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Menopausal state and rheumatoid arthritis: a systematic review and meta-analysis

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Abstract

Background Rheumatoid arthritis (RA) is a chronic inflammatory condition primarily affecting the joints. The higher prevalence of RA among females, combined with the known effects of sex hormones on immune function, has led researchers to investigate the potential relationship between menopausal status and the risk, severity, or progression of RA. This systematic review and meta-analysis aimed to determine the association between menopause and rheumatoid arthritis.

Methods In 2023, we conducted a comprehensive search across multiple databases, including Google Scholar, Scopus, PubMed/MEDLINE, Science Direct, Web of Science, EMBASE, Springer, and ProQuest. The search aimed to identify studies exploring the association between menopause and rheumatoid arthritis.

Results Our analysis revealed that post-menopausal women had a higher risk of developing rheumatoid arthritis compared to pre-menopausal women, with an estimated odds ratio of 1.35 (95% CI: 1.04–1.67). Additionally, women who experienced early menopause (defined as onset before age 45) showed significantly higher odds of developing RA, with an odds ratio of 2.97 (95% CI: 1.73–4.22).

Conclusion These findings highlight the importance of considering menopausal status when assessing the risk of RA development in women. The results suggest that post-menopausal women, particularly those who experience early menopause, may be at higher risk for developing RA. Further research in this area could provide valuable insights into potential preventive measures and targeted interventions for high-risk individuals.

Keywords Rheumatoid arthritis, Menopause, Early menopause, Women's health

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by symmetrical joint pain, swelling, and stiffness, predominantly affecting the small joints. It is notably more prevalent in women, with a global burden that has significantly increased over the past decades. The exact etiology of RA remains elusive, though it is believed to result from a complex interplay of multiple factors. While immune system disorders and deficiencies are considered central to its pathogenesis, various other elements contribute to its development, including age, gender, genetic predisposition, age at menopause, weight gain, and viral infections [1–3].

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According to the 2020 Global Burden of Disease report, approximately 17.6 million people worldwide were affected by RA, with projections suggesting this number will rise to 31.7 million by 2050, 69% of whom will be women [4].

RA is a common condition that affects women of all ages, but it is also likely influenced by physiological mechanisms unique to the female body. A woman's capacity to procreate naturally decreases with age [5]. For women, numerous systemic changes in the body begin at the conclusion of the reproductive phase.

Menopause is characterized by the ovaries' diminished responsiveness to gonadotropin stimulation, marking the end of a woman's reproductive years. The diagnosis of menopause is primarily based on hormonal assessments, with a key indicator being elevated levels of follicle-stimulating hormone (FSH). Clinically, menopause is confirmed when a woman has experienced an absence of menstrual periods for a minimum of 12 consecutive months, coupled with persistently high FSH levels [5].

This hormonal shift can have wide-ranging effects on various bodily systems. The reduction in these key hormones may contribute to decreased bone density, increasing the risk of osteoporosis. Many women experience vasomotor symptoms, commonly known as hot flashes, which can be disruptive to daily life. Vaginal health can also be affected, often resulting in dryness and discomfort. The hormonal fluctuations may impact mental well-being, potentially leading to mood disorders or other psychological changes [6]. These diverse effects highlight the significant impact of menopause on women's overall health and quality of life.

The transition to menopause is marked by a significant decline in estrogen levels, which has wide-ranging effects on various bodily systems. However, the specific impact of this estrogen deficiency on immune function remains incompletely understood [5, 7]. The higher prevalence of autoimmune conditions like rheumatoid arthritis (RA) in women compared to men suggests that estrogen plays a crucial role in the pathogenesis of these diseases. Given this potential link, there is a pressing need for more comprehensive research into the association between menopause-associated estrogen decline and the onset and progression of RA.

Despite these insights, data on the effect of age at menopause on RA risk remain inconsistent. Some studies have found no significant association [8, 9], while others have reported an inverse association between later age at menopause and RA development [10–12]. This systematic review and meta-analysis aim to clarify whether age at menopause is significantly associated with the risk of developing RA, providing a comprehensive evaluation of the existing evidence.

Materials and methods

To report systematic reviews and meta-analyses accurately and transparently, this study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards [13, 14]. Furthermore, its administrative protocol was recorded in the international perspective Register of systematic reviews (PROSPERO) under the code PROSPERO 2023 CRD42023441672 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023441672.

Search strategy

For this systematic review and meta-analysis, we conducted a comprehensive literature search up to May 2023. The search was limited to articles published in English and covered multiple databases, including Google Scholar, Scopus, PubMed/MEDLINE, Science Direct, Web of Science, EMBASE, Springer, and ProQuest.

To optimize our search, we used Medical Subject Headings (MeSH) terms either alone or in combination with other keywords, employing the Boolean operators "AND" and "OR" (see Supplementary Table 1 for the full search strategy). To ensure comprehensive coverage, we also examined the reference lists of identified publications for additional relevant articles.

The process of identifying, screening, and selecting relevant studies is illustrated in the PRISMA flowchart (Fig. 1).

Inclusion and exclusion criteria

After eliminating duplicates, we examined the titles and abstracts of related studies. Two authors then independently reviewed the full texts of the articles to determine whether they met the inclusion and exclusion criteria and to rate the articles' quality. Any disagreements between reviewers were settled by a single third party and through consensus.

The inclusion criteria for our study encompassed observational studies, specifically case-control, cohort, and analytical cross-sectional studies that investigated the association between menopausal status and rheumatoid arthritis. We required that these studies either reported odds ratios (ORs) with corresponding 95% confidence intervals (CIs) or provided sufficient data to calculate these measures. Additionally, studies needed to be available in full-text format and published in English to be included in our analysis.

For exclusion, we removed studies with non-analytical observational designs, such as case reports and case series. We also excluded descriptive cross-sectional studies that did not report odds ratios or equivalent measures of association. Studies lacking sufficient data to calculate or extract odds ratios were similarly excluded. However, we made an exception to include high-quality

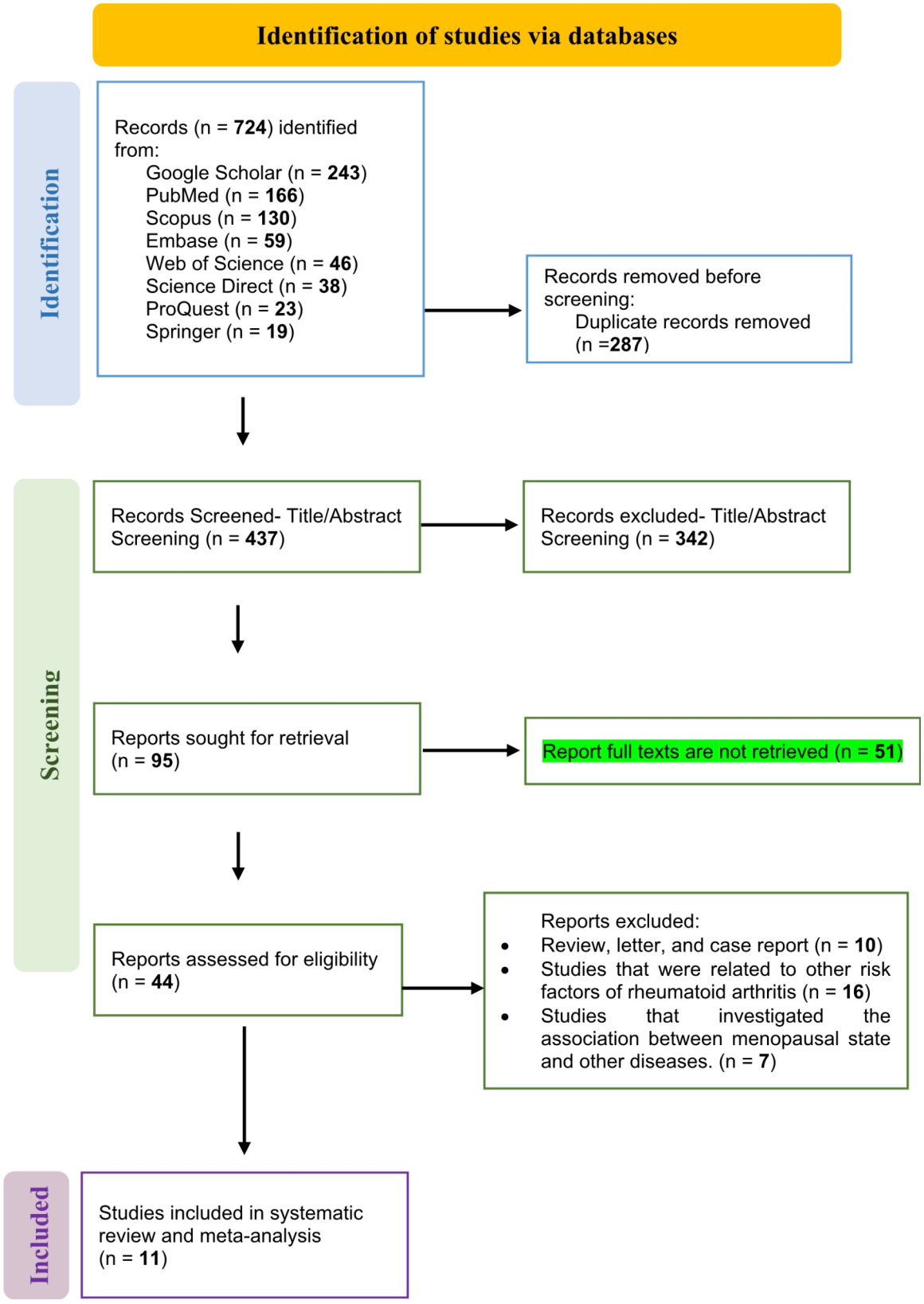

Fig. 1 Depicts the flowchart of studies included in the systematic review and meta-analysis, following the PRISMA guidelines

analytical cross-sectional studies that reported odds ratios or equivalent measures, as these provided valuable data consistent with our research objectives and met our other inclusion criteria.

Definitions

Natural Menopause: Normal menopause refers to the natural biological process in a woman's life when she reaches the end of her reproductive years. It is characterized by the permanent cessation of menstrual periods due to a decline in ovarian function and hormone production, particularly estrogen. Normal menopause typically occurs around 45 to 55, although individual variations exist [15].

Early Menopause: Early menopause, also known as premature menopause, occurs when a woman experiences the permanent cessation of menstrual periods and associated menopausal symptoms before age 45 [16].

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS), a tool specifically developed to evaluate the quality of non-randomized studies in systematic reviews. The NOS evaluates studies based on three main criteria: selection of study groups, comparability of groups, and assessment of outcome or exposure. Each study is rated and scored, with higher scores indicating better quality. A score of 6 or higher is considered good (low risk of bias), 3–5 as moderate (moderate risk of bias), and less than 3 as low quality (high risk of bias). Only studies with moderate and good quality were included in this meta-analysis [17].

The quality assessment process was carried out meticulously to ensure accuracy and reliability. Reviewers had unrestricted access to the journal and authors' names for a comprehensive evaluation. The first reviewer carefully read the entire article before completing and scoring the quality assessment checklist. The second reviewer independently conducted the same procedures. Any disagreements were resolved through group discussion to reach a consensus.

Data extraction

Our study employed a comprehensive, multi-step data extraction process. Initially, all selected articles were imported into EndNote X8, and duplicate entries were removed. Subsequently, two team members independently reviewed the remaining articles, screening titles and abstracts to eliminate irrelevant studies. The selection criteria were based on the relevance to our research topic and consistency with analytical study methodologies.

After identifying potentially relevant articles, the final selection was made through group discussion. The selected studies then underwent qualitative review and information extraction in the subsequent phases of our analysis.

Data analysis

We utilized forest plots to visually represent the association between menopausal status and rheumatoid arthritis (RA), displaying odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) for each study. In our analysis, an OR greater than one indicated a risk factor, while an OR less than one suggested a protective effect. To ensure consistency across all included studies, we converted hazard ratios (HRs) and incidence rate ratios (IRRs) from cohort studies to ORs. To assess heterogeneity among studies, we employed both Cochran's Q test and the I^2 index, which helped evaluate whether the observed differences in results across studies were due to chance or true heterogeneity. We addressed potential publication bias using Egger's regression test and applied the trim-and-fill method to account for possible missing studies due to publication bias. This approach allowed us to adjust the overall estimate by incorporating the estimated number of unpublished studies, thereby enhancing the robustness of our findings [18, 19].

We applied different statistical models based on the observed heterogeneity among studies. In the absence of significant heterogeneity, we employed a fixed-effects model. Conversely, when substantial heterogeneity was evident, we implemented a random-effects model to account for between-study variability.

To explore potential sources of heterogeneity, we conducted both univariate and multivariate meta-regression analyses. These analytical approaches helped identify factors that might explain the observed variations in results across studies.

All statistical analyses, including the meta-analysis and meta-regression, were performed using Stata software version 14.

Results

Study selection

Based on the inclusion criteria, 724 articles were initially selected from the current databases. During the screening process, 287 articles were identified as duplicates and removed. This left 437 articles for further review. After reading the full text, 426 studies were found to be ineligible and were excluded from the review. Ultimately, eleven studies were included in the analysis. Of these, seven studies reported the incidence of RA in post-menopausal women compared to pre-menopausal women [8, 20–25] and four studies reported the incidence of RA among women in early menopause compared to those who underwent menopause at a normal age [23, 26–28] (Fig. 1).

Characteristics of included studies

Table 1 presents a comprehensive overview of the characteristics of the included studies. The analysis encompassed 11 studies, comprising six cohort studies, two case-control studies, and three cross-sectional studies. The geographical distribution of these studies was as follows: four were conducted in the United States, two in Sweden, and one each in Canada, Iran, South Korea, Australia, and England.

All 11 journal articles included in this analysis underwent a risk of bias assessment using the Newcastle-Ottawa Scale (NOS) checklist. Based on this evaluation, all studies were determined to have a low risk of bias, as indicated in Table 1.

Meta-analysis

We conducted a random-effects meta-analysis incorporating seven studies to assess the odds of developing rheumatoid arthritis (RA) in post-menopausal women compared to pre-menopausal women. The analysis revealed a statistically significant increase in RA risk among post-menopausal women, with an odds ratio (OR) of 1.35 (95% confidence interval [CI]: 1.04 to 1.67) (Fig. 2). However, we observed substantial heterogeneity among the included studies, as indicated by a Q statistic of 31.81 ($p<0.001$) and an I^2 value of 81%. Both univariate and multivariate regression analyses showed that none of the examined variables (country, year, study quality, and study design) significantly contributed to this heterogeneity ($p>0.05$) (Table 2).

In a separate random-effects analysis, we examined the odds of developing RA in women who experienced early menopause (defined as onset before age 45) compared to those who underwent menopause at a normal age. This analysis demonstrated that women with early menopause had significantly higher odds of developing RA, with an OR of 2.97 (95% CI: 1.73 to 4.22) (Fig. 3). Again, we observed considerable heterogeneity among the included studies (Q statistic = 12.51, $p=0.006$; $I^2 = 76.0\%$). Notably, univariate and multivariate regression analyses indicated that the year of study publication might have contributed to this heterogeneity, as evidenced by coefficients of -0.359 and 0.351, respectively ($p<0.05$) (Table 2).

Publication bias

We assessed publication bias using funnel plots and Egger's test for both sets of studies in our meta-analysis.

For studies reporting the odds ratio of RA incidence among post-menopausal women compared to pre-menopausal women, we found no evidence of publication bias. The Egger's test yielded a biased estimate of -6.258 (95% confidence interval: -0.653 to 13.171; $p=0.067$), as illustrated in Fig. 4.

Table 1 Summary of the studies concerning the association between Menopausal State and rheumatoid arthritis

Author	Year	Country	Number of participants	Study design	Outcome	Comparison group	OR (95%CI)	QA
Neda Ghamarzad Shishavan, et al. [20]	2016	Iran	469	Case-control	RA	Post-menopause/Pre-menopause	2.97(1.98–4.46)	Low risk
Lauren E. et al. [26]	2015	Canada	534	Cohort	RA	Early menopas/ normal menopas	2.20(1.30–3.80)	Low risk
Mitra Pikwer, et al. [27]	2011	Sweden	30,447	Cohort	RA	Post-menopause/Pre-menopause	2.42(1.32–4.45)	Low risk
Yeonghee Eun et al. [22]	2020	South Korea	6056	Cohort	RA	Post-menopause/Pre-menopause	0.96(0.79–1.17)	Low risk
Camilla Bengtsson, et al.	2017	USA	121,700	Cohort	RA	Early menopas/ normal menopas	2.41(1.50-4.0)	Low risk
Camilla Bengtsson, et al. [23]	2017	USA	116,430	Cohort	RA	Post-menopause/Pre-menopause	2.79(1.76–3.81)	Low risk
Linda A. Merlino, et al. [8]	2003	USA	31,336	Cohort	RA	Post-menopause/Pre-menopause	0.80(0.51–1.25)	Low risk
Mitra Pikwer, et al. [21]	2012	Sweden	134	Case-control	RA	Early menopause(≤ 45 years)/ normal menopause	4.51(3.59–5.43)	Low risk
Beydoun, et al. [28]	2013	USA	1892	Cross-sectional data from the Third National Health and Nutrition Examination Survey	RA	Early menopas/ normal menopas	2.53(1.41–4.53)	Low risk
Szoeke, et al. [24]	2005	Australia	1897	Cross-sectional population-based survey	RA	Post-menopause/Pre-menopause	1.88(1.33–2.66)	Low risk
Jingjing Zhu1, et al. [25]	2021	UK	329,345	survey	RA	Post-menopause/Pre-menopause	1.05(0.98–1.11)	Low risk

Abbreviation: QA: Quality assessment, RA: Rheumatoid Arthritis

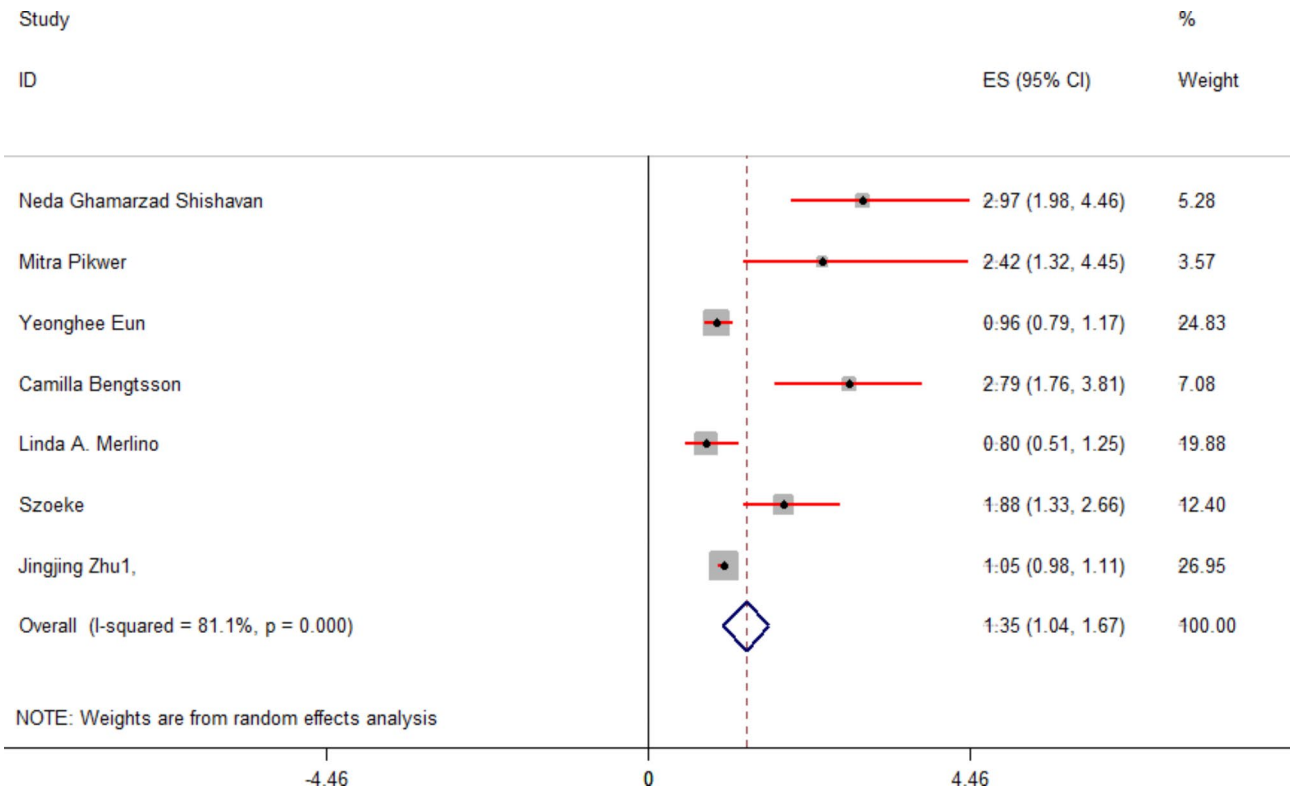

Fig. 2 Presents a forest plot illustrating the odds of rheumatoid arthritis (RA) incidence in post-menopausal women compared to pre-menopausal women

Table 2 Presents the results of univariate and multivariable meta-regression analyses, which were conducted to identify potential factors that may have contributed to the observed heterogeneity among the studies included in the meta-analysis

comparison group	Possible cause of heterogeneity	Univariate		Multivariable	
		Coefficient (95%CI)	*P*-value	Coefficient (95%CI)	*P*-value
Post-menopause/Pre-menopause	Location	-0.280(-0.630, 0.069)	0.116	-0.084(-0.686, 0.518)	0.784
	Risk of bias	-0.271(-0.802, 0.258)	0.235	-0.032 (-0.295, 0.231)	0.721
	Year	0.009(-0.084, 0.103)	0.843	0.011(-0.085, 0.109)	0.812
	study design	-0.468(-0.992, 0.055)	0.080	-0.386(-1.289, 0.5160)	0.401
Early menopause/ normal menopause	Location	-0.1700(-0.878, 0.538)	0.638	-0.046(-0.568, 0.475)	0.862
	Risk of bias	-0.422 (-0.917, 0.072)	0.082	-0.178 (-0.387, 0.031)	0.067
	Year	-0.359(-0.694, -0.025)	**0.035**	-0.351(-0.6965, -0.007)	**0.045**
	study design	-0.537(-2.669, 1.594)	0.621	-0.365(-2.903, 2.172)	0.778

However, for studies comparing RA incidence between women with early menopause and those with normal-age menopause, the funnel plot appeared asymmetric. The Egger's test revealed a significant bias estimate (bias = -14.712, 95% CI: -24.566 to -4.858; $p=0.023$), suggesting the presence of publication bias, as shown in Fig. 5.

To address this potential publication bias, we conducted a Trim-and-fill analysis using non-parametric methods. This analysis estimated the values of two censored studies and adjusted the overall odds ratio using a random-effects model. After correction, the odds ratio for RA incidence among women with early menopause compared to those with normal-age menopause was 3.16 (95% CI: 2.08–4.24).

Discussion

This study provides evidence of an increased risk of rheumatoid arthritis (RA) among post-menopausal women compared to pre-menopausal women. The random-effects analysis revealed a statistically significant association, with post-menopausal women having 35% higher odds of developing RA than their pre-menopausal counterparts. Furthermore, our analysis showed that women who experienced early menopause had nearly three times higher odds of developing RA than those who underwent menopause at a normal age. This finding highlights the potential impact of early menopause on RA development. The finding highlights the potential impact of early menopause on RA development.

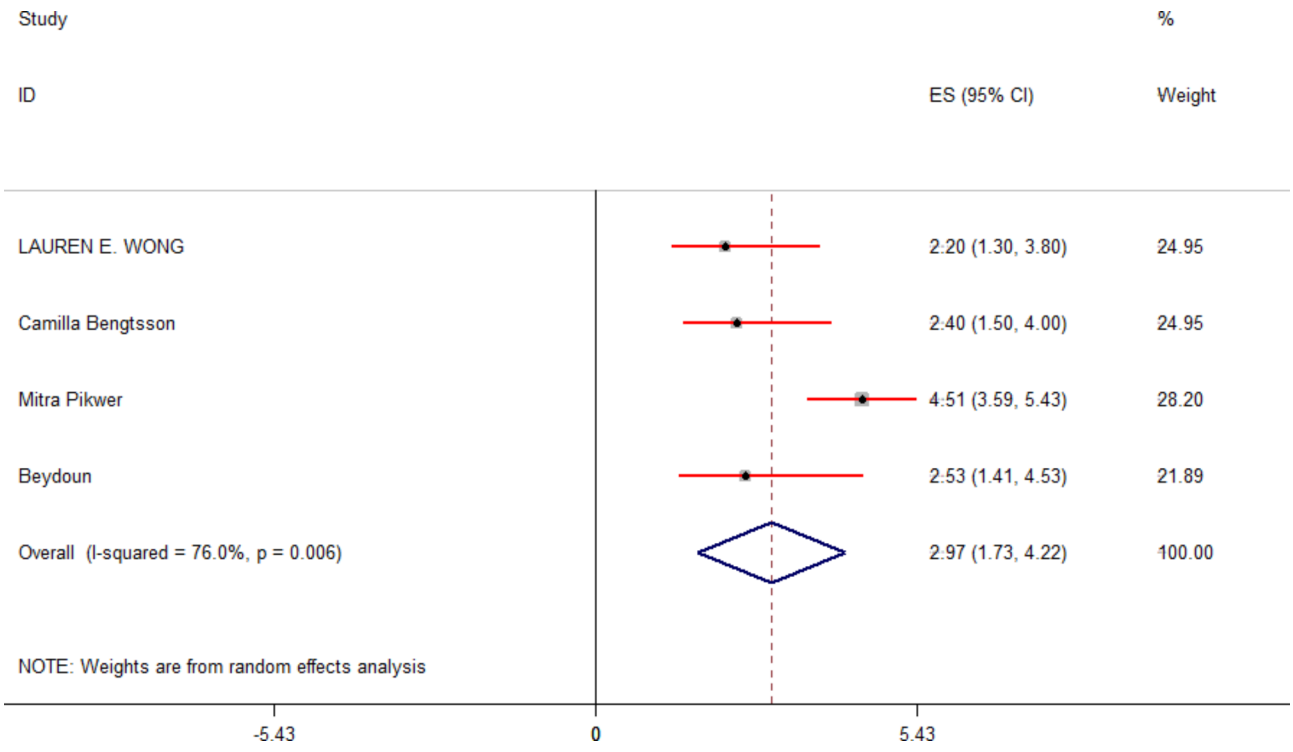

Fig. 3 Presents a forest plot illustrating the odds of rheumatoid arthritis (RA) incidence in women who experienced early menopause compared to those who underwent menopause at a typical age

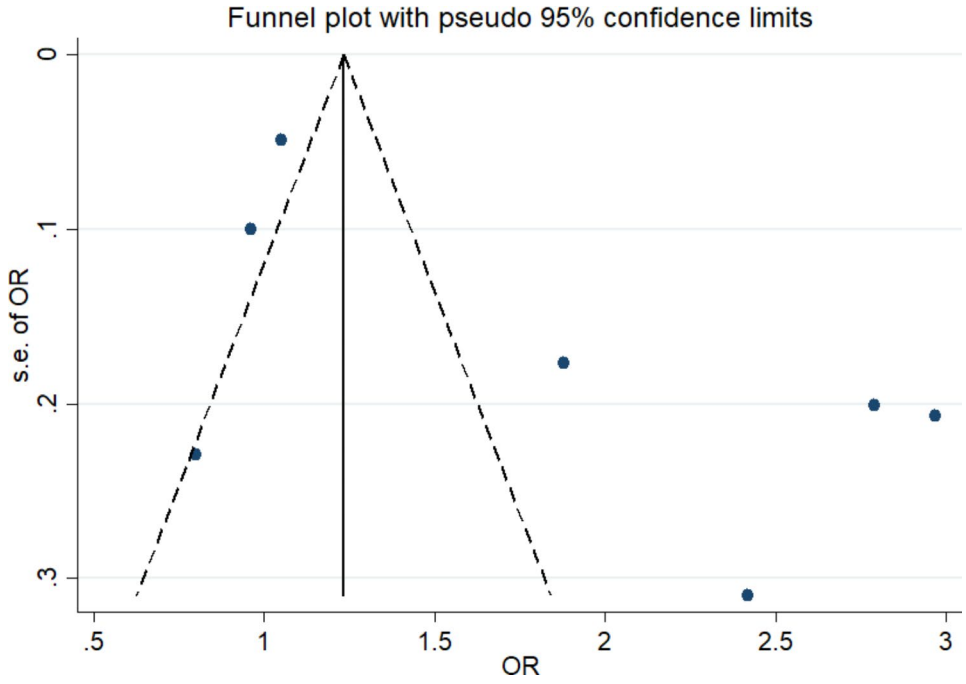

Fig. 4 Represents the funnel plot with pseudo 95% confidence limits for detecting publication bias regarding the risk of RA incidence among post-menopausal women compared to pre-menopausal women

Several studies support our findings. For example, a case-control study in northwest Iran indicated that early age at menopause is a risk factor for developing RA [11]. Pikwere et al. also identified early menopause as an independent predictor of RA, specifically associated with the seronegative type [10]. Data from the Nurses' Health Study (NHS) revealed that post-menopausal and early menopausal women were more likely to have RF-negative

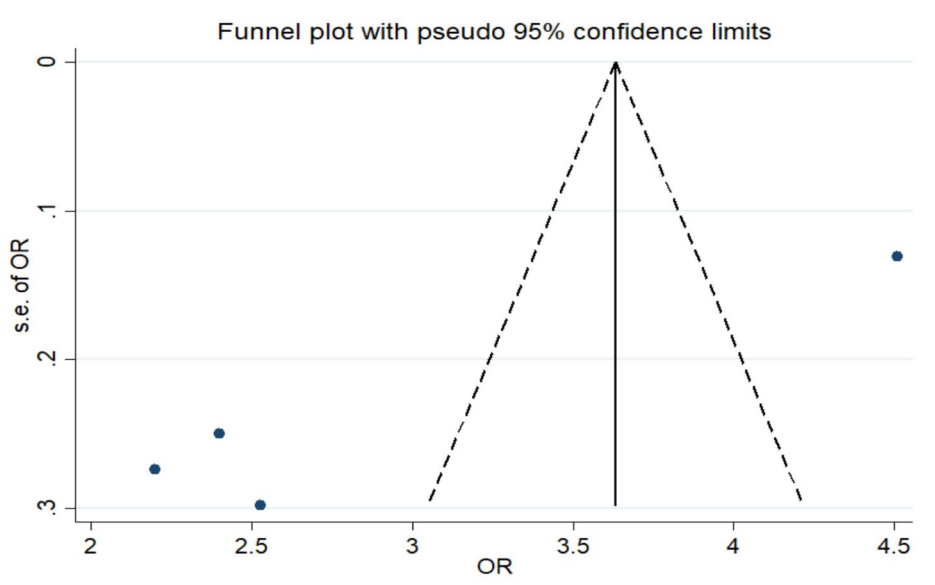

Fig. 5 Displays the funnel plot with pseudo 95% confidence limits for detecting publication bias regarding the risk of RA incidence among women in early menopause compared to women who underwent menopause at a normal age

RA [28]. Merlino et al. found an inverse association between age and the development of RA, suggesting that younger age at menopause increases RA risk [8]. Beydoun et al. reported that age at menopause was the only risk factor for RA development among post-menopausal women over 60 years [29]. A Canadian cohort study determined that menopause before age 45 was associated with an increase in seropositive RA and worsening self-reported pain [12].

However, there are some conflicting results. For instance, the NHS showed an increased risk for seronegative RA with early menopause Pikwere et al. reported a milder type of seronegative RA in the early menopausal group [28]. Other risk factors, such as a history of hormone replacement therapy (HRT) [8, 9] or polycystic ovary syndrome [8], have also been linked to RA development. The NHS reported that long-term HRT use (over eight years) was associated with an increased risk of seropositive RA [30].

Conversely, some studies, including those from South Korea [9] and Nonwage [31], showed a statistically insignificant or weakly positive association between age and menopausal state.

Discrepancies in results may stem from differences in study design, participant demographics, stages of reproductive aging, and ethnic features. The role of reproductive hormones around menopausal transition, particularly estrogen, in RA pathogenesis is significant. Estrogen has both immunosuppressive and immunostimulatory effects depending on its physiological level [32]. This dual effect may explain the varying impacts of HRT depending on dose and duration. While theoretically protective, long-term HRT use has been associated with increased RA risk [8, 22, 33]. Estrogen loss leads to a Th1-dominant immune response, which may drive RA pathogenesis [34]. Progesterone, on the other hand, inhibits Th1 and Th17 pathways and may have a protective effect [35, 36].

Women with early menopause may experience a less responsive and gradual decline in the hypothalamus-pituitary-gonadal axis (HPG), leading to hormonal changes that increase RA risk [37, 38]. However, Pikwer et al. found that early menopausal women tend to have a milder, seronegative form of RA [27], potentially due to different hormonal pathways. Additionally, smoking and HLA-DRB1 are well-known factors associated with severe, seropositive RA [39, 40].

Limitation

Our study has some limitations that should be recognized. Firstly, the studies we included in our analysis may have inherent biases and limitations since we relied on the existing literature. Differences in the design of the studies, sample sizes, and data collection methods across the studies may have introduced potential sources of bias. Another limitation of our study is the high heterogeneity observed among the included studies, which is a significant concern. The underlying reasons for the heterogeneity remain unclear despite utilizing random-effects models to address this issue. It is possible that unmeasured confounding factors or differences in participant characteristics, such as age, ethnicity, lifestyle factors, and comorbidities, may have influenced the results.

A third limitation of our study is that it primarily focused on comparing post-menopausal and pre-menopausal women without considering other stages of menopause, such as perimenopause. This limited focus may have resulted in an incomplete understanding of the relationship between different menopausal stages and the risk of developing RA. Fourth, the generalizability of our findings may be limited to the populations and settings represented in the included studies. Most of the studies were conducted in specific geographic regions, which could potentially restrict the applicability of our results to other populations.

An additional limitation of our study is that we were unable to access the full text of 51 articles during our literature search. While this is not uncommon in systematic reviews and meta-analyses, and our inaccessibility rate (7%) was lower than the average reported in similar studies, it is possible that some relevant data were missed. However, we made extensive efforts to obtain these articles and conducted sensitivity analyses to mitigate the potential impact of this limitation on our results.

Lastly, other factors not considered in our analysis, such as hormonal replacement therapy, genetic predisposition, and environmental factors, may also have impacted the association between menopausal status and the risk of developing RA. Despite these limitations, our study provides valuable insights into the relationship between menopausal status and RA risk, and serves as a foundation for future research in this area.

Advantages

Despite these limitations, our study has several notable strengths. Firstly, it is the first comprehensive meta-analysis specifically investigating the association between menopausal status and the risk of developing RA, providing valuable insights into this area. Secondly, by including a diverse set of studies from various geographical regions, our analysis offers a broader perspective on the global trends and associations. Lastly, this study highlights the need for further research in this field, laying the groundwork for future studies to build upon and address the identified gaps.

Conclusion

Our study reveals significant associations between menopausal status and the risk of rheumatoid arthritis (RA), with post-menopausal women showing a 35% increased risk of developing RA compared to pre-menopausal women. Moreover, we found that women who experience early menopause face nearly three times higher odds of developing RA than those who undergo menopause at a typical age. These findings underscore the importance of menopausal status as a potential risk factor for RA, with the substantial increase in RA risk associated with early menopause warranting particular attention from both clinicians and researchers. Our results suggest several avenues for future research, including investigation into the biological mechanisms underlying the association between menopause and RA risk, development of targeted preventive strategies for post-menopausal women (especially those who experience early menopause), and exploration of potential interventions to mitigate RA risk in these higher-risk groups.

Abbreviations

RA	Rheumatoid arthritis
GBD	Global Burden of Disease report
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
MeSH	Medical Subject Headings
CIs	Confidence intervals
NOS	Newcastle-Ottawa Scale
(HRs	Hazard ratios
IRRs	Incidence rate ratios
HRT	Hormone replacement therapy
NHS	National Health Service
HPG	Hypothalamus-pituitary-gonadal

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41927-024-00418-2.

Supplementary Material 1

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Author contributions

AGH and VR conceived and designed the study. MJ and NN conducted the literature search and screening. MJ and VR gathered the data. VR conducted the statistical analysis. VR, NN, and HK contributed to data interpretation. VR, NN, and AGH drafted the manuscript, which VR critically reviewed. All authors reviewed the final version before publication. [VR] assumed full accountability for the accuracy and reliability of the data analysis and had unrestricted access to the study's data.

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None.

Data availability

The authors recognize that the article and its supplementary material contain the necessary data to support the findings presented in this research.

Declarations

Ethics approval and consent to participate

We meticulously adhered to ethical standards for our systematic review and meta-analysis endeavors throughout this research. The study protocol received formal endorsement from the Ethics Committee of Jahrom University of Medical Sciences, with the designated code: IR.JUMS.REC.1401.116.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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