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The Age of Menopause and their Associated Factors: A Cross-Sectional Population-Based Study

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Abstract

Purpose: To characterize the onset of natural menopause and to investigate the associated factors with the age of menarche and natural menopause in a population aged 29-59 yrs in Sao Paulo, Brazil.

Methods: In total, 426 women underwent clinical evaluation and blood collection for biochemical analysis. Participants were classified as being in the premenopausal or natural menopausal stage.

Results: The results showed that the mean age of menarche was 12.7 yrs and that the mean age of menopause was 47.5 yrs. The associated factors with women who began menopause before an average age of 47 yrs were age (OR: 0.85), luteinizing hormone (OR: 0.93) and follicle-stimulating hormone (OR: 1.03). Menopause of <47 yrs was negatively associated with age and luteinizing hormone. Follicle-stimulating hormone levels were associated with an increased risk of menopause before 47 yrs.

Conclusions: The mean ages of menopause and menarche were characterized in this population. Follicle-stimulating hormone level was the unique parameter which increased early, raised the risk to occurrence of early menopause. In this study age of menarche, social-demographic factors, ethnicity and anxiety index were not associated with the age of menopause onset.

Keywords: Menopause; Menarche; Age; Follicle stimulating hormone; Luteinizing hormone

Abbreviations: AHI: Apnoea-Hypopnea Index; BMI: Body Mass Index; DBP: Diastolic Blood Pressure; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; NM: Natural Menopausal Stage; OSAS: Obstructive Sleep Apnoea Syndrome; PRM: Premenopausal Stage; PSG: Polysomnography; SBP: Systolic Blood Pressure; SEM: Standard Error of the Mean

Introduction

In healthy women, there are two important physical, hormonal and cultural events in the natural female reproductive cycle: menarche and menopause. Menarche, which is described as the first menstrual cycle, represents the beginning of female sexual maturation [1].

Menarche affects physical, psychological and sociocultural aspects in women, serving as a transition from childhood to adulthood.

Earlier menarche is associated with a more rapid onset of ovulatory cycles and a tendency to sustain higher levels of certain hormones of the luteal phase, increasing the risk of ovarian cancer [2].

Late menarche might decrease the risk of ovarian cancer, with an estimated 15% reduction in the risk, by decreasing a woman's lifetime number of ovulations [2].

Menopause is characterized by ovarian failure combined with amenorrhea for at least 12 months [3]. This complex biosocial and bio cultural period occurs spontaneously in a woman's midlife and refers to the permanent cessation of menses resulting from the loss of ovarian follicular function [3]. The timing of natural menopause may serve as a marker for the process of reproductive aging, with an earlier age at menopause indicating premature aging [4].

Menopause is relevant to population health, as the occurrence of menopause indicates an increased risk of the onset of certain chronic diseases [5,6]. Earlier menopause may expose a woman to an increased risk of cardiovascular diseases and osteoporosis, whereas later menopause may elevate the risk of endometrial and breast cancers [7,8]. Many studies have shown that variation in the age of menopause is associated with several factors, such as reproductive, demographic, socioeconomic, lifestyle and cultural factors [9,10].

In Brazil, the association between age at menarche and menopause has not been elucidated [11]. Several studies have addressed the mean ages of menarche and menopause in small populations. The mean age of menarche was found to vary from 2-12.6 yrs [12], according to the age of the participants, in a secular trends study conducted in Rio de Janeiro [12].

Other studies found decreases in age at menarche of approximately 2.6, 2.4 and 3.24 months per decade for women born between 1920 and 1979 [13], between 1932 and 1977 [14] and between 2001 and

2010 [15], respectively. This more recent study identified a mean age at menarche of approximately 12 yrs.

For menopause, the mean age also varies, ranging from 48.5 [16] to 51.2 yrs [17] in the Brazilian population. This Brazilian research is in accordance with literature worldwide and reflects a mixed ancestry [18]. Overall the mean age of menarche is 13.5 yrs, and the mean age of menopause is 49.2 yrs [10].

The mean ages at menarche and menopause vary substantially between women across different countries and across different ethnic groups [10]. Indeed, various factors have been associated with early and late menarche and menopause, such as such as socioeconomic conditions [19], general health and lifestyle [20], nutritional status [10,21] and physical activity [22]. Age at menarche seems to be closely related to extrinsic factors, such as living conditions, and especially energy expenditure, and age at menopause appears to be related to intrinsic factors, such as individual reproductive history [10].

In this sense, the current study sought to establish the age of menarche, the onset of natural menopause and to investigate some biological, demographic, social and lifestyle associated factors to age at menopause in a population sample of women.

Materials and Methods

Subjects

The study involved a population-based cross sectional study that included 472 women (20 to 80 yrs old), residing in Sao Paulo city in 2007. This research is part of the Sao Paulo Sleep Epidemiologic Study (EPISONO) [23]. This sample size was established to allow prevalence estimates with 3% precision [24]. A total of 1,101 participants were selected to participate in the study and answered questionnaires at home during the visits.

Of these, 59 refused to undergo a complete full-night polysomnography, leading to a final sample size of 1,042 (refusal rate=5.4%). In the EPISONO survey, a total of 1,042 individuals (among them 574 were women) were randomly selected by three-stage (census-tract, household and individual) cluster sampling. The sample was representative of the general population according to gender, age and socioeconomic status [25].

The study was approved by the Ethics Committee for Research at the Universidade Federal de São Paulo (CEP #0593/06) and registered with ClinicalTrials.gov (NCT00596713).

The method used to recruit participants in this cross-sectional study was similar to the conceptual framework used for the North American National Health Surveys [24]. In the first stage, to assure the representativeness of different levels of wealth, 96 districts (from the 1500 districts in which the city was divided for census purposes) were proportionally selected from the 4 homogenous socioeconomic macro-regions of Sao Paulo. Slums and shantytowns were excluded due to high criminal activity.

Households were selected if they were permanently occupied private homes, so clinics, schools, and other commercial and non-commercial establishments were excluded. In the second stage, the selection of a given household was made by randomly picking the first home and subsequently skipping a specified number, calculated by dividing the total number of homes by a fixed number, to select 11 households in each sector.

Each apartment in a building was considered a home, and counting was carried out from the upper floor to the lower floor. Finally, in the third stage of sampling, all eligible residents of each chosen home were ranged from the youngest to the oldest, and the participant was selected by means of 96 pre-established random tables, which designated the rank number to be chosen for each of the 11 households, from the 96 selected districts.

Based on these results, age (P=0.11), gender (P=0.55), and socio-economic status (P=0.38) distributions did not significantly differ between the participants who accepted PSG recording and those who refused. We concluded that the substitution did not introduce a significant selection bias.

Clinical assessment

A gynecological questionnaire was administered to the female participants [26]. General physical measurements were taken immediately before a polysomnography (PSG) was conducted during the subjects' habitual sleep time.

The morning after the PSG was administered, blood samples were taken following a 12-hour overnight fast to obtain progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and 17β-estradiol measurements using the chemiluminescence Acridinium ester method (ADVIA Centaur®/Siemens Healthcare Diagnostics, Inc., USA).

General physical measurements were taken by 2 trained technical and included systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), body weight (kg), height (m) and calculation of body mass index (BMI) using the formula (weight/height^2).

Gynecological evaluation

Regarding gynecological status, 574 participants included in this study were grouped into the following menopausal status: premenopausal (PRM) or natural menopausal (NM) stage, according to the Stages of Reproductive Aging Workshop [27].

PRM status was defined as an ongoing menstrual cycle and distributed into one of the following categories: follicular phase, anovulatory, periovulatory, in use of hormonal contraceptive, luteal phase. Follicular phase, women in the first 12 days of the menstrual cycle; luteal phase, women in the second half of the menstrual cycle; anovulatory, women experiencing amenorrhea, with FSH and LH concentrations higher than 30 mIU/ml; periovulatory, near the 14th day of the menstrual cycle, with an LH concentration of approximately 50 mIU/ml; and hormonal contraceptive use. In our study, we excluded 76 individuals with missing data in the PRM group. Thus, the PRM group consisted of 289 individuals.

Perimenopausal women (women in menopausal transition) were defined as those who had irregular menstrual cycles in the last year, FSH and LH concentrations more than 30 mIU/ml and a 17β-estradiol concentration greater than 30 pg/ml [28]. This group was excluded from the sample in this study, since this group has transitional characteristics of premenopause to postmenopause.

The postmenopausal group was defined as those who had either experienced amenorrhea for more than 1 year or who had FSH and LH concentrations higher than 30 mIU/ml. In this group, women were excluded due to menopause: history of hysterectomy and/or oophorectomy (surgical menopause). Finally, we excluded participants

with missing data for the menopause variable. Thus, the menopause group consisted of 137 individuals.

Therefore, the exclusion criteria of this study were participants with missing values for the following variables: surgical menopause (n=27), perimenopause (n=15), undetermined stage (n=10), as well as missing data regarding number of children (n=55), FSH (n=20), age of menopause (n=9), LH (n=5), systolic blood pressure (n=4) and age of menarche (n=3) (Figure 1).

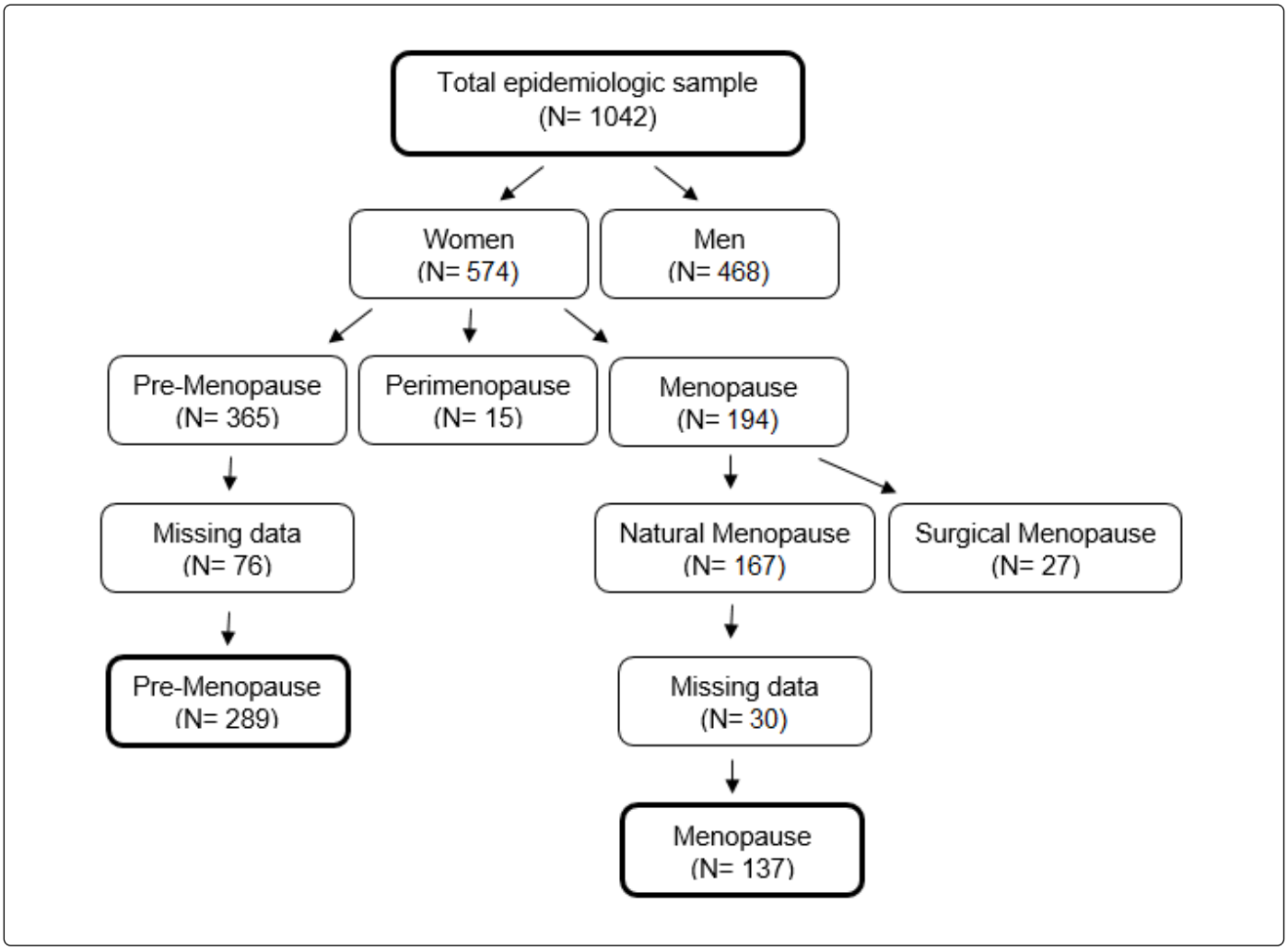

Figure 1: Flow sheet regarding the criteria for selecting patients for the study.

In this epidemiological study, women's health-related parameters were evaluated. The past life variables investigated included the number of pregnancies, the number of children, age at menarche and age at menopause, determined using a questionnaire [26,29].

Socio-demographic variables

Individuals self-reported their ethnic origin according to the following classifications used by the Brazilian Institute of Geography and Statistics: Caucasian, Afro-Brazilian and other/unknown. Social class was defined as high, middle or low according to the Brazilian Economic Classification Criteria (www.abep.org), with an annual household income greater than US $15,961, between US $4,561 and US $15,960 and lower than US $4,560, respectively.

Marital status was defined based on the presence of a partner. The group without a partner consisted of single, divorced and widowed women. The group with a partner was composed of married women and women in a stable relationship.

Physical activity, depression and anxiety index

The assessment of physical activity was based on the self-reporting of each individual. Responses were categorized as follows: those who reported no regular physical activity, women who practiced physical exercise one to two times per week and those who practiced physical exercise more than 3 times per week.

The Brazilian version of the Beck Depression Inventory was used to measure the magnitude of depression symptoms [30]. The questionnaire contains 21 items, with responses rated on a Likert scale ranging from 0-63 points (0-11: minimal depression; 12-19: mild depression; 20-35: moderate depression; and 36-63: severe depression). Values higher than 19 indicate the presence of depressive symptoms, based on validation performed by Cunha and colleagues (2001) [31].

The Brazilian version of Beck Anxiety Inventory was used to assess anxiety levels [32]. The questionnaire also consists of 21 statements,

with responses rated on a Likert scale from 0-63 points (0-10: minimal anxiety; 11-19: mild anxiety; 20-30: moderate anxiety; and 31-63: severe anxiety). Women were characterized as having anxiety symptoms when classified as having moderate or severe anxiety, based on previous validation [31].

Statistical analysis

All data that did not meet the assumptions of normality and homogeneity were Z-score transformed for suitable parametric evaluation. The statistical analysis for description of the sample group was performed using a general linear model. Chi-square tests were performed to determine the association between the variables. Binary logistic regression was used to reveal the predictors of natural menopause using the backward Wald method.

The dependent variable was a binary distribution of the mean age of menopause. Menopause started >47 yrs older were considered as reference for the inferential analysis. The cut point for the age of menopause was defined by the mean age of menopause at this population. The continuous variables independent chosen for the logistic regression were age, BMI, LH, FSH, estradiol, menarche and the numbers of pregnancies and children. Dichotomous independent variables were: ethnicity, social class and marital status. The significance level was set at 5%. The data are reported as the mean and standard error of the mean (SEM). All analyses were performed using SPSS 20 (SPSS Inc.).

Results

In total, 457 women from the EPISONO sample were analyzed in the current study, and 36.76% were classified as women in the postmenopausal period. Figure 2 depicts the frequency distribution of the sample by quinquennium and identify the PRM or natural menopause groups. Women aged 35-39 yrs and diagnosed with menopause were identified, whereas and no women over 60 yrs were in the PRM group (Figure 2).

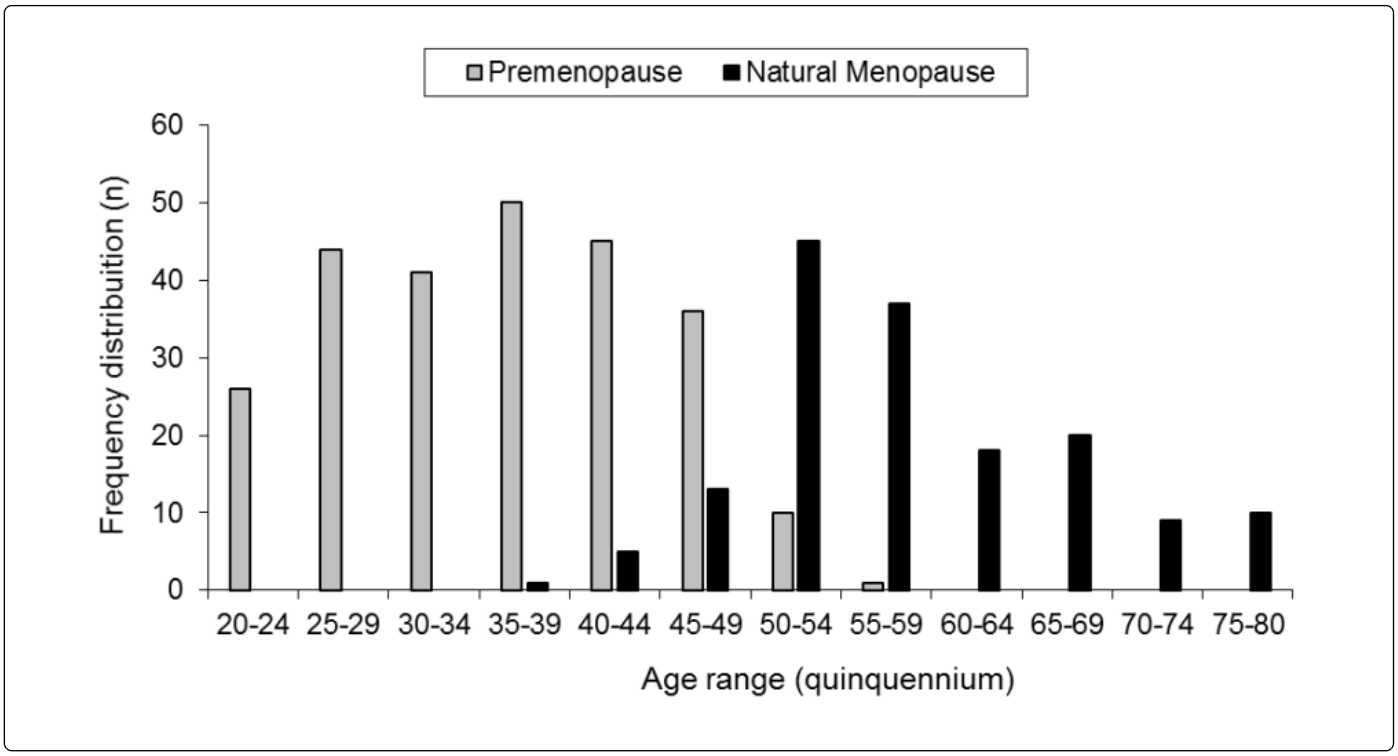

Figure 2: Distribution frequency of the women's reproductive cycle according to age in Sao Paulo (n=426).

Table 1 presents a comparative characterization of the PRM and menopausal groups and the results for the sample group. The results indicate differences on age (p<0.001), BMI (p<0.001), pregnancy (p<0.001) and children (p<0.001). Biochemical analysis of the following hormones also showed significant differences between the groups: FSH (p<0.001), LH (p<0.001) and estradiol (p<0.001). However, there were no significant differences in the reported age at menarche between the groups (p>0.05) (Table 1).

Variables	Total (n=426)	Pre-menopause (n=289)	Natural Menopause (n=137)	p value
Age (y)	43.3 ± 0.7	35.9 ± 0.5	58.9 ± 0.8*	<0.001
BMI (kg/m^2)	27.2 ± 0.3	26.4 ± 0.3	29.0 ± 0.4*	<0.001
Menarche (y)	12.7 ± 0.1	12.7 ± 0.1	12.9 ± 0.1	0.12

Pregnancy (N)	2.3 ± 0.1	2.0 ± 0.1	3.1 ± 0.2*	<0.001
Children (N)	1.9 ± 0.1	1.6 ± 0.1	2.4 ± 0.2*	<0.001
FSH (mUI/ml)	22.8 ± 1.4	6.9 ± 0.6	56.2 ± 2.3*	<0.001
LH (mUI/ml)	9.3 ± 0.8	34.8 ± 1.5	17.5 ± 0.9*	<0.001
Estradiol (pg/ml)	73.6 ± 4.2	97.8 ± 5.6	22.5 ± 2.0*	<0.001
Anxiety Beck	12.0% (51)	13.5% (39)	8.8% (12)	0.16
Depression Beck	11.5% (49)	12.1% (35)	10.2% (14)	0.568
Hypertension	47.4% (202)	35.6% (103)	72.3% (99)*	<0.001
Ethnicity (%/N)				0.448
Caucasian	56.1% (239)	55.0% (159)	58.4% (80)	
Afro-Brazilian	27.2% (116)	29.1% (84)	23.4% (32)	
Other/Unknown	16.7% (71)	15.9% (46)	18.2% (25)	
Social Class (%/N)				0.268
High-income	46.9% (200)	44.3% (128)	52.6% (72)	
Middle-income	43.4% (185)	45.3% (131)	39.4% (54)	
Low-income	9.6% (41)	10.4% (30)	8.0% (11)	
Marital status (%/N)				0.107
Single	35.4% (151)	32.9% (95)	40.9% (56)	
With partner	64.6% (275)	67.1% (194)	59.1% (81)	
Physical activity				0.001
No activity	70.9% (302)	75.1% (217)	62.0% (85)	
1-2 time/week	6.6% (28)	3.5% (10)	13.1% (18)*	
≥ 3 time/week	22.5% (96)	21.5% (62)	24.8% (34)	

Table 1: Descriptive parameters in the sample of women from Sao Paulo according to the women's reproductive life cycle (n=426). BMI=Body mass index, FSH=Follicle-stimulating hormone, LH=Luteinizing hormone. [*significant differences compared to the pre-menopause group].

The details of the frequency distribution presented in Table 1 show that the women did not have different levels of anxiety symptoms ($p>0.05$) or symptoms of depression ($p>0.05$). It is noteworthy that marital status did not vary between the groups evaluated ($p>0.05$). The parameters ethnicity ($p>0.05$) and social class ($p>0.05$) did not differ between the groups. Hypertension ($p<0.001$) and physical activity ($p<0.001$) was significant.

Table 2 describes the mean ages of both menarche and menopause in the sample according to ethnicity and the number of children. The mean ages at menopause among the ethnic groups analysed in the study were not different ($p>0.05$).

A tendency trend of a difference between groups was observed, indicating that Caucasians had a mean value higher than that of other groups. The mean value for age at menopause was higher in women who had no children compared with those who had more than 4 children (Table 2).

Variables	Age (yrs + SEM)	p value
Menopause		
Mean	47.5 ± 0.5	-
Ethnicity		0.098

Caucasian	48.4 ± 0.6	
Afro-Brazilian	46.1 ± 1.2	
Other/Unknown	46.0 ± 1.4	
Children		0.421
0	45.4 ± 2.3	
01-Mar	47.5 ± 0.6	
≥ 4	48.2 ± 1.2	
Menarche*		
Mean	12.9 ± 0.2	-
Ethnicity		0.638
Caucasian	12.7 ± 0.2	
Afro-Brazilian	13.2 ± 0.4	
Other/Unknown	13.2 ± 0.4	

Table 2: Mean ages of menopause and menarche onset according to ethnicity and parity in Sao Paulo (n=137). SEM (standard error of the mean) *Related results only for women in natural menopause.

However, there was greater variability in the group that had no children, and the results did not achieve the desired level of significance (p>0.05). The average age at menarche was associated with ethnicity. The Caucasian group had average values for the age of menarche below 13 yrs, although the results were not significantly different from those of other ethnic groups (p>0.05).

Table 3 details the effects in the menopausal groups (earlier menopause at age 47 *vs.* those who had menopause at 47 yrs or old).

The results were segmented into two blocks: gynaecological and socio-demographic variables (Table 3).

Variables		**<47 yrs (n=47)**	**≥ 47 yrs (n=90)**	**p value**
Gynecological variables	Menopause Age (y)	40.4 ± 0.7*	51.1 ± 0.3	<0.001
	Menarche (y)	13.0 ± 0.3	12.9 ± 0.2	0.872
	Body mass index (kg/m^2)	29.1 ± 0.8	28.9 ± 0.6	0.847
	FSH (mUI/ml)	55.6 ± 4.6	56.6 ± 2.6	0.845
	LH (mUI/ml)	33.1 ± 2.6	35.7 ± 1.9	0.412
	Estradiol (pg/ml)	28.0 ± 4.0*	19.6 ± 2.2	0.048
	Pregnancy (N)	2.6 ± 0.3	3.3 ± 0.2	0.073
Socio-demographic Variables	Ethnicity % (N)			0.075
	Caucasian	46.9% (22)	64.4% (58)	
	Afro-Brazilian	34.0% (16)	17.8% (16)	
	Other/Unknown	19.1% (9)	17.8% (16)	
	Social Class % (N)		0.539	
	High-income	55.4% (26)	51.1% (46)	
	Middle-income	34.0% (16)	42.2% (38)	
	Low-income	10.6% (5)	6.7% (6)	

	Marital Status % (N)		0.657	
	Single	38.3% (18)	42.2% (38)	
	With partner	61.7% (29)	57.8% (52)	
	Children (N)	2.0 ± 0.2*	2.6 ± 0.2	0.045

Table 3: Description of the sample according to the average age of natural menopause onset in Sao Paulo (n=137).

Here, we assess the effect of age at menopause on the socio-demographic variables. No significant differences were found between the frequency categories of the variables ethnicity (p>0.05), social class (p>0.05) and marital status (p>0.05). An effect of the number of children in women who had menopause <47 yrs compared with the other group was identified (p<0.05).

The aim was to identify the associated factors with earlier menopause. Among the gynecological variables that were assessed were age at menopause (p<0.001), age at menarche (p>0.05), BMI (p>0.05), FSH (p>0.05), LH (p>0.05), estradiol (p<0.05) and pregnancy (p>0.05) It was observed that the values of menopausal age were significantly lower in the group <47 yrs compared with the group ≥ 47 yrs (p<0.001). It was also observed that estradiol levels in women with early menopause were significantly higher compared with levels in the group with menopause ≥ 47 yrs (p<0.05). Other gynaecological variables did not reach the level of statistical significance

Logistic regression was performed to identify associated factors with menopause before 47 yrs because there are important clinical implications for women with early menopause. The adjusted model showed the most favorable Hosmer-Lemeshow goodness-of-fit (p>0.05) for the development of menopause (Nagelkerke R^2=0.35) (Table 4).

Variables	Crude Odds Ratio			Adjusted Odds Ratio		
	cOR value	CI 95%	p value	aOR value	CI 95%	p value
Age	0.89	0.84-0.94	<0.001	0.85	0.80-0.91	<0.001
LH	0.99	0.97-1.01	0.41	0.93	0.89-0.98	0.002
FSH	0.99	0.99-1.01	0.844	1.03	1.00-1.05	0.032
Body mass index	1.01	0.94-1.08	0.846	-	-	-
Estradiol	1.01	1.00-1.03	0.058	-	-	-
Menarche	1.02	0.85-1.22	0.871	-	-	-
Pregnancy	0.84	0.69-1.02	0.076	-	-	-
Children	0.76	0.58-0.99	0.043	-	-	-
Ethnicity						
Caucasian	REF			-	-	-
Afro-Brazilian	2.64	1.13-6.16	0.025	-	-	-
Other/Unknown	1.48	0.57-3.85	0.418	-	-	-
Social Class						
High	REF			-	-	-
Middle	0.75	0.35-1.59	0.446	-	-	-
Low	1.47	0.41-5.31	0.552	-	-	-
Marital Status						
Single	REF					
With partner	1.18	0.57-2.42	0.657	-	-	-

Table 4: Results of the logistic regression for factors associated with natural menopause before 47 yrs of age in Sao Paulo (n=137).

The analysis confirmed good model fit by an Omnibus test of Model Coefficients (P<0.001). The significant associated factors were age (aOR: 0.85; IC 95%: 0.80-0.91; p<0.001), LH (aOR: 0.93; IC 95%: 0.89-0.98; p=0.002) and FSH (aOR: 1.03; IC 95%: 1.00-1.05; p=0.032). Increases in age and LH levels represented a lower risk of developing menopause before 47 yrs old. An increase in FSH promoted a higher risk (3%) of menopause before 47 yrs.

Discussion

The present study describes the average age of natural menopause in a sample of women from Sao Paulo, Brazil. The results showed that women in Sao Paulo experienced natural menopause at approximately 47 yrs old. The age at menopause observed in our study is corroborated by previous studies [33,34].

Overall, the age at menopause worldwide is approximately 50 yrs [35]. In the literature, several studies have shown differences in the average age of natural menopause. In general, these ages are different according to the country, such as 45 yrs in Thailand [36], 46 yrs in South Africa [37], 48 yrs in Ghana [38] and 51 yrs in the USA [39].

However, even within the same country, differences in age at menopause can be observed between cities; Pedro and colleagues (2003) 17 reported the mean age to be 51 among women in Campinas, Brazil. In fact, there is no consensus about the average age of onset of natural menopause and about the factors related to the differences in age. Several factors have been reported to hasten or delay the onset of menopause. Certain factors are potentially associated with menopause, such as menarche, parity, socioeconomic status [40], obesity [41,42] and ethnicity [43,44].

Socioeconomic status is one of the important factors reported to be associated with menopausal age in the literature. Socioeconomic status is associated with various implications for life and, consequently, women's health, as are education, parity and nutrition. In general, low-income women have more children. Nulliparity is associated with early menopause, and multiparity is related to late menopause [39]. Indeed, we also observed that the parity exerted an effect on age at menopause. We did not find a statistically significant effect because the average age at menopause in nulliparous women was lower than in multiparous women.

We observed average ages of menopause of 45.4 yrs for nulliparous women, 47.5 for those who gave birth to 3 children and 48.2 for those who had more than 4 children, demonstrating a possible relationship between parity and age at menopause. The main hypothesis about this phenomenon is related to hormones, and especially estrogen. Despite an increase in estrogen levels during pregnancy, a high progesterone concentration in this phase can antagonize several estrogenic effects. Postpartum and during lactation, there is a significant decrease in estrogen levels. Multiparous women are less exposed to the action of estrogen and, for this reason, have lower rates of loss of oocytes and of occurrence of ovulatory cycles, thus delaying the onset of menopause.

Another factor that may also be related to socioeconomic status and menopause is nutritional status. An association has been observed between obesity and menopause [45]. The relationship between obesity and menopause is due to the high level of endogenous estrogen in fatty tissues [46]. This high level of estrogen can induce major stimulation of follicular growth, with a rapid decline in the number of follicles and consequent induction of early menopause. The reduction in ovarian function reduces the metabolism and the concentration of lean mass, decreases energy use and stimulates fat accumulation in adipose tissue [47].

It is emphasized that adipose tissue, beyond being an endocrine organ, is also the site of sex steroid metabolism and the synthesis of leptin [48]. High concentrations of leptin may also interfere with the production of follicular estradiol (E2) and consequently affect the maturation of preovulatory follicles [49]. Still, a high leptin level may influence steroidogenesis in granulosa cells through augmentation of FSH-stimulated E2 production [49].

Thus, this factor could influence the age of onset of menopause. Despite that hypothesis, a recent study shows no variation in age at menopause by ethnicity after controlling for relevant variables [50]. Although BMI is a factor possibly associated with menopausal age, we found no association between BMI and age at natural menopause in our sample. This lack of association may have been due to a limitation of our study, as this is a cross-sectional study in which the participants reported their age at the onset of menopause and in which current BMI data were included, but not BMI data previous to the period of menopause onset.

Menarche is another factor possibly associated with age at menopause. Certain studies have shown a correlation between age at menarche (<14 yrs) and the onset of early menopause [8,40]. In our study, we observed that the average age of menarche was 12 yrs. However, we found no significant direct association between age at menarche and age at menopause.

It has also been reported that ethnicity may have an effect on age at natural menopause. It has been observed that African-American women experience menopause two yrs earlier than do Caucasian women [43,44]. Interestingly, these women have earlier menarche than do Caucasian women, thus demonstrating a possible relationship between ethnicity, menarche and menopause. These differences in age at menopause according to ethnicity may be due to differences in the composition of body fat and in hormonal variation between races. One study showed an increase in FSH concentrations among Chinese- and Japanese-American women compared with Caucasian women [51]. In addition, that study showed a reduction in the estrone conjugate level (E1c) in Chinese, Japanese and African-American women compared with Caucasian and Hispanic women. Serum hormone concentrations are directly related to the menstrual cycle; follicular maturation; and, consequently, the age of menopause.

The present study evaluated the relationship of ethnicity with menopause and observed certain differences in the age of onset of menopause according to race. Whereas Caucasian women had an age at menopause of 48.4 yrs, Afro-Brazilian women and women of other races (Asian and Indian) had a mean age of 46 yrs for the onset of menopause. Thus, our findings corroborate the results of other studies [43,44] who showed that African-American women experience menopause approximately 2 yrs before Caucasian women. Regarding the relationship of the age of menarche with the age of menopause according to ethnicity, we did not observe a relationship. Although Caucasian women have a lower age at menarche in relation to other ethnic groups, these women did not show earlier menopause compared with other races.

Certain studies have shown that separated, divorced and widowed women experience menopause earlier compared with women who are married or in stable relationship [19,44,52,53]. In our study, we found no association between marital status and age at menopause onset. However, a higher percentage of women without a partner were

present in the group of postmenopausal women compared with the group of PRM women.

The age of menopause in a population is essential information about both an individual and public health. A cohort study showed that women who had menopause before 40 yrs of age had a 95% increased risk of mortality compared with women who experienced menopause at over 50 yrs of age [54]. The risk of mortality was also observed to increase in women who had an age at menopause of 40-49 yrs, who showed an increase in risk of 35% [54].

In our study, there was no statistically significant association between ethnicity, social class, marital status, pregnancy, children, BMI or menarche and age at natural menopause. Another factor beyond those previously analyzed that may be responsible for these results found in this sample of women from Sao Paulo. Recently we identified, in this sample, that the diagnosis of menopause and waist circumference were among the main factors associated with OSAS [55].

This is the first study to evaluate the mean ages of menopause and menarche in Sao Paulo city. The study involved a 3-stage cluster sample that was proportionally representative of the general population according to gender, age (20-80 yrs) and socioeconomic status. However, limitations included the small sample size, a lack of design for the aim, the fact that half of the sample was composed of men and a lack of information about the use of tobacco. As a cross-sectional study, there may also have been bias associated with the self-reported age of onset of menopause and previous history of menopause. Anxiety and depression indexes and information on physical activity were obtained via a survey. We aimed to find the association between these variables and the age of menopause onset (in data that were collected prospectively).

Apart from its limitations, this study contributes information on the age of menopause among women from Sao Paulo, Brazil. Menopause is a normal transition in a woman's reproductive life that involves many negative features. For this reason, know the age of menopause is important to the life and health of women. It is important to identify when to begin medical care for the prevention and treatment of related symptoms in this new phase of life and to identify the associated factors with this event.

Conclusions

This epidemiological study presents descriptive data that characterize the ages of menarche and menopause in the female population of the city of Sao Paulo, Brazil. It was observed that the mean and SEM of age at menarche was 12.7 ± 0.1 and of age at menopause was 47.5 ± 0.5 yrs. The study also aimed to identify associated factors with the diagnosis of earlier menopause.

Levels of LH and age have been considered to be "protectors" because a linear increase in these parameters decreases the likelihood of early menopause. This suggests that these factors are not strongly associated with the diagnosis of menopause. The main finding indicates that only factor positively associated with the diagnosis of menopause is increase of the FSH levels, which is directly related to the characterization of the menopausal stage. In this study age of menarche, social demographic factors, ethnicity and anxiety index were not associated with the age of menopause onset.

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Authors' Contributions

DNP, HH and MLA were responsible for the study concept. HH, LRB, MLA and ST performed the experiments. ACB, CH, DNP and KTN analysed the data. ACB, CH, DNP, HH, KTN and MLA drafted the manuscript. All authors critically reviewed content and approved the final version for publication.

References

1. Beausang CC, Razor AG (2000) Young western women's experiences of menarche and menstruation. Health Care Women Int 21: 517-528.
2. Gong TT, Wu QJ, Vogtmann E, Lin B, Wang YL (2013) Age at menarche and risk of ovarian cancer: a meta-analysis of epidemiological studies. Int J Cancer 132: 2894-2900.
3. WHO. Research on the Menopause. WHO technical report series 670. Geneva1981.
4. Nilsson P, Moller L, Köster A, Hollnagel H (1997) Social and biological predictors of early menopause: a model for premature aging. J Intern Med 242: 299-305.
5. Sowers MR, La Pietra MT (1995) Menopause: its epidemiology and potential association with chronic diseases. Epidemiol Rev 17: 287-302.
6. Jacobsen BK, Heuch I, Kvåle G (2004) Age at natural menopause and stroke mortality: cohort study with 3561 stroke deaths during 37-year follow-up. Stroke 35: 1548-1551.
7. Mondul AM, Rodriguez C, Jacobs EJ, Calle EE (2005) Age at natural menopause and cause-specific mortality. Am J Epidemiol 162: 1089-1097.
8. Kaczmarek M (2007) The timing of natural menopause in Poland and associated factors. Maturitas 57: 139-153.
9. Morabia A, Costanza MC (1998) International variability in ages at menarche, first livebirth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Am J Epidemiol 148: 1195-1205.
10. Thomas F, Renaud F, Benefice E, de Meeus T, Guegan JF (2001) International variability of ages at menarche and menopause: patterns and main determinants. Hum Biol 73: 271-290.
11. Otero UB, Chor D, Carvalho MS, Faerstein E, Lopes CES, et al. (2010) Lack of association between age at menarche and age at menopause: Pró-Saúde Study, Rio de Janeiro, Brazil. Maturitas 67: 245-250.
12. Lago MJ, Faerstein E, Sichieri R, Lopes CS, Werneck GL (2007) Relation between age at menarche and final height of women in the Pró-Saúde Study. Rev Assoc Med Bras 53: 20-24.
13. Kac G, Coel ASC, Melendez GV (2000) Secular trend in age at menarche for women born between 1920 and 1979 in Rio de Janeiro, Brazil. Ann Hum Biol 27: 423-428.
14. Lago JM, Faerstein E, Lopes CSD, Werneck GL, Pró-Saúde (2003) Rio de Janeiro Ba. Family socio-economic background modified secular trends in age at menarche: evidence from the Pró-Saúde Study. Ann Hum Biol 30: 347-352.
15. Castilho SD, Pinheiro CD, Bento CA, Filho AEA, Cocetti M (2012) Secular trends in age at menarche in relation to body mass index. Arq Bras Endocrinol Metabol 56: 195-200.
16. Aldrighi JM, Alecrin IN, Oliveira PR, Shinomata HO (2005) Smoking and earlier menopause. Rev Assoc Med Bras 51: 51-53.

17. Pedro AO, Neto AMP, Paiva LH, Osis MJ, Hardy E (2003) Age at natural menopause among Brazilian women: results from a population-based survey. Cad Saude Publica 19: 17-25.
18. Guindalini C, Colugnati FA, Pellegrino R, Santos-Silva R, Bittencourt LR, et al. (2010) Influence of genetic ancestry on the risk of obstructive sleep apnoea syndrome. Eur Respir J 36: 834-841.
19. Luoto R, Kaprio J, Uutela A (1994) Age at natural menopause and sociodemographic status in Finland. Am J Epidemiol 139: 64-76.
20. Parazzini F, Negri E, Vecchia CL (1992) Reproductive and general lifestyle determinants of age at menopause. Maturitas 15: 141-149.
21. Simondon KB, Simon I, Simondon F (1997) Nutritional status and age at menarche of Senegalese adolescents. Ann Hum Biol 24: 521-532.
22. Baker ER (1985) Body weight and the initiation of puberty. Clin Obstet Gynecol 28: 573-579.
23. Tufik S, Silva SR, Taddei JA, Bittencourt LR (2010) Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med 11: 441-446.
24. Korn EL, Graubard BI (1999) Analyses of health surveys. New York: John Wiley & Sons Inc.
25. Silva RS, Tufik S, Conway SG, Taddei JA, Bittencourt LR (2009) Sao Paulo Epidemiologic Sleep Study: rationale, design, sampling, and procedures. Sleep Med 10: 679-685.
26. Hachul H, Andersen ML, Bittencourt LR, Silva RS, Conway SG, et al. (2010) Does the reproductive cycle influence sleep patterns in women with sleep complaints? Climacteric13: 594-603.
27. Soules MR, Sherman S, Parrott E (2001) Stages of Reproductive Aging Workshop (STRAW). J Womens Health Gend Based Med 10: 843-848.
28. Hachul H, Andersen ML, Bittencourt L, Silva RS, Tufik S (2013) A population-based survey on the influence of the menstrual cycle and the use of hormonal contraceptives on sleep patterns in São Paulo, Brazil. Int J Gynaecol Obstet 120: 137-140.
29. Cramer DW, Xu H (1996) Predicting age at menopause. Maturitas 23: 319-326.
30. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4: 561-571.
31. Cunha JA (2001) Manual da versão em português das escalas Beck. São Paulo: Casa do Psicólogo.
32. Beck AT, Epstein N, Brown G, Steer RA (1988) An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 56: 893-897.
33. Luzardo MF PG (1970) Climaterio y menopausia. Rev Col Obstet Ginecol.
34. Gonzales GF, Villena A (1996) Body mass index and age at menarche in Peruvian children living at high altitude and at sea level. Hum Biol 68: 265-275.
35. Cramer DW, Xu H, Harlow BL (1995) Family history as a predictor of early menopause. Fertil Steril 64: 740-745.
36. Boulet MJ, Oddens BJ, Lehert P, Vemer HM, Visser A (1994) Climacteric and menopause in seven South-east Asian countries. Maturitas 19: 157-176.
37. Benjamin F (1960) The age of the menarche and of the menopause in white South African women and certain factors influencing these times. S Afr Med J 34: 316-320.
38. Kwawukume EY, Ghosh TS, Wilson JB (1993) Menopausal age of Ghanaian women. Int J Gynaecol Obstet 40: 151-155.
39. Kato I, Toniolo P, Akhmedkhanov A, Koenig KL, Shore R, et al. (1998) Prospective study of factors influencing the onset of natural menopause. J Clin Epidemiol 51: 1271-1276.
40. Li L, Wu J, Pu D (2012) Factors associated with the age of natural menopause and menopausal symptoms in Chinese women. Maturitas 73: 354-360.
41. Akahoshi M, Soda M, Nakashima E (2002) The effects of body mass index on age at menopause. Int J Obes Relat Metab Disord 26: 961-968.
42. Willett W, Stampfer MJ, Bain C (1983) Cigarette smoking, relative weight, and menopause. Am J Epidemiol 117: 651-658.
43. Frere G (1971) Mean age at menopause and menarche in South Africa. S Afr J Med Sci 36: 21-24.
44. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, et al. (1997) Prospective study of the determinants of age at menopause. Am J Epidemiol 145: 124-133.
45. Sherman BM, Wallace RB, Bean JA, Chang Y, Schlabaugh L (1981) The relationship of menopausal hot flushes to medical and reproductive experience. J Gerontol 36: 306-309.
46. Speroff L GR, Kase NC (1989) Clinical Gynecologic Endocrinology and Infertility. Baltimore: Williams & Wilkins.
47. Poehlman ET (2005) Transversing the menopause: change in energy expenditure and body composition. Coron Artery Dis 16: 511.
48. Meier U, Gressner AM (2004) Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. Clin Chem 50: 1511-1525.
49. Agarwal SK, Vogel K, Weitsman SR, Magoffin DA (1999) Leptin antagonizes the insulin-like growth factor-I augmentation of steroidogenesis in granulosa and theca cells of the human ovary. J Clin Endocrinol Metab 84: 1072-1076.
50. Gold EB, Crawford SL, Avis NE (2013) Factors related to age at natural menopause: longitudinal analyses from SWAN. Am J Epidemiol 178: 70-83.
51. Santoro N, Crawford SL, Lasley WL (2008) Factors related to declining luteal function in women during the menopausal transition. J Clin Endocrinol Metab 93: 1711-1721.
52. Stanford JL, Hartge P, Brinton LA, Hoover RN, Brookmeyer R (1987) Factors influencing the age at natural menopause. J Chronic Dis 40: 995-1002.
53. Gold EB, Bromberger J, Crawford S (2001) Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 153: 865-874.
54. Snowdon DA, Kane RL, Beeson WL (1989) Is early natural menopause a biologic marker of health and aging? Am J Public Health 79: 709-714.
55. Polesel DN, Hirotsu C, Nozoe KT (2015) Waist circumference and post menopause stages as the main associated factors for sleep apnea in women: a cross-sectional population-based study. Menopause 22: 835-844.