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Determinants and Predictors of Age at Menopause among Women in Southeastern Iran

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ABSTRACT

Aims Menopause age is an important indicator that not only indicates the end of a woman's reproductive period but also increases the risk of various middle-aged diseases and complications that can be prevented with timely interventions. This study examined the age of menopause and factors affecting it among Iranian women in southeastern Iran.

Instrument & Methods This population-based study was conducted among 2,649 postmenopausal women aged 35-70 years who participated in the Zahedan Cohort Study, a component of the Prospective Epidemiological Research Studies in Iran, in Zahedan from October 2015 to January 2019. Data were analyzed using t-tests, chi-square tests, ANOVA, and multivariable logistic regression.

Findings The average age at menopause was 49.01±5.39 years. Among the women, 8.5% experienced premature menopause, 7.5% early menopause, and 84% normal menopause. Premature menopause was associated with marital status (single: OR=2.48, 95%CI:1.23–5.1), body mass index (p=0.036), physical activity, depression, diabetes, and history of stillbirth. Early menopause was linked to marital status (p=0.027), infertility (OR=1.51, 95%CI:1.09–2.1), body mass index, physical activity, depression, and diabetes. Normal menopause was associated with educational status, marital status, physical activity, body mass index, hypertension, and age at menarche (all p<0.05).

Conclusion Genetic and social factors, including marital status and reproductive history, influence menopausal age, with distinct predictors characterizing premature and early menopause.

Keywords Menopause; Women; Cohort Study

CITATION LINKS

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Introduction

Menopause marks the end of the monthly menstrual cycle in females and is characterized by amenorrhea for 12 consecutive months due to decreased ovarian follicular function [1]. This transition is accompanied by a reduction in estrogen levels, resulting in the cessation of menstruation and reproductive capability [2]. The natural age of menopause is typically defined as after age 45 [3, 4]. Menopause may occur before the age of 40, which is known as premature ovarian failure [3]. Approximately 4% of females experience this transition before age 40 [5], or it may occur between ages 40 and 44, a condition called early menopause [3]. The average age of menopause varies globally: Europe, 54 years; North America, 51.4 years; Latin America, 48.6 years; Asia, 51.1 years [6]; and Iran, 50.4 years [7]. The age of menopause serves as a predictor of mortality and disease risk in women's later life stages. Early menopause is associated with increased risks of cardiovascular diseases, osteoporosis, and type 2 diabetes [7-9]. Epidemiological studies suggest a 2% reduction in mortality rates with adjustments in menopausal age [10], whereas late menopause is correlated with increased risks of endometrial and ovarian cancer [11-15].

Several factors may influence the age at menopause onset, including the use of contraceptive medications, body mass index (BMI), smoking and alcohol consumption, physical activity, socioeconomic status, genetic factors, education level, and environmental, socioeconomic, and lifestyle factors [16-18]. Identifying the factors that determine menopausal age is highly important. Understanding the genetic aspects of this phenomenon can enhance our knowledge of the causes of premature menopause, which in turn affects women's fertility [19]. Therefore, careful study and identification of factors that affect the age at menopause can help predict and better manage the health risks associated with this period. This can improve the quality of life for postmenopausal women and enable them to approach this important stage of life with greater awareness and preparation. While some studies have been conducted on menopause in Iran, there is a lack of research specifically focused on the age of menopause and its influencing factors in a large population of women in Zahedan. Understanding these parameters can provide valuable insights into women's health in this region and inform public health strategies. To address these gaps, we conducted a cross-sectional study to determine the age at menopause and identify factors associated with it among women living in Zahedan, Iran.

Instrument and Methods

Design and participants

This cross-sectional study used data from the Zahedan Cohort Study (ZCS), part of the Prospective Epidemiological Research Studies in Iran (PERSIAN), conducted in Zahedan, a city in southeastern Iran. ZCS is a prospective, population-based study, with data collection conducted between October 2015 and January 2019 in Zahedan, and a 15-year follow-up was planned.

The ZCS used a multistage stratified approach, where Zahedan city was divided into three areas (periphery, center, and upper city) based on municipal regions and socioeconomic class. A comprehensive health service center was randomly selected in each region, and all women who met the study eligibility criteria were enrolled at each center.

Inclusion criteria were women with a history of cancer, hysterectomy, or oophorectomy (unilateral or bilateral) before menopause, as well as those who had not yet experienced menopause. Of the 6,099 women who participated, 3,450 were excluded, and 2,649 were postmenopausal (defined as the absence of menstruation for at least 12 months). The menopausal status of women was categorized as premature menopause, early menopause, or normal menopause. Premature menopause was defined as occurring before age 40, early menopause as occurring between ages 40 and 44, and normal menopause as occurring after age 45 [3].

Instrument

Data were collected using a questionnaire whose validity and reliability have been confirmed in Persian cohort studies [20, 21].

Socioeconomic status was measured using the wealth score index (WSI), which considers various factors, including access to facilities, travel status, homeownership, number of bedrooms, monthly household income, annual domestic and international trips, and number of books read. WSI was calculated via multiple correspondence analysis (MCA). MCA is a widely used technique for analyzing categorical data; it aims to reduce large sets of parameters into smaller sets of components that summarize the information contained in the data. MCA can be regarded as an adaptation of principal component analysis (PCA) for categorical data [22]. Using the MCA method, the WSI was divided into three groups (poor, moderate, and rich) based on the scoring of the mentioned parameters.

The level of physical activity was calculated based on metabolic equivalent task hours (MET-hours/day). The participants' BMI was calculated (BMI<18.5 as underweight, 18.5-24.9 as normal, 25-29.9 as overweight, and 30 or more as obese) [23]. Triglyceride (TG)≥150mg/dl and cholesterol (CHOL)≥200mg/dl were considered elevated [24]. Current cigarette smokers were defined as individuals who had smoked at least 100 cigarettes in their lifetime and currently smoked either every day or on some days [25].

Stillbirth was defined as the death of the pregnancy product after the 20th gestational week [26]. Menarche age is the age at which a person

experiences their first menstruation. Menopause was defined as the passage of at least 12 months since the last menstruation [27]. To assess menopausal status, women were asked whether they had undergone menopause (yes/no). Furthermore, among women who had experienced menopause, the age at menopause completion was recorded.

Procedure

The questionnaire was administered and completed by trained personnel who collected information from the participants. The aims, foundation, and design of this study have been previously published [22]. Trained interviewers used a laptop-based questionnaire to gather data on participants' socio-demographics, anthropometrics, medical history, lifestyle, nutrition, and reproductive characteristics. Data were collected after participants provided written informed consent. The research team received the data from the ZCS supervisor in a coded, anonymous form, and the authors did not have access to participants' identification information. Trained personnel used validated questionnaires to collect data on sociodemographic characteristics, substance use, medical history, family history, socioeconomic status, and physical activity. Marital status was dichotomized as married and single, with the latter including never married, divorced, or widowed individuals. The level of physical activity was calculated based on metabolic equivalent task hours (MET-hours/day).

Data analysis

Individual characteristics were compared across menopausal age groups (premature, early, and normal) using the chi-square test and Fisher's exact test for categorical variables, and one-way analysis of variance (ANOVA) and the independent-samples t-test for quantitative variables. Multiple logistic regression analyses were used to assess the associations between independent variables and premature, early, and normal menopause. The normal menopause category was set as the reference category in this model. Potential confounding parameters were entered into the model in order of their hypothesized strength of association with menopausal age. Parameters with a p-value less than 0.2 were selected as confounders. All analyses were performed using SPSS 22.

Findings

A total of 2,649 women with a mean age of 57.21±5.80 years (range: 35–70) were included. There were significant differences among the three menopausal age groups in terms of age, educational status, job status, cardiac disease, depression, infertility, and diabetes (Table 1).

Table 1. Frequency of baseline characteristics of menopausal women

Parameter			Premature menopause	Early menopause	Normal menopause	p-Value
Educational status (year)	<6	2025 (76.4)	165 (73.3)	128 (64.6)	1732 (77.8)	0.001
	6-12	494 (18.6)	50 (22.2)	57 (28.8)	387 (17.4)	
	>12	130 (4.9)	10 (4.4)	13 (6.6)	107 (4.8)	
Married status	Single	20 (0.8)	0	4 (2)	16 (0.7)	0.108
	Married	2001 (75.5)	177 (78.7)	152 (76.8)	1672 (75.1)	
	Divorced/widow	628 (23.7)	48 (21.3)	42 (21.2)	538 (24.2)	
Job status	Housekeeper	2302 (86.9)	198 (88)	163 (82.3)	1941 (87.2)	0.028
	Employee	288 (10.9)	18 (8)	27 (13.6)	243 (10.9)	
	Others	59 (2.2)	9 (4)	8 (4)	42 (1.9)	
Physical activity (hour)	<41	2185 (82.5)	189 (84)	165 (83.3)	1831 (82.3)	0.76
	≥41	464 (17.5)	36 (16)	33 (16.7)	395 (17.7)	
Body mass index	<18.5	48 (1.8)	5 (2.3)	4 (2)	39 (1.8)	0.67
	18.5-24.9	612 (23.4)	48 (21.6)	39 (19.9)	525 (23.9)	
	25-29.9	996 (38.1)	79 (35.6)	82 (41.8)	835 (38.1)	
	≥30	955 (36.6)	90 (40.5)	71 (36.2)	794 (36.2)	
Socioeconomic status	Poor	915 (34.5)	71 (3.6)	60 (30.3)	784 (35.2)	0.18
	Moderate	857 (32.4)	73 (32.4)	59 (29.8)	725 (32.6)	
	Rich	877 (33.1)	81 (36)	79 (39.9)	717 (32.2)	
Cardiac disease	Yes	394 (14.9)	46 (20.4)	29 (14.6)	319 (14.3)	0.049
	No	2255 (85.1)	179 (79.6)	169 (85.4)	1907 (85.7)	
Depression	Yes	576 (21.7)	63 (28)	50 (25.3)	463 (20.8)	0.021
	No	2073 (78.3)	162 (72)	148 (74.8)	1763 (79.2)	
Infertility	Yes	241 (9.2)	30 (13.3)	22 (11.3)	189 (8.6)	0.033
	No	2388 (90.8)	195 (86.7)	172 (88.7)	2021 (91.4)	
Smoking	Yes	90 (3.4)	6 (2.7)	7 (3.5)	77 (3.5)	0.81
	No	2558 (96.6)	219 (97.3)	191 (96.5)	2148 (96.5)	
Hypertension	Yes	1229 (46.4)	97 (43.1)	81 (40.9)	1051 (47.2)	0.13
	No	1420 (53.6)	128 (56.9)	117 (59.1)	1175 (52.8)	
Diabetes	Yes	784 (29.6)	59 (26.2)	44 (22.2)	681 (30.6)	0.024
	No	1865 (70.4)	166 (73.8)	154 (77.8)	1545 (69.4)	
Stillbirth	Yes	337 (13.1)	35 (16.4)	17 (9)	285 (13.1)	0.087
	No	2240 (86.9)	178 (83.6)	172 (91)	1890 (86.9)	
Age at menarche (year)	Early (≤13)	836 (31.6)	61 (27.1)	60 (30.3)	715 (32.1)	0.28
	Late (>13)	1813 (68.4)	164 (72.9)	138 (69.7)	1511 (67.9)	

Menopausal age was significantly associated with educational status (p=0.001), job status (p=0.01), BMI (p=0.014), socioeconomic status (p=0.032), depression (p=0.005), infertility (p=0.006), hypertension (p=0.001), diabetes (p=0.005), and age at menarche (p=0.014) in the total sample (Table 2).

Table 2. Comparison of the mean menopausal age based on categorical parameters

Parameter	Total (n=2649)		Premature (n=225)		Early (n=198)		Normal (n=2226)	
	Mean	p-Value	Mean	p-Value	Mean	p-Value	Mean	p-Value
Educational status (year)								
<6	49.27±5.45	0.001	36.79±4.56	0.49	42.71±1.16	0.23	50.94±3.44	0.001
6-12	48.14±5.27		37.16±3.06		42.70±1.06		50.36±3.04	
>12	48.36±4.56		38.30±1.88		43.00±1.15		49.90±3.05	
Married status								
Single	47.85±3.54	0.11	0	0.64	42.50±1.29	0.027	49.19±2.45	0.04
Married	48.90±5.41		36.86±4.34		42.84±1.04		50.74±3.30	
Divorced/widow	49.37±5.38		37.19±3.58		42.30±1.22		51.01±3.57	
Job status								
Housekeeper	49.06±5.42	0.01	36.86±4.33	0.15	42.70±1.10	0.8	50.84±3.75	0.28
Employee	49.07±4.68		38.50±1.65		42.85±1.13		50.54±3.30	
Others	46.90±6.42		35.44±3.84		42.60±1.06		50.17±3.41	
Physical activity (hour)								
<41	48.92±5.40	0.058	37.19±4.16	0.68	42.72±1.12	0.73	50.72±3.35	0.03
≥41	49.44±5.35		36.89±4.20		42.70±1.02		51.11±3.43	
Body mass index								
<18.5	49.10±4.56	0.014	39.60±0.89	0.036	43.25±0.95	0.47	50.90±2.58	0.001
18.5-24.9	49.17±4.70		39.19±3.07		42.60±1.06		50.50±3.34	
25-29.9	49.54±4.82		39.90±3.84		42.80±1.07		51.00±3.26	
≥30	48.83±4.88		38.30±3.93		42.62±1.16		50.47±3.19	
Socioeconomic status								
Poor	49.12±5.45	0.032	36.66±4.50	0.32	42.53±1.11	0.25	50.75±3.57	0.095
Moderate	49.29±5.19		37.50±3.27		42.78±1.13		51.00±3.20	
Rich	48.63±5.51		36.67±4.61		42.84±1.06		50.62±3.28	
Cardiac disease								
Yes	48.75±5.83	0.3	37.11±4.01	0.339	42.83±1.10	0.59	50.76±3.35	0.3
No	49.06±5.31		36.89±4.24		42.70±1.10		50.97±3.45	
Depression								
Yes	49.17±5.27	0.005	37.07±4.27	0.43	42.69±1.10	0.4	50.46±3.21	0.41
No	48.45±5.79		36.50±3.97		42.83±1.09		51.16±3.49	
Infertility								
Yes	48.11±6.08	0.006	36.73±4.44	0.77	42.23±1.19	0.02	50.60±3.32	0.39
No	49.11±5.32		36.97±4.16		42.80±1.07		50.82±3.35	
Smoking								
Yes	48.99±5.38	0.32	36.98±4.16	0.39	42.43±0.97	0.46	51.31±3.50	0.16
No	49.57±5.70		35.50±5.20		42.74±1.10		50.76±3.35	
Hypertension								
Yes	48.61±5.31	0.001	37.02±4.48	0.72	42.84±1.09	0.68	51.16±3.49	0.001
No	49.48±5.45		36.82±3.78		42.69±1.10		50.46±3.29	
Diabetes								
Yes	49.47±5.32	0.005	36.93±4.47	0.95	42.66±1.14	0.64	50.90±3.57	0.06
No	48.82±5.41		36.97±3.30		42.75±1.09		50.70±3.27	
Stillbirth								
Yes	49.08±6.017	0.97	36.26±5.40	0.24	42.53±0.97	0.39	51.05±3.50	0.19
No	49.08±5.23		37.13±3.73		42.77±1.09		50.77±3.33	
Age at menarche (year)								
Early (≤13)	48.84±5.36	0.014	36.59±5.06	0.44	42.62±1.15	0.35	51.05±3.46	0.01
Late (>13)	49.39±5.45		37.07±3.83		42.78±1.08		50.67±3.32	

Single women had higher odds of premature menopause (p=0.023). Women with physical activity <41 MET-hours/day had higher odds of premature and early menopause (p=0.035 and p=0.04, respectively). Additionally, having diabetes increased the odds of premature and early menopause (p=0.02 and p=0.036, respectively). Women with a history of stillbirth had higher odds of premature menopause (p=0.03). Women with a history of depression had higher odds of premature and early menopause (p=0.012 and p=0.007, respectively). Women with a high BMI and a history of infertility had higher odds of early menopause (p=0.016 and p=0.013, respectively; Table 3).

Discussion

This study aimed to explore the determinants and predictors of age at menopause among Iranian women in the Zahedan Adult Cohort Study (PERSIAN) in Southeastern Iran. We investigated the risk factors for age at menopause, both in general and by classifying menopause as early, premature, or normal. The mean age of menopause in our sample (49.01±5.39 years) aligns with previous research conducted in Iran, where the average age at menopause has been reported to range from 48.3 to 49.6 years [28–33]. Notably, Iranian women tend to experience menopause earlier than their

counterparts in Europe (50.1–52.8 years) and North America (50.5–51.4 years). However, the menopausal age of our population was higher than that reported in the Middle East (46.9-47.8 years) and Latin America (41.6–45.9 years) [6]. The observed differences in menopausal age across geographical regions may be attributed to a combination of genetic, social, economic, and lifestyle factors [34]. For example, premature menopause is often linked to genetic disorders, autoimmune conditions, and certain medical interventions [35]. Additionally, early menopause may be influenced by an accelerated aging process due to both genetic predispositions and environmental factors [3]. Our analysis revealed no significant correlation between education level and age at menopause, consistent with other findings [17, 29, 36] but contrasting with studies reporting a significant relationship [17, 37].

Table 3. Multiple logistic regression results for risk factors associated with menopausal age

Parameter	Premature menopause vs. Normal menopause			Early menopause vs. Normal menopause		
	Adjusted OR	95% CI	p-Value	Adjusted OR	95% CI	p-Value
Educational status (year)						
<6	Ref					
6-12	1.14	(0.78, 1.66)	0.47	1.23	(0.74, 2.04)	0.41
>12	0.97	(0.51, 1.91)	0.95	0.95	(0.73, 1.27)	0.83
Married status						
Single	2.48	(1.23, 5.1)	0.023	1.33	(0.46, 3.85)	0.59
Married	1.14	(0.71, 1.45)	0.48	0.96	(0.73, 1.24)	0.79
Divorced/widow	Ref					
Body mass index						
<18.2	1.132	(0.39-3.24)	0.81	0.87	(0.21-0.98)	0.36
18.5-24.9	0.84	(0.56-1.27)	0.42	1.05	(0.82-1.33)	0.68
25-29.9	1.17	(0.8-1.52)	0.51	1.22	(1.1-1.62)	0.016
≥30	Ref					
Physical activity (hour)						
<41	1.23	(1.02, 1.63)	0.035	1.25	(1.12, 2.35)	0.04
≥41	Ref					
Socioeconomic status						
Poor	1.7	(0.51, 2.23)	0.2	1.31	(0.98, 1.74)	0.064
Moderate	1.8	(0.57, 2.17)	0.33	1.16	(0.88, 1.51)	0.27
Rich	Ref					
Depression						
Yes	1.3	(1.1, 1.84)	0.012	1.23	(1.02, 2.3)	0.007
No	Ref					
Diabetes						
Yes	1.51	(1.07, 2.13)	0.02	1.23	(1.1, 2.53)	0.036
No	Ref					
Hypertension						
Yes	0.786	(0.58-1.7)	0.1	1.18	(0.99-1.59)	0.053
No						
Stillbirth						
Yes	1.7	(1.2, 2.2)	0.03	1.68	(0.62, 2.13)	0.36
No	Ref					
Smoking						
Yes	0.98	(0.43-2.09)	0.912	1.13	(0.48-1.58)	0.68
No	Ref					
Infertility						
Yes	1.29	(0.81-2.06)	0.27	1.51	(1.09-2.1)	0.013
No	Ref					

OR: Odds ratio; CI: Confidence interval

Interestingly, single women were more likely to experience premature and early menopause than their married counterparts, particularly in cases of premature menopause, which aligns with the findings of Farjam *et al.* [37]. This observation underscores the potential role of social support structures in influencing menopausal timing. Physical activity was a significant predictor of menopausal age. Lower levels of physical activity were associated with increased odds of both premature and early menopause, which is consistent with some studies [6, 34] and contradicts others [38]. This aligns with the literature suggesting that active lifestyles may contribute positively to reproductive health outcomes in women. A higher BMI was linked to increased odds of early menopause, corroborating findings from previous research indicating that obesity can adversely affect hormonal balance and reproductive function [39, 40].

Socioeconomic status plays a critical role in determining the timing of menopause. Women from lower socioeconomic backgrounds had higher odds of experiencing premature and early menopause, although this relationship was not statistically significant in our analysis. However, several studies have reported a significant association between earlier age at normal menopause and lower social class [41–43]. Golshiri *et al.* report that women with lower socioeconomic status experience menopause at an earlier mean age, nearly three years earlier than

those with moderate socioeconomic status. Additionally, women with moderate socioeconomic status have an earlier mean age at menopause, approximately four years earlier than women with high socioeconomic status [44]. There is a link between early menopause and a heightened risk of cardiovascular disease and hypertension, highlighting the importance of monitoring health outcomes in this group [45, 46].

We observed associations between a history of hypertension and early onset of menopause; however, these relationships were not statistically significant. Fertility history appeared to affect the timing of menopause. Some studies indicate that women with a history of infertility or stillbirth experience menopause earlier than those without such a history [35, 44]. A history of stillbirth increased the odds of premature menopause, and a history of infertility increased the odds of early menopause, suggesting that reproductive events may have lasting effects on women's health trajectories.

Unexpected findings regarding smoking were obtained, while the literature often associates smoking with the earlier onset of menopause [47, 48]. Some studies have shown a statistically significant relationship between smoking and the age of menopause [49–51]. However, other studies, including the current one, did not find similar results [52]. This could be attributed to the small number of smokers in the cohort or the low prevalence of smoking among Iranian women.

Evidence suggests that diabetes may contribute to the early onset of menopause [53]. Specifically, women diagnosed with type 1 diabetes often experience menopause approximately five years earlier than their counterparts without diabetes [54]. However, some studies have failed to corroborate these findings. For example, Brand *et al.* report that women who develop diabetes before the age of 20 years experience earlier menopausal onset, whereas those diagnosed after the age of 50 years experience a delay in menopause [55]. Moreover, no significant correlation was found between diabetes onset between the ages of 20 and 50 years and the age at menopause. Women with a history of diabetes presented higher odds of experiencing premature and early menopause.

Additionally, women who began menstruating before the age of 13 years had elevated odds of both premature and early menopause. This observation aligns with certain studies but contradicts others in the literature [56–59]. The increased risk of depression during menopause has been attributed to biological vulnerability, with studies finding an association between greater variation in estradiol and follicle-stimulating hormone (FSH) levels and higher depressive symptoms [60]. A history of depression was also associated with increased odds of premature and early menopause, corroborating findings from Shea *et al.*, indicating a similar association between depression and menopausal timing [61].

The strengths of our study include its large sample size and comprehensive evaluation of various factors influencing menopausal age among women. A significant advantage of our research is the adjustment for numerous potential confounders, such as demographic information and medical history. However, we acknowledge several limitations in our study. First, data regarding outcomes and exposures were primarily self-reported, which may introduce misclassification and recall bias among participants. Moreover, recalling the exact time of menopause might also be subject to recall bias. Second, we excluded women over the age of 70 years, who might face more severe health challenges that could affect menopausal timing. Finally, the cross-sectional nature of our study limits our ability to establish causal relationships between various factors and age at menopause; thus, further longitudinal studies are warranted to elucidate these associations.

While genetic factors significantly influence the age at menopause, social factors, such as marital status and pregnancy also play important roles. Improving the health of premenopausal women requires a multidimensional approach that simultaneously includes regular physical activity, screening for mental disorders, healthy nutrition, diabetes prevention, and social support. Implementing community-based interventions and integrating screenings into primary care can lead to effective prevention of the physical and psychological consequences of this period and sustainably improve women's quality of life. It should be noted that menopause information relied on self-reports, potentially introducing reporting bias and misclassification of menopausal status.

Conclusion

Genetic factors, along with social and health-related factors, such as marital status, body mass index, physical activity, and reproductive history, influence menopausal age, with different factors predominating in premature versus early menopause.

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