2.57 (0.36–18.22)	2.71 (0.38–19.4)
≥56	1.29 (0.17–9.68)	1.02 (0.13–7.72)	—[b]	—[b]

[a]$P < 0.05$ Consider statistically significant.
[b]This was not reported due to few case number.
CI, confidence interval; IHD, ischemic heart disease.

Table 6. Association of Age at Menopause and Age of Incident Cardiovascular Event Based on the Presence of Metabolic Syndrome in Isfahan Cohort Study: 2001–2013

	Age at event		
Age at menopause	*Menopause with metabolic syndrome*	*Menopause without metabolic syndrome*	*Total (all menopause women)*
≤45	66.6 ± 10.0 *n* = 61	66.6 ± 10.6 *n* = 31	66.6 ± 10.2 *n* = 92
46–50	68.9 ± 8.84 *n* = 73	70.9 ± 10.5 *n* = 30	69.5 ± 9.35 *n* = 103
51–55	68.3 ± 8.81 *n* = 23	65.3 ± 6.18 *n* = 8	67.5 ± 8.22 *n* = 31
≥56	71.9 ± 11.8 *n* = 6	73.2 ± 5.26 *n* = 3	72.3 ± 9.71 *n* = 9
P	0.240	0.399	0.108

the women with menopause age of ≥56 years ($P = 0.11$); this difference was 5.3 years in women with MetS, as opposed to 6.6 years in women without MetS ($P = 0.4$ and $P = 0.24$, respectively). The Kaplan–Meier curve of cardiovascular event rates in postmenopause women based on age at menopause is represented in Figure 1.

Discussion

In this longitudinal study, younger menopause age was not associated with earlier CV events in 12 years follow-up of postmenopause women, in urban and rural districts of central Iran. Lower age at menopause was not related to increased incidence of CV events in this cohort of postmenopause women. In women without MetS, considering the low case number, a trend with increasing incidence of stroke was observed, in those with menopause age of ≤45 years.

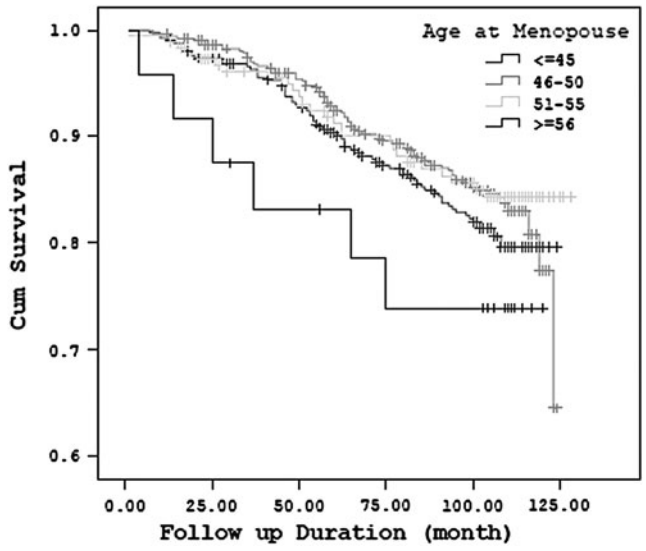

FIG. 1. Kaplan–Meier curve indicating cardiovascular event rates in postmenopause women based on age at menopause (≤45, 46–50, 51–55, ≥56 years) in ICS (2001–2013). ICS, Isfahan Cohort Study.

Timing of menopause varies in different countries based on ethnicity, race, genetic factors, life style (smoking, BMI, nutrition, physical activity, and parity), and socioeconomic status.[25] A meta-analysis of 21 studies revealed that the mean age at natural menopause in Iranian women was 48.18 years, which is in line with the current finding, 48.06 years (both surgical and natural menopause).[26] The mean age at menopause in Iran is earlier than those of developed countries, where the mean age of more than 50 years is frequently reported.[27,28] For instance, in a series of more than 95,000 of different ethnic/race women in the United States, the mean age at menopause was 51.4 years.[25] In our cohort study, in only 3% of the study population, menopause occurred at the age of ≥56 years.

Controversy still exists on the role of estrogen deficiency in the occurrence of CV events. Researchers have investigated the association of age at menopause and different types of CVD incidence. In an analysis of the Framingham Heart Study (FHS), 1430 women aged ≥60 years were followed up for the incidence of ischemic stroke; it was found that women with natural menopause age of ≤42 years had twice the risk of ischemic stroke.[14] In the Swedish Mammography Cohort study, after 13 years of follow-up, the HR of 1.40 (95% CI: 1.19–1.64) for the incidence of heart failure was reported in postmenopause women, with natural menopause age of 40–45 years, compared with those of 50–55 years.[29] A positive relationship was also reported in the analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort for both coronary heart disease and stroke.[30] Canonico et al. reported a U-shaped association between age at menopause and the incidence of venous thromboembolism (VTE), in an analysis of Women's Health Initiative Hormone Therapy (WHI HT) clinical trials, with increased risk of nonprocedure-related VTE in menopause age of <40 or >55 years.[31] A meta-analysis demonstrated that early menopause has a modest nonsignificant relationship with CVD, and it was proposed that artificial menopause has a more prominent association with CVD incidence, compared with natural menopause.[9]

In our cohort study, the most prevalent single factor in postmenopause women with MetS was high WC (95% prevalence), as for Franco et al. analysis of the women in the Framingham Offspring Study.[32] High WC is very common in all ICS women as well (90% prevalence with >80 cm cut point).[33] Three common combinations of MetS ("TG+HDL+HTN+WC, TG+HDL+WC, and TG+HTN+WC"), consist of two third of the postmenopause women with MetS. Regarding the HR for CV events, it seems that these three common groups have a lower risk for CV events, compared with the remaining groups. The finding that low HDL-C was not predictive for CV events in all ICS women, as for those at menopause may have a role for these low-risk combinations.[33]

In the present analysis of ICS data, natural menopause had no association with the occurrence of total CV events. In a subanalysis of postmenopause women without MetS, a trend with higher incidence of stroke, in menopause age of ≤45 years was observed (age-adjusted HR: 4.84, 95% CI: 0.99–23.5, $P = 0.05$). Although this observation is consistent with the findings of the FHS data analysis for stroke incidence,[14] concerning the few numbers of stroke events, it is difficult to distribute this finding to all postmenopause women without MetS.

Some have assumed that early menopause is a consequence of increased cardiovascular risk, instead of the

associated etiology. They have analyzed the data from the Framingham Heart Study, concluding that higher premenopausal serum TC increases in TC, relative weight and BP during follow up in the premenopausal period, are related to significant earlier age at menopause.[34] In the analysis of the MESA cohort, women with early menopause (<46 years) had higher mean of BMI and more often had diabetes and smoking.[30] In contrast, women with menopause age of ≤45 years in the current study, were younger at the time of enrollment in the study, compared with the rest of women and had lower total and LDL-C, in comparison with the subjects with menopause age of 51–55 years. Other traditional RFs and drug usage were not different in women regarding age at menopause, except for average BMI that was higher in 51–55 years group, compared with ≥56 years. MetS is a potent RF for CV events, and in ICS, the HR of MetS for IHD in women was 2.49 (95% CI: 1.58–3.86, $P < 0.001$).[16] In this study, MetS was a common RF in postmenopause women (58.4%), and ~70% of total CV events were identified in postmenopause women with MetS. No difference was observed between age at menopause and CV incidence, regarding the presence of MetS.

In the WHI HT cohort study, no association of reproductive factors such as parity, age at menarche, and time since menopause with VTE incidence was observed.[31] While the present study showed that the only reproductive factor that predicted CV events was history of multiple abortions (≥3; HR: 1.89, 95% CI: 1.06–3.34, $P = 0.029$), this association did not remain significant, after adjustment for age.

There is a lack of evidence on the association of early menopause and age at an incidence of CV events. In a case–control study of CAD patients, early postmenopausal status (≤3 years postmenopause) was the strongest RF for premature CAD with odds ratio of 4.55 (95% CI: 2.82–7.35).[35] In ICS, postmenopause women with menopause age of ≤45 years, suffered from CV events 5.7 years earlier, compared with women with menopause age of ≥56 years ($P = 0.11$); this difference was 5.3 years in women with MetS, as opposed to 6.6 years in women without MetS ($P = 0.4$ and $P = 0.24$, respectively). None of these differences in age of CV events was statistically significant.

The present study was a longitudinal cohort study with standard internationally accepted methodology and quality control protocols and a long-term follow-up and an acceptable number of cases to have a powerful analysis. The major limitation of the cohort was a relatively significant loss of subjects in follow-up.[19] Actually, the researchers did not separate natural menopause from surgical menopause because it might have led to loss of the study power. Some studies emphasize on surgical menopause, as more potent cardiovascular RF, compared with natural menopause. Recall bias is probably a problem as women may have been mistaken on recalling the exact date of last menstruation time, but it seems that these mistakes are not so significant to affect the results.

The present investigation indicated that younger age at menopause was not associated with statistically meaningful earlier CV events in women with and without MetS. Age at menopause was not predictive for total CV incidence. In women without MetS, early menopause was associated with a trend with increasing risk of stroke. Generally, considering age at menopause as a RF in cardiovascular risk assessment of menopause women remains the area of uncertainty and further studies are needed to address this issue.

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Authors' Contributions

A.S.: contributor in research, main writer. A.P.: contributor in research, main cowriter. M.S.: co principal investigator of research, contributor in writing. H.R.: contributor in research, contributor in writing. M.T.: contributor in research, contributor in writing. M.D.: contributor in research, statistical analyst, contributor in writing. S.O.: contributor in research, contributor in writing. M.S.: contributor in research, contributor in writing. N.S.: principal investigator, main reviser of the article.

Author Disclosure Statement

No conflicting financial interests exist.

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