

# Factors associated with age at natural menopause among elderly women in São Paulo, Brazil

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## Abstract

**Objectives:** To analyze factors associated with age at natural menopause in elderly women who are part of the Health, Well-Being and Aging Study—which is a representative sample of elderly residents of the municipality of São Paulo, Brazil.

**Methods:** Multivariate Cox proportional-hazards analysis using data from a total of 1,415 women with natural menopause. We included 163 women with hysterectomy, oophorectomy, and estrogen therapy as censored data.

**Results:** The median age of natural menopause was 50 years. In the multivariate Cox proportional hazards, smoking was associated with earlier age at natural menopause for the three cohorts (2000, 2006, and 2010). Current smokers had a 35% higher risk of earlier natural menopause (hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.12, 1.62) and former smokers had a 27% higher risk of earlier natural menopause (HR 1.27, 95% CI 1.09, 1.50), in comparison with never-smokers. Women with 8 years or more of formal education had a 33% lower risk of earlier natural menopause (HR 0.67, 95% CI 0.50, 0.89) than women with no education, and women who were separated, widowed, or divorced had a 15% higher risk of earlier natural menopause (HR 1.15, 95% CI 1.00, 1.31) in comparison with married women. Marital status and parity were associated with later age at natural menopause only in 2006.

**Conclusions:** We found significant associations of age at natural menopause with reproductive and lifestyle factors similar to some studies of women from developed countries.

**Key Words:** Aging – Brazil – Menopause.

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The World Health Organization (WHO) defines natural menopause (NM) as the ending of the reproductive life of a woman, frequently occurring when she is between 45 and 55 years old.<sup>1</sup> Several factors have been found to influence the timing of this natural process. Some well-known factors include sociodemographic variables such as income<sup>2</sup> and education<sup>3-6</sup>; reproductive variables such as the use of oral contraceptives,<sup>4,5,7</sup> parity,<sup>8,9</sup> and age at menarche<sup>6</sup>; and variables related to lifestyle such as smoking,<sup>2-6,8</sup> body mass index (BMI)<sup>2,3,8</sup> and physical activity.<sup>2,3,5</sup> Other factors such as race/ethnicity<sup>5</sup> and diet<sup>9</sup> still need more research.

Menopause can take place spontaneously without intervention (NM) or through surgery, such as a bilateral oophorectomy (surgical menopause). Depending on the age of onset,

menopause is frequently categorized as premature (aged 40 or less), early (aged between 40 and 45<sup>10</sup>), and late (aged 55 years or more).<sup>11</sup>

Age at natural and surgical menopause has been previously associated with some long-term adverse health outcomes. Some studies indicate that premature and early natural menopause increase cardiovascular risk,<sup>12,13</sup> whereas late menopause may raise breast cancer risk.<sup>14</sup> Moreover, early surgical menopause is linked to a higher risk of cardiovascular mortality, which is even higher for women who have not undergone hormonal treatment.<sup>15,16</sup>

In Latin America, very few studies analyzed factors associated with age at menopause. Two studies found an association between smoking, education, and parity<sup>17-19</sup> with earlier menopause, whereas a different study showed an association of current employment and parity with later menopause.<sup>20</sup> In Brazil, previous studies found that there is no relation with sociodemographic factors and smoking.<sup>21</sup> Others studies in Brazil and Mexico have shown no association between age at NM and age at menarche.<sup>22,23</sup>

Age at menopause differs across countries, and results in Brazil have previously disagreed with the literature. More studies are needed that include different age cohorts in developing countries, to better understand the factors associated with age at menopause and their associated risk to produce adverse health outcomes. The aim of this study was to determine the factors associated with age at natural

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Received April 2, 2018; revised and accepted June 11, 2018.

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Funding/support: This work was supported by CONICYT (Chilean National Commission for Scientific and Technological Research) “Becas Chile” Doctoral Fellowship program Grant number 72170038; and São Paulo Research Foundation (FAPESP, Grant number 09/53778-3).

Financial disclosure/conflicts of interest: None reported.

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menopause using data from three waves of a representative sample of elderly residents of São Paulo, Brazil.

## METHODS

### Sample

This analysis used data from the three waves (2000, 2006, and 2010) of SABE (Health, Well-being and Aging)—a study that began in 2000, and was coordinated by the Pan American Health Organization (PAHO) and originally involved seven Latin American countries. Its objective was to collect information on health and living conditions among the elderly population (people aged 60 or more).<sup>24</sup> In Brazil, SABE is a longitudinal study carried out in the municipality of São Paulo, coordinated by the University of São Paulo. Details about sample design have been described elsewhere.<sup>25,26</sup> Briefly, in its first wave in 2000, SABE's sample was constructed in two phases. In the first phase, households were selected by two-stage conglomerate sampling. The first stage was probabilistic, and was based on 72 census tracts selected by the Department of Epidemiology of the School of Public Health of the University of São Paulo (USP) using the National Household Sample Survey (PNAD). For the second stage, a minimum number of households visited per sector were calculated. At the end of the first phase, 1,568 older people were interviewed. The second phase consisted of 575 residents aged 75 or more in the districts where the interviews were conducted. This oversampling was introduced to compensate for the high rate of mortality in this age group, and to guarantee the longitudinal design of the study.<sup>27</sup> The final number of individuals interviewed in both phases was 2,143, out of which 1,265 were women. Sample weights were calculated by sex and population aged 60 years or more in the census carried out by the Brazilian Institute of Geography and Statistics (IBGE).

Data from the second wave were collected in 2006. From the 2,143 individuals analyzed in 2000, 1,115 were re-interviewed. The remaining 1,028 individuals included 649 deaths, 178 refusals, 139 not located, 51 changes to other municipalities, and 11 institutionalizations.<sup>28</sup> For this wave, a new cohort of 298 older people between the ages of 60 and 64 was added,<sup>29</sup> including 172 women. The third wave was conducted in 2010, which re-interviewed 748 individuals from the two previous cohorts, and a new cohort of 355 participants, of which 224 were women. Thus, a total of 1,661 women were included for analysis in this study.

### Data collection

Data collection was performed by trained interviewers through questionnaires proposed by the PAHO. These questionnaires were translated and adapted to be used in Brazil, and were reviewed by a specialized technical team.<sup>25,26</sup> The SABE questionnaires were approved by the Research Ethics Committee of the Faculty of Public Health of the University of São Paulo (FSP-USP) and the National Research Ethics Commission (CONEP).

### Variables

The outcome of interest was self-reported age at the last menstruation. Independent variables included education, categorized according to years of study (without formal studies, 1-7, and  $\geq 8$  years); marital status (married, widowed/separated/divorced, and never married); parity (nulliparity [without children], 1 or 2, and  $\geq 3$ ); and smoking history (currently smokes, has smoked but no longer smokes, and never smoked). All models were adjusted by year of birth as a continuous variable.

### Data analysis

We used Cox proportional-hazards models to evaluate factors associated with NM. Age at NM was the timing in the survival model. Women excluded from the total of 1,661 individuals included 201 with missing data on menopause, 36 with missing data in other relevant variables used in this study, 4 that mentioned they were still menstruating, and 5 with age at NM over 60. These exclusions left 1,415 women for the analysis. Of these, 1,252 women had NM and the rest ( $n = 163$ ) were censored at the age of surgery or hormonal treatment such as hysterectomy alone ( $n = 70$ ), hysterectomy with unilateral or bilateral oophorectomy ( $n = 81$ ), and estrogen therapy (ET) ( $n = 12$ ). If the woman had information about age of any surgery and ET, we considered age at surgery as the age censored. The sample weight of the SABE study was applied in all of the statistical analyzes. The assumption of a proportional hazard model was tested in the 2,000 sample, formed by most women of the study (89%), by log-log plot and log-rank for each variable. Median ages were obtained through Kaplan-Meier. Continuous variables were used in tests for trends in the Cox proportional-hazards models. The final Cox model was tested using the Akaike Information Criterion Statistic and adjusted by age and all of the variables. In addition, we performed a pooled hazard ratio (HR) and tested heterogeneity between cohorts by each variable included in the study. We considered a  $P$  value  $< 0.05$  as statistically significant for heterogeneity. The results of the variables that were statistically significant are shown separately by cohort.

## RESULTS

The median age of all women of the study was 67 years, with an age range from 60 to 97 years. The majority of women had NM (90.77%), presented 1 to 7 years of formal education (62.07%), had more than three successful births (59.79%), and never smoked (64.01%) (Table 1). Median age of hysterectomy (46.5 years) and hysterectomy with oophorectomy (47 years) were lower than for those with NM (50 years) and hormonal treatment (50 years). There were differences between the median ages at NM according to levels of education, marital status, parity, and smoking. Women who never married and were smokers (current and past) presented 2 years earlier age at NM in comparison with married women and nonsmokers (48 vs 50 years). Meanwhile, women without schooling and nulliparous presented 1 year earlier age at NM

**TABLE 1.** Baseline characteristics by relative distribution (%) and median ages at natural menopause, SABE study, Municipality of São Paulo, 2000-2006-2010

	Cohort 2000 (n = 1,060)	Cohort 2006 (n = 160)	Cohort 2010 (n = 195)	All women (n = 1,415)	
	%	%	%	%	Median age
Menopause status					
Natural menopause	82.98	99.29	100.00	90.77	50
Histerectomy	7.82	—	—	4.18	46.5
Histerectomy with uni/bilateral oophorectomy	8.42	0.71	—	4.64	47
Hormonal treatment	0.78	—	—	0.41	50
Education, y					
Without studies	19.03	16.26	0.87	13.77	49
1-7	64.96	60.74	57.18	62.07	50
≥8	16.01	23.00	41.95	24.15	50
Marital status					
Married	42.88	61.66	45.9	47.58	50
Separated/widowed/divorced	52.18	34.70	48.96	47.70	50
Never married	4.94	3.64	5.14	4.72	48
Parity					
Nulliparous	10.08	4.83	—	6.39	49
1-2	33.10	28.60	39.53	33.82	50
≥3	56.82	66.57	60.47	59.79	50
Smoking					
Never	71.22	57.26	54.53	64.01	50
Current	10.91	17.01	12.76	12.66	48
Former	17.87	25.74	32.71	23.33	48

<sup>a</sup>Percent according to complex sampling of SABE study according to each cohort.

in relation to women with 1 or more years of schooling and had one or more children (49 vs 50 years).

In the adjusted model for all women of the study (Table 2), smoking and marital status were associated with earlier age at NM. Both current smokers (HR 1.35, 95% CI 1.12, 1.62) and former smokers (HR 1.27, 95% CI 1.09, 1.50) had earlier age at NM than never-smokers. Regarding marital status, women who were separated, widowed, and divorced had earlier age at NM than married women (HR 1.15, 95% CI 1.00, 1.31). On the contrary, education was associated with later age at NM for women with 8 or more years of

schooling compared with those without schooling (HR 0.67, 95% CI 0.50, 0.89). Further, there was a significant linear tendency between years of schooling and age at NM ( $P < 0.001$ ). Almost all the associations were homologous between the cohorts. Never married and had one to two children were heterogeneous between the cohorts (Table 3). Women who never married (HR 0.12, 95% CI 0.03, 0.51), had one to two children (HR 0.15, 95% CI 0.04, 0.56), or more than three children (HR 0.16, 95% CI 0.04, 0.64) presented later age at NM in 2006 versus their references.

**TABLE 2.** Unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for age at natural menopause by baseline characteristics (SABE study, Municipality of São Paulo, 2000-2006-2010)

	Unadjusted		Adjusted <sup>a</sup>		Heterogeneity
	HR	95% CI	HR	95% CI	P
Education					
Without studies	1	Reference	1	Reference	
1-7	0.85	0.70, 1.03	0.82	0.66, 1.02	0.98
≥8	0.74	0.58, 0.95	0.67	0.50, 0.89	0.98
P trend					<0.001
Marital status					
Married	1	Reference	1	Reference	
Separated/widowed/divorced	1.14	1.01, 1.28	1.15	1.00, 1.31	0.84
Never married	1.27	0.94, 1.70	1.16	0.83, 1.62	<0.05
Parity					
Nulliparous	1	Reference	1	Reference	
1-2	0.88	0.70, 1.28	0.88	0.66, 1.17	<0.05
≥3	0.94	0.75, 1.19	0.90	0.69, 1.19	0.06
P trend					0.16
Smoking					
Never	1	Reference	1	Reference	
Current	1.38	1.15, 1.67	1.35	1.12, 1.62	0.10
Former	1.35	1.16, 1.57	1.27	1.09, 1.50	0.56

<sup>a</sup>Adjusted for all the variables in the table and year of birth as continuous variable of the three cohorts.

**TABLE 3.** Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for age at natural menopause by cohort, according to marital status and parity (SABE study, Municipality of São Paulo, 2000-2006-2010)

	Cohort 2000		Cohort 2006		Cohort 2010	
	HR <sup>a</sup>	95% CI	HR <sup>b</sup>	95% CI	HR <sup>c</sup>	95% CI
Marital status						
Married	1	Reference	1	Reference	1	Reference
Separated/widowed/divorced	1.11	0.94, 1.32	1.24	0.88, 1.74	1.11	0.83, 1.48
Never married	1.50	0.92, 2.43	0.12	0.03, 0.51	1.21	0.81, 1.82
Parity						
Nulliparous	1	Reference	1	Reference	—	—
1-2	0.83	0.60, 1.15	0.15	0.04, 0.56	1	Reference
≥3	0.92	0.67, 1.27	0.16	0.04, 0.64	0.86	0.67, 1.09

<sup>a</sup>Adjusted for all the variables in the table and year of birth of cohort 2000.

<sup>b</sup>Adjusted for all the variables in the table and year of birth of cohort 2006.

<sup>c</sup>Adjusted for all the variables in the table and year of birth of cohort 2010.

## DISCUSSION

Previous studies indicate that the median age at NM in developing countries is lower than in developed countries.<sup>2,30,31</sup> In this study, the median age at NM was 50 years, which was similar to Russian women,<sup>4</sup> but lower in studies involving women in the United States (52.5 years),<sup>5</sup> the Czech Republic (51 years),<sup>4</sup> Poland (51.25 years),<sup>32</sup> and Japan (52.1 years).<sup>8</sup> Women who had undergone hysterectomy or hysterectomy with oophorectomy unilateral or bilateral, presented median ages at NM lower than women who did not report any surgery.

In this study, median age in women without formal education was lower than in women who had 1 or more years of studies. This is similar to the results obtained in other studies conducted in Brazil,<sup>22</sup> México,<sup>33</sup> United States,<sup>34</sup> Europe,<sup>4</sup> and China.<sup>35</sup> Additionally, it was found that women with higher education had significantly higher age at NM. This result is also shown by other studies,<sup>3</sup> demonstrating a linear tendency between more years of studies and later age at NM.

The results should be of concern, given that Brazil is a country with very high educational inequalities. Brazilian adults with less education have more chronic diseases,<sup>36</sup> and lifestyle risks such as smoking and sedentary lifestyle.<sup>37</sup> Brazil's Human Development Index (HDI) has remained closely the same since 2015, with women representing one of the most vulnerable groups affected by education inequality.<sup>38</sup> Even if education does not have any direct influence on ovarian function, women with no schooling could share some reproductive and lifestyle risk factors that could affect age at menopause, such as smoking, sedentary and consequently high BMI, unhealthy diet, and chronic diseases.

Several studies have shown that women who never married presented earlier age at natural menopause than women married, separated, widowed, and divorced.<sup>4,5,39</sup> However, women who never married in 2006 had later NM in relation to women who were married. This result cannot be explained by parity, but in our sample, 89% were self-categorized as white women, 66.46% had high schooling (8 years or more), and 47% had 3 and more minimum wage (data not shown), and these characteristics have been associated with later age at NM by others studies.<sup>2</sup>

Consistent with other studies,<sup>6,8,34,35</sup> nulliparous women had lower median age at NM than women who had one or

more successful births. Even though there was a similar tendency of earlier age at NM between women who had one or two in comparison with those who had three children or more, we did not find a linear tendency between parity and later age at NM, probably because we considered women with one and two children together (due to low prevalence among the cohorts), whereas most of the other studies analyzed them separately.<sup>6,35</sup> For the 2006 cohort, women with ≥1 children had decreased risk of earlier age at NM compared with nulliparous women. Among Brazilian women, the age range more common to have a child is between 20 and 24 years. Women of our study crossed this age group between 1960 and 1974, when the fertility rate in Brazil was still high (6.28 and 5.76, respectively).<sup>40</sup> Thus, the majority of women had three children or more. One of the mechanisms that have been proposed by the literature to explain the association between parity and age at NM is the "incessant hypothesis." This refers to incessant ovulation with no resting time as pregnancy leads to a faster loss of oocytes, which, in turn, leads to an early menopause.<sup>41</sup> However, this is controversial due to the fact that the majority of ovarian follicles are eliminated by atresia. Thus, this association must be taken with caution since new in depth studies are needed.

The mechanism by which smoking affects age at menopause remains unclear, but there are some hypotheses that seek to explain it. Some studies indicate that polycyclic hydrocarbons may affect ovarian germ and follicle cells,<sup>42,43</sup> promoting the death of primordial oocytes.<sup>44,45</sup> Other studies suggest that tobacco toxins decrease levels of estrogen from synthesis inhibition and endocrine disruption,<sup>45-47</sup> or increased levels of 2-hydroxyestrogen,<sup>3,45,48,49</sup> producing an anti-estrogen effect that induces early menopause in women who smoked tobacco in relation to nonsmoking women. Several studies support the hypothesis that current smoking<sup>31,43,48,50,51</sup> and also past smokers<sup>6,46</sup> present an increased risk of early NM. In this study, current and former smokers had higher risk of earlier menopause in relation to nonsmokers. Median age at NM was similar for former smokers and current smokers, and both groups had a lower median age at NM compared with never-smokers.

These results are in contrast with other studies where past smokers were more likely to have similar age at NM than

nonsmokers.<sup>32,52</sup> However, our results agree with other studies regarding the association of being a former smoker and early NM,<sup>5,6,46</sup> suggesting that the ovarian damage from tobacco is irreversible.

This study has important limitations. First, some variables associated with age at NM, according to literature, were not included in this study, such as BMI, number of cigarettes, age at menarche, regularity of menstrual cycles, age at maternal menopause, and physical activity. The first reason is that age at menarche, regularity of menstrual cycles, and age at maternal menopause were not included in the SABE survey. Second, BMI had a high frequency of missing values (11.6%) due mainly to the difficulty in measuring the weight of older women from the 2000 cohort. Also, physical activity did not have continuity through the cohorts (the question regarding physical activity in the year 2000 was different than the one from 2006 and 2010). Therefore, both were not included in this study. Additionally, we consider smoking information as incomplete. Number of cigarettes was a question related to current smokers and did not include former smokers, and only 8.5% of women responded years of smoking (data not shown). Moreover, studies demonstrate that there is a dose-response between years of smoking and age at NM.<sup>50,52</sup> Third, this is a retrospective cross-sectional study. Women entered the SABE study postmenopausal. Causality and associations have to be analyzed with caution, because variables such as smoking and marital status may reflect a postmenopause status. Finally, there is a risk of recall bias because all of the variables used in this study were self-reported, and women entered the SABE study only if they were 60 years old or older. Women from the 2000 cohort were older, thus there could be an issue of a greater recall bias. However, the associations were homologous between the cohorts. Nevertheless, 94% of women had 13 or more points in the mini mental abbreviated score, which indicates no cognitive impairment.

Despite these limitations, this study is the first multicohort analysis in Brazil that demonstrates the presence of independent factors consistently associated with age at menopause.

## CONCLUSIONS

We found that education, marital status, and smoking were associated with age at NM, indicating that social and lifestyle determinants could affect age at menopause. Our results support the idea that reproductive factors are not the only ones involved in the complex process of ovarian aging. The results may have implications in the prevention of adverse health outcomes due to the association of earlier menopause with morbidity and mortality.

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