Association between socioeconomic position in earlier and later life and age at natural menopause: Estudo Pró-Saúde, Brazil

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This study was based on a prospective cohort of university staff in Rio de Janeiro, Brazil (the Estudo Pró-Saúde). In this article the association between socioeconomic position (SEP) earlier and later in life and age at menopause is investigated. The main indicators investigated were for earlier SEP: mother's and father's schooling; stature; leg and trunk length. For later SEP they were: schooling; home and/or car ownership. Median age at menopause was estimated and survival curves were generated by the Kaplan–Meier method, while the association between indicators of SEP and age at menopause was explored by means of Cox semiparametric models. Associations were found between earlier SEP – represented by trunk length – and earlier menopause and between later SEP – represented by the indicator 'present schooling' – and earlier menopause. The association between earlier and later SEP was confirmed. Adverse situations over the life course can impact age at menopause and related health outcomes.

Menopause is an important marker for cessation of reproductive capacity in women [1]. It occurs, on average, at 50 years of age [2], and may vary from country to country. In North America and Europe, it ranges from 48 to 52 years of age [3]. Early menopause, alternatively defined as occurring before the ages of 49 or 50 years [4], is associated with increased risk of osteoporosis [5] and cardiovascular disease [6] and, by contrast, with reduced risk of breast cancer [7] and endometrial cancer [8].

Ovarian follicles decline in number from birth through to perimenopause, when the rate accelerates. When a critical number of follicles is reached, menopause occurs [9]. Various factors are associated with early or late menopause. Tobacco use has been systematically and reliably related to early menopause [10,11]. Factors contributing to late menopause include the use of oral contraceptives [12], the woman's age at first childbirth [13] and irregular menstrual cycles [14]. There are no consistent results for other characteristics, such as schooling [15,16], BMI [17,18], age at menarche [16,19], short menstrual cycles [16,20], nulliparity [14] and race/color [21].

A number of studies suggest that adverse socioeconomic circumstances over the course of life, particularly in childhood, contribute to early menopause [22,23], but not all support that finding [11,24]. Leg length and trunk length measurements are considered important markers of childhood socioeconomic position (SEP) [25]. This is because conditions such as early weaning, precarious diet in childhood and childhood infections affect child growth, shortening these body segments [22,26–28]. In a woman's reproductive life, adverse conditions in the early periods of their life can influence the rate at which ovarian follicles decline [29], and there is evidence that shorter leg and trunk measurements in adult life are associated with early menopause [22].

Other studies consider the hypothesis that the number of oocytes may begin to decline earlier, during intrauterine life, given that formation of ovarian follicles peaks during fetal development. It is thus possible that the retardation of intrauterine growth associated with adverse conditions during pregnancy may cause a reduction in the number of ovarian follicles, resulting in early menopause [22,26].

Adverse socioeconomic circumstances occurring later in life may also be associated with early menopause [11,22,30]; various different markers of SEP suggest this association, such as occupation (earlier menopause among blue collar than white collar workers) and schooling (earlier menopause among those with less formal education) [31].

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Earlier and later life SEP tend to be correlated and, more importantly, might have a cumulative effect over a person's life course [22]. Few studies have investigated how earlier and later life SEP affects age at menopause [29]. Accordingly, the aim of this study is to investigate these relationships in a cohort of working women in Rio de Janeiro, Brazil.

Methods
Population
This research is based on a prospective study of technical and administrative staff at a university in Rio de Janeiro State, Brazil – the Estudo Pró-Saúde [32]. Baseline data were collected in 1999–2001 and the first follow-up occurred in 2006–2007. The data used for this article were collected at the baseline (1999), except for the anthropometric measurements, which were taken at first follow-up (2006–2007). All the 4428 technical administrative personnel at the university were invited to take part in the study. In the first stage, 4030 individuals (91% of the eligible population) participated; 2238 of them were women. In this article we excluded women aged ≤35 years (680 women) or those who had entered menopause in this age bracket (53 women), because of the strong likelihood that menopause may have occurred as a result of disease [33]. Women whose age at natural menopause, surgery or initiation of hormone therapy was not reported (n = 13) and those who were unable to report date of menarche (n = 30) were also excluded from the study population, which totaled 1462 women.

Measurements
Participants responded to a self-completed multidimensional questionnaire, applied at their workplace with the assistance of a previously trained team. Menstrual status was evaluated in the questionnaire by the follow filter question "Do you still menstruate?" (yes or no). It was followed by a question about time since last menstruation for those who answered "yes" to the previous one.

Information on age at menopause was obtained by the question: "At what age did you stop menstruating?" (less than 6 months ago; between 6 months and 1 year ago; more than 12 months ago).

A test–retest reliability study performed on a sample of university temporary workers from the same university, (n = 192) showed intraclass correlation coefficient for age at menopause of 0.97 (95% CI: 0.96–0.98).

For this study 11 independent variables were selected as indicators of earlier life SEP:

• Father's schooling (higher – completed university; other – did not complete fundamental, middle and higher education);

• Mother's schooling (higher – completed university; other – did not complete fundamental, middle and higher education);

• Height (cm);

• Leg length (short: ≤72 cm; medium: from 73 to 76 cm; and long: ≥77 cm);

• Trunk length (short: ≤82 cm; medium: from 83 to 86 cm; and long: ≥87 cm);

• Annual weight gain from age 20 years:

$$\frac{\textit{Weight taken at first collection} - \textit{reported weight at age 20 years}}{\textit{Age at first collection} - 20 \textit{ years}}$$

• Economic circumstances at age 12 years, obtained by the question: "How would you classify your family's economic situation when you were 12 years old; that is, your family's standard of living at that time?" (wealthy/moderate, poor/very poor);

• Age on starting work (years);

• Went without eating at age 12 years, obtained by the question: "When you were 12 years old, were there times at home when you went without eating for lack of money?" (yes or no);

• Place of residence at age 12 years (urban or rural);

• Color/race.

The trunk length measurement corresponded to sitting height (from seat surface to the crown of the head), calculated with the individuals sitting upright on a level bench, on a fixed base, with the head in the Frankfort position, feet on the floor and arms hanging loose. The leg length measurement was obtained by the difference between the individual's standing and sitting heights [34]. Five variables were selected as indicators of later life SEP:

• Woman's schooling (middle/higher; fundamental or less);

• Owning a house and/or car;

• Per capita income (classified by terciles as low/medium or high):

$$\frac{\textit{Family income}}{\textit{Number of people living in the same house}}$$

- Hours worked weekly;

- Standard of living during adolescence, obtained by asking: "Compared with the standard of living you have now, what was your family's standard of living like when you were 12 years old?" (better than it is now, the same, worse than it is now).

Other covariables included were:

- Tobacco use (smoker; never smoked/ex-smoker);

- Parity (childless, one or more children);

- BMI at age 20 years (using reported weight at age 20 years and height measured at the first collection) and current BMI;

- Marital status (married, separated/divorced/widowed, single).

Natural menopause has been defined by the WHO as: "The permanent cessation of menstruation resulting from the loss of ovarian follicular activity, recognized retrospectively after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause" [2]. In our study, menopause status was classified as 'natural' in participants who reported spontaneous cessation of menstruation more than 12 months earlier, and excluded those whose menstruation was interrupted due to surgery, hormone therapy or any other non-natural cause (e.g., pregnancy, radiation). The WHO defines perimenopause as the period immediately prior to, and the first year after, menopause [2]. In this study, women who reported having ceased menstruating less than 6 months, or from 6 months to 1 year, before the time the data were collected were considered to be in perimenopause.

Statistical analysis

Survival analysis – both nonparametric Kaplan–Meier estimations and Cox proportional hazards regression – were the main statistical tools utilized. The time to event was the reported age of menopause. Descriptive analysis was performed for all the variables and the median was estimated by survival analysis, whose curves were estimated by the Kaplan–Meier method, using the logrank test to evaluate differences between strata of the variables selected [35].

The effect of indicators for earlier and later life SEP on age at natural menopause was estimated using Cox's semiparametric (hazard ratios [HRs]) model [35]. Participants in either of the following situations at the interview date were

censored: still menstruating (n = 1044), or in perimenopause (n = 73). Women who reported surgical menopause from removal of ovaries with or without uterus were censored at the age they underwent surgery (n = 140).

Considering that socioeconomic variables tend to be highly correlated, a careful approach was adopted to the multivariate analysis. In order to discuss effects of earlier and later life SEP on time to menopause, two multivariate models were fitted. Beginning with trunk length, the main indicator of earlier life SEP, all other socioeconomic variables were evaluated one by one, and were kept in the model (only when affecting the association parameter of the main variable by 10% or more). The same approach was applied when analyzing schooling, a marker of later life SEP. Parity and smoking were included in both models. Schoenfeld and Martingale residuals were evaluated, and model fit was considered adequate. The analyses were performed using R version 2.7.2. software (Free Software Foundation, Inc., Boston, MA, USA).

Results

Natural menopause, the event of interest, occurred in 205 women. The median age for natural menopause was 52 years. The differences in behavior of the categories of the main variables – schooling and trunk length – can be observed from the Kaplan–Meier curves (Figure 1): less schooling (p = 0.075) and shorter trunk length (p = 0.006) are associated with early menopause.

In the univariate analysis (Table 1), women with short trunks (≤82 cm) show a 54% higher risk of early menopause (HR = 1.54; 95% CI: 1.03–2.33) than those with longer trunks. There was no significant association between leg length and age at menopause. The participant's father and mother having less schooling showed an association with early menopause, but this was not statistically significant.

For women with later life SEP (Table 2), the median age at menopause was 2 years earlier for women with less schooling, with the risk of early onset 46% higher than for women with a college education (HR = 1.46; 95% CI: 1.10–1.94). Possessions also showed an association with age at menopause. Participants who owned neither car nor home showed a 33% higher risk of early menopause (HR = 1.33; 95% CI: 0.97–1.82) than those who owned both. Nulliparas and smokers were also observed to enter menopause at an earlier age than women with children and those who had never smoked or had stopped smoking.
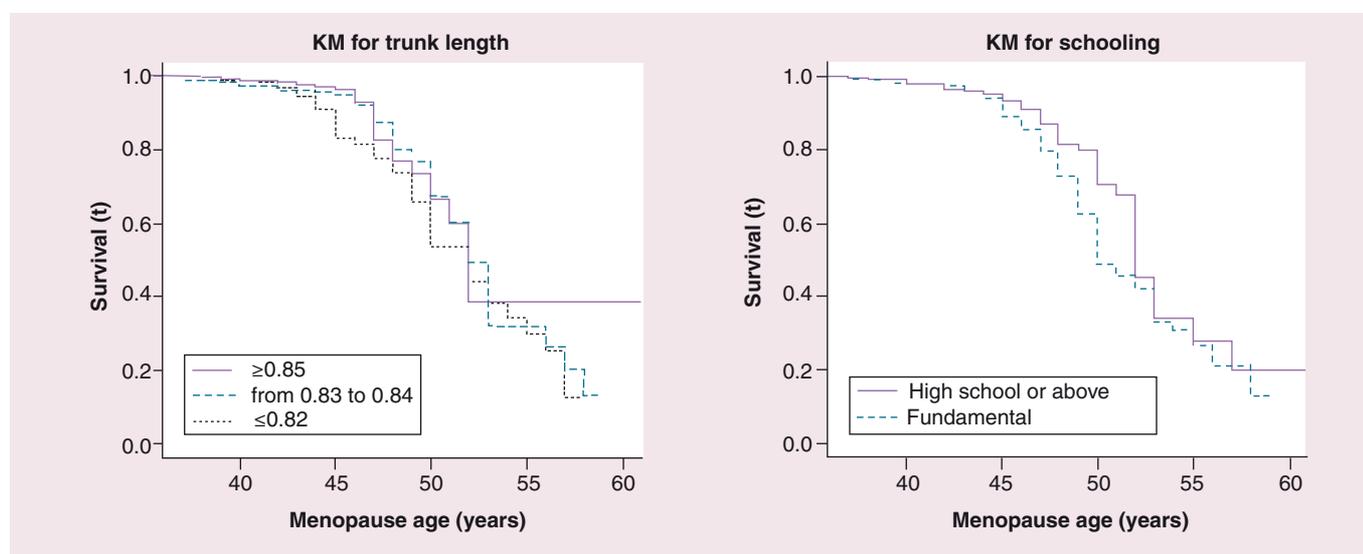
Figure 1. Survival curves for menopause age, according to indicators of earlier and later socioeconomic position.
KM: Kaplan–Meier.

Trunk length (earlier life SEP) and schooling (later life SEP) were the variables that showed statistical significance (although borderline in the case of schooling) after adjustment for the covariables (Table 3). The variables of father's schooling and home and/or car ownership were not retained in the final model, because the risk measurement did not vary. With each 1 cm increase in trunk length, the risk of early menopause diminished by 7% (HR = 0.93; 95% CI: 0.88–0.98). With regard to schooling, in the unadjusted model, a 46% higher risk of early menopause was observed in women with only fundamental schooling compared with those with college education. After adjustment for trunk length, parity and tobacco use, the magnitude of the association diminished to 35% (HR = 1.35; 95% CI: 0.94–1.96).

According to the residual analysis and linear correlation test, the indicators for earlier and later life SEP (Table 3, model 3 for trunk length and model 3 for schooling) proved proportional over time and showed no systematic pattern, indicating a good fit with the final models.

Discussion

In the study population, indicators of worse earlier life SEP (represented by trunk length) and later life SEP (represented by schooling) showed an association with early menopause. Women with shorter trunks showed a 7% higher risk of early menopause than those with longer trunks, while women with less schooling had a 35% higher risk of early menopause.

These results corroborate most of the studies that suggest, on the basis of various different indicators of SEP, an association between earlier and later life SEP and age at menopause. Vélez et al. reported that women with the least schooling showed a 17% higher risk of early menopause than women with high school education or more [36]. In a study by Hardy and Kuh, women classified in the most disadvantaged social class during childhood showed a 13% higher risk of early menopause than those in the least disadvantaged social class [37]. Lawlor et al. reported a cumulative effect of socioeconomic disadvantage over the course of a woman's life, so that the higher the score from ten indicators of SEP (indicating a worse position), the earlier the age at menopause [22].

Only two studies reported a lack of association between SEP and age at menopause [11,24]. The Brazilian study by Pedro et al. [24], in addition to finding no association between age at menopause and SEP-related risk factors (e.g., schooling, income) that have traditionally been studied, found no association for tobacco use and parity (which are practically a consensus in the literature today).

Accordingly, thought must be given to possible limitations, such as the type of statistical analysis used in the study and most others that take no account of 'time', which can be done using survival analysis. In a study by Hardy et al., the results are inconsistent depending on what indicators of SEP are used [11]. In other articles, the same authors, using the same study population (National Survey of Health and Development [NSHD]), found an association between adverse SEP and early menopause [29,37].

The present study found an association between trunk length and age at menopause, but not between leg length and age at menopause. This result can be compared only with a few studies in which age at menopause was investigated as the outcome. Lawlor *et al.* reported an association between shorter legs and trunks and early menopause based on a British cohort study (British Women's Heart and Health Study) [22].

The results of research into other outcomes confirm the direction of the association found with age at menopause. Adverse circumstances in early life (indicated by shorter leg length) lead to a higher risk of chronic diseases, such as resistance to insulin and coronary disease [22,38–40].

According to Li *et al.* [34] and Webb *et al.* [25], leg length is a more sensitive marker for

Table 1. Univariate regression of Cox hazard ratios for age at natural menopause and median age at menopause by characteristics of earlier socioeconomic position.

Selected characteristics	Descriptive statistics		Kaplan–Meier		Cox
	n	Natural menopause	Median	p-value[†]	HR[‡] (95% CI)
Father's schooling					
Higher	145	8	§	0.134	1
Other (middle/fundamental/no schooling)	1191	175	52		1.69 (0.83–3.44)
Mother's schooling					
Higher	58	2	50	0.487	1
Other (middle/fundamental/no schooling)	1346	183	52		1.59 (0.39–6.44)
Leg length (cm)					
Long: ≥73	566	63	52		1
Medium: from 71 to 72	324	38	52	0.639	1.03 (0.69–1.54)
Short: ≤70	294	46	52		1.19 (0.81–1.74)
Trunk length (cm)					
Long: ≥85	592	23	52		1
Medium: from 83 to 84	358	63	52	0.075	1.16 (0.75–1.77)
Short: ≤82	234	61	52		1.54 (1.03–2.33)
Economic situation at age 12 years					
Wealthy/moderate	657	87	52	0.785	1
Poor/very poor	797	116	52		0.96 (0.73–1.27)
Went without eating at age 12 years					
Yes	255	39	52	0.816	1
No	1201	165	52		1.04 (0.74–1.48)
Place of residence at age 12 years					
Urban	1140	129	52	0.298	1
Rural	297	71	52		1.16 (0.86–1.55)
Race/color					
Nonwhite	734	106	52	0.498	1
White	713	97	52		1.10 (0.83–1.45)
Other characteristics					
Stature (cm)	1184	147	–	–	0.96 (0.94–0.99)
Weight gain/year from 20 years of age	1374	185	–	–	0.77 (0.54–1.09)
Age started working (years)	1449	202	–	–	1.12 (0.84–1.47)

[†]*Logrank test.*
[‡]*Risk of natural menopause occurring earlier.*
[§]*Not available.*
HR: Hazard ratio.

Table 2. Univariate regression of Cox hazard ratios for age at natural menopause by indicators of later socioeconomic position, reproductive health and health-related behavior.

Selected characteristics	Descriptive statistics		Kaplan–Meier		Cox
	n	Natural menopause	Median	p-value†	HR‡ (95% CI)
Present schooling					
Middle/higher	1067	93	52	0.006	1
Fundamental or less	375	106	50		1.46 (1.10–1.94)
Home and/or car owner					
Car and/or home	590	55	52	0.066	1
Not car/home owner	881	135	52		1.33 (0.97–1.82)
Per capita income					
High	828	94	52	0.401	1
Medium/low	531	92	52		1.14 (0.85–1.52)
Current standard of living					
Worse than before	197	41	52		1
Same	330	46	52	0.492	0.79 (0.52–1.20)
Better than before	927	116	52		0.84 (0.59–1.21)
Tobacco use					
Never smoked or gave up	1013	140	52	0.008	1
Smoker	355	49	51		1.56 (1.12–2.17)
Parity					
Has children (≥1)	1096	157	52	0.001	1
Childless	270	37	50		1.88 (1.30–2.70)
Marital status					
Married	238	31	55		1
Separated	737	79	52	0.647	0.88 (0.58–1.33)
Single	416	81	52		1.00 (0.66–1.52)
Other characteristics					
Hours worked weekly	1403	196	–	–	1.01 (1.0–1.02)
BMI at 20 years of age (kg/m²)	1128	135	–	–	0.99 (0.97–1.01)
BMI at present (kg/m²)	1438	200	–	–	0.99 (0.97–1.02)

†Logrank test.
‡Risk of natural menopause occurring earlier.
HR: Hazard ratio.

malnutrition and for adverse circumstances in early childhood (<5 years old) [25,34], at which stage these segments grow faster than the trunk [27]. Trunk length, meanwhile, is affected more in the prepubertal period [27,39] by events such as parents' divorce and severe disease [27,28]. Parents' divorce before 15 years of age can act as a marker of early emotional stress and is related to precarious psychological health in adulthood [41]. The impact of stress in childhood and in adult life includes hypothalamic–pituitary–adrenal axis responsiveness, and can influence age at menopause [5,42].

It is possible that segments of Brazil's population with a life history of extreme poverty (deficient diet and deficient growth in infancy) are not represented in our study, which could explain the weak and insignificant association between leg length and age at menopause.

Other indicators of earlier life SEP have been evaluated in various studies. In relation to the occupation of parents, Hardy and Kuh reported that in women whose parents were 'manual' workers, menopause occurred at a younger age than those whose parents were from other social classes [37]. In the present study population, no

statistically significant association was identified between age at menopause and any other indicator of earlier life SEP, except trunk length. Substantial magnitudes of risk were observed in relation to father's schooling (HR = 1.69; 95% CI: 0.83–3.44) and mother's schooling (HR = 1.59; 95% CI: 0.39–6.44). The lack of statistical significance may result from the small number of events (natural menopause) in women whose parents (father) received a college education (n = 8).

With regard to indicators of later life SEP, the median age at menopause was 2 years earlier (50 years) in women with the least schooling than in those with college education (52 years). In the multivariate models, risk of early menopause for participants with the least schooling was attenuated from 46 to 35%, with borderline significance. This result is consistent with those of some other studies [14,15,22,36], but not with all of them [11,24,30,43].

One of the limitations of this study is the small number of women who reported natural menopause occurring more than 12 months earlier (n = 205), since the Pró-Saúde Study population consists of working age – and thus relatively young – women. Thus, the lack of statistical significance in some associations (e.g., father's and mother's schooling) may be altered in future analyses of this cohort as the participants age. In addition, although the information on age at menopause was found to be highly reliable, the validity of the retrospective collection of these data may be lower. It should also be remembered that all the participants in the study work at a public university

where socioeconomic disparities may not be very evident, unlike in the overall population. This factor may have interfered with the ability to identify significant associations between most of the characteristics examined and age at menopause.

Results of studies such as this one reinforce the argument that distal variables should be better researched in epidemiological studies, not just as covariables, but also as key variables. Adverse circumstances over the course of a life, such as malnutrition, childhood deprivation, parents' divorce and infections, can impact future health, and their role in menopause age as well as other aspects of reproductive health is still insufficiently understood [1,26,29].

Conclusion & future perspective

In this article an association was found between earlier life SEP (represented by trunk length) and later life SEP (represented by schooling) and age at menopause. Few studies have investigated specifically how indicators of earlier and later life SEP associate with age at menopause. The results of Hardy et al. [11], for example, diverge from those of two later two studies by the same authors using different indicators. The later studies examined exposure to breastfeeding in childhood [29] and to social class, occupation and parents' divorce [37]. A longitudinal study of 1583 British women (NSHD) highlighted the importance of factors such as parents' divorce, weight at age 2 years and mother's age at menopause [44]. Systematic reviews underline the importance of a reproductive health approach over a woman's life course and the contribution

Models	HR[†] (95% CI)
Table 3. Multivariate regression of Cox hazard ratios for age at natural menopause by indicators of earlier and later socioeconomic position.	
Indicator of SEP in childhood	
Crude model: trunk length[‡]	0.94 (0.89–0.98)
Model 1: trunk length + schooling	0.95 (0.91–0.99)
Model 2: model 1 + parity	0.93 (0.89–0.98)
Model 3: model 2 + smoking	0.93 (0.88–0.98)
Indicator of SEP in adulthood	
Crude model: schooling	1.46 (1.10–1.94)
Model 1: schooling + trunk length	1.35 (0.96–1.90)
Model 2: model 1 + parity	1.38 (0.97–1.96)
Model 3: model 2 + smoking	1.35 (0.94–1.96)

[†]*Risk of natural menopause occurring earlier.*
[‡]*Result of univariate regression using trunk length as continuous variable.*
HR: Hazard ratio; SEP: Socioeconomic position.

of early life factors to age at menopause, particularly precarious socioeconomic conditions, deficient childhood growth, not having been breastfed and parents' divorce [26]. Lawlor *et al.* studied 3513 women participants in the British Women's Heart and Health Study and showed that "adverse SEP in childhood, as well as in adulthood, are associated with an earlier age at menopause" [22].

Accordingly, in view of the lack of research directly to investigating the contribution of distal variables as key factors affecting age at menopause, further studies of population groups from different sociocultural contexts are necessary. Linear growth factors (leg and trunk lengths and stature) have already been acknowledged in the literature as markers of adverse situations in childhood and associated with chronic diseases, and should be explored in greater depth. Given its importance, the mechanism connecting schooling with age at menopause requires better clarification. The mechanisms that explain the association between early and late SEP and age at menopause should be better studied and understood to ensure that prevention measures can be taken in specific groups.

Executive summary

Reasons for studying indicators of earlier & later socioeconomic position & age at menopause
- Age at menopause is related to adverse health outcomes.
- Socioeconomic position has not been widely studied, especially in Latin America, as a determinant of age at menopause.
- Studies suggest that adverse situations in a woman's life course are associated with early or later age at natural menopause, with health consequences.

Age at menopause
- An associated indicator of earlier socioeconomic position is trunk length.
- An associated indicator of later socioeconomic position is schooling.

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- of interest
- of considerable interest

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