

Original Article

An Explanation for Variation in Age at Menopause in Developing Countries Based on the Second National Integrated Micronutrient Survey in Iran

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Abstract

Background: It is reported that women in developing countries reach menopause earlier compared to developed countries. This seems to be due to underestimation of age at menopause as pre-menopause women who will reach menopause at older ages are commonly excluded in cross-sectional settings. In this study, we propose an estimation method which can deal with this bias. We also assessed major determinants of menopause.

Methods: The second national integrated micronutrient survey in Iran completed in 2015 is a population-based study with a nationally representative sample of 4,898 Iranian women aged 50 to 60 years. We used data on menopause status and menopausal age (asked retrospectively) to estimate the median survival time. We also used Logistic regression to model menopausal status on the current age and to estimate the median age, at which 50% of women will experience menopause. Demographic, lifestyle, and anthropometric determinants were also examined.

Results: The estimated age at menopause was 51.2 (51.0–51.3) years in the logistic model and 50.5 (48.1, 53.7) years in survival analysis. In both models, the age at menopause was significantly lower among rural and underweight women. In addition, survival analysis showed that smokers and women with smaller family size had significantly lower age at menopause.

Conclusion: While many studies stress a gap in age at menopause between developed and developing countries, this study with a reliable estimation method showed that such a gap might originate from an underestimation of age at menopause in developing countries rather than a real difference.

Keywords: Age at menopause, Determinants, Bias estimate, Developing countries, Iran

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Introduction

Menopause is a turning point in every woman's life; it impacts their quality of life in terms of physical and emotional changes. Joint pains, weight gain, hot flashes and fluctuations in mood are some of its side effects.¹ It has been shown that early menopause increases the duration of exposure to risk factors of certain chronic diseases such as osteoporosis,² cardiovascular diseases,¹ and diabetes.³ Therefore, expanding knowledge on this issue could assist policy makers to allocate better health service for the post-menopause period.

Several studies have so far addressed the age at menopause

and its determinants in developed countries. In contrast, there is a limited number of studies in developing countries, most of which lack appropriate statistical methods and sufficient sample size. Most studies used simple summary measures to estimate the menopausal age of a population.^{4–7} A gap found in such studies is that these research studies usually exclude women who have not reached menopause yet and will experience it in older ages. This exclusion leads to underestimation of menopausal age.

Additionally, the existing evidence on the age at menopause and the risk factors of menopause is controversial.^{8,9} A number of risk factors have been suggested for early menopause in the literature. Reports on the association between smoking and earlier age at menopause are consistent.^{10–12} However, the association of obesity and physical activity with age at menopause remains inconclusive.¹³ Thus, a national population-based study with a relatively large sample size is needed to provide representative estimates of age at menopause and the effects of associated factors in Iran.

In this study, we report findings from part of the Second National Integrated Micronutrient Survey (NIMS-II), which was conducted by the School of Nutritional Sciences and Dietetics of Tehran University of Medical Sciences, Tehran, Iran. The merits of our study lie in its large national sample size and novel statistical models for the likely unbiased estimates of menopausal age. We

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Figure 1. The geographic presentation of the study regions.

used two alternative statistical methods to analyze the data and compared the results of these methods. The findings of the current study can be generalized to the entire population of Iran, given its large and representative sample.

Materials and Methods

This study used data on menopausal age and its determinants from the NIMS-II which is a population-based survey completed in 2015¹⁴. The participants included 4,898 Iranian women aged 50 to 60 years who were apparently healthy or without diseases. Data was collected using structured questionnaires and anthropometric measurements. Below, we present details on sampling design, study variables, data cleaning, and analysis methods.

Sampling design

We divided Iran into 11 study regions (zones) with almost equal population size based on the similarities in geographic and socio-economic characteristics (Figure 1). Socio-economic characteristics were not measured directly and we relied on nutritional expert opinion to determine these regions.

The number of participants included per region was 400 women, which is appropriate for estimating non-rare events. Within each region, 80 clusters were randomly selected using one-stage cluster sampling. Each cluster consisted of 5 women, aged 50-60 years. In both urban and rural areas, we used the recent sampling frame of Statistical Center of Iran (census 2011) to define a sampling frame of households. In each cluster, we randomly selected one household from the household sampling frame. We collected the data of participants from this household and neighboring households to reach a cluster of size 5. The number of clusters

in urban and rural areas of each stratum was a proportion of the population size. When an individual was not available (after being called 3 times), a new participant was substituted from the same cluster. The total number of study participants (4,898) outnumbers the estimated minimum sample size (4,400) for 11 regions.

Since we selected an equal number of women in each region, we used a sampling weight to adjust the weight of each observation proportional to the regions' population size. In all analyses presented in the results section, we used appropriate sampling weights.

Study variables

Menopausal status and age when a woman reaches menopause are main outcome variables. Menopause is defined as the absence of menstrual periods for at least 12 consecutive months¹⁴. Furthermore, study variables include demographic characteristics, history of hysterectomy, age at hysterectomy, cultural and lifestyle behaviors (family size and smoking), socio-economic factors (house size) and anthropometric indices, which consisted of body mass index (BMI) and waist circumference. Smoking status of women was determined by asking whether they were current smokers. We used the house size as a proxy variable for socio-economic status and family size as a proxy variable for the number of children for each woman and their cultural behavior. Anthropometric indices were measured through physical examinations.

Data cleaning

We excluded 283 women whose age at interview was less than 50 years based on study inclusion criteria. Furthermore, participants for whom age or age at menopause was missing

Table 1. Variable definition in survival analysis and logistic regression.

Participants	Survival Analysis		Logistic regression	
	Event	Time to event	Event	Age variable
Menopause women	Failure	Age at menopause	Menopause	Age at interview
Pre-menopause women	Censor	Age at interview	Non-menopause	Age at interview
Hysterectomy women	Censor	Age at hysterectomy	Non-menopause	Age at hysterectomy

Table 2. General characteristics of study participants.

Characteristics	Number	Percentages
Menopausal status		
Postmenopausal	3262	72.1
Premenopausal	826	18.3
Hysterectomy or oophorectomy	436	9.6
Area of residence		
Urban	2,878	63.6
Rural	1,646	36.4
Current smoker		
No	4,462	98.6
Yes	62	1.4
Family size		
1–2	720	15.9
3–4	2,004	44.3
5–6	1,233	27.3
≥7	566	12.5
House size		
≤ 70 m ²	910	20.2
71–100 m ²	1393	31.0
101–120 m ²	677	15.1
121–150 m ²	632	14.0
≥151 m ²	887	19.7
Body Mass Index		
Underweight (<18.5)	83	1.8
Normal (18.5–24.9)	1,055	23.4
Overweight (25–29.9)	1,674	37.1
Obesity (≥30)	1,698	37.7
Waist circumference		
<80	626	13.8
80–87.9	905	20.0
≥88	2993	66.2

(n=64), and observations for women whose menopausal age was reported higher than the age at interview (n=27) were excluded. Plausible range recommendation for BMI variable (kg/m²)¹⁵ was employed and 14 implausible BMI values (BMI<14 or BMI>50) were replaced by missing values. However, the number of excluded observations were less than 2% of the sample that could have negligible effects on findings.

Statistical analysis

We examined the association of cultural and lifestyle behaviors, socio-economic determinants and anthropometric indices with age at menopause and menopausal status using survival analysis and logistic regression, respectively.

Survival analysis

The outcome parameter to estimate in this study is median menopausal age. However, a number of included participants had

not reached menopause at the time of survey. These women will reach menopause in older ages. A typical estimation of median age at menopause excludes this group of participants, thus leading to a biased estimate of menopausal age. Survival analysis can properly handle these censored observations¹⁶.

For the survival analysis, time to event (T) was defined as time from birth to menopause or censorship. Menopause defined as event and perimenopause and hysterectomy cases were considered as censor. For a premenopausal woman, age at interview, and for a person with hysterectomy, age at the time of surgery were considered as time to censorship. The information about the definition of event and time to event for different groups is defined in Table 1. For both premenopausal and hysterectomy women, we did not know the exact age of menopause. The only information is that their menopausal age is later than the age at interview and age at surgery, respectively. We preferred to use this partial information in a survival model rather than excluding them.

Table 3. Assessment of the relation of age at menopause and its determinants using two alternative models: Cox proportional hazard (PH) model and logistic regression.

Characteristics	Cox PH Model			Logistic Regression	
	Median ANM ^a	Adjusted HR ^d (95% CI)	P-Value ^b	Adjusted OR ^d (95% CI)	P-Value ^c
Area of residency			0.010		<0.001
Urban	50.7	1.00		1.00	
Rural	50.3	1.09 (1.01–1.18)		1.35 (1.12–1.62)	
Current smoker			0.012		0.091
No	50.5	1.00		1.00	
Yes	49.2	1.41 (1.07–1.87)		1.88 (0.88–4.05)	
Family size			0.026		0.982
1–2	50.3	1.00		1.00	
3–4	50.6	0.94(0.85–1.04)		0.90 (0.69–1.17)	
5–6	50.6	0.92 (0.82–1.02)		0.98 (0.74–1.30)	
³ 7	50.5	0.88 (0.77–0.99)		0.95 (0.68–1.33)	
Body Mass Index			0.049		0.009
Underweight (<18.5)	49.7	1.00		1.00	
Normal (18.5–24.5)	50.4	0.79 (0.62–1.01)		0.73 (0.33–1.61)	
Overweight (25–29.9)	50.4	0.76 (0.60–0.97)		0.61(0.28–1.32)	
Obesity (≥30)	50.7	0.75(0.59–0.96)		0.58 (0.27–1.27)	
House size			0.549		0.322
≤70 m ²	50.4	1.00		1.00	
71–100 m ²	50.5	0.98 (0.89–1.08)		0.85 (0.67–1.09)	
101–120 m ²	50.5	1.01 (0.90–1.14)		0.87 (0.66–1.16)	
121–150 m ²	50.6	0.98 (0.87–1.11)		0.79 (0.59–1.06)	
³ 150 m ²	51.0	0.90 (0.81–1.01)		0.73 (0.56–0.95)	

^aANM: Age at Natural Menopause using Kaplan-Meier method. ^bP-values obtained from multivariate Cox regression. ^cP-values obtained from multivariate logistic regression. ^dNote that for easier interpretation, the hazard ratios and odds ratios reported in the table are based on categorical scale not ordinal scale.

We used Kaplan-Meier method to obtain descriptive information on median age at menopause for the entire study population or within the subgroups of important determinants such as smoking behavior and residential area. Log-rank test was used to compare age at menopause between these subgroups. For multivariate analysis, all variables that were significant in the univariate analysis were included. Cox proportional hazards model was used to quantify the impact of each determinant on age at menopause in the presence of other covariates. We considered variables such as BMI and waist circumference as continuous variables in the analysis. Family size was divided into 4 categories of almost equal length (1–2, 3–4, 5–6, ³7) and it was used on an ordinal scale with categories ranging from 1 to 4, respectively. House size was used in its original continuous format. However, values larger than 300 square meters were changed to 300 square meters.

Logistic regression

For logistic regression, menopause status was defined as a binary outcome (menopause and non-menopause). A woman who had undergone hysterectomy was considered as being non-menopausal at the age of hysterectomy. This modification helps us to keep hysterectomy cases in the analysis. The other participants were considered menopausal and non-menopausal at the age at the time of interview (Table 1). Median age at menopause, that is the age when 50% of women experienced menopause, could be directly estimated by logistic regression when age is the only

variable entered in the model. We also used this model to find the determinants that affect menopausal status of women.

All statistical analyses of this article (including survival analysis, logistic regression, and regression) were conducted using Stata software (Version 12), and p-values less than 0.05 were considered significant.

Results

The general characteristics of the study participants are demonstrated in Table 2. The majority of participants (72.1%) were in postmenopausal period; 18.3% of the participants had not reached menopause yet; and 9.6% had undergone hysterectomy or oophorectomy and therefore never experienced a natural menopause (Table 2).

Estimation of age at menopause and its determinants using survival analysis

Figure 2 depicts the pattern of age at natural menopause and age at hysterectomy using the Kaplan-Meier method in urban and rural areas. The occurrence of menopause was not considerably different between urban and rural areas. The median age at menopause in urban areas, rural areas, and the country were 50.7 (48.2, 53.9), 50.3 (48.0, 53.4), and 50.5 (48.1, 53.7) years, respectively. Notably, hysterectomy was almost twice as common in urban areas as rural areas (Figure 2).

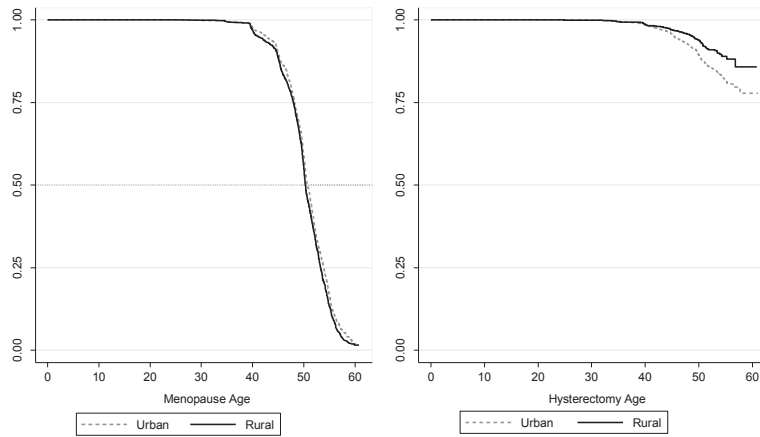


Figure 2. Survival function of age at menopause and age at hysterectomy by region (urban/rural), results of a sample of 4524 Iranian middle-aged women.

The results of Cox proportional model indicated that urban women, higher BMI, and larger family size delay the age at menopause (P value < 0.05). In contrast, current smoking accelerated age at menopause significantly (P value < 0.05). The median age at menopause among smokers was marginally 1.3 years lower than non-smokers. Univariate analysis showed that age at menopause was significantly correlated with the socio-economic variable. However, it was non-significant in multivariate analysis (Table 3). We retained this variable in the multiple model, so that readers can compare it with the results of other studies investigating the effect of socio-economic status on age at menopause. Furthermore, with or without socio-economic status, the coefficients for other variables remain intact.

Estimation of age at menopause and menopause determinants using logistic regression

For logistic regression, we used the same data and predictors as survival analysis except that it was not necessary to exclude 17 cases who had missing values for age at menopause. The menopause occurrence was earlier in the rural compared to

the urban population (Figure 3). The estimated median age at menopause in urban areas, rural areas, and the entire country were 51.4 (51.2–51.6), 50.6 (50.1–50.9), and 51.2 (51.0–51.3) years, respectively.

The percentage of premature menopause, i.e. menopause occurring before 40 years of age,¹⁷ was also determined using logistic regression. On average, 3.2% (2.1–5.0) of the participants had premature menopause, which was more common in rural than urban areas [4.0% (2.5–6.3) vs. 2.7% (1.7–4.3)].

In addition, we explored the association of explanatory variables with menopausal status of women and compared the results with those of survival analysis (Table 3). Area of residence and BMI were statistically significant in both models (P value < 0.05). Smoking and family size were significant determinants in survival analysis, but non-significant in logistic regression.

Two directions of effects regarding the relationship between BMI and menopause could be considered; first, a causal effect of BMI on menopause and second, a reverse causal effect. If the latter proves valid, then as time from menopause goes on, BMI is expected to increase. We tested this hypothesis with a linear

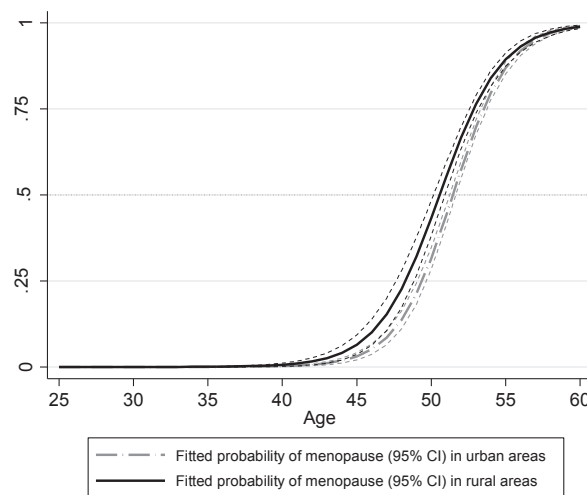


Figure 3. Estimated probability of menopause using logistic regression by region (urban/rural).

regression model, in which time since menopause was considered as the independent variable and BMI as the dependent variable. In this regression, we controlled for the confounding effect of age. The analysis showed no significant relationship between the two variables, which indirectly supported the former assumption, i.e. causal effect of BMI on age of menopause.

Discussion

The values of median age at menopause based on logistic regression and survival analysis were 51.2 and 50.5 years, respectively. This shows that different analysis models produce different estimates. Both methods have advantages and disadvantages. The limitation of the first one is the probability of bias in recalling age at menopause or hysterectomy that may have been reached a long time ago. There is no such limitation for the second method since it only relies on information of patient's current status. Thus, we believe that logistic regression can estimate the median age at menopause more reliably, especially in the middle-aged women.

There are differences between age at menopause reported in this study and in previous studies conducted in Iran. In a cross-sectional study in Yazd province of Iran on 346 women, the mean age at menopause was estimated to be 48 years among postmenopausal women.¹⁸ Similar findings were obtained in another community based study of 1,397 women aged 45–63 years old in northern areas of Iran¹⁹. The reason for this difference is that previous studies usually fall short of the accurate estimations of median age at menopause and overlook premenopausal women in their analysis. A higher age at menopause in this study could be due to both using more sophisticated methodology that decreased the degree of underestimation and also the health improvement of Iranian women in the recent years.

Age at menopause in this study is also significantly higher than the age reported in other studies in developing countries such as Turkey (47 years old), Pakistan (46), and India (48).^{5,6,20} Age at menopause in developed countries is higher than 50 years, for instance 50.0 years in Switzerland, 50.9 in Sweden, 51.0 in Finland, 51.7 in Spain, 52.0 in France, and 52.6 in the United States^{21,22}. A comparison of age at menopause between developing and developed countries indicates a gap ranging 2-3 years. Many studies have emphasized this gap,^{23,24} however, further assessment showed that this gap might be due to analysis methods and shortcomings, not a significant difference.

The results of survival analysis revealed that urban residency, higher BMI, and larger family size delay menopause whereas smoking was significantly associated with earlier menopause. These findings confirm the results of previous studies.^{24–27} Logistic regression only found area of residency and BMI as statistically significant predictors. An explanation for conservative findings of the logistic regression is that it does not have information on the effect of determinants when the age of women is under 50 years. Regardless of being significant or not, the determinants had the same directions in both methods.

Smoking had the largest effect among the determinants; it significantly decreased the age at menopause, by 1.3 years. This is consistent with the recent findings on the effects that smoking has on earlier menopause. Another study reported 1–2 years decrease in age at menopause as a result of smoking²⁸. The effect size for smoking in this research was observed in a sample with relatively

small number of smokers. More reliable effect size can be obtained from case-control studies with a larger number of smokers.

Our findings of direct relationship between menopause and BMI are consistent with results obtained from prior research.²⁹ Further assessment of the effect of BMI showed that the major difference in menopausal age was between the underweight group and other BMI groups. Moreover, our previous results that BMI did not increase after menopause indicated that BMI is a causal determinant of age at menopause.

We found that the median age at menopause in rural areas was lower than urban areas. A study conducted in Iran in 2000 analogously showed that the median age at menopause is 49.9, 49.2, and 49.6 years in urban and rural settings and in the total population, respectively.²⁷ There are several social, economic, and lifestyle differences between urban and rural areas of Iran, therefore adjusting for area of residency makes the odds ratio of house size non-significant in the multivariate analysis. It seems that area of residence could be a suitable proxy for socio-economic status in Iran.

Many studies conducted in this area excluded women who had gone hysterectomy since they were supposedly unable to systematically handle them in the right way. Nevertheless, in this article, we figured out a new strategy in both survival and logistic models that enabled us to include them in the analysis.

We used survival analysis and logistic regression to take advantage of both possible methodologies in this cross-sectional study. The cross-sectional design of the collected data can influence assessment of causal relationships. Many studies conducted in Western countries have used prospective designs with long follow-up duration which preclude the bias due to the high percentage of censored observation and the bias in recalling the exact age of menopause. Thus, accurate assessment of age at menopause, determinants and symptoms can be done using prospective studies with large-sample sizes, which have not been conducted in Iran so far. Moreover, we assessed the effect of smoking exposure using the self-report current smoking status, which could be considered as one of the limitations of this study.

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Conflicts of interest

None of the authors declares any conflict of interest with the study.

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