Universidade de São Paulo
Faculdade de Saúde Pública

**Idade da menopausa em mulheres idosas do Município
de São Paulo: fatores associados e análise de sobrevida**

Alejandra Andrea Román Lay

Tese apresentada ao Programa de Pós-
Graduação em Saúde Pública para a
obtenção do título de Doutor em Ciências.

Área de concentração: Epidemiologia.

Orientador: Prof. Dr. Alexandre Dias
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Roman A. Idade da menopausa em mulheres idosas do Município de São Paulo: fatores associados e análise de sobrevivência [tese]. São Paulo: Faculdade de Saúde Pública da Universidade de São Paulo; 2018.

Resumo

Introdução: O crescimento do número de idosos no Brasil tem aumentado o interesse em identificar os determinantes da sua sobrevivência e da incidência de doenças crônicas. A menopausa é definida como a cessação permanente da menstruação e está associada à diminuição da secreção de estrógenos por perda da função folicular, marcando o fim da fase reprodutiva na vida feminina. A idade da menopausa tem sido associada em alguns estudos internacionais com a mortalidade e algumas causas de morbidade, mas faltam estudos sobre o tema no Brasil. Esta tese será apresentada por meio de 3 artigos. O primeiro analisou os fatores associados à idade da menopausa natural em mulheres do estudo SABE (Saúde, Bem-estar e Envelhecimento). O tabagismo e a escolaridade estiveram estatisticamente associados com uma menopausa mais cedo nas três coortes analisadas: 2000, 2006 e 2010. Mulheres fumantes atuais tiveram 35% maior risco de ter menopausa precoce (HR=1.35, 95% CI: 1.12, 1.62) e as ex-fumantes 27% maior risco (HR=1.27, 95% CI: 1.09, 1.50), em comparação com as mulheres que nunca fumaram. Em relação à escolaridade, as mulheres com 8 anos ou mais de estudos tiveram 33% menor risco de menopausa precoce (HR=0.67, 95% CI: 0.50, 0.89) comparadas às mulheres sem escolaridade. Estado civil e número de filhos estiveram associados a uma menopausa mais tardia na coorte 2006. No segundo artigo, foi realizada uma análise de sobrevivência segundo a idade da menopausa natural das mulheres pertencentes à coorte 2000. Foram identificados 444 óbitos de mulheres até 2016. Mulheres com menopausa precoce tiveram 48% de maior risco de mortalidade geral (HR=1.48, 95% IC: 1.03, 2.14) comparadas às mulheres com idade de menopausa entre os 50 e 54 anos (referência). Em relação à mortalidade específica, mulheres entre 41 e 49 anos apresentaram o dobro de risco de mortalidade por neoplasias em comparação com o grupo de referência. No terceiro artigo, foi realizada uma revisão sistemática e meta-análise dos fatores reprodutivos associados à menopausa natural. Os três fatores estudados apresentaram uma associação com a menopausa tardia. As mulheres com uso de anticoncepcionais orais em relação às aquelas que não relataram uso de anticoncepcionais orais (HR=0.86, CI=0.79, 0.92), as com idade da menarca ≥ 13 anos comparadas às aquelas com idade da menarca < 13 anos (HR=0.88, CI=0.84, 0.93) e aquelas que relataram ter um filho ou mais comparadas com as que não tiveram filhos (HR=0.80, CI=0.76, 0.85).

Palavras-chaves: Menopausa, análise de sobrevivência, idosos, estudo SABE, anticoncepcionais orais, menarca, número de filhos, meta-análise.

Roman A. Age at menopause among elderly women in the São Paulo Municipality: Associated factors and survival analysis [thesis]. São Paulo: School of Public Health, University of São Paulo; 2018.

Abstract

Introduction: The increase of the elderly population in Brazil has raised concerns about their care and the determinants of survival and incidence of chronic diseases. Menopause is defined as the permanent end of a woman's menstruation and is associated with the decline of the release of estrogens due to loss of follicular function, indicating the end of the reproductive phase of a woman's life. Age at menopause has been linked with mortality and morbidity in international studies. The first article of this thesis analyzed the factors associated with age at natural menopause among women of the SABE study cohort (Health, Well-Being, Aging). Smoking and education were associated with earlier menopause for the three waves analyzed: 2000, 2006 and 2010. Current smokers had 35% higher risk of earlier natural menopause (HR=1.35, 95% CI: 1.12, 1.62) and former smokers had 27% higher risk of earlier natural menopause (HR=1.27, 95% CI: 1.09, 1.50), in comparison with never smokers. Regarding education, women with 8 years or more of formal education had 33% lower risk of earlier natural menopause (HR=0.67, 95% CI: 0.50, 0.89) than women with no education. Marital status and parity were associated with later age at natural menopause only in 2006. In the second article, a survival analysis was performed according to age at natural menopause in women from SABE 2000. We found a total of 444 deaths from 2000 to 2016. Women with earlier menopause had 48% increased risk of all-cause mortality (HR=1.48, 95% IC: 1.03, 2.14) compared to women with age at menopause between 50 and 54 years (reference group). Regarding cause-specific mortality, women with ages at natural menopause between 41 and 49 had twice the risk of cancer mortality compared to the reference group. In the third article, we performed a systematic review and meta-analysis of the reproductive factors associated with natural menopause. The three factors analyzed were statistically associated with later menopause: women with use of oral contraceptives before menopause compared to women with no use of oral contraceptive (HR=0.86, CI=0.79, 0.92), women with age at menarche ≥ 13 compared to women with age at menarche < 13 years (HR=0.88, CI=0.84, 0.93) and those with one or more live births compared to nulliparous women (HR=0.80, CI=0.76, 0.85).

Keywords: Menopause, survival analysis, elderly, SABE study, oral contraceptives, menarche, parity, meta-analysis.

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1 INTRODUÇÃO

1.1 TRANSIÇÃO DEMOGRÁFICA: O ENVELHECIMENTO

Devido à rápida transição demográfica, o mundo está envelhecendo progressivamente. Em 2017, o número de pessoas com 60 anos ou mais era de 962 milhões e as estimativas internacionais apontam que o número mais do que dobrará até 2050 para 2,1 bilhões de pessoas (UN, 2017). Essa aceleração na proporção da população será maior nos países em desenvolvimento. Estima-se que, em 2050, 80% dos idosos do mundo viverão em países em desenvolvimento (SHETTY, 2012).

A transição demográfica produz uma modificação na estrutura etária da população, levando a uma inversão na pirâmide populacional. A pirâmide populacional do Brasil que era larga para as crianças passa a ter maior quantidade de pessoas idosas no vértice. O processo de envelhecimento é contínuo, originado uma pirâmide populacional em forma de barril (ALVES, 2014). Segundo estimativas do Instituto Brasileiro de Geografia e Estatística (IBGE), em 2017 o grupo etário de crianças de 0 a 4 anos era de 14,3 milhões, já em 2060 serão apenas 8,9 milhões de crianças. Em relação aos idosos, em 2017 corresponderam a 12,5% da população total do Brasil, enquanto estimativas apontam que em 2060 corresponderão a 33,7% da população total (IBGE, 2013).

No Brasil existe uma tendência de redução do crescimento populacional. Em 2017, o país tinha 207,6 milhões de pessoas, terá 223,1 milhões em 2030 e 218,17 milhões em 2060 (IBGE, 2013). Segundo estimativas da Organização das Nações Unidas (ONU), o crescimento demográfico vai seguir desacelerando até 2050 (UN, 2004). Entre os fatores responsáveis por essa transição demográfica estão as quedas nas taxas de mortalidade infantil e de fecundidade, a melhoria da qualidade vida e o diagnóstico e tratamento precoce das doenças crônicas, o que trará como consequência um aumento na expectativa de vida.

No Brasil, a maior diminuição da mortalidade aconteceu entre 1980 e 1991, sendo mais importante entre os menores de 1 ano (IBGE, 2010). A taxa de mortalidade infantil diminuiu 90,9% de 1940 até 2016. O forte declínio na taxa se deve principalmente a medidas preventivas como vacinação em massa, aumento do acesso à atenção pré-natal, entre outros avanços de saúde pública (IBGE, 2017).

A taxa de fecundidade vem decrescendo em quase todos os países do mundo. Entre 2010 e 2015 esteve abaixo do nível de substituição em 83 países incluindo o Brasil, correspondendo a 46% da população mundial (UN, 2004). No Brasil, a taxa de fecundidade vem decrescendo progressivamente desde a década de 1970 e é considerado o principal fator responsável pela diminuição da velocidade do crescimento populacional. Em 2000, o número médio de filhos por mulher era de 2,39 filhos, enquanto que em 2030 será de 1,51 filho e estima-se que se manterá por volta de 1,50 filho até 2060 (IBGE, 2013). Entretanto, existem importantes diferenças entre grupos populacionais. Mulheres brancas tendem a ter uma maior proporção de nenhum filho (41,6%) em comparação com mulheres pretas ou pardas (35,9%). Em relação à escolaridade, mulheres com até 7 anos de estudo apresentam uma menor proporção de nenhum filho (22,1%) em relação às mulheres com 8 anos ou mais de estudo (43,5%) (IBGE, 2016).

A expectativa de vida no Brasil em 2017 foi de 76 anos e sua previsão nos próximos anos é que continue a aumentar, chegando aos 81,2 anos em 2060. Espera-se que esse aumento da expectativa de vida será maior em mulheres (84 anos) que para os homens (78 anos) (IBGE, 2013).

1.2 TRANSIÇÃO EPIDEMIOLÓGICA: DOENÇAS INFECCIOSAS PARA DOENÇAS CRÔNICAS

No Brasil, a forte queda na taxa de mortalidade está relacionada com o início da transição epidemiológica. A proporção de causas de óbito por doenças infecciosas tem diminuído consistentemente, aumentando a importância de causas de óbito relacionadas ao envelhecimento da população, como câncer e doenças cardíacas (IBGE, 2017). Como consequência dessa transição, as doenças crônicas não transmissíveis (DCNT) se tornaram as principais causas de morbidade, incapacidade e mortalidade de pessoas idosas, a um custo crescente para os indivíduos, as famílias e o Estado (ILC-UK, 2011).

A prevalência das DCNT está aumentando em todo o mundo, sendo maior em países em desenvolvimento (ISLAM et al., 2014). A Organização Mundial da Saúde (OMS) estima que mais de 40 milhões de pessoas morrem anualmente por DCNT no mundo. Além disso, são consideradas responsáveis por 15 milhões de óbitos prematuros, ocorridos entre 30 a 69 anos, sendo que aproximadamente 80% dessas mortes acontecem em países com renda baixa e

média (WHO, 2018). No Brasil, atualmente 72% das mortes são por DCNT (MINISTÉRIO DE SAÚDE, 2011), classificadas segundo a OMS em causas cardiovasculares, câncer, respiratórias crônicas e diabetes (WHO, 2018).

As DCNT têm uma origem multifatorial, sendo influenciadas por fatores de risco modificáveis como tabagismo, sedentarismo, dieta pouco saudável e alcoolismo, e fatores de risco metabólicos como pressão sistólica alta, hiperglicemia, hipercolesterolemia e índice de massa corporal (IMC) (GBD, 2015). O conjunto dos fatores de risco metabólicos é conhecido como síndrome metabólica, sendo precursor de doenças cardiovasculares e diabetes mellitus (SAMSON e GARBER, 2014).

A síndrome metabólica aumenta com a idade em homens e mulheres, mas em idades mais avançadas é maior em mulheres. Existem também diferenças em relação aos fatores de risco entre os sexos com o aumento da idade. Nas mulheres, aumenta a prevalência de obesidade abdominal, hipercolesterolemia, hipertensão e hiperglicemia, enquanto nos homens aumenta a prevalência de hipertensão e hiperglicemia (NAQVI et al., 2015).

No Brasil, a Pesquisa Nacional de Saúde (PNS), realizada em 2013, encontrou-se que 24% dos adultos consomem bebida alcoólica uma vez ou mais por semana e 27,1% dos homens praticaram atividade física no nível recomendado pela OMS, enquanto entre as mulheres só 18,4% praticaram algum esporte. A prevalência de tabagismo entre os adultos foi de 15%, com uma importante diferença segundo o nível de escolaridade. Adultos sem instrução ou com fundamental incompleto apresentam maior proporção de fumadores (20,2%), principalmente em relação a adultos com superior completo (8,8%) (IBGE, 2014).

As mulheres apresentam ainda fatores de risco exclusivos do sexo feminino (APPELMAN et al., 2015; RIJTER et al., 2015). Comorbidades na gestação como pré-eclâmpsia e diabetes gestacional, além da menopausa precoce, aumentam o risco de doenças cardiovasculares (RIJTER et al., 2015). O aumento de risco cardiovascular entre mulheres aumenta a partir dos 50 anos, coincidindo com o início do climatério e o aparecimento ou exacerbação dos componentes da síndrome metabólica (NETO et al., 2010).

1.3 Climatério e menopausa

Em 1999, a OMS padronizou os conceitos da área com o objetivo de melhorar as definições sobre o climatério e a menopausa. As nomenclaturas identificadas foram:

Menopausa: definida como a cessação permanente da menstruação por perda de função ovariana. Menopausa natural acontece depois de 12 meses consecutivos de ausência de menstruação sem causas patológicas.

Peri-menopausa: corresponde ao período antes da menopausa e um ano depois dela.

Transição menopáusica: referente ao período antes da menopausa com ciclos menstruais irregulares.

Climatério: a transição na vida reprodutiva da mulher a um período não reprodutivo.

Síndrome climatérico: quando mulheres apresentam sintomas no climatério. O conjunto de sintomas é chamado síndrome climatérico.

Pré-menopausa: pode se referir ao período de 1 ou 2 anos antes da menopausa ou a toda a fase antes do início da menopausa.

Pós-menopausa: período que começa após a menopausa.

Além das nomenclaturas definidas pela OMS, existem outras que têm passado por algumas alterações, como as definições de *menopausa prematura* e *menopausa induzida*. Segundo a OMS, a menopausa prematura é aquela que acontece antes dos 40 anos de idade (UTIAN, 1999). Atualmente ainda se utiliza esse corte de idade como uma definição geral, mas foram também adicionados dois conceitos: menopausa precoce e menopausa tardia. A menopausa precoce é aquela que ocorre entre os 40 e 44 anos de idade (SHUSTER et al., 2010), e a menopausa tardia ocorre após os 55 anos (OSSEWAARDE et al., 2005).

Em relação à definição de menopausa induzida, a OMS menciona que a mulher pode apresentar menopausa “artificial” através de um tratamento terapêutico, por exemplo, por radiação nos casos de câncer, ou através de cirurgias, como a ooforectomia bilateral (UTIAN, 1999). Atualmente, a menopausa devido a cirurgias é conhecida como menopausa cirúrgica (HUANG et al., 2018).

No Brasil, o Ministério da Saúde modificou e adicionou informação à nomenclatura indicada pela OMS, estabelecendo que a menopausa pertence a uma fase do climatério, que é definido como uma parte biológica da vida da mulher que compreende a transição do período reprodutivo e não reprodutivo, ocorrendo normalmente entre os 40 a 65 anos e dividido em pré-menopausa, peri-menopausa e pós-menopausa. A pré-menopausa se inicia após os 40 anos e é caracterizada pela diminuição da fertilidade em mulheres com ciclos menstruais regulares. A peri-menopausa tem início dois anos antes da última menstruação e termina um ano após com ciclos menstruais irregulares, enquanto a pós-menopausa se inicia um ano após o último ciclo menstrual (NETO et al., 2010).

A partir dessa informação, é possível esquematizar o climatério numa linha de tempo como na sequência:

Figura 1. Fases do climatério

Segundo a OMS, a faixa etária mais frequente para a menopausa natural é entre 45 e 55 anos (WHO, 1996). No Brasil, a idade média de menopausa é estimada em 51,2 anos (PEDRO et al., 2003).

Vários fatores têm sido associados com a menopausa natural em idades mais jovens, como habito de fumar, baixa escolaridade (SCHOENAKER et al., 2014), idade de menarca precoce e não ter filhos (MISHRA et al., 2017), enquanto a menopausa tardia tem sido

associada com ser casada (SIEVERT et al., 2001) e apresentar sobrepeso (TAO et al., 2014). Adicionalmente, outros estudos encontraram uma associação da dieta com a menopausa tardia, principalmente em relação ao consumo de peixe, legumes (DUNNERAM et al., 2018), frutas e proteínas (DORJGOCHOO et al., 2008).

1.3.1 Menopausa e mortalidade

Alguns estudos apontam que a menopausa precoce e a prematura podem estar associadas a uma mortalidade precoce nas mulheres, enquanto uma menopausa tardia aumentaria a sobrevida geral. Um estudo realizado nos EUA (MONDUL et al., 2005), numa amostra de 68.154 mulheres, encontrou uma associação da idade de menopausa com todas as causas de mortalidade, sendo que as mulheres com idade de menopausa entre 40 e 44 anos apresentaram um maior risco de mortalidade geral do que aquelas que tiveram a menopausa entre os 50 e 54 anos. No mesmo estudo, o risco de mortalidade aumentou quando foi analisada a mortalidade específica por doença arterial coronária. No mesmo ano, um estudo na Holanda demonstrou que as mulheres com idade da menopausa acima de 55 anos tiveram um aumento da expectativa de vida em dois anos comparadas com mulheres com idade de menopausa menor de 40 anos (OSSEWAARDE et al., 2005).

Em 2006, um estudo de The Jichi Medical School Cohort Study encontrou que as mulheres Japonesas com idade da menopausa menor de 40 anos tiveram o dobro de risco de mortalidade geral, comparadas às mulheres com idade da menopausa entre 45 a 49 anos (AMAGAI et al., 2006).

Em 2007, outro estudo analisou a idade da menopausa natural e mortalidade específica por doença cardiovascular e câncer em mulheres asiáticas, encontrando que as mulheres com idade da menopausa menor de 40 anos tiveram 32% maior risco de mortalidade geral comparada às mulheres com idade da menopausa entre 45 a 49 anos. Ao analisar a mortalidade por causa específica, mulheres com idade de menopausa menor de 40 anos tiveram 53% maior risco de mortalidade por doença cardiovascular, e o dobro de risco de câncer comparado com o grupo de referência (HONG et al., 2007).

Em 2013, Li et al., utilizando os resultados do estudo The Black Women's Health Study encontraram que o risco de mortalidade geral, específica por doença cardiovascular, câncer e por todas as demais causas, foi maior nas mulheres afro-americanas com idade da

menopausa menor que 40 anos, quando comparadas com mulheres com idade da menopausa entre os 50 a 54 anos.

Em 2014, WU et al., analisou a idade da menopausa em quintis, encontrando que as mulheres chinesas com idade da menopausa menor de 46.64 anos tiveram maior risco de mortalidade geral, específica por câncer e doença isquêmica do coração, comparadas com as mulheres com idade de menopausa entre os 48.80 e 50.15 anos (quartil de referência incluindo a mediana do estudo de 49.58).

Em 2016, um estudo de meta-análise analisou a idade da menopausa e risco de mortalidade cardiovascular e geral. Foram selecionados apenas 10 estudos dos 197 artigos originalmente encontrados. Após a análise estatística, as mulheres que apresentaram idade da menopausa menor de 40 anos tiveram 18% maior risco de mortalidade geral e 11% maior risco de mortalidade por doença coronária, comparadas com mulheres que apresentaram idade da menopausa entre os 45 a 54 anos (GONG et al., 2016).

1.3.2 Menopausa e morbidade

1.3.2.1 Doença arterial coronariana e acidente vascular cerebral (AVC)

Alguns estudos internacionais têm indicado que a menopausa prematura aumenta o risco de doenças cardiovasculares. Em 2006, um estudo de coorte de mulheres dinamarquesas encontrou que a menopausa entre 40 e 45 anos esteve associada com o aumento do risco de doença coronariana, tanto em mulheres que tiveram histerectomia ou ooforectomia precoce, como em mulheres com menopausa natural (LØKKEGAARD et al., 2006).

Em 2009, o Estudo de Framingham analisou AVC em mulheres segundo a idade da menopausa e encontrou que aquelas que apresentaram idade da menopausa antes dos 42 anos tiveram o dobro de risco de apresentar AVC comparadas com mulheres com menopausa aos 42 anos ou mais (LISABETH et al., 2009).

Em 2017, um estudo com mulheres chinesas encontrou que as mulheres que apresentaram menopausa antes dos 45 anos tiveram 33% maior chance de doença arterial coronariana comparadas com as mulheres que apresentaram menopausa entre os 45 e 52 anos. Entre essas mesmas mulheres, houve 69% maior chance de AVC em relação ao grupo de referência (SHEN et al., 2017).

1.3.2.2 Neoplasias

Existem poucos estudos analisando a associação entre a menopausa tardia e o aumento do risco de câncer de mama. Em 1999, um estudo das mulheres pertencentes a um projeto de rastreamento de câncer de mama (corte de DOM) encontrou que as mulheres com idade da menopausa igual ou inferior a 44 anos tiveram 34% menor risco de câncer de mama comparadas com mulheres com idade da menopausa acima dos 54 anos. Entretanto nesse estudo não foram excluídas as mulheres com menopausa induzida, o que pode ter superestimado o risco de câncer nas mulheres de 44 anos ou menos (MONNINKHOF et al., 1999).

Em 2012, um estudo que incluiu 118,964 mulheres com câncer de mama de 117 estudos epidemiológicos, encontrou que o risco de câncer de mama aumentou 2% por cada aumento de ano da menopausa (COLLABORATIVE GROUP ON HORMONAL FACTORS IN BREAST CANCER, 2012).

1.3.2.3 Osteoporose

Em 2012, um estudo longitudinal acompanhou 390 mulheres inicialmente com 48 anos do Norte de Europa. Foi analisada a associação entre a idade da menopausa e a incidência de osteoporose quando essas mulheres chegaram aos 77 anos. Encontrou-se que as mulheres com idade da menopausa menor que 47 anos apresentaram 83% maior risco de incidência de osteoporose, 68% maior risco de fratura por fragilidade e 59% maior risco de mortalidade geral comparadas às mulheres com idade da menopausa aos 47 anos ou mais (SVEJME et al., 2012).

1.3.2.4 Depressão

Recentemente, uma meta-análise encontrou uma relação inversa entre a idade da menopausa e o risco de depressão, sendo que mulheres com idade da menopausa aos 40 anos ou mais apresentaram 50% menor risco de depressão comparadas às mulheres com idade da menopausa <40 anos (GEORGAKIS et al., 2016).

No Brasil, as mulheres têm uma taxa de mortalidade menor que os homens. Os estados com maior expectativa de vida entre as mulheres são o estado de Santa Catarina (82,4), Espírito Santo (82,2), Distrito Federal (81,5), Rio Grande do Sul e São Paulo (81,1) (IBGE, 2017).

Segundo projeções da população brasileira, em 2018 55,6% do total de idosos são mulheres, aumentando para 62,4% na faixa etária de 80 anos e mais (IBGE, 2013).

Projeções indicam que em 2030 haverá 1,2 bilhões de mulheres pós-menopáusicas no mundo (WHO, 1996). Como mencionado, a idade da menopausa pode influenciar na morbidade e mortalidade das mulheres, originando uma preocupação para o sistema de saúde.

Apesar de existirem estudos internacionais respaldando as associações, esses ainda são escassos e compostos em sua maioria por mulheres brancas, existindo poucos estudos realizados em mulheres latinas. Adicionalmente, não existem trabalhos de análise de sobrevivência segundo a idade da menopausa natural na América Latina, este é primeiro estudo a realizar uma análise quantitativa.

A alta proporção de mulheres entre os idosos brasileiros e os resultados encontrados em estudos internacionais sobre a relação da idade da menopausa com a morbidade e a mortalidade fazem com que os resultados deste projeto possam contribuir para a área de saúde dos idosos e especificamente para o planejamento de políticas públicas para mulheres idosas no Brasil.

2 OBJETIVOS

2.1 OBJETIVO GERAL

- Analisar os fatores relacionados à idade da menopausa natural e a sua relação com a mortalidade entre as mulheres do estudo SABE (Saúde, Bem-Estar e Envelhecimento) do Município de São Paulo.

2.2 OBJETIVOS ESPECÍFICOS

- Identificar os fatores socioeconômicos e reprodutivos associados à menopausa natural.
- Analisar a associação entre a idade de menopausa e a mortalidade por todas as causas e mortalidades específicas (cardiovascular, respiratória e neoplasias).
- Identificar na literatura fatores reprodutivos associados à idade da menopausa natural.

3 METODOLOGIA

3.1 ESTUDO SABE

A análise foi do tipo longitudinal e utilizou os resultados do estudo SABE: Saúde, Bem-estar e Envelhecimento, realizado nos anos 2000, 2006 e 2010. Trata-se de um inquérito multicêntrico originalmente coordenado pela Organização Pan-Americana de saúde sobre as condições de vida dos idosos em sete países de América Latina e Caribe (LEBRÃO e LAURENTI, 2005). A partir do 2006, o estudo do Município de São Paulo foi transformado em um estudo de coorte. Atualmente a coorte leva quatro ondas: 2000, 2006, 2010 e 2015. O estudo no Brasil é coordenado por uma equipe de pesquisadores da Faculdade de Saúde Pública (FSP) da Universidade de São Paulo (USP).

3.2 AMOSTRA

A primeira onda, no ano 2000, denominada coorte A00, corresponde a uma amostra representativa de idosos de 60 anos ou mais residentes na área urbana do Município de São Paulo. A amostra do SABE foi construída em duas fases. Na fase 1 se estabeleceu que 5.882 domicílios fossem visitados. O sorteio desses domicílios foi realizado através de amostragem por conglomerado, em dois estágios. O primeiro estágio foi probabilístico e baseado em 72 setores censitários selecionados pelo Departamento de Epidemiologia da Faculdade de Saúde Pública da USP, utilizando o cadastro da Pesquisa Nacional por Amostra de Domicílios (PNAD) (CRUZ et al., 2012). Para o segundo estágio, calculou-se o número mínimo de domicílios visitados por setor, dividindo o número total de domicílios pelo número de setores censitários do primeiro estágio ($5.882/72=81,69$ aproximado a 90). O número total de endereços de cada setor censitário foi agrupado em segmentos de 10 domicílios, e em cada setor foram sorteados 9 segmentos, originando 90 domicílios a serem visitados. Ao concluir a primeira fase, 1.568 idosos foram entrevistados (GOMEZ et al., 2013). A segunda fase foi composta por 575 residentes de 75 anos ou mais, nos distritos em que as entrevistas foram realizadas. Esse acréscimo foi feito para compensar a mortalidade, completar o número adequado de entrevistas nessa faixa etária e garantir o desenho longitudinal do estudo. O número total de indivíduos entrevistados em ambas as fases foi de

2.143 idosos (OLIVEIRA et al., 2007). Foram calculados os pesos amostrais segundo a amostragem, faixa etária, sexo e tamanho da população de 60 anos ou mais recenseada pelo IBGE residentes no Município de São Paulo no 1998. O peso dado os questionários foi calculado de acordo com cada setor censitário correspondente (CRUZ et al., 2012).

Dos 2.143 idosos da onda de 2000, 1.115 foram entrevistados novamente em 2006. Para analisar a ocorrência de óbitos, foi realizada uma pesquisa das Declarações de Óbito (DO) pertencentes à Fundação Sistema Estadual de Análise de Dados (SEADE) e ao Programa de Aprimoramento de Informações de Mortalidade (PRO-AIM). Para a localização dos sobreviventes foi utilizada a informação do questionário do ano 2000, como o endereço, informação pessoal como telefone pessoal ou dos familiares e o uso da mídia impressa. Os idosos não encontrados foram categorizados como não localizados (TAMANINI et al., 2011). As entrevistas não realizadas corresponderam a 1028 idosos, sendo 649 óbitos, 177 recusas, 139 idosos não localizados, 52 mudanças para outros municípios e 11 institucionalizações (CRUZ et al., 2012). Para a onda de 2006, uma nova amostra de idosos de 60 a 64 anos foi incluída, denominada coorte B06. Essa nova amostra foi composta por idosos residentes do Município de São Paulo em 2006. No total foram selecionados 376 idosos e realizadas 298 entrevistas – sendo os 78 faltantes devido a 72 recusas, 1 óbito e 5 mudanças de moradia. Assim, no total foram entrevistados 1.413 idosos (DELLAROZA et al., 2013).

A onda de 2010 denominada coorte C10, aconteceu entre 2010 e 2011. Em relação à amostra original (A00), as perdas de seguimento corresponderam a 44,2% idosos que faleceram, 20,9% por outros motivos tais como mudança de cidade, não localizados e rejeição de participar (TAMANINI et al., 2016), e 34,9% foram entrevistados novamente. Os pesos amostrais foram recalculados segundo o Censo 2010. A amostra final foi composta por 748 idosos da onda de 2000, 242 da onda de 2006 e adicionaram-se também 355 novos idosos de 60 a 64 anos (CORONA et al., 2014). Assim, no total 1.345 idosos foram entrevistados (**Figura 2**).

Figura 2. Desenho amostral do Estudo SABE

3.3 COLETA DE DADOS

A coleta de dados foi realizada por entrevistadores treinados, por meio de questionários específicos propostos pela Organização Pan-Americana da Saúde (OPAS/OMS), traduzidos e adaptados para serem usados no Brasil. Cada questionário foi revisado por uma equipe técnica especializada. O questionário foi composto por 11 blocos temáticos identificados por letras: informações pessoais (seção A), avaliação cognitiva (B), estado de saúde (C), estado funcional (D), medicamentos (E), uso y acesso a serviços (F), rede de apoio familiar e social (G), história de trabalho e fontes de receita (H), características da moradia (J), antropometria (K) e mobilidade e flexibilidade (L). Em 2006, adicionou-se a seção maus tratos (M) e, em 2010, cuidadores (N).

A coleta de dados foi realizada por entrevistas nos domicílios, em duas etapas com um intervalo de 6 meses entre as duas. A primeira etapa correspondeu ao preenchimento das

secções do questionário A até J e a segunda etapa foi da K à L, pertencente a antropometria e testes de mobilidade e flexibilidade (MAIA et al., 2006).

Os dados de óbitos para os objetivos deste estudo, foram obtidos por médio de linkage em 2016. Foram utilizados os dados pessoais dos idosos pertencentes à primeira coorte do ano 2000 e nome dos pais disponíveis no questionário do 2006. Os dados utilizados foram nome completo, ano de nascimento, sexo, nome de mãe e do pai e endereço. Os dados de mortalidade foram fornecidos pelo Programa de Aprimoramento das Informações de Mortalidade no Município de São Paulo (PRO-AIM).

3.4 VARIÁVEIS DO ESTUDO

O questionário do estudo SABE possui uma grande variedade de dados sobre características sociodemográficas e do estado de saúde. Para o desenvolvimento deste estudo, foram utilizados os resultados das seções A (Informações pessoais) e C (Estado de saúde) do questionário do ano 2000, 2006 e 2010.

Seção A

Variáveis sociodemográficas, como idade (ano de nascimento como variável continua), estado civil (casada, viúva, separada/divorciada/nunca casou), escolaridade em anos (sem anos de escolaridade, 1 a 7, ≥ 8 anos). A raça autorreferida (branca, parda e outras) foi utilizada só na coorte 2000.

Seção C

As variáveis reprodutivas da mulher incluídas foram quantidade de filhos (sem filho, 1, 2, ≥ 3 e sem filho, 1 a 2, ≥ 3), idade da última menstruação autorreferida na pergunta *Que idade tinha quando menstruo pela última vez?* (continua e categorizada em ≤ 40 , 41-44, 45-49, 50-54 (referência), ≥ 55), antecedente e idade de histerectomia e histerectomia com ooforectomia (sim ou não), e a realização de tratamento hormonal de estrogênio (sim ou não). Em relação aos fatores de risco de saúde, foi analisado o tabagismo categorizado em nunca fumou, atualmente fuma e fumou, mas já não fuma.

Em relação às variáveis relacionadas com o estado de saúde, foi analisado o número de doenças crônicas (sem doença, 1 a 2, ≥ 3). Considerou-se hipertensão arterial, diabetes

mellitus, doença crônica pulmonar e osteoporose como doenças crônicas. Essa variável foi usada apenas na coorte 2000.

Dados de mortalidade

Foram utilizados os dados das causas básicas de óbitos, categorizadas segundo a Classificação Internacional de Doenças, décima revisão (CID-10). Para analisar a mortalidade específica cardiovascular foi usado o capítulo IX, mortalidade respiratória o capítulo X e neoplasias o capítulo II.

Variáveis da meta-análise

Menopausa natural foi definida segundo a OMS como ausência de menstruação de pelo menos 12 meses consecutivos por motivos naturais (WHO, 1996). As variáveis independentes de interesse foram menarca precoce (geralmente definida como ≤ 12 anos), número de filhos vivos e uso de anticoncepcionais orais.

3.5 ANÁLISE DOS DADOS

Para analisar os fatores associados à idade da menopausa natural, foram analisadas as mulheres pertencentes às coortes 2000, 2006 e 2010. Utilizou-se modelos de regressão de Cox, nos quais a idade da menopausa natural foi o tempo no modelo de sobrevivência. As variáveis de interesse foram escolaridade, estado civil, número de filhos e tabagismo. A amostra inicial de 1.661 mulheres, foi diminuída para 1.415 devido aos critérios de exclusão. Foram excluídas da análise as mulheres com dados faltantes na idade da menopausa ($n=201$), dados faltantes em outras variáveis utilizadas no estudo ($n=36$), mulheres que autoreferiram ainda menstruar ($n=4$) e 5 mulheres com menopausa referida acima dos 60 anos. Das 1.415 mulheres, 1.252 tiveram menopausa natural e 163 mulheres foram censuradas na idade da histerectomia ($n=70$), histerectomia com ooforectomia ($n=81$) e mulheres com tratamento hormonal ($n=12$). Para o cálculo das medianas segundo as variáveis selecionadas, foi utilizado o estimador de Kaplan-Meier. A heterogeneidade entre as coortes foi testada por meio de uma análise quantitativa utilizando os resultados das três coortes com pooled-Hazard Ratio.

Para analisar a mortalidade geral e específica segundo a idade da menopausa, foram analisadas as mulheres que ingressaram no estudo no ano 2000. Das 1.265 mulheres da amostra inicial, 842 foram analisadas. As 423 mulheres restantes foram excluídas da análise

por não terem informação sobre a idade da menopausa (n=188), dados faltantes em outras variáveis do estudo (n=53), ainda menstruavam (n=3), idade da menopausa cima dos 60 anos (n=3), histerectomia (n=70) e histerectomia com ooforectomia (n=80). Através do linkage foram identificados 467 óbitos. Adicionalmente, foram excluídos os óbitos por causas externas (n=13) e óbitos sem causa definida (n=13). Assim no total foram analisados 444 óbitos. Para a análise estatística, foram utilizados modelos de regressão de Cox, onde a idade da menopausa natural categorizada foi a principal variável de interesse. Outras variáveis nos modelos foram ano de nascimento, escolaridade, estado civil, raça, número de filhos, tabagismo, número de doenças crônicas e tratamento hormonal. Foram censuradas mulheres que não foram a óbito, outorgando a idade que tinham no último linkage (sobrevida até o dia 13 de setembro 2016). Os desfechos de interesse foram mortalidade geral, mortalidade cardiovascular, respiratória e por neoplasias.

A suposição de proporcionalidade do modelo de Cox ao longo do tempo foi testada por log-rank e resíduos de Schoenfeld. No estudo de fatores associados à menopausa natural, foi testado na coorte 2000 por ter a maior quantidade de mulheres (89% da amostra total).

Finalmente, para o estudo de meta-análise utilizou-se as escalas de Newcastle-Ottawa (NOS) para avaliação da qualidade dos artigos. O risco de viés de publicação foi testado por meio de Egger's test e Begg's test. Para a análise quantitativa, utilizou-se os modelos randômicos e forest plot na apresentação dos resultados, e a heterogeneidade foi avaliada pelo Cochran's Q test and I².

Todas as análises foram realizadas no programa STATA 13. Para as análises realizadas por meio de modelos de regressão de Cox, foi utilizado o peso amostral, testando as variáveis com o qui-quadrado de Rao-Scott.

4 ASPECTOS ÉTICOS DA PESQUISA ENVOLVENDO SERES HUMANOS E AUXÍLIOS À PESQUISA

Depois de ser explicado aos idosos os objetivos do estudo, foi realizada a entrevista com o compromisso de não divulgação dos dados da identidade dos participantes. Os idosos consentiram em participar por meio de assinatura após a leitura do termo de consentimento livre e esclarecido.

A primeira coorte, de 2000, foi aprovada pela Comissão Nacional de Ética em Pesquisa (CONEP), em 17/06/1999 (parecer nº315/99). No ano 2006, a segunda onda do SABE, foi aprovada pelo Comitê de Ética em Pesquisa (COEP) da Faculdade de Saúde Pública da Universidade de São Paulo, em 14/03/2006 (parecer nº 83/06), e a terceira onda do SABE foi aprovada pelo Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo em 5/03/2010 (protocolo nº 2044).

O Estudo SABE é financiado no Brasil pela Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP). Conta com os seguintes processos; desde o 1/12/2005 até 30/11/2009 (processo 05/54947-2), 01/04/2010 até 31/03/2015 (processo 09/53778-3) e desde o 01/05/15 até 30/04/19 (processo 14/50649-6).

5 RESULTADOS E DISCUSSÃO

Artigo 1- Aceito pela revista Menopause (Fator de Impacto: 2,67), com publicação prevista para fevereiro 2019.

Título: Factors associated with age at natural menopause among elderly women in São Paulo, Brazil.

Autores:

Alejandra Andrea Roman Lay, MPH^{a,b}

Yeda Aparecida de Oliveira Duarte, PhD^c

Alexandre Dias Porto Chiavegatto Filho, PhD^a

^a Department of Epidemiology, School of Public Health, University of São Paulo, Brazil.

^b Faculty of health sciences, Universidad de Tarapacá, Chile.

^c School of Nursing, University of São Paulo, Brazil.

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, 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 35% higher risk of earlier natural menopause (HR=1.35, 95% CI: 1.12, 1.62) and former smokers had 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 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 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 NM with reproductive and lifestyle factors similar to some studies of women from developed countries.

Keywords: Menopause, aging, Brazil.

1. Introduction

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 (1). Several factors have been found to influence the timing of this natural process. Some well-known factors include sociodemographic variables such as income(2) and education (3–6); reproductive variables such as the use of oral contraceptives(4,5,7), parity(8,9) and age at menarche(6); and variables related to lifestyle such as smoking(2–6,8), Body Mass Index (BMI)(2,3,8) and physical activity(2,3,5). Other factors such as race/ethnicity(5) and diet(9) still need more research.

Menopause can take place spontaneously without intervention (natural menopause) 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(10)) and late (aged 55 years or more) (11).

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

In Latin America, very few studies analyzed factors associated with age at menopause. Two studies found an association between smoking, education, and parity(17,18,19) with earlier menopause, while a different study showed an association of current employment and parity with later menopause (20). In Brazil, previous studies found that there is no relation with sociodemographic factors and smoking(21). Others studies in Brazil and Mexico have shown no association between age at NM and age at menarche (22,23).

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

2. Methods

2.1 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)(24). 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(25,26). 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 was 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 the high rate of mortality in this age group, and to guarantee the longitudinal design of the study(27). 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 was 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(28). For this wave, a new cohort of 298 older people between the ages of 60 and 64 was added(29), 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.

2.2 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(25,26). 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).

2.3 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 to 7, and ≥ 8 years); marital status (married, widowed/separated/divorced and never married); parity (nulliparity (without children), 1 or 2, and ≥ 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.

2.4 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 that 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 2000 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 statistical significant for

heterogeneity. The results of the variables that were statistically significant are shown separately by cohort.

3. 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 one to seven 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 that never married and smokers (current and past) presented two years earlier age at NM in comparison with married women and non smokers (48 vs 50 years). Meanwhile, women without schooling and nulliparous presented one year earlier age at NM in relation to women with one 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 other hand, 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 1 to 2 children (HR=0.15, 95% CI: 0.04, 0.56) or more than 3 children (HR=0.16, 95% CI: 0.04, 0.64) presented later age at NM in 2006 vs their references.

4. Discussion

Previous studies indicate that the median age at NM in developing countries is lower than in developed countries(2,30,31). In this study, the median age at NM was 50 years, which was similar to Russian women(4), but lower in studies involving women in the U.S (52.5

years)(5), the Czech Republic (51 years)(4), Poland (51.25 years)(32), and Japan (52.1 years)(8). Women who had undergone hysterectomy or hysterectomy with oophorectomy uni 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 one or more years of studies. This is similar to the results obtained in other studies conducted in Brazil(22), México(33), U.S(34), Europe(4), and China(35). Additionally, it was found that women with higher education had significantly higher age at NM. This result is also shown by other studies(3), 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(36), and lifestyle risks such as smoking and sedentary lifestyle(37). 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(38). 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(4,5,39). 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 (eight 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(2).

Consistent with other studies(6,8,34,35), 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) while most of studies analyze them separately(6,35).

For the 2006 cohort, women with ≥ 1 children had decreased risk of earlier age at NM compared to nulliparous. Among Brazilian women, the age range more common to have a child is between 20 to 24 years old. 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) (40). Thus, the majority of women had three children or more. One of the mechanism that have be 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(41). 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(42,43) promoting the death of primordial oocytes(44,45). Other studies suggest that tobacco toxins decrease levels of estrogen from synthesis inhibition and endocrine disruption(45–47), or increased levels of 2-hydroxyestrogen(3,45,48,49), producing an anti-estrogen effect that induces early menopause in women who smoked tobacco in relation to non-smoking women. Several studies support the hypothesis that current smoking(31,43,48,50,51) and also past smokers(6,46) present an increased risk of early NM. In this study, current and former smokers had higher risk of earlier menopause in relation to non-smokers. 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 non-smokers(32,52). However, our results agree with other studies regarding the association of being a former smoker and early NM(5,6,46), 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 Body Mass Index (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 include 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(50,52). Third, this is a retrospective cross-sectional study. Women entered the SABE study post-menopausal. Causality and associations have to be analyzed with caution, since variables such as smoking and marital status may reflect a post-menopausal status. Finally, there is a risk of recall bias since 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.

In spite of these limitations, this study is the first multi-cohort analysis in Brazil that demonstrates the presence of independent factors consistently associated with age at menopause.

5. 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 ageing. 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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Table 1. Baseline characteristics by relative distribution (%^a) 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
Menopausal status					
Natural menopause	82.98	99.29	100.00	90.77	50
Hysterectomy	7.82	-	-	4.18	46.5
Hysterectomy with uni/bilateral oophorectomy	8.42	0.71	-	4.64	47
Hormonal treatment	0.78	-	-	0.41	50
Education (years)					
Without studies	19.03	16.26	0.87	13.77	49
1 to 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 to 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

^a Percent according to complex sampling of SABE study according to each cohort.

(-)Without observations.

Table 2. Unadjusted and adjusted Hazard ratios (HR) with 95% confidence intervals (CI) for age at natural menopause by baseline characteristics, SABE study, Municipality of São Paulo, 2000-2006-2010.

	Unadjusted		Adjusted		Heterogeneity
	HR	CI 95%	HR	CI 95%	p-value
Education					
Without studies	1	Reference	1	Reference	
1 to 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 to 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

^a Adjusted for all the variables in the table and year of birth as continuous variable of the three cohorts.

Table 3. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) 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 ^a	CI 95%	HR ^b	CI 95%	HR ^c	CI 95%
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 to 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

(-) Without observations.

^a Adjusted for all the variables in the table and year of birth of cohort 2000.

^b Adjusted for all the variables in the table and year of birth of cohort 2006.

^c Adjusted for all the variables in the table and year of birth of cohort 2010.

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Título: Age at natural menopause and mortality: a survival analysis
of elderly residents of São Paulo, Brazil.

Autores:

Alejandra Andrea Roman Lay, MPH^{a,b}

Carla Ferreira do Nascimento, MPH^a

Yeda Aparecida de Oliveira Duarte, PhD^c

Alexandre Dias Porto Chiavegatto Filho, PhD^a

^a Department of Epidemiology, School of Public Health, University of São Paulo, Brazil.

^b Faculty of health sciences, Universidad de Tarapacá, Chile.

^c School of Nursing, University of São Paulo, Brazil.

Abstract

Objectives: To conduct a survival analysis according to age at natural menopause (NM) in a representative sample of elderly women from the Municipality of São Paulo, Brazil.

Study design: We analyzed data from the Health, Well-Being and Aging study (SABE), a cohort that started in 2000. Mortality data, occurring up to September 2016, was obtained by linkage from the Program for Mortality Information of São Paulo (PRO-AIM).

Main outcome measures: We used Cox regression to analyze all-causes, and cause-specific mortality from cardiovascular diseases, respiratory diseases and cancer, according to age at menopause, categorized in ≤ 40 , 41-44, 45-49, 50-54 (reference) and ≥ 55 .

Results: After 16 years of follow up, there were 444 deaths, of which 199 were from cardiovascular diseases, 73 from respiratory diseases and 65 from cancer. After adjustment for socioeconomic, reproductive and lifestyle factors, having an early menopause (41-44) was associated with an increased risk of all-causes mortality (HR=1.48, 95% IC: 1.03, 2.14) relative to NM at 50-54 years. Women with age at NM between 41-44 and 45-49 had twice the risk of cancer mortality compared to the reference group. We did not find significant associations between age at NM and cause-specific mortality for respiratory and cardiovascular diseases.

Conclusions: Our findings suggest that early menopause is associated with all-cause mortality in the largest city of Latin America. In addition, earlier age at NM was associated with cancer mortality. These results suggest that age at NM may be a biomarker for mortality, irrespective of country of residence.

Keywords: Menopause, aging, mortality, cardiovascular, cancer.

Highlights

- Early age at natural menopause presented increased risk of all-cause mortality
- Menopause between 41-49 years was associated with higher risk of cancer mortality
- Neither premature nor early menopause were associated with cardiovascular mortality
- Neither premature nor early menopause were associated with respiratory mortality
- This is the first longitudinal study of age at menopause and mortality in Latin America

1. Introduction

Natural menopause is defined as the absence of menstrual periods due to loss of ovarian follicular function[1], which frequently occurs between the ages of 45 and 55[2]. Menopause under 40 years is defined as premature menopause[3], between 40 and 45 is known as early menopause[4] and after the age of 55 as late menopause[5].

A few studies have found an association between age at natural menopause and adverse health outcomes. Premature and early menopauses have been shown to be associated with greater risk of all-cause mortality[6] as well as an increased risk of cardiovascular diseases[7] and coronary heart mortality[8,9]. On the other hand, late menopause has been associated with a higher risk of breast[10], uterine and ovarian cancers[5].

Studies on age at menopause and mortality have been mostly conducted in developed countries. To our knowledge, there are no published studies analyzing the association between natural menopause and mortality in Latin America. Previous analyzes have shown that age at menopause is earlier on average for women living in Latin America in comparison with those living in developed countries[11,12], which could lead to an increased risk of early mortality. Also, the presence of wide disparities regarding socioeconomic factors may adversely affect age at menopause and its consequent effect on mortality[8]. The objective of this study is then to analyze the association between age at menopause and all-cause, and cause-specific, mortality in a representative sample of elderly women from São Paulo, Brazil.

2. Methods

2.1 Study population

We analyzed data from the SABE (Health, Well-being and Aging) study conducted in São Paulo Municipality, Brazil. The SABE study was originally coordinated by the Pan American Health Organization (PAHO) in the year 2000, collecting information about health and lifestyle from a representative sample of elderly residents of São Paulo, Brazil. SABE study design has been described elsewhere[13,14]. Briefly, the sample was constructed in two segments. The first segment was a probabilistic sample based on 72 census tracts obtained from 263 census sectors drawn by conglomerate sample from the National Household Sample Survey (PNAD). In this segment, 1,568 participants were interviewed.

The second segment was formed by 575 residents in areas where previous interviews had been conducted, to compensate the higher mortality of individuals over 75 years and to complete the number of interviews in this age group. A total of 2,143 individuals were interviewed, out of which 1,265 were women[13].

The weights of the questionnaires were calculated according to the corresponding census sector. For questionnaires carried out in non-drawn lots, the weights were calculated according to the population of older individuals living in the Municipality of São Paulo in 1998[14].

2.2 Data collection

The questionnaires were adapted by the PAHO to be applied in Portuguese. Interviewers were trained professionals and each questionnaire was reviewed by a specialized technical team. The SABE study was 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, Nº 315/99).

2.3 Outcome

Our outcomes of interest were all-cause mortality and the underlying cause-specific mortality for cardiovascular diseases, respiratory diseases and cancer. Mortality data was obtained through linkage of SABE data and the death registry database from the Program for Improvement of Mortality Information in the Municipality of São Paulo (PRO-AIM) until September 13th 2016, and the underlying cause of death for each individual was collected. We classified causes of death according to the International Classification of Diseases (ICD), 10th revision. Cardiovascular deaths were those included in chapter IX, i.e. diseases of the circulatory system (I00-I99); respiratory mortality in chapter X, i.e. diseases of the respiratory system (J00-J99); and cancer mortality in chapter II, i.e. malignant neoplasms (C00-C97), in situ neoplasm (D00-D09), benign neoplasms (D10-D36) and neoplasms of uncertain or unknown behavior (D37-D48). Recent analyzes have shown that the information regarding the underlying causes of death in Brazil is of good quality, in accordance with international standards [15].

2.4 Data analysis

In 2000, 1,265 women were included in the SABE study, of which we excluded 188 without menopause data, 3 that self-reported still having menstruation, 3 with menopause over 60 years, 70 reporting hysterectomy, 80 reporting hysterectomy with uni or bilateral oophorectomy and 53 with missing data in variables of this study. These exclusions left 868 women for the analyzes. In addition, from 2000 to 2016, there were a total of 467 deaths (55.46% of the elderly sample), of which we excluded 13 deaths from external causes and 13 without cause of death, yielding a total of 842 women of which 444 died. We applied Cox regression model to analyze the association of age at natural menopause with all-cause mortality, cardiovascular mortality, respiratory mortality and cancer mortality. Women not found to be dead were censored at their attained age by 13 September 2016 (n=398).

All the variables were obtained from the SABE 2000 questionnaire. Our main independent variable was self-reported age at natural menopause, categorized in 5 groups (≤ 40 , 41-44, 45-49, 50-54 (reference) and ≥ 55), following the literature[2-5] and adjusted in two models. First, model 1 was adjusted by social and demographic characteristics: year of birth (continuous), education (without formal studies, 1 to 7 and ≥ 8 years), marital status (married, widowed and separated/divorced/never married) and race (self-reported as white, mixed and others). For model 2, we added to model 1 reproductive and lifestyle characteristics: parity (without, 1, 2, ≥ 3), smoking (never smoked, currently smokes, and former smoker), number of chronic diseases (none, 1 to 2 and ≥ 3) and estrogen therapy (ET) (never used, has used).

Survival curves were constructed for every variable and tested with long-rank tests. The proportional hazard assumption was tested by Schoenfeld residuals. The sample weight of the SABE study was applied in all of the statistical analyzes. Associations between the categories of natural menopause and variables of the study were measured by Rao-Scott chi-square.

3. Results

Median age at first interview was 71 years and the majority (58.52%) was 70 years or older at the start of the study. Median age at natural menopause was 50 years (interquartile range: 46-52). There were 444 deaths during the 16 years of follow-up, of which 45% were cardiovascular, 16% respiratory, 15% cancer and 24% other causes.

There were no significant statistical differences between the categories of age at natural menopause and parity, marital status, race, smoking, number of chronic diseases and estrogen therapy (Table 1). Meanwhile, the proportion of women without formal education decreased as the age of menopause increased ($p < 0.05$).

In Table 2, model 2, women with early menopause (41-44 years) had 48% higher risk of all-cause mortality compared to the reference group (HR= 1.48, 95% CI: 1.103, 2.14). In Tables 3 and 4, it is shown that there were no significant association between age of natural menopause and cardiovascular and respiratory mortality.

In Table 5, after adjusting for all the variables in model 2, the risk of cancer mortality in women with early menopause was 2.1 times higher than that of the reference group (95% CI: 1.00, 4.42). In addition, presenting age at menopause between 45 and 49 was associated with an increased risk of cancer mortality in model 1 (HR= 2.04, 95% CI: 1.11, 3.76), maintaining the significance when reproductive and lifestyle variables were added to model 2 (HR=2.15, 95% CI: 1.13, 4.08).

4. Discussion

Women with early menopause presented a statistically significant increased risk of early mortality. These results are similar to previous studies in developed countries that have shown associations between early [6,8] and earlier [16] menopause with all-cause mortality. However, the risk of all-causes mortality for Brazilian women seems to be higher than for these studies. Mondul et al.[8] reported, in a study of US women, an increased risk of 5% in comparison with natural menopause between the ages of 50 and 54, while Li et al.[6] found a higher risk of 33% in US black women with early menopause compared to the same age category as reference. On the other hand, a study by Hong et al.[9] of South Korean women did not find statistically significant association of early menopause with all-cause mortality. Women with later menopause had decreased risk of all-cause mortality, consistent with previous studies [5,17], although our results were not statistically significant.

Women with premature menopause had the lowest education levels, similar to previous studies that showed a linear tendency between age at natural menopause and education [18,19]. Further, lower education has been associated with earlier menopause in studies with diverse populations of women [18, 20-21]. One study found that Brazilian women with less formal education have an increased risk of sedentary behavior, smoking and self-reported

hypertension compared to women with a college degree [22]. Women without formal education may share common characteristics, such as risk factors and lifestyle behaviors that may directly affect ovarian function, affecting the age of menopause. Furthermore, worldwide, women are more vulnerable to high socioeconomic inequalities when compared with men [23,24]. Brazil is one of four American Latin countries with higher Gini coefficient (over 0.50) [23]. According to The Brazilian Institute of Geography and Statistics (IBGE), in 2016 the Gini coefficient of Brazil was 0.525, and the Southeast Region, where São Paulo is situated, presented the second highest coefficient [24]. This scenario of very high inequality is also reflected in the mortality according to socioeconomic characteristics and gender. Brazilian women with low income and schooling have higher mortality rates of acute myocardial infarction compared to women with high socioeconomic status [25]. Due to these factors, we analyzed mortality separately in two models. The first model adjusted for only socioeconomic variables, while the second model added reproductive and lifestyle behaviors.

We did not find significant associations of premature and early menopause with cardiovascular mortality, similar to others studies where neither premature[1] nor early menopause [26] were associated with cardiovascular mortality. In addition, we did not find an association between age at menopause and respiratory mortality. This result contrasts with a previous study of US women where early menopause was associated with an increased risk of respiratory mortality[8].

On the other hand, we found a significant association between earlier menopause and cancer mortality. In addition, there seems to be a linear tendency between age at menopause and cancer mortality, as later menopause was consistently associated with lower risk of cancer mortality, albeit being non-significant. There are a few international studies that analyzed age at menopause and cancer mortality. Previous studies found an association between premature menopause [9], early menopause [27] and earlier menopause [16] with an increased risk of overall cancer mortality, and some have associated early menopause with a reduced risk of breast cancer [10,28, 29]. However, others studies found no association between early and earlier age at menopause with cancer mortality [6,8,17]. While, a study found that later menopause was associated with an increased risk of uterine and ovarian cancer[5]. It is not yet clear the physiological pathway by which age at menopause could increase the risk of breast cancer and ovarian cancer, but it is known that women with later

menopause have been more exposed to estrogen in their lifetime. Estradiol metabolism is associated with genotoxic metabolites in breast and ovarian cancer, increasing the initiation of carcinogenesis in breast tissue and ovarian surface epithelium (OSE) [30,31, 32]. In our sample, the highest risk was among women with NM between 45 and 49 years, neither early nor later menopause, which had twice the risk of breast cancer than women in the reference group (50-54 years). There were also ten deaths due to gynecological causes: three endometrial, three ovarian, three uterine and one vaginal cancer. Similar to breast cancer, women with menopause between 45 and 49 had twice the risk of gynecological cancer compared to the reference group. Even if our results shown a tendency, it must be analyzed with caution since we did not have information about risk factors associated with estrogen exposed cancer, such as inherited history of cancer, BMI and diet. Further studies with larger samples need to be conducted in developing countries to test the association of age at menopause with cause-specific cancers associated with estrogen, such as breast, endometrial and ovarian cancer.

This study has some limitations. First, we had to exclude 241 (19%) of the original sample due to missing information regarding age at menopause and other variables of the study, decreasing the sample size. Second, almost all the variables used, with exception of birth year, were self-reported. This means that memory bias could be an issue here due to the age of the women who entered to the study (all were at least 60 years old, with a median age of 71), especially regarding age at menopause. Third, in our study there was not a lot of deaths at the extremes of ages at menopause (youngest and oldest), as around 70% of the deaths occurred among women aged between 45 and 54 years old, so there could be an issue of small sample size for these extremes. Finally, we could not obtain mortality information of women who died outside of São Paulo.

Despite these limitations, to our knowledge, this is the first longitudinal study of age at menopause and mortality with women living in a Latin American country. Our results are overall similar to those found in cohorts from developed countries, indicating that age at menopause may be a biological marker of early mortality.

Contributors

ARL was responsible for study conception and design, analysis and interpretation of data, and drafting the article.

CFN was responsible for analysis and interpretation of data.

YD was responsible for acquisition of data, study design and interpretation of data.

ACF was responsible for study design, analysis and interpretation of data, and revising the article.

All authors have contributed to revising the article and approved the final manuscript.

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Table 1. Baseline characteristics by relative distribution (%^a) according to age at natural menopause (NM). SABE study, Municipality of São Paulo, 2000.

Characteristics	Age at natural menopause					p value ^c
	≤40	41-44	45-49	50-54 ^b	≥55	
Age at NM (%)	8.37	7.75	32.83	39.87	11.18	
Birth year (median)	1927	1929	1929	1928	1927	0.32
Education						
Without studies	35.79	16.99	22.45	16.57	9.92	0.01
1 to 7	52.3	65.56	64.9	67.32	64.88	
≥8	11.91	17.45	12.66	16.11	25.2	
Marital status						
Married	34.12	39.05	39.1	46.76	43.69	0.06
Widowed	43.9	35.05	44.29	41.56	48.63	
Separated/divorced/never married	21.98	25.9	16.61	11.68	7.68	
Race						
White	66.85	78.56	68.14	75.27	77.57	0.37
Brown	27.24	14.18	23.75	16.32	14.84	
Others	5.91	7.26	8.11	8.41	7.59	
Parity						
Nulliparous	17.84	11.51	12.09	8.57	5.95	0.26
1	11.64	11.08	10.72	11.5	12.15	
2	11.41	25.97	16.91	18.65	28.92	
≥3	59.11	51.43	60.28	61.28	52.98	
Smoking						
Never	67.72	79.32	62.99	73.82	74.83	0.07
Current	15.97	6.29	11.89	11.27	10.06	
Past	16.31	14.39	25.12	14.91	15.11	
Number of chronic diseases						
Without	24.04	29.05	25.22	22.19	29.37	0.60
1 to 2	59.45	64.21	61.01	65.93	55.3	
≥3	16.51	6.74	13.76	11.88	15.33	
Estrogen therapy						
Never use	72.14	68.21	75.47	72.61	67.13	0.63
Ever use	27.86	31.79	24.53	27.39	32.87	

^a Percent according to complex sampling of SABE study according to 2000 cohort.

^b Reference category.

^c p value of Rao-Scott Chi-Square Test.

Table 2. All-cause mortality according to age at natural menopause (NM). SABE study, Municipality of São Paulo, 2000.

Age at NM	Person-years	No. of deaths	All-cause mortality			
			Model 1 ^a		Model 2 ^b	
			HR	(95% IC)	HR	(95% IC)
≤40	6072	45	1.27	(0.88,1.83)	1.18	(0.79,1.76)
41-44	5374	38	1.38	(0.94,2.03)	1.48	(1.03,2.14)
45-49	21414	138	1.17	(0.87,1.58)	1.11	(0.81,1.52)
50-54	29157	172	1.00	(ref.)	1.00	(ref.)
≥55	8387	51	0.84	(0.54,1.32)	0.85	(0.55,1.31)

^a Adjusted by birth year, education, marital status and race.

^b Adjusted by birth year, education, marital status, race, parity, smoking, number of chronic diseases and estrogen therapy.

Table 3. Cardiovascular mortality according to age at natural menopause (NM). SABE study, Municipality of São Paulo, 2000.

Age at NM	Person-years	No. of deaths	Cardiovascular mortality			
			Model 1 ^a		Model 2 ^b	
			HR	(95% IC)	HR	(95% IC)
≤40	1939	23	1.17	(0.65,2.09)	1.03	(0.57,1.86)
41-44	900	11	0.83	(0.38,1.78)	0.89	(0.41,1.93)
45-49	5304	64	1.09	(0.72,1.66)	1.04	(0.67,1.60)
50-54	6682	80	1.00	(ref.)	1.00	(ref.)
≥55	1761	21	0.89	(0.54,1.45)	0.87	(0.54,1.40)

^a Adjusted by birth year, education, marital status and race.

^b Adjusted by birth year, education, marital status, race, parity, smoking, number of chronic diseases and estrogen therapy.

Table 4. Respiratory mortality according to age at natural menopause (NM). SABE study, Municipality of São Paulo, 2000.

Age at NM	Person-years	No. of deaths	Respiratory mortality			
			Model 1 ^a		Model 2 ^b	
			HR	(95% IC)	HR	(95% IC)
≤40	758	9	1.34	(0.57,3.12)	1.26	(0.51,3.09)
41-44	488	6	0.74	(0.23,2.39)	0.89	(0.28,2.82)
45-49	1650	20	0.96	(0.50,1.84)	0.85	(0.44,1.65)
50-54	2749	32	1.00	(ref.)	1.00	(ref.)
≥55	551	6	0.38	(0.13,1.05)	0.37	(0.12,1.08)

^a Adjusted by birth year, education, marital status and race.

^b Adjusted by birth year, education, marital status, race, parity, smoking, number of chronic diseases and estrogen therapy.

Table 5. Cancer mortality according to age at natural menopause (NM). SABE study, Municipality of São Paulo, 2000.

Age at NM	Person-years	No. of deaths	Cancer mortality			
			Model 1 ^a		Model 2 ^b	
			HR	(95% IC)	HR	(95% IC)
≤40	343	4	0.84	(0.26,2.65)	0.84	(0.26,2.66)
41-44	543	7	1.99	(0.93,4.26)	2.10	(1.00,4.42)
45-49	1967	25	2.04	(1.11,3.76)	2.15	(1.13,4.08)
50-54	1962	24	1.00	(ref.)	1.00	(ref.)
≥55	435	5	0.36	(0.11,1.16)	0.40	(0.13,1.24)

^a Adjusted by birth year, education, marital status and race.

^b Adjusted by birth year, education, marital status, race, parity, smoking, number of chronic diseases and estrogen therapy.

Artigo 3- Não submetido.

Título: Reproductive factors and age at natural menopause: A systematic review and meta-analysis.

Autores:

Alejandra Andrea Roman Lay, MPH^{a,b}

Carla Ferreira do Nascimento, MPH^a

Alexandre Dias Porto Chiavegatto Filho, PhD^a

^a Department of Epidemiology, School of Public Health, University of São Paulo, Brazil.

^b Faculty of health sciences, Universidad de Tarapacá, Chile.

Abstract

Objectives: To analyze the association between age at natural menopause and reproductive factors such as age at menarche, parity and use of oral contraceptives.

Methods: We analyzed Pubmed, Scielo, Scopus and LILACS databases to search for selected studies, based on previous study protocol. We performed a systematic review and meta-analysis to pool adjusted Hazard Ratios (HRs) and then present the results with a forest plot.

Results: A total of 29 articles were selected for the quantitative analysis. We found a later age of natural menopause for women with previous use of oral contraceptives (OC) compared to women with no use of OC (HR=0.86, CI=0.79, 0.92), for women with age at menarche ≥ 13 years compared to women with age at menarche < 13 years (HR=0.88, CI=0.84, 0.93), and for women with ≥ 1 live birth compared to nulliparous women (HR=0.80, CI=0.76, 0.85).

Conclusions: Despite differences in results between countries and study design, our findings suggest that previous use of OC, age at menarche ≥ 13 and having at least one live birth are associated with later menopause. The results suggest that these factors could be markers of later ovarian aging.

Keywords: Natural menopause, oral contraceptives, menarche, parity, meta-analysis.

1. Introduction

Natural menopause is defined as amenorrhea for at least 12 months after the last menstrual period without pathologic or surgical causes¹, and usually occurs between 45 and 55 years old². It is common to categorize age at natural menopause into premature (under 40 years)³, early menopause (between 40 and 44 years)⁴, and late (over 55 years)⁵. Premature and early menopause have been associated with an increase in all-cause mortality^{6,7}, while late menopause has been associated with higher life expectancy⁸. Worldwide, women are increasing their life expectancy, and it is estimated that they will spend on average two thirds of their lives being postmenopausal⁹. Further, post-menopausal women, independently of age at menopause, have a higher risk of increased metabolic syndrome and cardiovascular diseases^{10,11}.

Median age at menopause varies between countries, and different distributions of local characteristics could affect age at natural menopause, making it difficult to directly extrapolate international results. There are a few international studies that found associations of age at natural menopause with different individual factors, e.g. lifestyle and social factors such as smoking¹², Body Mass Index (BMI)¹³ and education¹⁴, and reproductive factors such as menarche, parity¹⁵ and use of oral contraceptives¹⁶, but to our knowledge there are no pooled analyzes that tested the association of reproductive factors with age at natural menopause using a broad literature review.

The aim of this study was then to perform a meta-analysis of observational studies that analyzed the associations of age at menarche, parity and use of oral contraceptives with age at natural menopause.

2. Methods

We conducted this review according to the guidelines of PRISMA¹⁷ and Meta-analysis of Observational Studies in Epidemiology¹⁸.

2.1 Study selection and eligibility criteria

We performed a literature review from Pubmed, Scielo, Scopus and LILACS databases. Our research was time limited until July 6, 2017. Two reviewers performed separately the research, using the following terms: “reproductive factors”, “menarche”, “parity”, “oral contraceptives” and “menopause”. There were no restriction of year or language (More

details in Appendix 1). The inclusion criteria was being an observational study and analyzing the association of age at natural menopause as a continuous variable as the dependent variable in a Cox proportional hazards model, with age at menarche, parity or use of oral contraceptives as exposures.

We excluded clinical trials, case reports, case-control, guidelines, reviews and articles that were not full text available (i.e. usually much older studies or conference abstracts). In addition, we decided to exclude studies with age at natural menopause categorized as premature, early and later; or any other categorization such as using the median age as a cut off point for early and later menopause. Studies that compared women with natural and surgical menopause were also excluded.

2.2 Data extraction and assessment of quality

The two investigators (ARL and CFN) analyzed every title and abstract independently through double blind review. Data extraction and evaluation of the studies were made by both investigators. For studies that did not present complete information, we constructed 2 X 2 tables to get the crude effect estimates with 95% CI. There were six studies¹⁹⁻²⁴ that did not have all the information about the factors or menopausal status. In these cases, we contacted the authors via email. Of the six authors contacted, three responded and one²⁰ offered the possibility to re-run the statistical analysis again, however due to waiting time we decided to use only available data.

For assessment of the quality of the studies, we used the Newcastle-Ottawa Scale (NOS) for cohort studies²⁵. For cross-sectional studies, we used the adapted NOS²⁶. The final score of the studies are presented in Appendix 2. We categorized the cut off points of the studies into low, moderate and high quality. For cohort studies, we categorized low as ≤ 3 , moderate as 4-6 and high as ≥ 7 , and for cross-sectional, low (≤ 4), moderate (5-7) and high (≥ 8)²⁷. Publication bias was tested by Egger's test and Begg's test⁷.

2.3 Statistical analysis

We used Stata 13.0 software to analyze the original data and generate the results through a forest plot. We used random effects models to obtain the pooled-effect estimates expressed in hazard ratios (HR), with 95% confidence intervals (CI). Heterogeneity between the studies was measured by Cochran's Q test and I^2 . We considered the cuts off points of I^2 suggested

by Higgins et al.²⁸, i.e. categorized into no heterogeneity (0%), low (<25%), moderate (25-75%) and high (>75%).

3. Results

There were 27790 articles originally identified, 11936 from PubMed, 15487 from EMBASE and 367 from LILACS. After removing 6839 duplicated articles, there were 20951 left, of which we excluded 20859 due to not including a relevant exposure (n=18665) or the relevant outcome (n=597), and 1597 that were clinical trials, case-control, case reports, guidelines and reviews, or articles not fully available. Of the remaining 92 articles, we further excluded 57 articles: 19 articles including only postmenopausal women without a comparison group, 2 articles that compared natural menopause with surgical menopause, 7 articles without any of our variables of interest, 9 articles with neither association measures of our interest nor descriptive tables with this information, 1 article that included women with natural and surgical menopause together, 3 articles that analyzed the same population (the results of one of the articles were included), 1 article for presenting results stratified by smoking, 1 article that was a meta-analysis, and 14 articles with age at menopause as categories (Appendix 3 presents the details of the exclusions), leading to a total of 35 articles^{19-24,29-57}. We further excluded 7 cross-sectional studies^{22,29-34} from our final analysis due to low quality (score of ≤ 4 points on the NOS-Scale), two studies where the categorization of the variables could not be included in any analysis^{24,35} and one study with Relative Risk (RR)⁵⁷, leading to a total of 12 cohort studies^{21,36-46} and 13 cross-sectional studies^{19-20,23,47-56} for our quantitative analysis (n=25). One cohort study was re-categorized and evaluated as cross-sectional because of the very short time between the waves⁵⁶.

The characteristics of the selected studies are presented in **Table 1**. The studies were published between 1987 and 2016. In total, there were 638.739 women included in our analysis. Almost all studies considered age at natural menopause according to the World Health Organization (WHO), defined as the absence of menstruation for at least 12 consecutive months². However, there were two studies that considered menopausal status as >6 months^{19,46}, three studies with no explicit definition of natural menopause^{20-21,55} and one study without a specific time for natural menopause⁵⁶. The characteristics of the studies according to adjustment factors is presented in Appendix 4. Of all the selected articles, there was only one that we had to use unadjusted results from the univariate analysis in order to be able to include the variables of interest³⁹.

3.1 Oral contraceptives and onset of natural menopause

For the oral contraceptive analysis, we included 13 studies: 7 cohorts and 6 cross-sectional, resulting in 334,720 women analyzed. The final results of the meta-analysis for use of oral contraceptives and age of natural menopause are presented in **Figure 1**. Despite a high heterogeneity between the studies ($I^2=79.9\%$, $p<0.001$), we found that women with OC had later age at NM (HR=0.86, 95%CI=0.79, 0.92). In results stratified by study design, we did not find significant heterogeneity for cohorts studies ($I^2=42.2\%$, $p=0.10$) and found that women who used OC before reaching menopause had later age at NM compared to women that did not use OC (HR=0.85, 95%CI=0.79, 0.91). Regarding cross-sectional studies, there was a statistically significant heterogeneity between studies (80.3%). However, the pooled HR was similar to the pooled HR obtained for all studies, as women with OC had later age at NM compared to women with no use of OC (HR=0.85, 95%CI=0.73, 0.99).

3.2 Age at menarche and onset of natural menopause

For the age at menarche analysis, we included 10 studies: 4 cohort and 6 cross-sectional studies. In total there were 258,893 women analyzed. We excluded from this analysis one study that used age at menarche ≥ 11 years as the reference group³⁷ and one study with age at 12 years or more as the comparison group⁴⁷.

In **Figure 2**, it is shown that there was moderate heterogeneity between all studies ($I^2=46.9\%$, $p=0.05$), and women with age at menarche at 13 years or more had later age at NM compared to women with ages at menarche <13 years old (HR=0.88, 95%CI=0.84, 0.93).

3.3 Parity and onset of natural menopause

For the parity analysis, we included 19 studies: 9 cohorts and 10 cross-sectional studies. We had to exclude from the quantitative analysis 2 studies because they did not include nulliparous women as the reference^{19,41}, and one study had the same cohort population as another⁵³. In all selected studies the reference group was nulliparous women. The results for parity are presented in **Figure 3**. There was a high heterogeneity between the studies ($I^2=73.9\%$, $p<0.001$). The results show that women with one live birth had later age at NM in comparison with nulliparous women (HR=0.80, 95%CI=0.76, 0.85).

3.4 Publication bias

We tested the three analyzes for publication bias, and found that only the parity results were significant for Egger's test, and none was significant for Begg's test (oral contraceptives: $p=0.06$ and 0.62 , respectively; age at menarche: $p=0.20$ and $p=0.18$; and women with one or more live birth: $p=0.02$ and $p=0.23$).

4. Discussion

The study found that the use of oral contraceptives (OC), age at menarche ≥ 13 years and having one or more live births were associated with later onset of natural menopause. This is the first meta-analysis that tested the association between reproductive factors and age at natural menopause using a unified methodology. Regarding OC, this is the first meta-analysis to summarize the association with age at NM. For the other two factors, while there is one previous meta-analysis that analyzed the association of nulliparous and early menarche with premature and early menopause¹⁵, it was solely based on nine studies included in the International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE). In 2011, a previous systematic review⁵⁸ found an association between OC and later menopause, but a quantitative analysis was not performed due to inconsistency among the included studies.

Although there was a high heterogeneity between the selected studies, our results were similar for the selected cohort and cross-sectional studies. Even though studies have frequently shown an association of oral contraceptives with later NM, there are few that aim to explain its physiological pathways. Menopausal transition is characterized by high serum levels of follicle stimulating hormone (FSH)⁵⁹. Vries et al⁴⁴ found that OCs suppress the levels of FSH, delaying age at menopause. Another hypothesis is the incessant ovulation, the same proposed to explain an increased risk of earlier NM in nulliparous women. According to this theory, OCs suppress ovulation, increasing the "survival time" of the follicles in the ovaries, delaying natural menopause⁶⁰. However, this is still controversial since almost all follicles are lost by atresia rather than ovulation. Women with age at menarche at 13 or more years had later age at NM compared to women with age at menarche at ≤ 12 years. We performed a subanalysis including just the studies with women with age at menarche at 14 years or more, and found that they also presented earlier age at NM (HR=0.89, CI=0.86, 0.93), with low heterogeneity between 8 studies ($I^2=27.7\%$, $p=0.20$) (data not shown). In

addition, a recent study found that age at menarche over 15 years slightly decreased the risk of NM between 1 and 5%, however the same study found that the reproductive period, i.e. the time between menarche and menopause, was 9 times higher in women with age at menarche ≤ 9 years compared to age at menarche ≥ 17 years⁶¹. Since age at menarche is highly influenced by genetics, prenatal, maternal and childhood characteristics⁶²⁻⁶³, it is difficult to establish a linear relation between age at menarche and NM.

Regarding parity, women also had later age at NM. We found that parity was the reproductive factor with highest later natural menopause. The mechanism of which parity could reduce the risk of earlier NM is thought to be the same as previously mentioned for OC, with both decreasing ovulatory cycles and delaying menopause^{44,60}.

This study has a few strengths and limitations. Our strengths are the population size (n=638.739), the largest overall study to our knowledge to analyze the association of reproductive factors with age at NM. Second, we included studies published worldwide, with no language restriction, while most meta-analyzes include only studies in English.

Regarding the limitations, the main issue is that we found moderate to high heterogeneity for the OC and parity analyzes. For the OC results, this heterogeneity can be partially attributed to the inclusion of small studies. The studies with the highest heterogeneity were those with the smallest sample size^{37,55}. Regarding parity, there was high heterogeneity for both types of study designs. Regarding cohort studies, there were two studies with very high later NM, and both studies included specific populations at risk: one study analyzed women with HIV infection³⁷ and the other women with depression⁴². Regarding cross-sectional studies, there were large differences mainly for three studies^{49,51,52} which could not be explained by sample size or year of publication. Also, these high heterogeneity studies analyzed data from different countries. Two studies included Brazilian women^{49,52} and one Chinese women⁵¹. In the Brazilian studies, the population was employees of Rio de Janeiro University, with a high degree of education, similar to the Chinese study⁵¹ where only 19% of the women presented low education level. Another possible issue is that we included six studies with dichotomous variable (nulliparous versus had one child or more) which presented high heterogeneity ($I^2=83.8\%$, $p<0.001$), with a pooled HR that could overestimate the overall obtained for all studies (HR=0.67, CI=0.53, 0.86) (data not shown). Finally, we decided to include studies with moderate quality assessment, which could increase the heterogeneity between the results.

Despite these limitations, our results bring new knowledge to the discussion about the association of reproductive factors with age at natural menopause. This is expected to be a growing epidemiologic area of interest for the near future as women spend increasingly more time of their lives postmenopausal.

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Table 1. Summary of the eligible studies.

Study	Country	Design	Samples sizes	Early menarche Assessment	Parity Assessment	OC or HC ^a	Measure of NM	Adjustment factors
Dölleman et al. 2015 ³⁶	The Netherlands	Cohort	1,163	Uncontrolled	Uncontrolled	Current vs previous	Continuous HR	None.
Calvet et al. 2015 ³⁷	Brazil	Cohort	667	≥11 vs <11	Nulliparity vs ≥1	Yes vs No	Continuous HR	Age at menarche, parity, use of OC, Smoking, BMI, Chronic hepatitis C, CD4 count and AIDS.
Stepaniak et al. 2013 ³⁸	Russia, Poland and six Czech towns	Cohort	12,676	Uncontrolled	Uncontrolled	Yes vs No	Continuous HR	Age, population, education, marital status, smoking, BMI, physical activity, alcohol consumption, supplementation with vitamins and minerals, hormonal contraceptives, HRT.
Gold et al. 2013 ³⁹	US	Cohort	3,253	Uncontrolled	*Nulliparity vs 1,2,3, ≥4	Never vs Ever	Continuous HR	Race/ethnicity, smoking, self-reported health, educational level, alcohol, current employment, physical activity and baseline weight. *None
Morris et al. 2012 ⁴⁰	UK	Cohort	50,678	Uncontrolled	Nulliparity vs 1,2, ≥3	Uncontrolled	Continuous HR	Age, smoking and BMI.
Nagata et al. 2012 ⁴¹	Japan	Cohort	3,115	≤12 vs 13-14,15-16, ≥17	1 vs nulliparity, 2, ≥3	No vs Yes	Continuous HR	Age.
Dratva et al. 2009 ³⁵	Spain, France, Belgium, Switzerland, UK, Norway, Sweden, Iceland	Cohort	4,606	Continuous	≥2 vs Nulliparity-1	Uncontrolled	Continuous HR	Country, age at menarche, parity, smoking, BMI and physical activity.

	and Estonia.							
Cassou et al. 2007 ⁴²	France	Cohort	226	≤12 vs ≥13	Nulliparity vs ≥1	Years of use	Continuous HR	Education, age at menarche, parity and high job.
Nagel et al. 2005 ⁴³	Germany	Cohort	4,807	≤11 vs 12,13,14, ≥15	Nulliparity vs 1-2, ≥3	No vs Yes	Continuous HR	Age, education, parity, age at first full pregnancy, breast feeding, OC use, HRT use, age at menarche, time till regular menses, physical activity, smoking and BMI.
Vries et al. 2001 ⁴⁴	The Netherlands	Cohort	8,701	Uncontrolled	Nulliparity vs 1-2, ≥3	Years of use	Continuous HR	Parity, smoking, BMI, health insurance, year of birth and years of OC use.
Gold et al. 2001 ⁴⁵	US	Cohort	14,620	Uncontrolled	Nulliparity vs ≥1	Never vs Ever	Continuous HR	Site, smoking, Use of oral contraceptives, livebirths, educational attainment, marital status, race/ethnicity, employment and history of heart disease.
Kato et al. 1998 ⁴⁶	US	Cohort	4,694	≤11 vs 12,13,≥14	Nulliparity vs 1,2,≥3	Uncontrolled	Continuous HR	Age.
Do et al. 1998 ²¹	Australia	Cohort	5,593	11-14 vs ≤10 and ≥15	Nulliparity vs 1-2, ≥3	Uncontrolled	Continuous HR	Birth year, age at menarche, parity, smoking, education and occupation.
Pallikadavath et al. 2016 ²⁹	India	Cross-sectional	630,361	Uncontrolled	Nulliparity vs 1,2,3, ≥4	No vs Yes	Continuous HR	Education, wealth quintiles, religion, caste, residence, region, ever been sterilized, abortion and

								marital status.
Brand et al. 2015 ⁴⁷	France, Italy, Spain, UK, Netherlands, Greece, Germany, Denmark and	Cross-sectional	258,898	<12 vs ≥12	Uncontrolled	Never vs Ever	Continuous HR	Age at menarche, number of full-term pregnancies, ever use of OCs and HRT, BMI, smoking status, alcohol consumption, physical activity and education.
Zsakai et al., 2015 ⁴⁸	Hungary	Cross-sectional	1,932	Uncontrolled	Nulliparous vs 1,2,3,≥4	No vs Yes	Continuous HR	Birth cohorts.
Emaus et al. 2013 ¹⁹	US	Cross-sectional	97,945	11-12 vs ≤10, 13-14, ≥15	Never pregnant vs 1, ≥2	Uncontrolled	Continuous HR	Physical activity, race/ethnicity, smoking, BMI, age at menarche, age at first full-term pregnancy, ever pregnant, never pregnant.
Mendes et al. 2013 ⁴⁹	Brazil	Cross-sectional	1,222	Uncontrolled	Nulliparity vs 1-2, ≥3	Uncontrolled	Continuous HR	Smoking, education, alcohol consumption.
Sievert et al. 2013 ⁵⁰	Hawaii	Cross-sectional	545	Uncontrolled	Parous vs nulliparous	Uncontrolled	Continuous HR	Ethnicity, financial comfort, BMI, smoking and marital status.
Pérez-Alcalá et al. 2013 ²²	Spain	Cross-sectional	575	<12 vs 12-14, ≥14	Nulliparous vs 1-2,3,≥4	No vs yes	Continuous HR	None.
Yasui et al. 2012 ²³	Japan	Cross-sectional	24,152	≤11 vs 12, ≥13	0 vs ≥1	No vs Yes	Continuous HR	BMI, cycle regularity, unilateral oophorectomy, ever smoke before menopause and birth year.
Li et al. 2012 ⁵¹	China	Cross-sectional	20,275	<14 vs ≥14	0 vs 1, ≥2	Uncontrolled	Continuous HR	Education, income, BMI and smoking.
Otero et al. 2011 ⁵²	Brazil	Cross-sectional	1,366	Uncontrolled	≥1 vs Nulliparity	Uncontrolled	Continuous HR	None.
Otero et al. 2010 ⁵³	Brazil	Cross-sectional	1,462	Continuous	≥4 vs 0,1-3	Ever vs never	Continuous HR	None.

Vélez et al. 2010 ²⁴	Argentina, Barbados, Brazil, Chile, Cuba, Mexico and Uruguay.	Cross-sectional	4,056	Uncontrolled	1-4 vs nulliparous, ≥ 5	Uncontrolled	Continuous HR	Childhood circumstances (perception of health, rural residence, hunger during infancy), education, occupation and smoking.
Aydin et al. 2010 ³⁰	Turkey	Cross-sectional	1,106	Continuous	No vs ever gave birth	Never vs ever	Continuous HR	None.
Henderson et al. 2008 ²⁰	US	Cross-sectional	95,704	<11 vs 11-12, 13-14, 15-16, ≥ 17	Nulliparity vs 1,2-3, ≥ 4	Uncontrolled	Continuous HR	Ethnicity, smoking, age at menarche, parity and BMI.
Kaczmarek et al. 2007 ⁵⁴	Poland	Cross-sectional	7,183	<14 vs ≥ 14	Nulliparous vs 1,2, ≥ 3	No vs Yes	Continuous HR	Educational level, usual menstrual cycle length, smoking and self-reported health status.
Pierl et al. 2007 ⁵⁵	Germany	Cross-sectional	792	<12 vs 12-13, >13	Nulliparous vs 1-2, ≥ 3	Never vs ever ^a	Continuous HR	OC use, HT use, parity, smoking, thyroidal medicaments.
Ortiz et al. 2006 ³¹	Puerto Rico	Cross-sectional	792	Uncontrolled	Nulliparity vs 1-2, ≥ 3	Never vs Ever	Natural menopause vs pre-menopausal OR	Age.
Schoenbaum et al. 2005 ³²	US	Cross-sectional	571	Uncontrolled	≥ 4 vs 0-1,2-3	Uncontrolled	Menopausal status vs pre-menopausal OR	HIV, drug use, physical activity and age.
Palmer et al. 2003 ⁵⁶	US	Cross-sectional	17,070	≥ 15 vs <11, 11, 12-13, 14	Nulliparous vs 1,2,3, ≥ 4	Uncontrolled	Continuous HR	Smoking, education, BMI, unilateral oophorectomy and vigorous physical activity.
Bromberger et al. 1997 ³³	US	Cross-sectional	185	Uncontrolled	Yes vs no	No vs yes*	Continuous RR	Race, menstrual cycles, smoking, weight reduction diet, parity and education. *None.

Gonzales et al., 1997 ³⁴	Peru	Cross-sectional	640	Continuous	Continuous	No vs Yes	Continuous HR	None.
Stanford et al. 1987 ⁵⁷	US	Cross-sectional	2,406	≤11 vs 12,13, ≥14	Nulliparous vs 1-2,3-4, ≥5	No vs yes	Menopausal vs Premenopausal RR	None.

^a Hormonal contraceptives

Figure 1. Hazard ratios (HRs) with 95% confidence intervals (CIs) for age of natural menopause and use of Oral Contraceptives (OC) stratified by study design.

Figure 2. Hazard ratios (HRs) with 95% confidence intervals (CIs) for onset of natural menopause and age at menarche at 13 or more years.

Figure 3. Hazard ratios (HRs) with 95% confidence intervals (CIs) for onset of natural menopause and women with one or more live birth.

Appendix 1

Study protocol

PhD candidates Alejandra Roman Lay and Carla Ferreira do Nascimento, in collaboration with Professor Alexandre Dias Porto Chiavegatto Filho, all from the School of Public Health of the University of São Paulo performed this meta-analysis as an extension of an analysis about factors associated with age at menopause in women from the Municipality of São Paulo, Brazil.

Title

Reproductive factors and age at natural menopause: A systematic review and meta-analysis.

Background

There are growing concerns about the timing at which natural menopause occurs. Early menopause has been associated with greater risk of incident heart failure¹, cardiovascular mortality and all-cause mortality^{2,3}, while later menopause has been associated with breast cancer risk⁴. A better understanding of determinants of natural menopause could help in the prevention of adverse outcomes. To our knowledge this is the first meta-analysis analyzing reproductive factors (early menarche, nulliparity and oral contraceptive) associated with age at menopause.

Aim

To evaluate the association between reproductive factors and age at natural menopause.

Research plan

This study will be guided by PRISMA checklist and flow diagram.

Variables of interest

Exposure

Early menarche: Menarche is the onset of menstruation. We included 13 years old as the cut-off, as it is the frequently used in the literature.

Parity: Number of live births. According to the World Health Organization (WHO) it is “the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life”⁷. We analyzed the question “Did you ever have a live birth?”, and categorized the number of births as 0 and ≥ 1 .

Oral contraceptives: Refers to use of oral contraceptives before reaching menopause. It is usually presented as a dichotomous variable categorized as yes or no, or never used/ever used. In addition, we are going to consider studies with a general denomination as hormonal contraceptives (not restrictive to oral).

Outcome

The outcome of interest is age at natural menopause, defined by the World Health Organization (WHO) as the presence of amenorrhea for at least 12 months after the last menstrual period, for natural reasons and not others like bilateral oophorectomy⁸.

Search strategy

Last date of research: 06/07/2017

Terms used in PubMed, Scielo, Scopus and LILACS databases:

English

((Reproductive AND factors) OR menarche OR (parity OR deliveries) OR (“oral contraceptives” OR hormonal)) AND ((menopause)) NOT animals OR NOT “animals”.

Spanish

((Reproductivos AND factores) OR menarca OR hijos OR (“contraceptivo oral” OR hormonal)) AND ((menopausia)) AND NOT “animales”.

Portuguese

((Reprodutivos AND fatores) OR menarca OR filhos OR (“anticoncepcionais orais” OR hormonal)) AND ((menopausa)) AND NOT “animais”.

Study selection

Articles will be eligible if they meet the inclusion criteria based on titles, abstract and full text available. This study does not have year and language restrictions.

Inclusion criteria

- Cohort, cross-sectional studies providing complete information (effect estimate in HR or RR, IC and p value) for the association between early menarche, parity and use of oral contraceptives with age at menopause.
- Studies with of age at menopause as a continuous variable, included in Cox proportional hazard models.

Exclusion criteria

- Clinical trials.
- Case-control.
- Case reports.
- Letters to the editor.
- Guidelines.
- Articles that are not full-text available.
- Studies in which women with natural and surgical menopause were analyzed together.
- Without the relevant exposures, i.e. articles with titles, abstract or full-text available without the reproductive variables of interest.
- Without the relevant outcome, i.e. articles with titles, abstract or full-text available without age at natural menopause.

Data extraction and assessment of quality of studies

The search results will be analyzed independently by the two reviewers. Differences will be discussed between them, and if there is no agreement a third reviewer will resolve. If necessary, we will send e-mails to authors of articles with incomplete information or

variables classified differently from our study, or if exposure variable were analyzed as continuous.

For assessment of quality, we will use the Newcastle-Ottawa Scale (NOS) for cohort studies. Regarding comparability, we will consider age as the most important adjustment factor and smoking and education as additional adjustment factors. The adapted Newcastle-Ottawa Scale will be used for cross-sectional studies⁹.

Risk of bias

Publication bias will be tested by Egger's test and Begg's test including at least 10 articles.

Statistical analysis

Data will be analyzed using Stata 13.0 software. Heterogeneity between the studies will be tested using Cochran's Q test and I^2 . A Cochran's Q test <0.10 will indicate heterogeneity. We are going to use the cuts off point suggested by Higgings JPT et al.¹⁰ for categorizing I^2 into no heterogeneity (0%), low heterogeneity ($<25\%$), moderate heterogeneity (25-75%) and high heterogeneity ($>75\%$). Depending on the results, we will use fixed-effect model if heterogeneity is low, otherwise we will use a random effects model. The final results will be presented by a forest plot.

Appendix 2

Evaluation of 38 studies included by the Newcastle-Ottawa Scale (NOS)

	Selection	Comparability	Outcome	Total
Dölleman ¹¹	4	2	2	8
Calvet ¹²	3	1	2	6
Stepaniak ¹³	4	2	2	8
Gold 2013 ¹⁴	4	1	2	7
Emaus ¹⁵	1	2	2	5
Morris ¹⁶	4	2	2	8
Nagata ¹⁷	2	2	1	5
Dratva ¹⁸	3	2	1	6
Henderson ¹⁹	3	1	1	5
Cassou ²⁰	2	1	2	5
Nagel ²¹	3	1	2	6
Vries ²²	4	2	2	8
Gold 2001 ²³	4	1	1	6
Kato ²⁴	1	2	2	5
Do ²⁵	2	2	2	6
Pallikadavath ²⁶	2	0	1	3
Brand ²⁷	3	2	2	7
Zsakai ²⁸	3	1	2	6
Mendes ²⁹	3	0	2	5
Sievert ³⁰	3	1	1	5
Pérez-Alcalá ³¹	1	0	1	2
Yasui ³²	1	2	2	5
Li ³³	2	1	2	5
Otero 2011 ³⁴	3	0	2	5
Otero 2010 ³⁵	3	1	2	6
Vélez ³⁶	5	1	2	8
Aydin ³⁷	1	1	1	3
Kaczmarek ³⁸	4	1	2	7
Pierl ³⁹	3	2	2	7
Ortiz ⁴⁰	1	0	2	3
Schoenbaum ⁴¹	1	1	1	3
Palmer ⁴²	3	1	2	6
Bromberger ⁴³	0	0	2	2
Gonzales ⁴⁴	1	0	2	3
Stanford ⁴⁵	2	1	2	5

Appendix 3

PRISMA Flow Diagram

Excluded studies and reasons for exclusion.

Ref	First Author, Year	Journal	Reason(s) to exclusion
46	Abdollahi et al., 2013	Medical Journal of the Islamic Republic of Iran	Only postmenopausal women, without group to compare.
47	Dorjgochoo et al., 2008	Menopause	Only postmenopausal women, without group to compare.
48	Golshiri et al., 2016	Journal of Menopausal Medicine	Only postmenopausal women, without group to compare.
49	Shobeiri et al., 2014	International Journal of Fertility & Sterility	Only postmenopausal women, without group to compare.
50	Rumianowski et al., 2016	Gesundheitswesen	Only postmenopausal women, without group to compare.
51	Esmaili et al., 2013	The Iranian Journal of Obstetrics, Gynecology and Infertility	Only postmenopausal women, without group to compare.
52	Ayatollahi et al., 2002	Iranian Journal of Medical Sciences	Only postmenopausal women, without group to compare.
53	Hidayet NM et al., 1999	Eastern Mediterranean Health Journal	Only postmenopausal women, without group to compare.
54	Liu et al., 2016	International Journal of Clinical and Experimental Medicine	Only postmenopausal women, without group to compare.
55	Rojas et al., 1993	Revista Colombiana de Obstetricia y Ginecología	Only postmenopausal women, without group to compare.
56	Pérez et al., 1996	Revista Cubana de Endocrinología	Only postmenopausal women, without group to compare.
57	Farahmand et al., 2013	Journal of Obstetrics and Gynaecology Research	Only postmenopausal women, without group to compare.
58	Benjamin , 1960	South African Medical Journal	Only postmenopausal women, without group to compare.
59	Rizk et al., 1998	Maturitas	Only postmenopausal women, without group to compare.
60	Johnston, 2003	Collegium Antropologicum	Only postmenopausal women, without group to compare.
61	Garrido-Latorre et al., 1996	International Journal of Gynecology & Obstetrics	Only postmenopausal women, without group to compare.

62	Kaur et al., 20098	The anthropologist	Only postmenopausal women, without group to compare.
63	Aghoozi et al., 2014	Journal of Babol University of Medical Sciences	Only postmenopausal women, without group to compare.
64	Balić et al., 2014	Menopause: The Journal of the North American Menopause Society	Only postmenopausal women, without group to compare.
65	Dvornyk et al., 2006	Maturitas	Compare natural menopause with surgical menopause.
66	Pokoradi AJ., 2011	American Journal of Obstetrics & Gynecology	Compare natural menopause with surgical menopause.
67	Reynolds et al., 2005	American Journal of Human Biology	Without variable of our inclusion.
68	Pedro et al., 2003	Cadernos de Saúde Pública	Without variable of our inclusion.
69	Ahuja, 2016	Journal of Mid-Life Health	Without variable of our inclusion.
70	<u>Blümel</u> et al, 2006	Menopause: The Journal of the North American Menopause Society	Without variable of our inclusion.
71	Mishra et al., 2007	Menopause: The Journal of the North American Menopause Society	Without variable of our inclusion.
72	Taffe et al., 1997	Maturitas	Without variable of our inclusion.
73	Ashrafi et al., 2008	International Journal of Gynecology & Obstetrics	Without variable of our inclusion.
74	Johnston, 2001	American Journal of Human Biology	Without association measures of our interest or tables information.
75	Reynolds et al., 2001	Annals of Human Biology	Without association measures of our interest or tables information.
76	Luoto et al., 1994	American Journal of Epidemiology	Without association measures of our interest in variables of interest.
77	Brambilla et al., 1989	Journal of Clinical Epidemiology	Without association measures of our interest or tables information.
78	Gonzales et al., 1997	Menopause: The Journal of the North American Menopause Society	Without association measures of our interest or tables information.
79	Reynolds et al., 2003	Annals of Human Biology	Without association measures of our interest or tables information.
80	OlaOlorun et al., 2009	Climacteric, The Journal of the International Menopause Society (IMS)	Without association measures of our interest or tables information.
81	Torgerson et al., 1994	Maturitas	Without association measures of our interest or tables information.

82	Sievert et al, 2003	Human Biology	Analyze women with natural and surgical together.
83	Nagata et al., 1998	Maturitas	Same population and results of other study included.
84	Kaczmarek, 2007	Przegląd Menopauzalny	Same population and results of other study included.
85	Ortiz et al., 2003	Puerto Rico Health Sciences Journal	Same population and results of other study included.
86	Calentano et al., 2003	Tumori Journal	Results estratified by smoking.
87	Mishra et al., 2017	Human reproduction	Meta-analysis
88	van Noord et al., 1997	Fertility and sterility	Age at menopause categorized.
89	Pirincci et al., 2016	Journal of Women & Aging	Age at menopause categorized.
90	Meschia et al., 2000	Maturitas	Age at menopause categorized.
91	Parazzini et al., 2007	Maturitas	Age at menopause categorized.
92	Agaba et al., 2017	Journal of Virus Eradication	Age at menopause categorized.
93	Zaldivar et al., 1995	Ginecología y obstetricia de México	Age at menopause categorized.
94	Dasgupta et al., 2015	American Journal of Human Biology	Age at menopause categorized.
95	Snowdon et al., 1989	American Journal of Public Health	Age at menopause categorized.
96	Gudmundsdottir et al., 2013	Journal Climacteric	Age at menopause categorized.
97	Parazzini et al., 1992	Maturitas	Age at menopause categorized.
98	Ortega-Ceballos et al., 2006	Salud Pública de México	Age at menopause categorized.
99	Cassou et al., 1997	Maturitas	Age at menopause categorized.
100	Ozdemir et al., 2004	Maturitas	Age at menopause categorized.
101	Vehid et al., 2006	Saudi Medical Journal	Age at menopause categorized.

Appendix 4

Table 2. Adjustment factors by article selected.

	Sociodemographic factors							Reproductive factors					Lifestyle factors						
	Age	Race/ethnicity	Country	Occupation	Education	Income	Marital status	Parity	Pregnant	Age at menarche	Use of OC	Hormonal contraceptives	Menstrual cycle	Oophorectomy	Smoking	Body mass index (BMI)	Alcohol consumption	Physical activity	Weight
Dölleman ¹¹																			
Calvet ¹²										x	x				x	x			
Stepaniak ¹³	x		x		x		x					x			x	x	x	x	
Gold, 2013 ¹⁴																			
Morris ¹⁶	x														x	x			
Nagata ¹⁷	x																		
Dratva ¹⁸			x					x		x					x	x		x	
Cassou ²⁰				x	x			x		x									
Nagel ²¹	x				x			x	x	x	x	x	x		x	x		x	
Vries ²²	x							x			x				x	x			
Gold, 2001 ²³		x	x	x	x		x				x				x				
Kato ²⁴																			
Do ²⁵	x			x	x			x		x					x				
Pallikadavath ²⁶					x		x												
Brand ²⁷					x				x	x	x				x	x	x	x	
Zsakai ²⁸	x																		
Emaus ¹⁵		x							x	x					x	x			
Mendes ²⁹					x										x		x		
Sievert ³⁰		x					x								x	x			
Pérez-Alcalá ³¹																			
Yasui ³²	x												x	x	x	x			
Li ³³					x	x									x	x			

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6 CONSIDERAÇÕES FINAIS

A literatura internacional apresenta poucos estudos sobre os fatores que afetam a menopausa em países latino-americanos. Nesta tese foi analisada a idade de menopausa natural nas mulheres do estudo SABE segundo diferentes aspectos. No artigo 1 foram analisadas as mulheres das três coortes 2000, 2006 e 2010, enquanto que no artigo 2 foi analisado um acompanhamento de 16 anos da mortalidade nas mulheres da coorte 2000. Nos dois artigos foram utilizados modelos de regressão de Cox para a análise de fatores associados e para a análise de sobrevivência segundo a idade da menopausa.

Assim, o principal objetivo do estudo foi analisar a associação da mortalidade e de fatores socioeconômicos, reprodutivos e de risco com a idade da menopausa. No artigo 1, verificou-se uma associação entre tabagismo e menor idade da menopausa, tanto nas ex-fumantes como fumantes atuais. A escolaridade também apresentou uma associação significativa com a idade da menopausa, sendo verificado que quanto mais anos de escolaridade, mais tardia é a menopausa. Os resultados são similares a estudos realizados em países desenvolvidos, indicando que a associação da idade da menopausa com a escolaridade e o tabagismo independente do país em estudo. Isso é de importante relevância já que o Brasil é um dos países da América Latina com maior desigualdade socioeconômica e educacional.

O segundo objetivo da tese foi analisar a mortalidade segundo a idade da menopausa, originando o primeiro estudo da América Latina a analisar essa associação. A distribuição das causas de óbito da amostra foi de 45% por doenças cardiovasculares, 37% por doenças respiratórias e 18% por neoplasias. As mulheres que apresentaram idade da menopausa entre os 41 a 44 anos de idade tiveram maior risco de mortalidade geral comparadas às mulheres com menopausa entre os 50 e 54 anos (referência). Além disso, mulheres com idade da menopausa entre os 45 e 49 anos tiveram o dobro do risco de mortalidade por neoplasias comparadas ao grupo de referência.

O artigo 3 foi o primeiro estudo a analisar os fatores reprodutivos associados à idade da menopausa por meio de uma revisão bibliográfica e posterior meta-análise dos resultados. Encontrou-se que o uso de anticoncepcionais orais, idade da menarca igual ou maior a 13 anos, e ter um ou mais filhos, estiveram associados com uma menopausa tardia.

Em todos os países, tanto os desenvolvidos como os em desenvolvimento, as mulheres estão vivendo em média mais do que os homens. Estima-se que as mulheres vão passar dois terços

das suas vidas sendo pós menopáusicas. É importante a elaboração de políticas públicas para não só aumentar a expectativa de vida dos idosos, mas também para melhorar a qualidade de vida e garantir uma velhice saudável. No presente estudo, verificou-se que tanto os fatores reprodutivos como também alguns fatores sociodemográficos e fatores de risco como o consumo de tabaco, estão associados à idade da menopausa natural. A identificação dos fatores de risco para a menopausa precoce pode trazer contribuições para a saúde pública. Especificamente, no desenvolvimento de medidas preventivas na área de saúde das idosas, dados os efeitos negativos da menopausa precoce na incidência de doenças cardiovasculares e na mortalidade precoce.

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ANEXOS

Anexo 1. Documento de aprovação do Estudo SABE 2000

UNIVERSIDADE DE SÃO PAULO
FACULDADE DE SAÚDE PÚBLICA
COMITÊ DE ÉTICA EM PESQUISA DA FSP/USP - COEP
Av. Dr. Arnaldo, 715 - CEP 01246-904 - São Paulo - Brasil
Telefones: (55-11) 3066 7742 - fax (55-11) 3064 7314

J7

Of.COEP/67/99

24 de maio de 1999

Pelo presente, informo que o Comitê de Ética em Pesquisa, aprovou, em sua 3.ª/99, Sessão Ordinária, de 19.05.99, de acordo com os requisitos da Resolução CNS/196/96, o Projeto de Pesquisa "AS CONDIÇÕES DE SAÚDE DOS IDOSOS NA AMÉRICA DO SUL E CARIBE", apresentado pelo pesquisador Ruy Laurenti, devendo ser remetido à CONEP conforme as normas da Resolução 196/96.

Atenciosamente,

Prof.Dr. Paulo Antonio de Carvalho Fortes
Vice-Coordenador do Comitê de Ética em Pesquisa da FSP-COEP

Anexo 2. Documento de aprovação do Estudo SABE 2006

Universidade de São Paulo
Faculdade de Saúde Pública

COMITÊ DE ÉTICA - COEP

Av. Dr. Arnaldo, 715 – Assessoria Acadêmica - CEP 01246-904 – São Paulo – Brasil
Telefones: (55-11) 3066-7779 – e-mail: coep@fsp.usp.br

Of.COEP/83/06

14 de março de 2006

Pelo presente, informo que o Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo-COEP, **aprovou** o Protocolo de Pesquisa n.º 1345, intitulado: “PROJETO SABE-2005 – SAÚDE, BEM-ESTAR E ENVELHECIMENTO. AS CONDIÇÕES DE SAÚDE E DE VIDA DOS IDOSOS NO MUNICÍPIO DE SÃO PAULO”, apresentado pela pesquisadora Maria Lúcia Lebrão.

Atenciosamente,

Helena Akemi Wada Watanabe
Professora Doutora

Vice-Coordenadora do Comitê de Ética em Pesquisa da FSP-COEP

Anexo 3. Documento de aprovação do Estudo SABE 2010

COMITÊ DE ÉTICA EM PESQUISA – COEP/FSP

Universidade de São Paulo
Faculdade de Saúde Pública

OF.COEP/23/10

5 de março de 2010.

Prezado(a) Pesquisador(a) e Orientador(a),

O Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo – COEP/FSP, **analisou**, de acordo com a Resolução N.º 196/96 do Conselho Nacional de Saúde – CNS e suas complementares, o protocolo de pesquisa n.º **2044**, intitulado **"ESTUDO SABE 2010: SAÚDE, BEM-ESTAR E ENVELHECIMENTO - ESTUDO LONGITUDINAL SOBRE AS CONDIÇÕES DE VIDA E SAÚDE DOS IDOSOS NO MUNICÍPIO DE SÃO PAULO"**, área temática **GRUPO III**, sob responsabilidade do(a) pesquisador(a) **Maria Lucia Lebrão**, e considerou que a pendência anteriormente apresentada por este COEP foi atendida. Protocolo de pesquisa **APROVADO "AD-REFERENDUM"**.

Cabe lembrar que conforme Resolução CN /196/96, são deveres do (a) pesquisador (a): **1. Comunicar**, de imediato, qualquer alteração no projeto e aguardar manifestação deste CEP (Comitê de Ética em Pesquisa), para dar continuidade à pesquisa; **2. Manter sob sua guarda e em local seguro**, pelo prazo de 5 (cinco) anos, os dados da pesquisa, contendo fichas individuais e todos os demais documentos recomendados pelo CEP, no caso eventual auditoria; **3. Comunicar**, formalmente a este Comitê, quando do encerramento deste projeto; **4. Elaborar e apresentar relatórios parciais e final**; **5. Justificar**, perante o CEP, interrupção do projeto ou a não publicação dos resultados.

Atenciosamente,

Claudio Leone
Professor Titular

Coordenador do Comitê de Ética em Pesquisa - COEP

Ilm.º Sr.º

Prof.ª Tit. Maria Lucia Lebrão

Departamento de Epidemiologia da FSP/USP

Anexo 4. Termo de consentimento Livre e Esclarecido

Termo de Consentimento Livre e Esclarecido

O estudo SABE é um estudo longitudinal sobre as condições de vida e saúde das pessoas de 60 anos e mais no Município de São Paulo, que teve início em 2000, continuou em 2006 e retorna em 2010. Esse é um estudo realizado pela Faculdade de Saúde Pública da Universidade de São Paulo, com financiamento da FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) e Ministério da Saúde.

Os objetivos do estudo são:

1. Descrever as condições de vida das pessoas de 60 anos e mais
2. Descrever as condições de saúde das pessoas de 60 anos e mais;
3. Avaliar o acesso e utilização dos serviços disponíveis e a contribuição da família para o cuidado das pessoas com 60 anos e mais;
4. Avaliar, por meio de testes de sangue e de urina, as possíveis doenças que podem acometer as pessoas de 60 anos e mais,

Inicialmente serão tomadas medidas como peso, estatura e gordura corporal, exame de força muscular manual e provas de eficiência física (caminhar, agachar, dobrar, levantar e sentar em uma cadeira), **respeitadas as restrições de cada um**, e exame bucal.

Em um segundo momento, serão colhidas amostras de sangue e de urina, seguindo rotinas padronizadas por pessoal capacitado e treinado para este fim,

supervisionado por profissional qualificado.

Por último, o participante responderá a um questionário sobre seu estado de saúde.

Serão tomadas todas as medidas necessárias para assegurar a confidencialidade de toda informação dada e não será revelada a identidade de

qualquer participante do estudo. Se for encontrada alguma anormalidade no exame bucal ou nos testes de laboratório, o participante da pesquisa será informado e encaminhado a um serviço ao qual poderá recorrer em caso de necessidade.

As amostras de sangue poderão ser armazenadas, se o participante autorizar, por tempo indeterminado, sem identificação nominal, de forma segura e em local especialmente preparado para a conservação das mesmas, sob responsabilidade da Dra Maria Lúcia Lebrão. Assim como em outras pesquisas no país e no mundo, essas amostras são fundamentais para futuras análises que possam ampliar o conhecimento sobre as doenças em estudo, contribuindo para o avanço da ciência.

No caso de hospitalização, autorizo, adicionalmente, que o/a representante do SABE, devidamente credenciado/a, copie dados constantes na papeleta de internação, bem como resultados de exames realizados durante minha internação.

Foi-me informado que se eu tiver alguma dúvida ou pergunta adicional sobre este estudo posso telefonar para **Profa.Dra. Maria Lucia Lebrão**, coordenadora do Estudo nos telefones **3061-7105** ou **3061-7815** ou para o **Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da USP**, no telefone **3061-7779**.

Meu consentimento em participar é voluntário e sem coerção ou força e estou ciente de que, fora o desconforto da picada para a coleta de sangue, minha participação na pesquisa não representa risco para a minha integridade física ou mental e nem benefício direto. Entendo que tenho o direito de terminar a entrevista no momento em que desejar e que poderei retirar meu consentimento a qualquer tempo, bastando para isso entrar em contato com a pesquisadora ou o Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da USP.

Assim, declaro que compreendi e estou de acordo com o exposto acima e, também, que o sangue e urina colhidos sejam utilizados:

☐ somente para exames hematológicos e bioquímicos, no momento

☐ para exames hematológicos e bioquímicos, no momento, e que o soro do sangue e a urina sejam guardados para exames posteriores.

Por este meio aceito colaborar com o Estudo SABE: - Saúde, bem-estar e envelhecimento no Município de São Paulo – 2010”.

_____	_____
Nome	Data

_____	_____
Assinatura Profa. Dra. Maria Lúcia Lebrão	

Pesquisadora responsável

Anexo 5. Questionário do estudo SABE 2000

SEÇÃO A - INFORMAÇÕES PESSOAIS

HORA DE INÍCIO: [] [] : [] []

DECLARAÇÃO VOLUNTÁRIA

Antes de começar, gostaria de assegurar-lhe que esta entrevista é completamente voluntária e confidencial. Se houver alguma pergunta que o Sr não deseje responder, simplesmente me avise e seguiremos para a próxima pergunta.

A.1a

Em que mês e ano o(a) Sr(a) nasceu?

MÊS [] []

ANO [] [] [] []

A.6

Qual a última série de que grau, na escola, o Sr. obteve com aprovação?

ANOTE A SÉRIE DO ÚLTIMO GRAU APROVADO E REGISTRE SÓ A OPÇÃO QUE CORRESPONDA A ESSE GRAU.

Primeiro grau (ou primário + ginásio) 01 [] []

Segundo grau (antigo clássico e científico) 02 [] []

Primeiro grau + auxiliar técnico 03 [] []

Técnico de nível médio (ex: técnico em contabilidade, laboratório) 04 [] []

Magistério - segundo grau (antigo normal) 06 [] []

Graduação (nível superior) 07 [] []

Pós-graduação 08 [] []

NS 988

NR 999

A.12 (PREGUNTA OPCIONAL)

Qual destas opções o descreve melhor?

BRANCO (de origem européia) 1

MESTIÇO (combinação de branco e índio) 2

MULATO (combinação de branco e negro) 3

NEGRO 4

INDÍGENA 5

ASIÁTICO 6

OUTRA 7

NS 8

NR 9

HISTÓRIA DE UNIÕES

A.13a

Com relação ao seu estado marital, alguma vez o(a) Sr.(a) foi casado(a) ou teve uma união livre?

SIM 1

NÃO 2 →

NR 9

VÁ PARA
A.18

A.18

Quantos filhos e filhas nascidos vivos o(a) Sr.(a) teve?

NÃO INCLUA ENTEADOS, FILHOS ADOTIVOS, ABORTOS OU FILHOS NASCIDOS MORTOS.

NÚMERO DE FILHOS: [] []

NS 98

NR 99

SEÇÃO C - ESTADO DE SAÚDE

C.4

Alguma vez um médico ou enfermeiro lhe disse que o(a) Sr(a) tem pressão sanguínea alta, quer dizer, hipertensão?

SIM 1
 NÃO 2
 NS 8
 NR 9

VÁ PARA
C.5

C.5

Alguma vez um médico ou enfermeiro lhe disse que o(a) Sr(a) tem diabetes, quer dizer, níveis altos de açúcar no sangue?

SIM 1
 NÃO 2
 NS 8
 NR 9

VÁ PARA
C.6

C.7

Alguma vez um médico ou enfermeiro lhe disse que tem alguma doença crônica do pulmão, como asma, bronquite ou enfisema?

SIM 1
 NÃO 2
 NS 8
 NR 9

VÁ PARA
C.8

C.11f

Em que ano ou com que idade foi diagnosticada a osteoporose?

ANO [] [] [] [] []

IDADE [] [] []

NS 9998

NR 9999

C.18 FILTRO

Sexo do entrevistado

MULHER.....1

HOMEM.....2 → VÁ PARA C.19

C.18e

A senhora fez histerectomia, isto é, uma cirurgia para tirar o útero e os ovários, ou apenas o útero?

SIM, ÚTERO E OVÁRIOS 1
 SIM, APENAS ÚTERO 2
 NÃO 3
 NS 8
 NR 9

VÁ PARA
C.18g

C.18f

Que idade tinha quando lhe fizeram a histerectomia?

IDADE [] [] []

NS 998

NR 999

VÁ PARA
C.18h

<p>C.18g</p> <p>Que idade tinha quando menstruou pela última vez?</p>	<p>IDADE [][]</p> <p>AINDA MENSTRUA 00</p> <p>NS 98</p> <p>NR 99</p>
<p>C.18h</p> <p>A senhora tomou alguma vez ou toma atualmente estrógeno, isto é, hormônio de mulher para a menopausa, através de comprimidos, adesivos (emplastos) ou creme?</p>	<p>SIM 1</p> <p>NÃO 2</p> <p>NS 8</p> <p>NR 9</p> <p>VÁ PARA C.20</p>
<p>C.18i</p> <p>Com que idade começou a tomar hormônios para a menopausa?</p>	<p>IDADE [][]</p>
<p>C.24</p> <p>O Sr. tem ou teve o hábito de fumar?</p> <p>LEIA CADA OPÇÃO ATÉ OBTER UMA RESPOSTA AFIRMATIVA.</p>	<p>FUMA ATUALMENTE 1</p> <p>JÁ FUMOU, MAS NÃO FUMA MAIS 2 → VÁ PARA C.24b</p> <p>NUNCA FUMOU 3</p> <p>NS 8</p> <p>NR 9</p> <p>VÁ PARA C.25a</p>

Anexo 6. Currículo lattes orientador

Alexandre Dias Porto Chiavegatto Filho

Endereço para acessar este CV: <http://lattes.cnpq.br/5517850224634709>

Última atualização do currículo em 04/09/2018

Possui graduação em Economia pela FEA/USP, doutorado direto em Saúde Pública pela FSP/USP e pós-doutorado na Universidade de Harvard. É professor doutor do Departamento de Epidemiologia da FSP/USP na área de estatísticas de saúde, orientador dos programas de pós-graduação em Saúde Pública e Saúde Global da USP e coordenador de cursos sobre o uso do R para a análise de dados e sobre machine learning em saúde. Atuou como professor convidado (2016) e pesquisador visitante (2017) na Universidade de Harvard. Atualmente é o Pesquisador Principal de pesquisas financiadas pela FAPESP, CNPq e Fundação Lemann. Em 2015-2016 foi responsável pelo curso online Big Data em Saúde no Brasil da parceria USP-Coursera, que teve mais de 8.500 alunos matriculados e representantes de todos os Estados brasileiros. É o diretor do Laboratório de Big Data e Análise Preditiva em Saúde (Labdaps) da FSP/USP. Tem experiência em pesquisas na área de saúde pública, com ênfase em estatísticas de saúde. **(Texto informado pelo autor)**

Identificação

Nome

Alexandre Dias Porto Chiavegatto Filho

Nome em citações bibliográficas

Chiavegatto Filho, A.D.P.;CHIAVEGATTO FILHO, A. D. P.;Chiavegatto Filho, Alexandre Dias Porto;Filho, Alexandre Dias Porto Chiavegatto;PORTO CHIAVEGATTO FILHO, ALEXANDRE DIAS;Chiavegatto Filho, Alexandre DP;Chiavegatto, Alexandre Dias Porto;Chiavegatto Filho, Alexandre;Filho, Alexandre Chiavegatto;CHIAVEGATTO FILHO, ALEXANDRE D P;CHIAVEGATTO FILHO, A D P

Anexo 7. Currículo lattes aluno

Alejandra Andrea Roman Lay

Endereço para acessar este CV: <http://lattes.cnpq.br/7974594829262480>

Última atualização do currículo em 08/09/2018

Possui graduação em Fisioterapia-Universidad de Tarapacá (UTA-2009), Mestrado em Saúde Pública com menção em Epidemiologia (UTA-2012) e atualmente Doutoranda em Saúde Pública pela Universidade de São Paulo (USP), bolsista da Comissão Nacional de Investigación Científica e Tecnológica (CONICYT) de Chile . Já foi fisioterapeuta em centros de atenção primária (Arica-Chile) e professora da Universidad de Tarapacá. Tem experiência nos seguintes temas: Saúde Pública e epidemiologia, doenças respiratórias e cardiovasculares, envelhecimento, mortalidade e saúde reprodutiva da mulher. **(Texto informado pelo autor)**

Identificação

Nome	Alejandra Andrea Roman Lay
Nome em citações bibliográficas	LAY, A. R.;ROMAN-LAY, ALEJANDRA;ROMAN LAY ALEJANDRA ANDREA;ROMAN LAY, ALEJANDRA ANDREA