



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

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ABSTRACT

Objectives: To systematically review the evidence on the association between age at natural menopause (NM) and reproductive factors such as age at menarche, parity and ever use of oral contraceptives.

Study design: A literature search was carried out in PubMed, Scielo, Scopus and LILACS databases, without restriction of publication year until July 6, 2017. We excluded clinical trials, case-control studies, case reports and studies using statistical methods other than Cox proportional hazard models to assess the factors associated with age at NM. Cross-sectional studies evaluating women aged < 50 years were also excluded. Random-effects models were used to pool the estimates. We registered the systematic review in the International Prospective Register of Systematic Review (PROSPERO) in August 2018, CRD42018099105.

Results: We identified 30 articles to include in the meta-analysis. We found that previous ever use of oral contraceptives (OC) (HR = 0.87, CI = 0.82, 0.93), age at menarche ≥ 13 years (HR = 0.90, CI = 0.84, 0.96), and having at least one live birth (HR = 0.79, CI = 0.74, 0.85) were associated with a later age of NM.

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.

1. Introduction

Natural menopause is defined as amenorrhea for at least 12 months after the last menstrual period without pathologic or surgical causes [1]. It is common to categorize age at natural menopause into premature (under 40 years) [2], early menopause (between 40 and 44 years) [3], normal menopause (usually between 45 and 55 years) [4] and late menopause (over 55 years) [5]. Premature and early menopause have been shown to increase all-cause mortality [6,7], while later menopause has been associated with higher life expectancy [5] and also with adverse health outcomes such as an increased risk of breast cancer [8]. Different factors have been associated with the age at presentation of menopause: while smoking and underweight are associated with earlier menopause [9,10], high education is related to later menopause [11]. In addition, there are a few international studies that found associations of age at natural menopause with reproductive factors such as menarche, parity [12] and use of oral contraceptives [13]. A better managements of determinants affecting age at menopause could

prevent adverse outcomes in women's health.

To our knowledge there are no pooled analyzes that summarize the evidence on the association of reproductive factors with age at natural menopause. In this study, we carried out a systematic review and meta-analysis on the associations of age at menarche, parity and ever use of oral contraceptives with age at NM.

2. Methods

We conducted this review according to the guidelines of PRISMA [14] and Meta-analysis of Observational Studies in Epidemiology [15].

2.1. Study selection and eligibility criteria

We performed the literature review in Pubmed, Scielo, Scopus and LILACS databases. We collect all the articles indexed in the databases without restriction of year of publication until the last day of our search, July 6, 2017. Two reviewers performed separately the literature

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search, using the following terms: “reproductive factors”, “menarche”, “parity”, “oral contraceptives” and “menopause”. There was no language restriction (More details in S1 file). We included observational studies; cohorts and cross-sectional studies providing complete information (effect estimated in HR, IC and p value) that analyzed the association of age at natural menopause (as continuous variable) with age at menarche, parity or ever use of oral contraceptives, using the Cox proportional hazards model.

We excluded clinical trials, case reports, case-control, letters to the editor, guidelines, reviews and articles whose full text was not available (i.e. usually much older studies or conference abstracts). In addition, we excluded 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 or pre-menopausal versus menopausal status were also excluded. In addition, we excluded cross-sectional studies with only women under 50 years at study entry because they did not include the total age range considered as normal (45–55 years).

2.2. Data extraction and assessment of quality

Two investigators (ARL and CFN) analyzed the titles and abstracts independently, then also extracted the data and evaluated the studies independently. Six studies [16–21] did not provide all the information on the menopausal status or the associated factors that were evaluated. We contacted the authors via email, and three provided the requested information, and another [17] 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 studies [22]. For cross-sectional studies, we used the adapted NOS [23]. The final scores of the studies are presented in S2 file. 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) [24]. Publication bias was tested using Egger’s test and Begg’s test [7].

2.3. Statistical analysis

We used Stata 13.0 in the data analysis and the hazard ratios (HR) were pooled using a random effects models. The results were stratified by study design. Heterogeneity between the studies was measured using Cochran’s Q test and I^2 . We considered the cut off points of I^2 suggested by Higgins et al. [25], i.e. categorized into no heterogeneity (0%), low ($< 25\%$), moderate (25–75%) and high ($> 75\%$). In addition, we conducted subanalysis for the associations of OC, age at menarche and parity according to sample size; small (< 1000 women), medium (< 5000 women) and large studies (≥ 5000 women).

3. Results

Fig. 1 shows the study selection flow chart. In the literature search, we identified 27790 articles, 11936 from PubMed, 15487 from EMBASE and 367 from LILACS. After removing 6839 duplicated articles, 20951 were reviewed, of which we excluded 20860 due to not including a relevant exposure ($n = 18665$) or the relevant outcome ($n = 597$), and 1598 that were clinical trials, case-control, case reports, guidelines and reviews, or articles not fully available. Of the remaining 91 articles, we further excluded 61 articles: 19 articles that included only postmenopausal women without a comparison group, 2 articles that compared natural menopause with surgical menopause, 7 articles that did not evaluate any of our variables of interest, 7 studies that did not use Cox proportional hazard models, 1 study with variables of our inclusion, but that did not add Cox regression model, 1 study where the

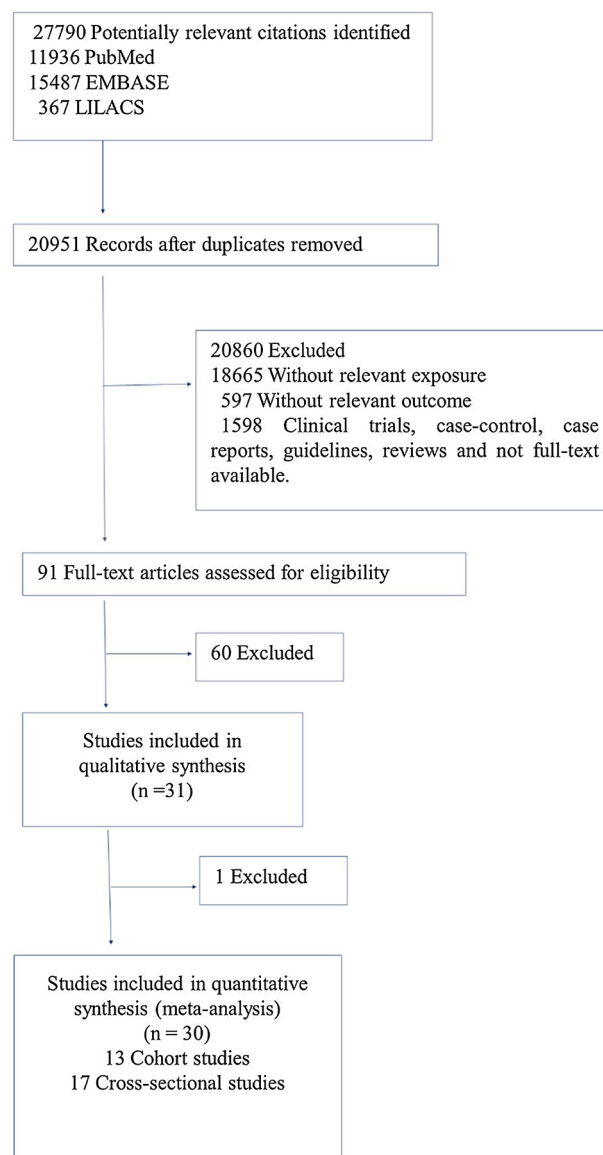


Fig. 1. PRISMA Flow Diagram.

results were not expressed in HR with their respective CI, 1 article that included only women under 50 years at study entry, 1 article that evaluated women with natural and surgical menopause, 4 articles that analyzed the same population (the results of one of the articles had already been included), 1 article that presented the results stratified by smoking, 1 article that was a meta-analysis, and 14 articles that categorized age at menopause (S3 presents the details of the exclusions), leading to a final total of 31 articles [13,16–21,26–49]. We further excluded 1 study where the categorization of the variable parity could not be included in any analysis [21], leading to a total of 13 cohort studies [13,18,26–36] and 17 cross-sectional studies [16,17,19,20,37–49] for our quantitative analysis ($n = 30$). One cohort study was re-categorized and evaluated as cross-sectional because of the very short time between the waves [48].

The characteristics of the selected studies are presented in Table 1. The studies were published between 1997 and 2015. In total, 646,458 women were included in our analysis. Most of the studies considered age at natural menopause according to the World Health Organization (WHO) definition, i.e. the absence of menstruation for at least 12 consecutive months [4]. However, there were two studies that considered menopausal status as > 6 months [16,36], three studies with no

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 [26]	The Netherlands	Cohort	1,163	Uncontrolled	Uncontrolled	Current vs previous Yes vs No	Continuous HR	None.
Calvet et al. 2015 [27]	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 [28]	Russia, Poland and six Czech towns	Cohort	12,676	Uncontrolled	Uncontrolled	No vs Yes	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 [13]	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.
Morris et al. 2012 [29]	UK	Cohort	50,678	Uncontrolled	Nulliparity vs 1,2, ≥ 3	Uncontrolled	Continuous HR	*None Age, smoking and BMI.
Nagata et al. 2012 [30]	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 [31]	Spain, France, Belgium, Switzerland, UK, Norway, Sweden, Iceland and Estonia.	Cohort	4,606	Continuous	≥ 2 vs Nulliparity-1	Uncontrolled	Continuous HR	Country, age at menarche, parity, smoking, BMI and physical activity.
Cassou et al. 2007 [32]	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 [33]	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 [34]	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 total years of OC use.
Gold et al. 2001 [35]	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 [36]	US	Cohort	4,694	≤ 11 vs 12,13, ≥ 14	Nulliparity vs 1,2, ≥ 3	Uncontrolled	Continuous HR	Age.
Do et al. 1998 [18]	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.
Brand et al. 2015 [37]	France, Italy, Spain, UK, Netherlands, Greece, Germany, Denmark and Hungary	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 [38]	Hungary	Cross-sectional	1,932	Uncontrolled	Number of gestations	No vs Yes	Continuous HR	Birth cohorts.
Emaus et al. 2013 [16]	US	Cross-sectional	97,945	11-12 vs ≤ 10, 13-14, ≥ 15	Age at first full-term pregnancy (in years) and parity	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 [39]	Brazil	Cross-sectional	1,222	Uncontrolled	Nulliparity vs 1-2, ≥ 3	Uncontrolled	Continuous HR	Smoking, education, alcohol consumption.
Sievert et al. 2013 [40]	Hawaii	Cross-sectional	545	Uncontrolled	Parous vs nulliparous	Uncontrolled	Continuous HR	Ethnicity, financial comfort, BMI, smoking and marital status.
Pérez-Alcalá et al. 2013 [19]	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 [20]	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 [41]	China	Cross-sectional	20,275	< 14 vs ≥ 14	0 vs 1, ≥ 2	Uncontrolled	Continuous HR	Education, income, BMI and smoking.
Otero et al. 2011 [42]	Brazil	Cross-sectional	1,366	Uncontrolled	≥ 1 vs Nulliparity	Uncontrolled	Continuous HR	None.

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Table 1 (continued)

Study	Country	Design	Samples sizes	Early menarche Assessment	Parity Assessment	OC or HC ^a	Measure of NM	Adjustment factors
Otero et al. 2010 [43]	Brazil	Cross-sectional	1,462	Continuous	≥ 4 vs 0,1-3	Ever vs never	Continuous HR	None.
Vélez et al. 2010 [21]	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 [44]	Turkey	Cross-sectional	1,106	Continuous	Number of births continuous	Never vs ever	Continuous HR	None.
Henderson et al. 2008 [17]	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 [45]	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.
Pieri et al. 2007 [46]	Germany	Cross-sectional	792	< 12 vs 12-13, > 13	Nulliparous vs 1,2, ≥ 3	Never vs ever ^b	Continuous HR	OC use, HT use, parity, smoking, thyroidal medicaments.
Ortiz et al. 2006 [47]	Puerto Rico	Cross-sectional	792	Uncontrolled	Nulliparity and 1 vs 2-3, ≥ 4	Never vs Ever	Continuous HR	Age.
Palmer et al. 2003 [48]	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.
Gonzales et al., 1997 [49]	Peru	Cross-sectional	640	Continuous	Continuous	No vs Yes	Continuous HR	None.

^a Results without adjustment factors.

^b Hormonal therapy.

explicit definition of natural menopause [17,18,46] and one study without a specific time for natural menopause [48]. The characteristics of the studies according to control for confounding factors are presented in S4. Of all the selected articles, there was only one that we had to use crude results in order to be able to include the variables of interest [13].

3.1. Oral contraceptives and onset of natural menopause

For the oral contraceptive analysis, we included 17 studies: 7 cohorts and 10 cross-sectional, resulting in 337,833 women analyzed (Fig. 2). We observed a moderate heterogeneity between the studies ($I^2 = 66.4\%$, $p < 0.001$), and women who ever used OC had later age at NM (HR = 0.87, 95%CI = 0.82, 0.93). In the analysis stratified by study design, we did not find significant heterogeneity for cohorts studies ($I^2 = 0\%$, $p = 0.45$) and found that women who ever used OC before reaching menopause had later age at NM (HR = 0.87, 95% CI = 0.83, 0.91). Regarding cross-sectional studies, there was a statistically significant heterogeneity between studies (75.1%). 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 = 0.87, 95% CI = 0.76, 0.98). Results of the subanalysis show that smaller studies had greater heterogeneity and the decreased risk of earlier NM was not statically significant ($I^2 = 80.9\%$, $p < 0.001$; HR = 0.85, 95% CI = 0.63,1.13), while medium studies had low heterogeneity compared to larger studies, i.e. medium ($I^2 = 17.2\%$, $p = 0.30$; HR = 0.89, 95% CI = 0.81,0.97) and large ($I^2 = 69.4\%$, $p = 0.011$; HR = 0.88, 95% CI = 0.82,0.95).

3.2. Age at menarche and onset of natural menopause

For age at menarche, we included 9 studies: 4 cohort and 5 cross-sectional studies. In total 232,010 women were analyzed. We excluded from this analysis studies in which age at menarche < 13 years old was not included as reference [18,27,37,41,45,48].

Fig. 3 shows that there was moderate heterogeneity between studies ($I^2 = 38.7\%$, $p = 0.11$), and women with age at menarche at 13 years or more had later age at NM (HR = 0.90, 95%CI = 0.84, 0.96). We performed a subanalysis using age at menarche as a continuous variable. There were four studies [31,43,44,49]; one cohort [31] and three cross-sectional studies [43,44,49], with moderate heterogeneity between the studies ($I^2 = 60.5\%$, $p = 0.05$) and age at menopause was negatively associated with age at menarche (HR = 0.95), but the confidence interval barely included the reference (95% CI = 0.90,1.00). According to sample size, from larger to smaller studies, there is a trend of decreased risk of earlier NM, despite not being statically significant in medium and small studies; 9% (HR = 0.91, 95% CI = 0.88,0.95), 13% (HR = 0.87, 95% CI = 0.71,1.06) and 22% (HR = 0.78, 95% CI = 0.56,1.08) respectively.

3.3. Parity and onset of natural menopause

Regarding parity, we included 19 studies: 9 cohorts and 10 cross-sectional studies. Four studies were excluded because nulliparous women were not considered as the reference [21,30,31,43], and two studies that did not consider parity as number of live births [16,38]. The results for parity are presented in Fig. 4. There was a high heterogeneity between the studies ($I^2 = 76.8\%$, $p < 0.001$), and parous women had later age at NM (HR = 0.79, 95% CI = 0.74, 0.85).

Only two cross-sectional studies presented parity as continuous variable [44,49], and we did not observe any association between the number of births and age at NM (HR = 1.18, 95% CI = 0.89,1.55). Similar to OC and menarche, there is a tendency of decreased risk of earlier NM according to sample size, for small studies (HR = 0.60, 95% CI = 0.50,0.73), medium (HR = 0.80, 95% CI = 0.73,0.88) and large studies (HR = 0.86, 95% CI = 0.84,0.88).

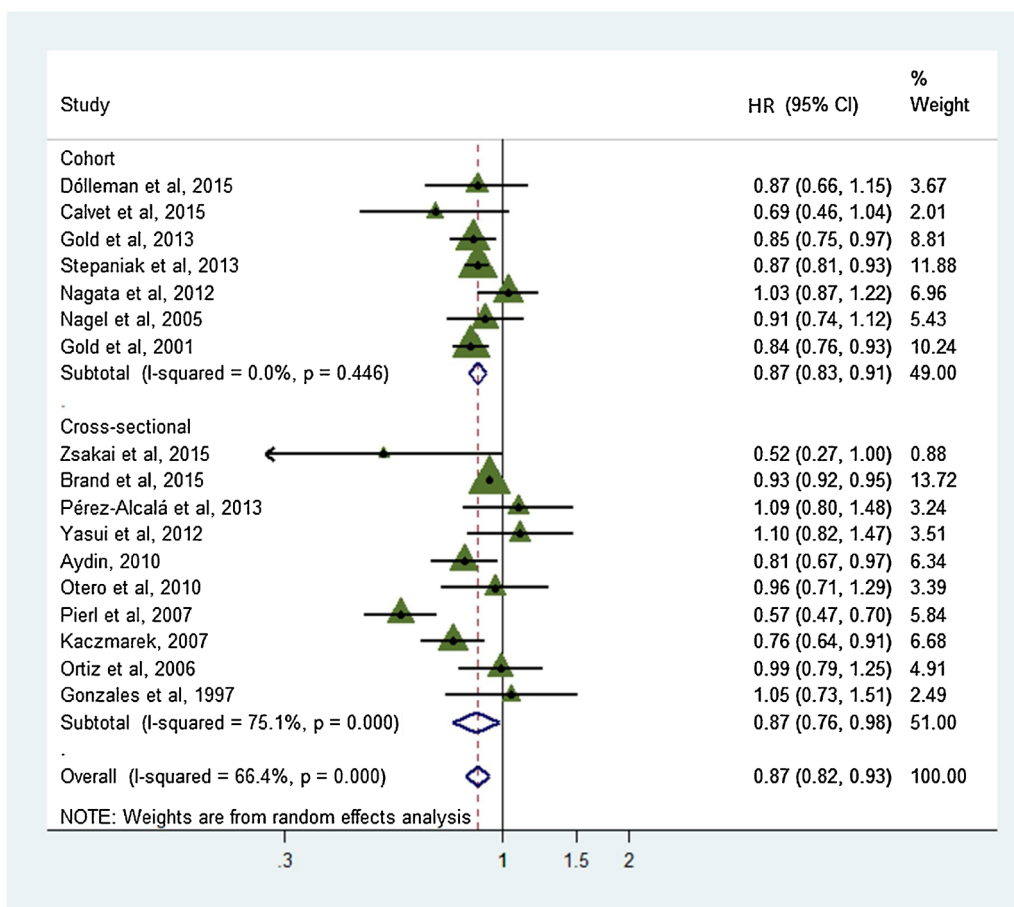


Fig. 2. Hazard ratios (HRs) with 95% confidence intervals (CIs) for age of natural menopause and use of Oral Contraceptives (OC) stratified by study design.

3.4. Publication bias

Regarding publication bias, we observed that for parity the Egger’s test was statistically significant ($p < 0.05$), whereas for the OCs exposure we did not observe any evidence of bias.

4. Discussion

In this meta-analysis, we observed that the ever use of oral contraceptives (OC), age at menarche ≥ 13 years and having one or more live births were associated with later age at natural menopause. Regarding OC, this is the first meta-analysis to summarize its association with age at NM. For the other two factors, while there is a previous meta-analysis that analyzed the association of nulliparous and early menarche with premature and early menopause [12], 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 review [50] 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 heterogeneity among the studies, our results were similar for cohort and cross-sectional studies, regardless of the country of origin, sample size and adjustment factors. We included 17 studies evaluating the association of OCs and age at natural menopause: 7 studies found a significant association between OCs and later menopause, 5 studies found that this association was not significant and 4 studies showed an inverse relationship, however none was significant.

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) [51]. Vries et al. [34] 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 menopause [52]. However, this is still controversial since almost all follicles are lost by atresia rather than ovulation.

In the analysis of age at menarche and menopause, all studies found an association to later menopause, however in 5 studies the association was not significant. 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. Most studies included age at menarche ≥ 14 years. Therefore, we performed a subanalysis including just those studies with two studies whose reference was < 14 years, finding that they also presented earlier age at NM (HR = 0.89, 95% CI = 0.86, 0.93), with low heterogeneity among 9 studies ($I^2 = 18.4\%$, $p = 0.28$) (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 years [53]. Since age at menarche is highly influenced by genetics, prenatal, maternal and childhood characteristics [54,55], it is difficult to establish a

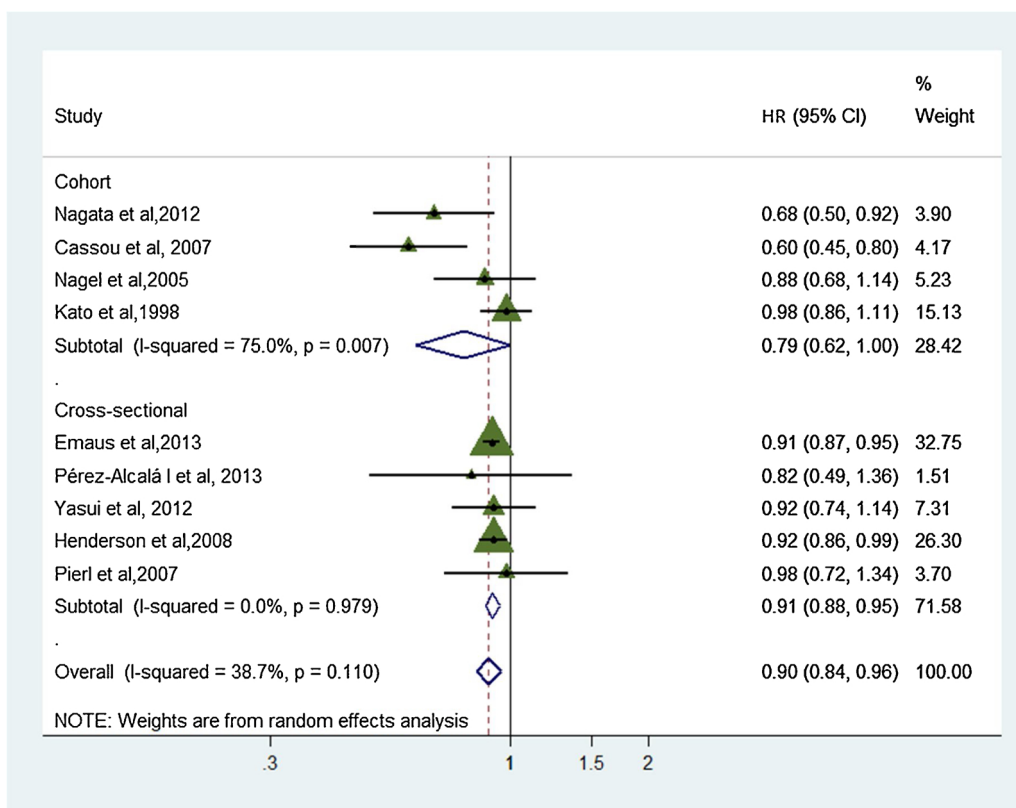


Fig. 3. Hazard ratios (HRs) with 95% confidence intervals (CIs) for onset of natural menopause and age at menarche at 13 or more years.

linear relation between age at menarche and NM.

Regarding parity, parous women had later age at NM. 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 [34,52].

This study has a few strengths and limitations. Our strengths are the population size (n = 646,458), 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-analyses include only studies in English.

Regarding the limitations, retrospective studies that analyze age at menopause may be prone to recall bias. The more time women spend being consulted about their menopausal age, the less chance they have of remembering their exact date, especially in older individuals. Women tend to refer numbers for age at NM that are easy to remember, so they tend to decrease or slightly increase their age by remembering the whole year closer to their real age of menopause. For example, when the real age of menopause is 48 years, she may refer menopause age at 50 [56]. Similarly, a recall bias may occur at age at menarche, especially given the very long that has passed. All the studies included used self-reported age at menarche and not status quo method or prospective recall. Therefore, the results for the association of age at menarche and menopause should be analyzed with caution.

We could not analyze the length of OC use. Of all the articles included, there were four studies that analyzed it (26,32,34,44). However, these four studies categorized the length of OC differently, making it difficult to include their results in a pooled-HR. In addition, there were two studies that collected this information but did not use it (37–38).

For OC analysis, 42% of the heterogeneity can be attributed to the inclusion of small studies (sample size less than 1000 women) [19,27,46,47,49] and the inclusion of studies with inverse association (earlier age at menopause) between OC and age at natural menopause [19,20,30,49]. Finally, in parity analysis, 48% of the heterogeneity was explained by small studies [19,27,32,40,46], country classification (developed versus developing countries) [27,39,42] and population at risk [27,32].

We had strict exclusion criteria to avoid tendentious results. We excluded case-control studies because women who are controls may become cases if our outcome is natural menopause, and all studies where statistical analysis was not Cox proportional hazard models. In addition, we excluded one cross-sectional study with postmenopausal women under 50 years of age at menopause that were not followed in time, because these left out the normal age range considered by the WHO as a natural menopause (45–55), which could bias the results towards an earlier menopause.

Our findings may have an influence in the reproductive life of women. If the use of OCs delays menopause, fertility would also be prolonged. Currently, there is a tendency to delay motherhood and many women choose eggs freezing as an option. However, this procedure has associated risks such as ovarian hyperstimulation syndrome. In addition, the cost of egg preservation is high, not being an accessible method for all women [57], so the OCs is currently the widely used method to avoid pregnancy.

In conclusion, 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 postmenopausal time in their lives.

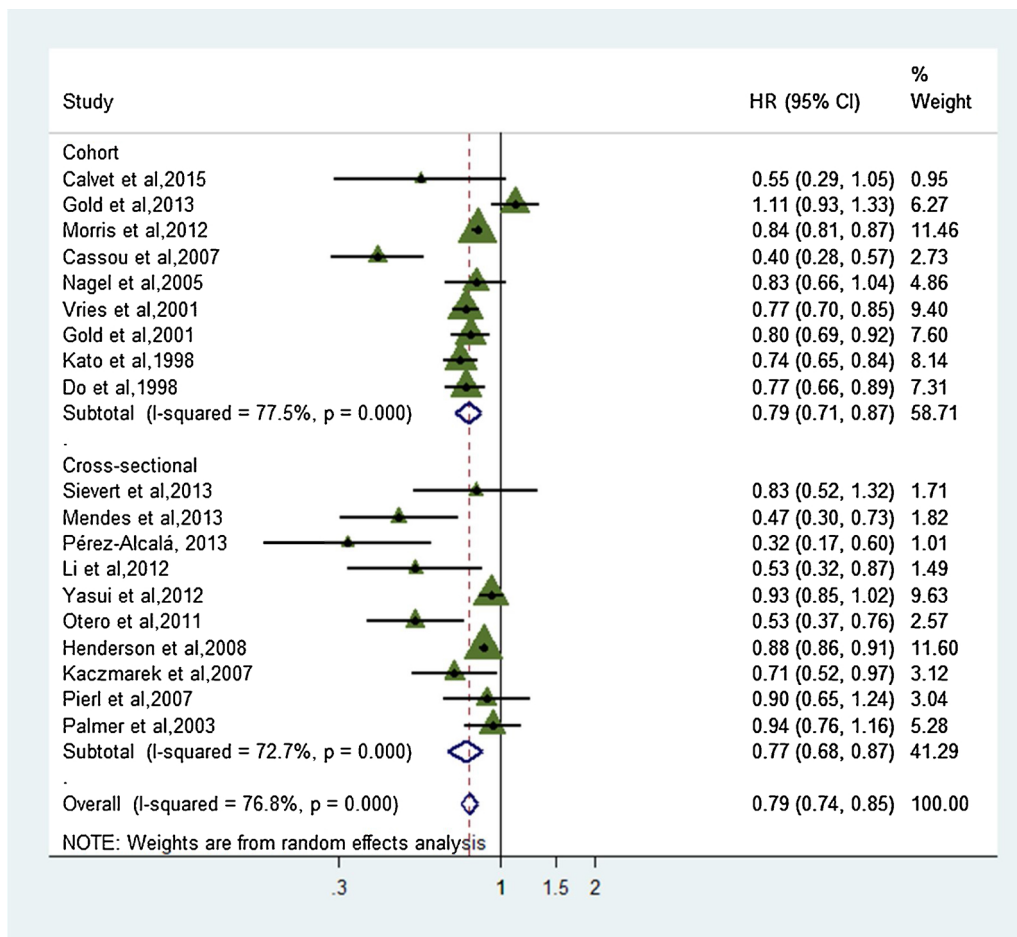


Fig. 4. Hazard ratios (HRs) with 95% confidence intervals (CIs) for onset of natural menopause and women with one or more live birth.

Contributors

Alejandra Andrea Roman Lay was responsible for study conception and design, analysis and interpretation of data, and drafting the article.

Carla Ferreira do Nascimento was responsible for analysis and interpretation of data.

Bernardo Lessa Horta was responsible for study design, analysis and interpretation of data.

Alexandre Dias Porto Chiavegatto Filho was responsible for study design, analysis and interpretation of data.

All authors contributed to revision of the article and approved the final version.

Conflict of interest

The authors declare that they have no conflict of interest.

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Provenance and peer review

This article has undergone peer review.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.maturitas.2019.10.012>.

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