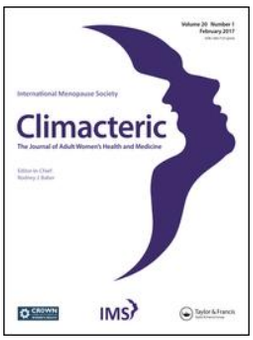

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ORIGINAL ARTICLE

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

S. Golezar[a], F. Ramezani Tehrani[b], S. Khazaei[c], A. Ebadi[d] and Z. Keshavarz[e]

[a]Student Research Committee, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [b]Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [c]Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran; [d]Behavioral Sciences Research Center, Life Style Institute, Nursing Faculty of Baqiyatallah University of Medical Sciences, Tehran, Iran; [e]Midwifery and Reproductive Health Research Center and Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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.

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Prevalence; primary ovarian insufficiency; early menopause; meta-analysis

Introduction

The perpetual cessation of menstrual cycles for 12 successive months occurring without any perceived psychological or pathological causes is called natural menopause[1,2]. The mean age of women experiencing natural menopause has been reported as 51.4 years[3].

The age at which menopause occurs is under the influence of various factors including genetic, hormonal, environmental, and lifestyle-related ones[4,5]. 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 menopausal level[6–8], this is considered to be primary ovarian insufficiency (POI), which is also called premature menopause or premature ovarian failure. Also, there is early menopause (EM) which occurs between the ages of 40 and 45 years[4,9].

Although mostly considered an idiopathic disorder, POI could also be due to autoimmune complications, genetic causes, inflammatory conditions, or metabolic syndromes[10]. POI and EM occur either spontaneously or as a result of medical interventions, including chemotherapy or bilateral oophorectomy[9,10].

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[4,9,11].

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[10–12]. 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[6]. 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[4].

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

CONTACT Zohreh Keshavarz keshavarzzohre@yahoo.com School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guide to enhance reporting of the systematic review and meta-analysis[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[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[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[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 $\geq 70\%$ 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[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

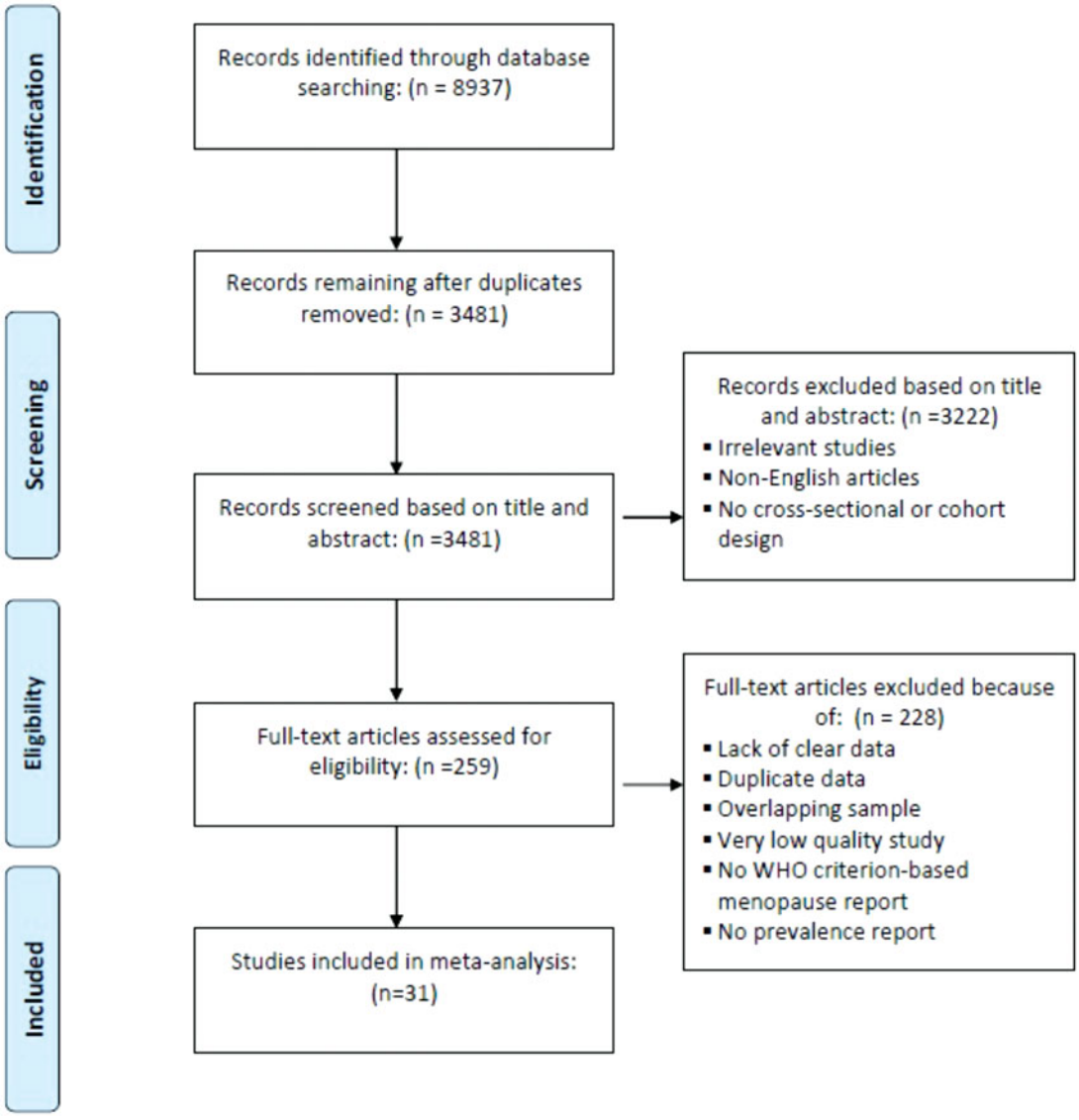

Figure 1. Flow chart of the literature search for the systematic review and meta-analysis. WHO, World Health Organization.

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 ($\beta = 0.002$, $p = 0.18$).

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.

Reference number	First author (year)	Country of study; race/ethnicity	Study design	N (natural menopause)	Age at entry, mean (range)	Mean ± SD BMI	Mean ± SD age at menopause	Median age at menopause	Quality score
17	Sullivan *et al.* (2017)	United States; 77% White, 12% Black, 11% other	Population-based cohort (Women's Health Initiative Clinical Trial Cohort)	25,499	62.66 (50–79)	28.5	_	_	High
18	Shamsa and Al Hashimi (2017)	Iraq	Multi center cross-sectional study	302	Above 40	_	48.8 ± 6.7	49.5	High
19	Muka *et al.* (2017)	The Netherlands	Cohort (population-based Rotterdam Study)	3639	66.9 ± 9.6	27.0 ± 4.4	50.0 ± 4.4	–	High
20	Pirincci *et al.* (2016)	Turkey	Cross-sectional	688	55.6 ± 9.3 (40–90)	–	47.4 ± 3.7	48	High
21	Rahman *et al.* (2015)	Sweden	Population-based cohort (Swedish Mammography Cohort)	22,416	(49–83)	–	51 ± 3.7	–	High
22	Ryan *et al.* (2014)	France	Population-based cohort study	3842	74.1	–	–	–	High
23	Bansal *et al.* (2014)	India	Cross-sectional (Rural Health Training Center composed of 15 villages)	100	(40–60)	–	45.9 ± 3.5	46	Medium
24	Li *et al.* (2013)	United States; African-American women	Population-based cohort (Black Women's Health Study)	11,212	53.32	28.62	_	50	High
25	Brand *et al.* (2013)	EPIC countries (Italy, Spain, the United Kingdom, the Netherlands, France, Germany, Sweden, and Denmark)	Prospective case–cohort study nested within EPIC (European Prospective Investigation into Cancer and Nutrition)	3250	59.2 ± 5.8	26.3 ± 4.6	48.6 ± 4.9	–	High
26	Anolue *et al.* (2012)	Nigeria; 100% Igbo	Cross-sectional (13 rural areas)	349	58 ± 7.9	_	47 ± 4.2	47	Medium
27	Delavar and Hajiahmadi (2011)	Iran	Cross-sectional	740	51.7 ± 5.4 (45–63)	29.2 ± 5.0	47.7 ± 4.9	48	High
28	OlaOlorun and Lawoyin (2009)	Nigerian women, possibly 100% West African	Cross-sectional community-based study	489	52.6 ± 4.8 (40–60)	_	48.5 ± 4.6	49	High
29	Løkkegaard *et al.* (2006)	Denmark	Cohort (The Danish Nurse Cohort Study)	7102	Above 44 years	–	49.2	50	High
30	Amagai *et al.* (2006)	Japan	Population-based cohort (Jichi Medical School [JMS] Cohort Study)	3797	61 ± 6.7 (36–89)	23.24	48.3 ± 4.8	_	High
31	Hong *et al.* (2007)	South Korean	Population-based cohort (Kangwha Cohort Study)	2658	66.0 ± 8.2 (<55)	_	46.9 ± 4.9	48	High
32	Ossewaarde *et al.* (2005)	Netherlands	Population-based cohort (breast cancer screening cohort)	10,078	57.4 ± 4.3 (48–68)	26 ± 4	49.0 ± 4.5	50	High
33	Choi *et al.* (2005)	South Korean	Cohort (Korean Elderly Pharmacoepidemiologic Cohort)	5731	>65 (69.8 ± 5.5)	–	49.6 ± 4.6	–	High
34	Rödström *et al.* (2005)	Sweden	Cohort	565	72.6 (70, 74, 78), 24-year follow-up	_	49.95 ± 3.99	_	High
35	Jacobsen *et al.* (2004)	Norwegian women	Cohort	19,731	61.8 (34–74)	_	48.4 ± 4.1	49	High
36	PMIS Group (2003)	Italy	Multi-center cross-sectional study	15,253	57 (55–71)	_	_	_	High
37	Sievert and Hautaniemi (2003)	Mexico	Cross-sectional community-based study	451	50.1 ± 6.3 (28–70)	29 ± 4.9	46.7 ± 4.7	49.6	Medium
6	Luborsky *et al.* (2003)	United States; 51.6% Caucasian, 24.87% Black, 15.85% Hispanic, 3.51% Chinese, 4.16% Japanese	Cross-sectional analysis of population-based cohort (The Study of Women Across the Nation [SWAN])	1994	(40–55)	–	–	–	High

(*continued*)

Table 1. Continued.

Reference number	First author (year)	Country of study; race/ethnicity	Study design	N (natural menopause)	Age at entry, mean (range)	Mean ± SD BMI	Mean ± SD age at menopause	Median age at menopause	Quality score
38	Adamopoulos *et al.* (2002)	Greek women	Hospital records cross-sectional	1815	(24–70)	–	47.9 ± 2.5	50.2	High
39	Yahya and Rehan (2002)	Pakistan	Cross-sectional (20 rural areas)	130	59.8 ± 7.4 (36–80)	–	49 ± 3.6	50	Low
40	Luoto *et al.* (2002)	United States	Cross-sectional analysis of cohort (Atherosclerosis Risk in Communities [ARIC] Study)	1688	57.8 (45–64)	–	–	–	High
41	Jacobsen *et al.* (1999)	California; 100% White (Hispanic)	Cohort (The Adventist Health Study)	6182	(25–100)	–	49.2 ± 4.5	–	High
42	Nagata *et al.* (1998)	Japan	Cross-sectional	1445	51.5 ± 2.1 (45–55)	22.2 ± 2.7			High
43	Cooper and Sandler (1998)	United States; 84.8% White, 15.2% non-White	Population-based cohort (National Health and Examination Survey I)	2562	(50–86)	–	48.8 ± 5.08	48	High
44	Kato *et al.* (1998)	United States (New York, Florida)	Population-based cohort (New York University Women's Health Study)	2035	42.8 (34–61)	–	–	51.3	High
45	Stanford *et al.* (1987)	United States; 94.66% White, 2.2% Black, 2.8% Other	Cross-sectional analysis of community-based study (Breast Cancer Detection Demonstration Project)	1423	(26–62)	–	–	51.1	High
12	Coulam *et al.* (1986)	Minnesota	Birth cohort	568	(18–22) birth cohort	–	–	–	Medium

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

the prevalence of spontaneous POI and EM between 1987 and 2018. Thirty-one studies have been included in this meta-analysis. Different studies have reported different POI and EM prevalence rates; varying standards of living, lifestyles, and races could justify the wide inconsistency.

In the current study, the overall prevalence of POI and EM was calculated as 3.7% and 12.2%, respectively. In the previous studies, a 1% prevalence of POI and a 5% prevalence of EM have been reported[10–12]. The reason for the lower prevalence rates reported in these studies compared with those of our study could be because in these studies the prevalence of POI and EM has been reported among the total population (premenopausal and postmenopausal women), while we have studied the prevalence only in postmenopausal women.

A meta-analysis of nine population-based cohort studies reported the prevalence of POI and EM in menopause women as 2% and 7.6%, respectively[4]. The study was of a smaller scale compared with the present study regarding the sample size (51,450 vs. 157,731), the number of studies included (9 vs. 31), and the number of nations investigated (only including the United Kingdom, Scandinavia, Australia, and Japan).

In the present study, the prevalence of age at natural menopause (ANM) was also calculated based on the countries' HDI level as well as the type and quality of the studies. Living standard factors such as income and educational level had not been reported in other studies. So, we used the 2018 HDI update to rank the countries included in the study. The index consists of education, life expectancy, and income per capita[16]. In our meta-analysis, 23 studies had been carried out in very high HDI countries. The prevalence of POI and EM (3.6% and 10.3%, respectively) was lower in these countries, while the highest prevalence of POI was in medium HDI countries (4.9%), and the highest prevalence of EM was in low HDI countries (23.8%).

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[4,47,49,50].

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%,

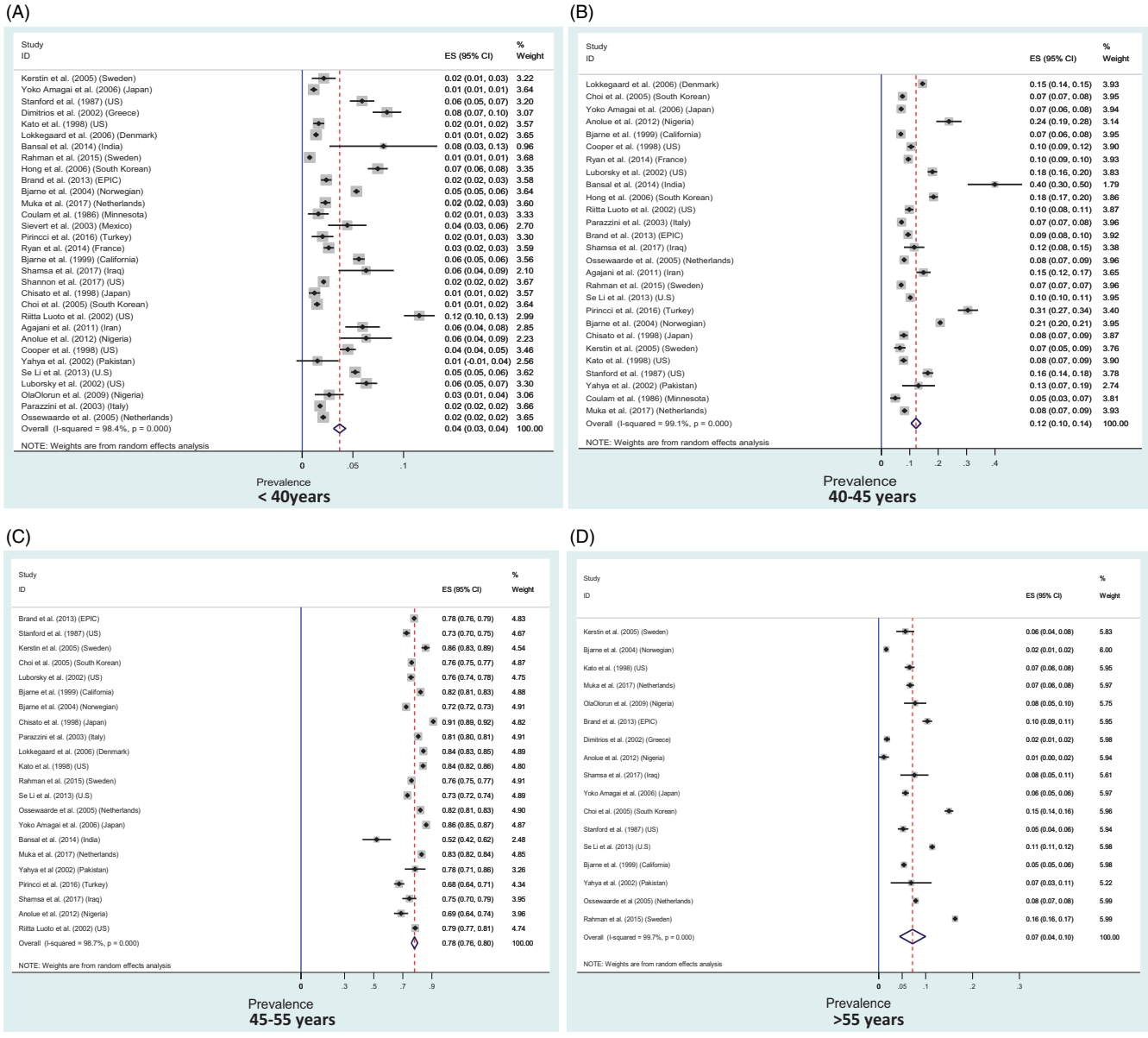

Figure 2. Forest plot showing the prevalence for menopause age classification: (A) premature menopause ($n = 31$ studies), (B) early menopause ($n = 28$ studies), (C) normal menopause ($n = 22$ studies), and (D) late menopause ($n = 17$ studies). CI, confidence interval; ES, effect size.

Table 2. Subgroup analysis based on HDI categorization, study type, and quality of the study.

	<40 years old			*40–45 years old*			*45–55 years old*			*>55 years old*		
	Prevalence	*95% CI*	p-*Value*	*Prevalence*	*95% CI*	p-*Value*	*Prevalence*	*95% CI*	p-*Value*	*Prevalence*	*95% CI*	p-*Value*
HDI category												
Very high	3.6	(2.9, 4.2)	<0.001	10.3	(8.5, 12.1)	<0.001	80	(77.6, 82.4)	<0.001	7	(4.5, 10.8)	<0.001
High	4.1	(1.5, 6.6)	0.019	22.6	(7.3, 38)	0.004	67.5	(63.9, 71.1)	<0.001	–	–	–
Medium	4.9	(0.8, 8.9)	0.002	20.8	(7.6, 33.9)	0.002	68.9	(56, 81.8)	<0.001	7.4	(4.9, 9.8)	<0.001
Low	4.3	(0.8, 7.9)	0.017	23.8	(19.3, 28.3)	<0.001	68.8	(63.9, 73.6)	<0.001	4.3	(0, 10)	0.19
Study type												
Cross-sectional	4.4	(3.2, 5.7)	<0.001	16.7	(12.9, 20.4)	<0.001	74.2	(69.2, 79.2)	<0.001	4.7	(2.5, 6.8)	<0.001
Cohort	3.3	(2.5, 4.1)	<0.001	9.8	(7.6, 12.1)	<0.001	80	(77.3, 82.7)	<0.001	8.4	(4.8, 12.1)	<0.001
Quality of study												
High	3.7	(3.1, 4.3)	<0.001	11.8	(10, 13.6)	<0.001	78.4	(76.2, 80.7)	<0.001	7.7	(4.7, 10.6)	<0.001
Moderate	6.3	(3.8, 8.8)	<0.001	23.8	(19.3, 28.3)	<0.001	68.8	(63.9, 73.6)	<0.001	1.1	(0, 2.2)	0.049
Low	1.5	(0, 3.6)	0.16	3.1	(7.3, 18.9)	<0.001	78.5	(71.4, 85.5)	<0.001	6.9	(2.5, 11.3)	<0.001
Overall	3.7	(3.1, 4.3)	<0.001	12.2	(10.5, 14)	<0.001	78.1	(75.9, 80.3)	<0.001	7.2	(4.5, 10)	<0.001

CI, confidence interval; HDI, Human Development Index.

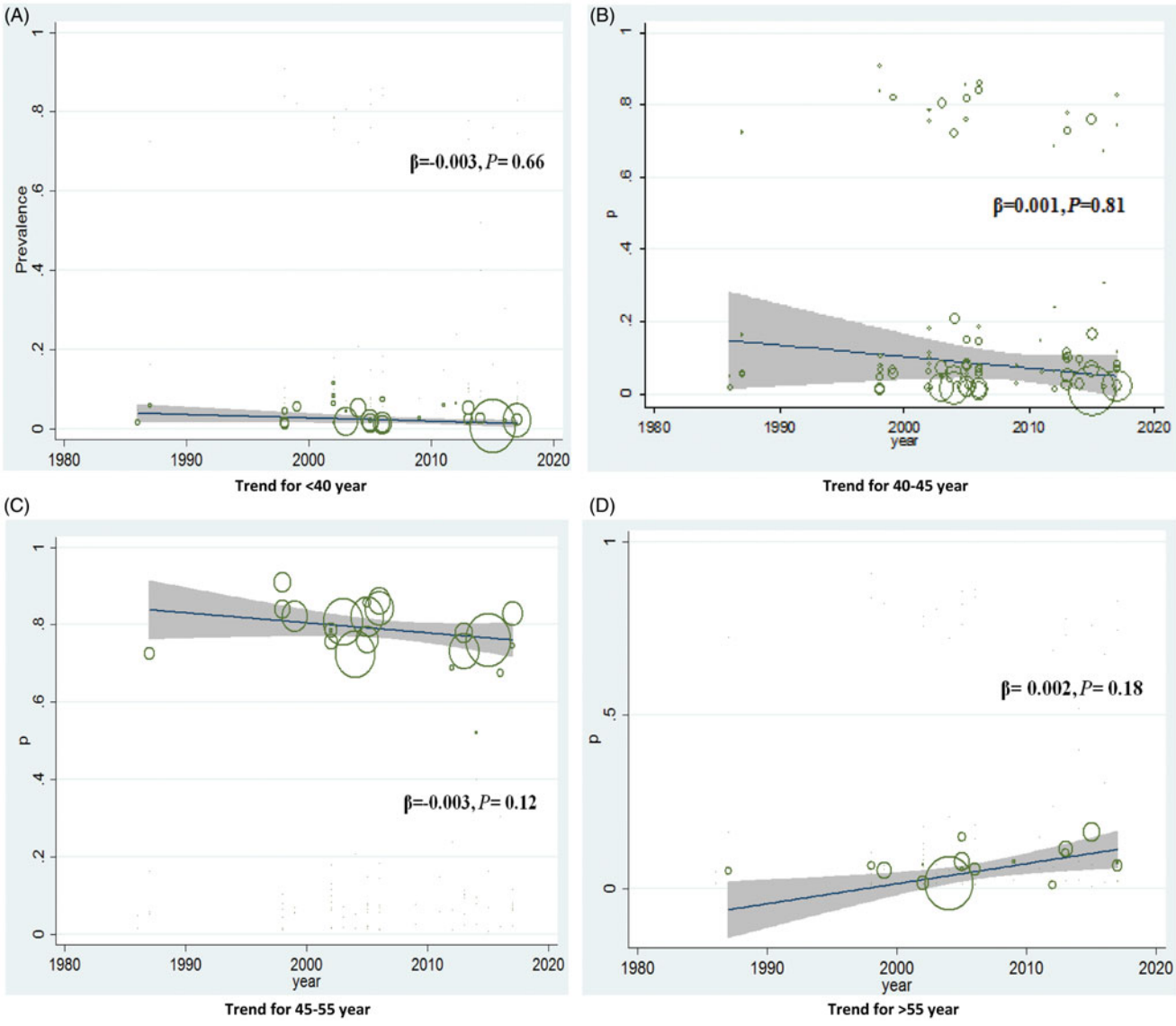

Figure 3. Meta-regression plots of change in the prevalence of (A) premature menopause, (B) early menopause, (C) normal menopause, and (D) late menopause according to the dates of the studies.

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 expectancy[51].

Closely related to the physical and psychological health of women, the ANM is indicative of ovarian function and aging[47,48]. 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 progesterone[4,11,46–48].

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 disorders[49]. 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 fitness[53].

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 studies[12,34]. 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 lives[46]. 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

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)[54].

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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ORCID

S. Golezar http://orcid.org/0000-0001-6062-8164
F. Ramezani Tehrani http://orcid.org/0000-0002-4609-065X
S. Khazaei http://orcid.org/0000-0001-5918-2310

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