The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis

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The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis

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ABSTRACT

Objective: The aim of this study was to estimate the global prevalence of primary ovarian insufficiency (POI) and early menopause (EM).

Methods: A comprehensive literature search was performed in several databases to retrieve relevant English articles published between 1980 and 2017. To assess the methodological quality of the studies, the Newcastle-Ottawa Scale was used. The heterogeneity of results across the studies was assessed using Cochran’s Q test and quantified by the $I^2$ statistic. Prevalence estimates of all studies were pooled using a random-effects meta-analysis model at a confidence level of 95%.

Results: A total of 8937 potentially relevant articles were identified from the initial searches. Thirty-one studies met the inclusion criteria and were included in this meta-analysis. The pooled prevalence of POI and EM was calculated as 3.7% (95% confidence interval: 3.1, 4.3) and 12.2% (95% confidence interval: 10.5, 14), respectively. The prevalence of POI was higher in medium and low Human Development Index countries. The prevalence trend did not change over time.

Conclusion: The prevalence of POI and EM in women is considerable. The results of this study could contribute to consciousness-raising of health policy-makers toward the necessity of prioritizing, planning, and allocating health resources as preventive and treatment interventions for these women.

Introduction

The perpetual cessation of menstrual cycles for 12 successive months occurring without any perceived psychological or pathological causes is called natural menopause. The mean age of women experiencing natural menopause has been reported as 51.4 years.

The age at which menopause occurs is under the influence of various factors including genetic, hormonal, environmental, and lifestyle-related ones. However, if amenorrhea occurs at an earlier age (i.e., before the age of 40 years) accompanied with a serum follicle stimulating hormone increase to the mean age of women experiencing natural menopause has been reported as 51.4 years.

Although mostly considered an idiopathic disorder, POI could also be due to autoimmune complications, genetic causes, inflammatory conditions, or metabolic syndromes. POI and EM occur either spontaneously or as a result of medical interventions, including chemotherapy or bilateral oophorectomy.

POI and EM are associated with both psychosocial and physiological problems. An increased risk for osteoporosis and fractures, overall cardiovascular disease, stroke, type 2 diabetes, and total mortality have been reported for women with spontaneous POI or EM.

POI has been reported as affecting about 1% of women younger than age 40 years and EM as affecting 5% of women between 40 and 45 years of age. The Study of Women’s Health Across the Nation (SWAN) reported a 1.1% prevalence of POI among women; in terms of ethnicity, 1% of Caucasian, 1.4% of African American, 1.4% of Hispanic, 0.5% of Chinese, and 0.1% of Japanese women experienced POI. In a pooled study of 51,450 postmenopausal women from nine cohort studies, 2% and 7.6% of women were reported as having POI and EM, respectively.

To date, there is a scarcity of data on the prevalence of POI and EM worldwide. Hence, we performed a systematic review of studies on the prevalence of POI and EM in different countries over various time periods. The review posed this question: what is the global prevalence of POI and EM?

Materials and methods

We conducted this meta-analysis to estimate the global prevalence of POI and EM. We utilized the Preferred
Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guide to enhance reporting of the systematic review and meta-analysis\textsuperscript{13}.

**Search strategy**

Through a comprehensive literature search, the major electronic bibliographic databases PubMed, Scopus, Cochrane, ScienceDirect, and Google Scholar were searched for relevant articles published between 1980 and 2018. The search was done using MeSH keywords including: ‘Premature Ovarian Failure’, ‘Primary Ovarian Insufficiency’, ‘POI’, ‘POF’, ‘Premature Menopause’, ‘Early Menopause’, ‘age at menopause’, ‘menopause’, and ‘prevalence’ separately or in combination, applying AND & OR operators. To find more studies, the references in the relevant papers were also followed up. The search was carried out by two independent researchers. All searches were limited to cohort and cross-sectional studies published in English.

**Eligibility criteria and study selection**

The inclusion criterion was menopause age as defined in the classification of menopause by the World Health Organization (WHO). The menstrual status of the menopausal subjects was classified into four age groups: ‘POI’ if younger than 40 years, ‘early’ if between 40 and 45 years, ‘normal’ if between 45 and 55 years, and ‘late’ if older than 55 years\textsuperscript{14}.

Exclusion criteria were: no menopause report based on the WHO criteria; no report of prevalence; no clear data; overlapping sample; and studies of very low quality. A modified version of the Newcastle-Ottawa Scale for cross-sectional and cohort studies was used to assess the methodological quality of the studies\textsuperscript{15}.

**Data extraction**

The following information was extracted from full-text articles by two authors (SG and SK): author(s); date; title; study design; characteristics of study population, such as body mass index (BMI) and age at entry to study; natural menopause population; prevalence of menopause for the identified age groups; mean and median of age at menopause; and mean and standard deviation (SD) of the data.

To prevent extraction errors, all authors performed a control check between the final data used in the meta-analysis and those of the original publications.

**Quality assessment**

To allocate each paper a score, checklists of validated quality assessment for cohort and cross-sectional studies were used. The Newcastle-Ottawa scale criteria of selection, comparability, and outcome were used to evaluate all studies included in the meta-analysis\textsuperscript{15}.

Two reviewers (SG and SK) independently assessed the quality of the studies; they were blinded to the authors’ identities, affiliations, and journal titles. Disagreements among reviewers were resolved by discussion until consensus was reached. Studies with a score of <20% were considered ‘very low’, 20–40% as ‘low’, 40–70% as ‘medium’, and ≥70% as ‘high’ quality.

**Statistical analysis**

At first, the variance of each study was calculated through the variance of the binomial distribution given that the prevalence rate had a binomial distribution. Then, each study was given a weight proportional to its inversed variance.

The heterogeneity of results across the studies was checked using Cochran’s $Q$ test ($p < 0.10$) and was quantified by the $I^2$ statistic. An $I^2$ statistic greater than 50% was considered to represent significant heterogeneity across the studies. Subgroup analysis was conducted based on the Human Development Index (HDI) categorization, which subsumes different countries under four categories: low, medium, high, and very high\textsuperscript{16}; study type; and quality of the study.

In order to provide a weighted-mean estimate of the pooled prevalence of menopause for the identified age groups across the included studies, a random-effects meta-analysis model was employed at a confidence level of 95%.

All meta-analyses and meta-regressions were performed using Stata software version 12 (Stata Corp, College Station, TX, USA).

**Results**

Figure 1 shows the results of the literature search and selection process based on the PRISMA flow chart for systematic reviews.

A total of 8937 potentially relevant articles were identified through the initial searches. After removing duplicates 3481 articles remained, and then 3222 articles were excluded by screening titles and abstracts, and the full texts of 228 remaining articles were retrieved from different sources. Finally, 31 studies met the inclusion criteria and were included in this meta-analysis.

**Study characteristics**

A detailed description of the characteristics of the included studies is reported in Table 1. These studies were published between 1986 and 2017. The sample size of the included articles varied from 130 to 25,499 participants. Out of the 31 included studies, 14 were cross-sectional and 17 were cohort. The quality score was high for 26 studies, medium for four studies, and low for one study. The mean age (range), mean ± SD of BMI, mean ± SD of age at menopause, and median age at menopause for each study are presented in Table 1.

**Evaluation of heterogeneity and meta-analysis**

The results for Cochran’s $Q$ test and $I^2$ statistics revealed significant heterogeneity among the included studies for the
prevalence of ‘POI’, ‘early’, ‘normal’, and ‘late’ menopause and thus a random-effects model was used for analysis. The pooled prevalence of ‘POI’, ‘early’, ‘normal’, and ‘late’ menopause was 3.7% (95% confidence interval [CI]: 3.1, 4.3), 12.2% (95% CI: 10.5, 14), 78.1% (95% CI: 75.9, 80.3), and 7.2% (95% CI: 4.5, 10), respectively (Figure 2).

Subgroup analysis

In order to reduce heterogeneity, we performed subgroup analysis based on HDI categorization, study type, and quality of the study. As presented in Table 2, the prevalence of POI was higher in medium and low HDI countries (4.9% and 4.3%, respectively). The lowest prevalence of EM was for very high HDI countries (10.3% [95% CI: 8.5, 12.1]), while the lowest normal menopause was for low HDI countries (68.8% [95% CI: 63.9, 73.6]).

With regards to the study type, cross-sectional studies had a higher prevalence of POI (4.4% vs. 3.3%) and EM (16.7% vs. 9.8%), while cohort studies reported a higher prevalence of normal (77.3% vs. 69.2%) and late (8.4% vs. 4.7%) menopause. Finally, high-quality studies had a higher prevalence of late menopause (7.7% [95% CI: 4.7, 10.6]), and medium-quality studies had a higher prevalence of POI (6.3% [95% CI: 3.8, 8.8]) and EM (23.8% [95% CI: 19.3, 28.3]).

Trend analysis

To show changes in the prevalence of ‘POI’, ‘early’, ‘normal’, and ‘late’ menopause according to the dates of the studies, meta-regression was used. As shown in Figure 3, the decreasing trend for the prevalence of ‘POI’, ‘early’, and ‘normal’ menopause was not statistically significant ($p > 0.05$). Also, the increasing trend for late menopause was not significant ($b = 0.002, p = 0.18$).

Discussion

The present large-scale study is the first systematic review and meta-analysis of cohort and cross-sectional studies on
Table 1. General characteristics of the studies in the systematic review and meta-analysis of the global prevalence of premature and early menopause.

<table>
<thead>
<tr>
<th>Reference number</th>
<th>First author (year)</th>
<th>Country of study; race/ethnicity</th>
<th>Study design</th>
<th>% (natural menopause)</th>
<th>Age at entry, mean (range)</th>
<th>Mean ± SD BMI</th>
<th>Mean ± SD age at menopause</th>
<th>Median age at menopause</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Sullivan et al. (2017)</td>
<td>United States; 77% White, 12% Black, 11% other</td>
<td>Population-based cohort (Women's Health Initiative Clinical Trial Cohort)</td>
<td>25,499</td>
<td>62.66 (50–79)</td>
<td>28.5</td>
<td>–</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>18</td>
<td>Shamsa and Al Hashimi (2017)</td>
<td>Iraq</td>
<td>Multi center cross-sectional study</td>
<td>302</td>
<td>Above 40</td>
<td>–</td>
<td>48.8 ± 6.7</td>
<td>49.5</td>
<td>High</td>
</tr>
<tr>
<td>19</td>
<td>Muka et al. (2017)</td>
<td>The Netherlands</td>
<td>Cohort (population-based Rotterdam Study)</td>
<td>3639</td>
<td>66.9 ± 9.6</td>
<td>27.0 ± 4.4</td>
<td>50.0 ± 4.4</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>20</td>
<td>Pirincci et al. (2016)</td>
<td>Turkey</td>
<td>Cross-sectional</td>
<td>688</td>
<td>55.6 ± 9.3 (40–90)</td>
<td>–</td>
<td>47.4 ± 3.7</td>
<td>48</td>
<td>High</td>
</tr>
<tr>
<td>21</td>
<td>Rahman et al. (2015)</td>
<td>Sweden</td>
<td>Population-based cohort (Swedish Mammography Cohort)</td>
<td>22,416</td>
<td>50.0 ± 4.4</td>
<td>–</td>
<td>51 ± 3.7</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>22</td>
<td>Ryan et al. (2014)</td>
<td>France</td>
<td>Population-based cohort study</td>
<td>3842</td>
<td>74.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>23</td>
<td>Bansal et al. (2014)</td>
<td>India</td>
<td>Cross-sectional (Rural Health Training Center composed of 15 villages)</td>
<td>100</td>
<td>(40–60)</td>
<td>–</td>
<td>45.9 ± 3.5</td>
<td>46</td>
<td>Medium</td>
</tr>
<tr>
<td>24</td>
<td>Li et al. (2013)</td>
<td>United States; African-American women</td>
<td>Population-based cohort (Black Women’s Health Study)</td>
<td>11,121</td>
<td>53.32</td>
<td>28.62</td>
<td>–</td>
<td>50</td>
<td>High</td>
</tr>
<tr>
<td>25</td>
<td>Brand et al. (2013)</td>
<td>EPIC countries (Italy, Spain, the United Kingdom, the Netherlands, France, Germany, Sweden, and Denmark)</td>
<td>Prospective case–cohort study nested within EPIC (European Prospective Investigation into Cancer and Nutrition)</td>
<td>3250</td>
<td>59.2 ± 5.8</td>
<td>26.3 ± 4.6</td>
<td>48.6 ± 4.9</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>26</td>
<td>Anolue et al. (2012)</td>
<td>Nigeria; 100% Igbo</td>
<td>Cross-sectional (13 rural areas)</td>
<td>349</td>
<td>58 ± 7.9</td>
<td>–</td>
<td>47 ± 4.2</td>
<td>47</td>
<td>Medium</td>
</tr>
<tr>
<td>27</td>
<td>Delavar and Hajajahmadi (2011)</td>
<td>Iran</td>
<td>Cross-sectional</td>
<td>740</td>
<td>51.7 ± 5.4 (45–63)</td>
<td>29.2 ± 5.0</td>
<td>47 ± 4.9</td>
<td>48</td>
<td>High</td>
</tr>
<tr>
<td>28</td>
<td>OluOlorun and Lawoyin (2009)</td>
<td>Nigerian women, possibly 100% West African</td>
<td>Cross-sectional community-based study</td>
<td>489</td>
<td>52.6 ± 4.8 (40–60)</td>
<td>–</td>
<td>48.5 ± 4.6</td>
<td>49</td>
<td>High</td>
</tr>
<tr>
<td>29</td>
<td>Løkkegaard et al. (2006)</td>
<td>Denmark</td>
<td>Cohort (The Danish Nurse Cohort Study)</td>
<td>7102</td>
<td>Above 44 years</td>
<td>–</td>
<td>49.2</td>
<td>50</td>
<td>High</td>
</tr>
<tr>
<td>30</td>
<td>Amagai et al. (2006)</td>
<td>Japan</td>
<td>Population-based cohort (Jichi Medical School [JMS] Cohort Study)</td>
<td>3797</td>
<td>61 ± 6.7 (36–89)</td>
<td>23.24</td>
<td>48.3 ± 4.8</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>31</td>
<td>Hong et al. (2007)</td>
<td>South Korean</td>
<td>Population-based cohort (Kangwha Cohort Study)</td>
<td>2658</td>
<td>66.0 ± 8.2 (&lt;55)</td>
<td>–</td>
<td>46.9 ± 4.9</td>
<td>48</td>
<td>High</td>
</tr>
<tr>
<td>32</td>
<td>Ossewaarde et al. (2005)</td>
<td>Netherlands</td>
<td>Population-based cohort (breast cancer screening cohort)</td>
<td>10,078</td>
<td>57.4 ± 4.3 (48–68)</td>
<td>26±4</td>
<td>49.0 ± 4.5</td>
<td>50</td>
<td>High</td>
</tr>
<tr>
<td>33</td>
<td>Choi et al. (2005)</td>
<td>South Korean</td>
<td>Cohort (Korean Elderly Pharmacoepidemiologic Cohort)</td>
<td>5731</td>
<td>&gt;65 (69.8 ± 5.5)</td>
<td>–</td>
<td>49.6 ± 4.6</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>34</td>
<td>Rödström et al. (2005)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>565</td>
<td>72.6 (70, 74, 78), 24-year follow-up</td>
<td>–</td>
<td>49.95 ± 3.99</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>36</td>
<td>PMIS Group (2003)</td>
<td>Italy</td>
<td>Multi center cross-sectional study</td>
<td>15,253</td>
<td>57 (55–71)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>High</td>
</tr>
<tr>
<td>37</td>
<td>Sievert and Hautaniemi (2003)</td>
<td>Mexico</td>
<td>Cross-sectional community-based study</td>
<td>451</td>
<td>50.1 ± 6.3 (28–70)</td>
<td>29 ± 4.9</td>
<td>46.7 ± 4.7</td>
<td>49.6</td>
<td>Medium</td>
</tr>
<tr>
<td>6</td>
<td>Luborsky et al. (2003)</td>
<td>United States; 51.6% Caucasian, 24.87% Black, 15.85% Hispanic, 3.51% Chinese, 4.16% Japanese</td>
<td>Cross-sectional analysis of population-based cohort (The Study of Women Across the Nation [SWAN])</td>
<td>1994</td>
<td>(40–55)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>High</td>
</tr>
</tbody>
</table>

(continued)
Table 1. Continued.

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Fast author/year</th>
<th>Country of study, race/ethnicity</th>
<th>Study design</th>
<th>Study design</th>
<th>Study design</th>
<th>Study design</th>
<th>Study design</th>
<th>Study design</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>Adamopoulos et al. (2002)</td>
<td>Greece, women</td>
<td>Hospital records cross-sectional study</td>
<td>1815 (24-70)</td>
<td>59.8 (45-80)</td>
<td>1888</td>
<td>Mean ± SD age at menopause</td>
<td>47.9 ± 2.5</td>
<td>50.2</td>
</tr>
<tr>
<td>39</td>
<td>Yahya and Rehan (2002)</td>
<td>Pakistan</td>
<td>Cross-sectional study (20 rural areas)</td>
<td>130</td>
<td>59.8 ± 7.4</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>49.2 ± 4.5</td>
<td>47.9 ± 2.5</td>
</tr>
<tr>
<td>40</td>
<td>Luoto et al. (2002)</td>
<td>United States</td>
<td>Cross-sectional analysis of cohort (Atherosclerosis Risk in Communities [ARIC] Study)</td>
<td>4182</td>
<td>49 ± 3.6</td>
<td>50</td>
<td>Median age at menopause</td>
<td>49 ± 3.6</td>
<td>50</td>
</tr>
<tr>
<td>41</td>
<td>Jacobsen et al. (1999)</td>
<td>California; 100% White (Hispanic)</td>
<td>Cohort study (The Adventist Health Study)</td>
<td>1445</td>
<td>51.5 ± 2.7</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>48.8 ± 5.08</td>
<td>50</td>
</tr>
<tr>
<td>42</td>
<td>Nagata et al. (1998)</td>
<td>Japan</td>
<td>Cross-sectional study</td>
<td>2035</td>
<td>42.8 ± 3.61</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>42.8 ± 3.61</td>
<td>50</td>
</tr>
<tr>
<td>43</td>
<td>Cooper and Sandler (1998)</td>
<td>United States; 84% White, 12.8% non-White</td>
<td>Population-based cohort (New York University Women's Health Study)</td>
<td>1423</td>
<td>2562</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>2562</td>
<td>50</td>
</tr>
<tr>
<td>44</td>
<td>Kato et al. (1998)</td>
<td>United States (New York, Florida)</td>
<td>Cross-sectional analysis of community-based study (Breast Cancer Detection Project)</td>
<td>1423</td>
<td>2562</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>2562</td>
<td>50</td>
</tr>
<tr>
<td>45</td>
<td>Stanford et al. (1987)</td>
<td>California, 100% White, 22% Black, 28% Other</td>
<td>Cross-sectional analysis of community-based study (Breast Cancer Detection Project)</td>
<td>1423</td>
<td>2562</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>2562</td>
<td>50</td>
</tr>
<tr>
<td>46</td>
<td>Coulam et al. (1986)</td>
<td>Minnesota</td>
<td>Body mass index (BMI): Prentice Menopausal Study</td>
<td>568</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>50</td>
<td>50</td>
<td>High</td>
</tr>
<tr>
<td>47</td>
<td>-</td>
<td>-</td>
<td>Birth cohort</td>
<td>568</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>50</td>
<td>50</td>
<td>High</td>
</tr>
<tr>
<td>48</td>
<td>-</td>
<td>-</td>
<td>Birth cohort</td>
<td>568</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>50</td>
<td>50</td>
<td>High</td>
</tr>
<tr>
<td>49</td>
<td>-</td>
<td>-</td>
<td>Birth cohort</td>
<td>568</td>
<td>50</td>
<td>Mean ± SD age at menopause</td>
<td>50</td>
<td>50</td>
<td>High</td>
</tr>
</tbody>
</table>

BMI, body mass index; PMIS, Progetto Menopausa Italico Study; SD, standard deviation.

There are some socioeconomic factors associated with ANM, including education level, social class, occupation, and income level. Moreover, studies have shown that natural menopause is experienced by women living in developed countries several years later than those in developing countries.46–49 Likewise, findings of a meta-analysis show a relationship between lower education and earlier ANM. Besides, the study revealed a similar relationship between occupation and ANM. Although the authors described the underlying mechanism of this association as unclear, they stated that lifestyle elements such as smoking, physical activity, BMI, and diet may be intervening factors.48 In addition to socioeconomic factors, menopause timing is affected by reproductive and genetic factors, such as race, ethnicity, maternal ANM, menarche age, and parity.44,47,49,50

In the present study, depending on the study types, the prevalence rate of POI and EM was lower in cohort studies compared with cross-sectional studies, which might be due to their larger sample size (130,864 for cohort studies vs. 26,867 for cross-sectional studies).

Based on the quality of the studies, the prevalence rates of POI and EM for high-quality studies were 3.7% and 11.8%,
Figure 2. Forest plot showing the prevalence for menopause age classification: (A) premature menopause (n = 31 studies), (B) early menopause (n = 28 studies), (C) normal menopause (n = 22 studies), and (D) late menopause (n = 17 studies). CI, confidence interval; ES, effect size.

<table>
<thead>
<tr>
<th>HDI category</th>
<th>Prevalence &lt;40 years old</th>
<th>95% CI</th>
<th>p-Value</th>
<th>Prevalence 40–45 years old</th>
<th>95% CI</th>
<th>p-Value</th>
<th>Prevalence 45–55 years old</th>
<th>95% CI</th>
<th>p-Value</th>
<th>Prevalence &gt;55 years old</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>3.6</td>
<td>(2.9, 4.2)</td>
<td>&lt;0.001</td>
<td>10.3</td>
<td>(8.5, 12.1)</td>
<td>&lt;0.001</td>
<td>80</td>
<td>(77.6, 82.4)</td>
<td>&lt;0.001</td>
<td>7</td>
<td>(4.5, 10.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>4.1</td>
<td>(1.5, 6.6)</td>
<td>0.019</td>
<td>22.6</td>
<td>(7.3, 38)</td>
<td>0.004</td>
<td>67.5</td>
<td>(63.9, 71.1)</td>
<td>&lt;0.001</td>
<td>–</td>
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<tr>
<td>Medium</td>
<td>4.9</td>
<td>(0.8, 8.9)</td>
<td>0.002</td>
<td>20.8</td>
<td>(7.6, 33.9)</td>
<td>0.002</td>
<td>68.9</td>
<td>(56.8, 81.8)</td>
<td>&lt;0.001</td>
<td>7.4</td>
<td>(4.9, 9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>4.3</td>
<td>(0.8, 7.9)</td>
<td>0.017</td>
<td>23.8</td>
<td>(19.3, 28.3)</td>
<td>0.001</td>
<td>68.8</td>
<td>(63.9, 73.6)</td>
<td>&lt;0.001</td>
<td>4.3</td>
<td>(0.1, 10)</td>
<td>0.19</td>
</tr>
<tr>
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<tr>
<td>Cross-sectional</td>
<td>4.4</td>
<td>(3.2, 5.7)</td>
<td>&lt;0.001</td>
<td>16.7</td>
<td>(12.9, 20.4)</td>
<td>&lt;0.001</td>
<td>74.2</td>
<td>(69.2, 79.2)</td>
<td>&lt;0.001</td>
<td>4.7</td>
<td>(2.5, 6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cohort</td>
<td>3.3</td>
<td>(2.5, 4.1)</td>
<td>&lt;0.001</td>
<td>9.8</td>
<td>(7.6, 12.1)</td>
<td>&lt;0.001</td>
<td>80</td>
<td>(77.3, 82.7)</td>
<td>&lt;0.001</td>
<td>8.4</td>
<td>(4.8, 12.1)</td>
<td>&lt;0.001</td>
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<td>Quality of study</td>
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<tr>
<td>High</td>
<td>3.7</td>
<td>(3.1, 4.3)</td>
<td>&lt;0.001</td>
<td>11.8</td>
<td>(10.3, 13.6)</td>
<td>&lt;0.001</td>
<td>78.4</td>
<td>(76.2, 80.7)</td>
<td>&lt;0.001</td>
<td>7.7</td>
<td>(4.7, 10.6)</td>
<td>&lt;0.001</td>
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<tr>
<td>Moderate</td>
<td>6.3</td>
<td>(3.8, 8.8)</td>
<td>&lt;0.001</td>
<td>23.8</td>
<td>(19.3, 28.3)</td>
<td>&lt;0.001</td>
<td>68.8</td>
<td>(63.9, 73.6)</td>
<td>&lt;0.001</td>
<td>1.1</td>
<td>(0.2, 2.2)</td>
<td>0.049</td>
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<tr>
<td>Low</td>
<td>1.5</td>
<td>(0.3, 3.6)</td>
<td>0.16</td>
<td>3.1</td>
<td>(7.3, 18.9)</td>
<td>&lt;0.001</td>
<td>78.5</td>
<td>(71.4, 85.5)</td>
<td>&lt;0.001</td>
<td>6.9</td>
<td>(2.5, 11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall</td>
<td>3.7</td>
<td>(3.1, 4.3)</td>
<td>&lt;0.001</td>
<td>12.2</td>
<td>(10.5, 14)</td>
<td>&lt;0.001</td>
<td>78.1</td>
<td>(75.9, 80.3)</td>
<td>&lt;0.001</td>
<td>7.2</td>
<td>(4.5, 10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; HDI, Human Development Index.
respectively; while for medium-quality studies they were 6.3% and 23.8%, respectively; and for low-quality studies, they were 1.5% and 3.1%, respectively. In the present meta-analysis, all studies were of high quality and only five of them were of medium or low quality.

The trend analysis in this study was indicative of an increasing menopause age, although not significant. The menopause age in different nations and communities is reportedly increasing because of diet and general health, besides life expectancy51.

Closely related to the physical and psychological health of women, the ANM is indicative of ovarian function and aging47,48. Studies show that women with early or late ANM are likely to experience adverse health outcomes. They also report early ANM as being associated with health-threatening conditions, including an increased risk of osteoporosis, cardiovascular disease, stroke, type 2 diabetes, and total mortality, due to a decrease in the levels of female sex hormones such as estrogen and progesterone4,11,46–48.

Studies have shown that a 1-year reduction in the ANM increases total mortality by about 2%32,52. Also, women experiencing natural menopause before age 45 years are at a more increased risk of a premature decline in cognitive function and mood disorders49. POI adversely affects women’s psychological health and quality of life, so it is necessary to provide women experiencing EM with integrated physical, psychological, and reproductive health care as well as preventive strategies to maintain their long-term fitness53.

There are some limitations to our study. First, the ANM was mostly derived from self-report and cross-sectional data that may lead to recall bias. It is worth noting that baseline data were extracted for all but two of the cohort studies12,34. Some studies posit that the reported age of menopause may be inaccurate, while others conclude that women have no problem recalling it due to its importance in their lives46. Young menopausal women (age >40 years) remember their age at menopause better than those with a later onset. Still, other studies suggest that special events (such as

Figure 3. Meta-regression plots of change in the prevalence of (A) premature menopause, (B) early menopause, (C) normal menopause, and (D) late menopause according to the dates of the studies.
menopause before age 40 years or after age 55 years) are easier to remember compared with normal events (such as menopause between ages 50 and 54 years)84.

Second, only studies published in English were included in this meta-analysis and this could be another source of bias.

Finally, we were unable to obtain enough data for assessment of the relationship between moderator factors (such as education, occupation, parity, smoking, menarche age, etc.) and menopause in different studies.

Conclusion
The prevalence of EM and POI in women is considerable. Genetic and racial factors besides social, economic, and lifestyle-related ones trigger the incidence of EM and POI. Due to the bio-psychosocial effects of EM and POI, the results of the present meta-analysis could contribute to consciousness-raising of health policy-makers toward the necessity of prioritizing, planning, and allocating health resources as preventive interventions for improving lifestyle and standards of living.

The results could also have a share in awareness-raising of the health-care providers toward the importance of providing integrated care and treatment interventions for improving quality of life and decreasing the long-term sequelae of POI and EM women.

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Conflict of interest
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