REVIEW ARTICLE

Relationship Between Female Reproductive Factors and Osteoporosis among Postmenopausal Women in Malaysia: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Numerous studies in Malaysia have investigated the potential link between female reproductive factors and osteoporosis in postmenopausal women; however, a comprehensive synthesis of these findings is lacking. This systematic review seeks to elucidate the association between female reproductive factors and bone health indices in postmenopausal Malaysian women. A comprehensive search of PubMed, Scopus, and the Cochrane Library databases was conducted up to October 2024. Inclusion criteria comprised case-control and cross-sectional studies that reported comparisons, correlations, or regression analyses involving years-since-menopause, parity, or lactation with osteoporosis. Qualitative analysis was conducted on eight cross-sectional studies and one case-control study. Five out of the nine studies indicated a relationship between years-since-menopause and osteoporosis. Additionally, two out of four studies found a relationship between parity and osteoporosis, while two out of three studies demonstrated a relationship between lactation and osteoporosis. Quantitatively, a meta-analysis was performed for five studies, with a pooled sample size of 1134 postmenopausal women. A significant negative correlation emerged between years-since -menopause and osteoporosis indices (Fisher's correlation coefficient: -2.51 [95% CI-0.305-0.195], p<0.001, fixed-effect model, I^2 97%). Unfortunately, the available data on parity and lactation history were insufficient for meta-analysis of correlation. Limitations in the regression data did not allow for meta-analysis. The findings underscore the potential importance of years-since-menopause as a reproductive factor associated with osteoporosis in postmenopausal Malaysian women. Additional research is imperative to substantiate this association and contribute to the development of a robust risk assessment tool.

Keywords
bone health, fragility fracture, osteoporosis, post menopause, reproductive factors

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INTRODUCTION

Osteoporosis is a prevalent global health concern, commonly diagnosed through assessment of bone mineral density (BMD).[1] A study conducted in Klang Valley, a densely populated region in Malaysia's capital, approximately 9.9% of Malaysian men and 20.1% of Malaysian women over the age of 50 were found to have osteoporosis.[2] These figures align with another study conducted in Selangor, another populous state in Malaysia, which reported that the prevalence of osteoporosis among men aged over 40 ranged from 7.5% to 15.8%, while for women in the same age group, the prevalence was between 17.6% and 27.0%.[3]

Dual-energy X-ray absorptiometry (DXA) is the gold standard, employing T-scores to evaluate BMD at the lumbar spine or proximal femur. According to World Health Organization (WHO) guidelines, osteoporosis is identified when BMD falls 2.5 standard deviations or more below the mean for young adults (T-score ≤−2.5), while osteopenia is diagnosed when the T-score falls between -1 and -2.5.[4] While DXA is integral in clinical settings, its cost limits widespread accessibility. In contrast, quantitative ultrasonography (QUS) offers a portable, radiation-free, and cost-effective alternative for bone health screening, using methods like broadband ultrasound attenuation (BUA) and speed of sound (SOS).[5] However, the T-scores generated by QUS may differ from DXA.[6] Another valuable tool for detecting bone loss is the measurement of bone resorption markers, such as N- and C-telopeptides of type I collagen (NTX and CTX), which reflect the enzymatic breakdown of the bone matrix.[7,8]

Oestrogen is essential for maintaining BMD as it inhibits bone resorption. A decline in oestrogen levels accelerates bone loss and increases the risk of fractures.[9] Recent research from Korea has highlighted the independent fracture risk associated with shorter lifetime exposure to endogenous oestrogen.[10] During the postpartum period, particularly while breastfeeding, oestrogen levels are temporarily suppressed, and they consistently decline after menopause.[11] Some studies suggest that earlier menopause increases the risk of osteoporotic fractures.[12-16] Additionally, pregnancy and lactation impact maternal bone health;[17] however, the long-term relationship between these factors and postmenopausal osteoporosis remains debated.[9,13,18-21] Consequently, reproductive factors such as menopausal age, parity, and lactation are frequently studied in osteoporosis research, as they significantly influence cumulative oestrogen exposure.[11,22-24]

Despite substantial racial and ethnic differences in BMD and fracture incidence,[25] limited epidemiologic data exist on osteoporotic fractures in Asian women, particularly in Malaysia. While previous studies have examined reproductive factors in Malaysian postmenopausal women, their findings have been inconsistent.[11,22-24] This study is the first to systematically review and meta-analyse the available evidence regarding the relationship between female reproductive risk factors and osteoporosis within the Malaysian population.

Our primary goal is to develop an effective Malaysian-specific osteoporosis screening tool that relies less on DXA scans and more on strong predictors. Effective risk assessment models begin by identifying the strength of these risk factors. This systematic review aims to establish the relationship between female reproductive factors and bone health indices in postmenopausal Malaysian women. The objective is to pool data qualitatively and quantitatively on the relationship between reproductive factors (years-since-menopause (YSM), parity, and lactation) and osteoporosis in this population.

MATERIALS AND METHODS

Data source and search strategy

A systematic search was conducted across three prominent databases (PubMed, Scopus, and the Cochrane Library) using a curated set of keywords: Postmenopause* OR Post-menopause* OR Menopause* AND Malaysia OR Malaysian* AND osteoporosis OR "fragility fracture" OR "bone loss" OR osteoporotic OR "osteoporotic fracture" OR fracture (Table I). Studies published between 1975, and October 2024 were considered, with eligibility restricted to articles in English or Malay, and studies affiliated with Malaysia. The search followed the PICO framework, where Population (P) referred to postmenopausal women in Malaysia, and Outcome (O) included bone health indices, osteoporosis, fragility fracture, or bone loss. These criteria formed the basis for the search strings employed in this study.

Table I: The curated set of keywords for the systematic search conducted on 27th October 2024

Database	Keywords string
Pubmed	("postmenopaus*"[All Fields] OR "post menopaus*"[All Fields] OR "menopaus*"[All Fields]) AND ("malaysia"[MeSH Terms] OR "malaysia"[All Fields] OR "malaysia s"[All Fields] OR "malaysian*"[All Fields]) AND ("osteoporosis"[MeSH Terms] OR "osteoporosis"[All Fields] OR "osteoporoses"[All Fields] OR "osteoporosis, postmenopausal"[MeSH Terms] OR ("osteoporosis"[All Fields] AND "postmenopausal"[All Fields]) OR "postmenopausal osteoporosis"[All Fields] OR "fragility fracture"[All Fields] OR "bone loss"[All Fields] OR ("osteoporotic"[All Fields] OR "osteoporotics"[All Fields]) OR "osteoporotic fracture"[All Fields] OR ("fractur"[All Fields] OR "fractural"[All Fields] OR "fracture s"[All Fields] OR "fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields] OR "fractured"[All Fields] OR "fractures"[All Fields] OR "fracturing"[All Fields]))
Scopus	((postmenopaus*) OR (post-menopaus*) OR (menopaus*)) AND ((osteoporosis) OR ("fragility fracture") OR ("osteoporotic fracture") OR (osteoporotic) OR (fracture) OR ("bone loss")) AND ((malaysia) OR (malaysian*)) AND (LIMIT-TO (AFFILCOUNTRY , "malaysia")) AND (LIMIT-TO (DOCTYPE , "ar"))
Cochrane Library	Postmenopaus* OR Post-menopaus* OR Menopaus* (Title/ Abstract/Keyword) AND osteoporosis OR 'fragility fracture' OR 'bone loss' OR osteoporotic OR 'osteoporotic fracture' OR fracture (Title/ Abstract/Keyword) AND Malaysia OR Malaysian* (Title/ Abstract/Keyword)

STUDY SELECTION

The selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[26] Nine studies were included in the qualitative analysis, all exploring the relationship between reproductive factors (YSM, parity, lactation) and osteoporosis, specifically those discussing correlation and/or regression among postmenopausal women in Malaysia. Only studies with full texts available were considered. Exclusion criteria included studies that did not assess these associations, focused on injectable contraception, examined unrelated reproductive risk factors, lacked bone health measurements, or were interventional or case reports. Studies in languages other than English or Malay were also excluded.

Specifically, inclusion criteria were studies examining the relationship between YSM, parity, lactation, and osteoporosis in postmenopausal women in Malaysia, using observational designs (cross-sectional, case-control, cohort). Excluded were duplicates, unrelated studies, unclear methodologies, interventional studies, and those not in English or Malay.

QUALITY ASSESSMENT

The quality of the included studies underwent evaluation using the Newcastle-Ottawa Scale (NOS) tailored for cross-sectional and case-control studies.[27] The NOS includes eight items across three domains: subject selection (four items), comparability (one or two items), and outcome (two or three items). Total NOS scores were calculated by dividing the achieved score by the maximum attainable score (14 points). Studies scoring >75% (11-14 points) were deemed "high quality," 50-75% (7-10 points) as "moderate quality," and ≤50% (0-6 points) as "low quality".[28]

RISK OF BIAS ASSESSMENT

The risk of bias in the studies was assessed using the Joanna Briggs Institute (JBI) tool.[29] For cross-sectional studies, the checklist included eight questions covering criteria such as subject selection, exposure and outcome measurement, confounding factors, and statistical analysis. For case-control studies, the checklist included ten questions focusing on the comparability of groups, exposure measurement, confounding factors, and outcome assessment, with responses similarly categorized. Responses were categorized as 'Yes/low risk,' 'No/high risk,' or 'Cannot tell/unclear risk'.

DATA EXTRACTION

Data were extracted from the selected studies on the following: (1) study type, (2) total population size, (3) population source, (4) bone-related parameters, (5) population categorization, (6) findings from comparison/ regression/correlation analyses, and (7) conclusions regarding the relationship between risk factors (YSM, parity, and lactation) and bone health. Two independent reviewers (S.Z.M. and S.H.N.) assessed all articles, with disagreements resolved through discussion with the second and third authors (M.N.A.T. and M.A.S.).

META-ANALYSIS

Fisher's z transformation was applied to convert correlation coefficients to Fisher's z scores for meta-analysis.[30] These scores were pooled to estimate the overall correlation using MedCalc® Statistical Software version 22.014 (MedCalc Software Ltd, Ostend, Belgium). A significance level of $p<0.05$ was considered significant. For data comparing osteoporotic versus non-osteoporotic groups, continuous data were pooled as mean values with standard deviations (SDs) using Review Manager 5 (RevMan 5) version 5.4 analytical software for an overall estimate of the effect size. The pooled mean difference (MD) with 95% confidence intervals (CIs) was used as the effect measure. A random effects model was applied to account for heterogeneity, denoting the extent of variation in effect sizes within the meta-analysis, and was quantified using the I^2 index (ranging between 0 and 100%), with a p-value of <0.05 indicating significant heterogeneity. Funnel plots were created to assess publication bias, with asymmetry suggesting potential bias.

ETHICAL APPROVAL

As this systematic review and meta-analysis involve a secondary analysis of published data, ethical approval was not required.

RESULTS

ARTICLE IDENTIFICATION AND SELECTION

The initial search identified 814 articles, of which 646 were excluded during title screening for irrelevance. After removing duplicates using EndNote®, 216 articles were retained for abstract and title screening. Following this, 21 full-text articles were retrieved for eligibility assessment based on the inclusion and exclusion criteria. Twelve articles were excluded, leaving nine articles (eight cross-sectional studies and one case-control study) that met all criteria (Figure 1).

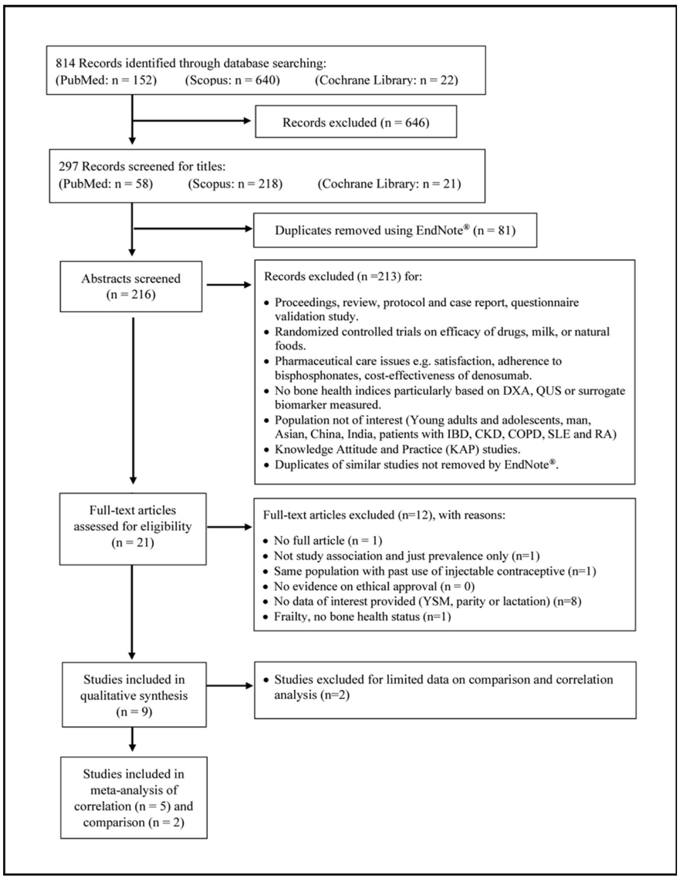

Figure 1: PRISMA flow chart.

All nine included studies are summarized in the evidence tables under the respective sections. One case-control study compared continuous data on YSM and parity between osteoporosis (case) and non-osteoporosis (control) postmenopausal women.[31] Another cross-sectional study categorized populations into osteoporotic and non-osteoporotic groups before comparison.[22] Two studies did not clearly define osteoporosis status or conduct correlation analyses, leading to their exclusion from the meta-analysis.[24,32] Data from these studies were qualitatively synthesized. Five of the included cross-sectional studies provided complete correlation data and were included in the meta-analysis for the correlation of YSM.[8,11,22,33,34]

QUALITY ASSESSMENT

One cross-sectional study and the case-control study received scores of 11 and 13 points, respectively, categorizing them as high-quality studies. The eight cross-sectional studies scored between 9 and 10 points, classifying them as moderate quality. Several cross-sectional studies that used purposive or convenience (non-random) sampling from a single centre received a score of 0 for the representativeness of the target population. One study used random sampling from a single ethnicity and centre,[8] earning a score of 1, while others used purposive sampling from multiple centres,[22,35] earning a score of 1 for representativeness.

Most studies met the target sample inclusion rate, but none provided data on non-respondents after exclusion criteria were applied. Studies that used either gold-standard or validated non-gold-standard tools for outcome assessment received an additional point. Similarly, controlling for confounders resulted in a one-point difference in scores.

RISK OF BIAS ASSESSMENT

All included studies achieved at least 75% "Yes/low risk" responses in the risk of bias assessment, with each study scoring ≥6 "Yes/low risk" in total. Studies that did not control for potential risk factors were categorized as "Cannot tell/unclear risk" for identifying confounders,[11,33,34] as these factors have not been confirmed as true confounders. The remaining studies controlled for confounders using multiple linear regression. Additionally, studies employing non-gold standard but validated tools for measuring osteoporosis, such as QUS and bone resorption biomarkers, were also categorized as "Cannot tell/unclear risk" for using objective, standard criteria for measuring the condition.

RELATIONSHIP BETWEEN YEARS-SINCE-MENOPAUSE (YSM) AND STEOPOROSIS

Table II presents the results from nine studies examining the relationship between YSM and osteoporosis in postmenopausal women in Malaysia. One study reported that osteoporotic women (n=20) had a longer YSM (9.5±6.08 years) than non-osteoporotic women (n=20) (6.10±4.32 years, p=0.048).[31] In contrast, another study found no significant difference in YSM between osteoporotic (n=144) and normal women (n=57) (p=0.06), with values of 4.63±3.08 years and 3.74±3.22 years, respectively.[22] Another study also reported no significant difference in bone resorption markers (CTx and NTx) between postmenopausal women with <10 years or >10 YSM.[32] The continuous data from two studies were pooled in a meta-analysis (77 osteoporotic women versus 164 controls). Seven studies with unavailable YSM data were excluded.[8,11,24,32-35] The forest plot in Figure 2(A) shows a trend favouring longer YSM in osteoporotic women, but this was not statistically significant (Overall Mean Difference=1.64; 95% CI:−0.61 to 3.89; P=0.15). Heterogeneity was moderate (I^2=52%, p>0.05), and the symmetrical funnel plot indicated no publication bias (Figure 2 (B)).

Table II: Evidence table - Years-since-menopause (YSM)

First author	Type of study and population (sample size and source)	Bone-related parameters	Categorization of population	Comparison/ correlation/ regression analysis	Relationship/ Association (Presence or absence)
Lim et al.[8]	Cross-sectional study conducted in 217 healthy postmenopausal Chinese women that were recruited from the (NACSCOM) in Kuala Lumpur Malaysia.	CTX1: serum collagen type 1 cross-linked CTx	NA	Comparison analysis: NA Bivariate Pearson correlation: • YSM was not significantly correlated with serum CTX1 (r= -0.109; p>0.05). Hierarchical regression analysis: • YSM is not a predictor of bone loss (CTX1): B=NA; β= -0.053; p=0.624).	Absent
Md Isa et al.[11]	Cross-sectional study. In total, 116 post-menopausal women were selected; All subjects were recruited from the Orthopaedic and menopause clinic at Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia.	BMD using DXA scan.	BMD status: Osteopenia (n=61) Osteoporosis (n=55)	Comparison analysis: NA Pearson correlation: • YSM was significantly negatively correlated with BMD (*r* = -0.284, *P*=0.001). Regression analysis: NA	Present but weak relationship.
Mohammadi et al.[22]	Cross-sectional study. 201 postmenopausal women aged ranged from 45 to 71 years, with a mean age of 53.6 ± 3.6 years; All subjects were recruited from menopause clinics at Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB).	Calcaneal QUS The mean BMD defined as BUA and T-score ≤ 1.8 at calcaneus was the threshold to determine osteoporosis and normal density.	Non-osteoporotic (n=144) Osteoporotic (n=57)	Comparison using Student's t-test: • Osteoporotic subjects had longer YSM (4.63±3.08) than the normal subjects (3.74±3.22) (p=0.06). Pearson's correlation: • YSM negatively correlated with BUA (*r* = -0.176, *p*<0.005). Correlation analysis: NA Stepwise regression: • YSM was not a predictor of BUA (Result not shown).	Present.

Cont'd

First author	Type of study and population (sample size and source)	Bone-related parameters	Categorization of population	Comparison/ correlation/ regression analysis	Relationship/ Association (Presence or absence)
Chin et al.[24]	Cross-sectional study. 344 women (mean age 61.8 ± 7.6) were recruited from a tertiary medical centre in Kuala Lumpur, Malaysia.	Bone health was determined using calcaneal QUS device. ● SOS (m/s) ● BUA (dB/MHz) ● T-score ● Stiffness index (SI)	● BUA (n=320) ● SI (n=319) ● T-score (n=318)	Comparison analysis: NA Correlation analysis: NA Stepwise multiple linear regression between QUS indices and variables of interest: ● YSM was a negative predictor of BUA (B=-0.018, SEB= 0.003; β= -0.306; p<0.001), SI (B= -0.562, SEB= 0.081; β= -0.358; p< 0.001) T-score (B=-0.054, SEB=0.008; p<0.001). YSM is not a significant predictor of SOS (data not shown in table).	May be present.
Chan et al.[31]	Case-control; Postmenopausal women with (n=20) or without osteoporosis (n=20); Subjects were randomly drawn postmenopausal women with or without osteoporosis from a bone health study in Klang Valley, Malaysia.	Lumbar spine (average of L1-L4) and hip BMD were computed automatically by the DXA scan. ● T-score ≤-2.5 indicates osteoporosis, between -2.5 and -1 indicates osteopenia, and more than >-1 indicates normal bone health.	● Normal group (n=20): T-score >-1 ● Osteoporosis group (n=20): T score ≤-2.5	Comparison using univariate (t-test): Osteoporotic group had longer YSM (9.50 ± 6.08 year) than normal group (6.10 ± 4.32 year) than (*p* = 0.048). Correlation analysis: NA Regression analysis: NA	Present
Hapidin et al.[32]	Cross-sectional study. A total of 51 healthy premenopausal women and 99 healthy postmenopausal women were recruited. Mean age for all subjects was 55.8 ± 7.11 years; All subjects were recruited from lower income family, based on Pendapatan Garis Kemiskinan (PGK) 2009 by Economic Planning Unit, Prime Minister's Department Malaysia.	Biochemical markers of bone resorption can be used clinically to predict future bone loss. ● CTx and NTx of type 1 collagen	● Healthy pre-menopausal group (n=51). ● Postmeno-pausal A group (n=65) who had been in menopausal state for less than 10 years. ● Postmeno-pausal B groups (n= 34) who had been in menopausal state for more than 10 years.	Comparison using ANOVA: The mean for CTx level was significantly different (p<0.05) between pre-menopausal group and both post-menopausal A and B. However, there was no difference between post-menopausal A and B. The mean serum CTx of the subjects were: Pre-menopaused (0.2833 ± 0.1769 ng/mL) ● Post-menopaused A (0.423 ± 0.2529 ng/mL) ● Post-menopausal B (0.510 ± 0.241 ng/mL) The mean for NTx level was significantly different (p<0.05) between pre-menopausal group and both post-menopausal A and B. However, there were no difference between post-menopausal A and B. The mean serum NTx of the subjects were: ● Pre-menopaused (15.203 ± 15.2025 nM BCE) ● Post-menopaused A (17.900 ± 7.7959 nM BCE) ● Post-menopausal B (19.351 ± 7.3775 nM BCE) Correlation analysis: NA Multiple linear regression using simultaneous multiple regression analysis: ● Duration of menopause was a significant positive predictor influencing CTx (B= 0.007; SEB=0.002; β= - 0.265 (p<0.05) and NTx (B= 0.013; SEB=0.005; β= 0.211) bone resorption marker (n=150; p<0.05)	Maybe absent since there is no difference in bone resorption markers between post-menopausal A and post-menopausal B.

Cont'd

First author	Type of study and population (sample size and source)	Bone-related parameters	Categorization of population	Comparison/ correlation/ regression analysis	Relationship/ Association (Presence or absence)
Mohd Hatta et al.[33]	Cross-sectional study. 87 post-menopausal women; All subjects were recruited from the orthopaedic and menopause clinics of Hospital Tengku Ampuan Afzan Kuantan, Pahang, Malaysia	FRAX® was used to calculate the risk for major and hip fracture probability in 10 years. • BMD result of the osteopenic range (T-score of less than −1 and greater than −2.5 SD).	FRAX 10-year risk score: • Major osteoporotic fracture (9.7%) • Hip fracture (3.5%)	Comparison analysis: NA The Pearson correlation coefficient showed a significant positive but weak correlation between year of menopause and FRAX major osteoporotic ($r=0.581$, $p < 0.001$) and hip fracture probability ($r=0.495$, $p < 0.001$). Regression analysis: NA	Present
Lim et al.[34]	Cross-sectional study. A total of 514 disease-free, uterus-intact, non -HRT-using women aged 45 years and older were recruited into the study; Subjects were recruited from residential areas around a tertiary referral hospital, but subjects from other areas responded as well after being informed by friends.	BMD using DXA. • Bone mass at the spine and hip (g/cm²) • Hip and spine T -score.	• Pre-menopausal (year 0) n=308 • Post-menopausal (n= 205) Overall, 42.1% postmenopausal women and 11.1% premenopausal women were osteoporotic.	Comparison analysis: NA Pearson's correlation: YSM negatively correlated with BMD: • Spine T-score ($r= -0.439$, $p< 0.001$). • Spine Z-score ($r= -0.289$, $p< 0.001$), • hip T-score ($r= -0.441$, $p< 0.001$), • hip Z-score ($r= -0.186$, $p< 0.001$). Regression analysis: NA	Present
Mohammadi et al.[35]	Cross-sectional study. A total of 201 postmenopausal, disease-free women. Their ages ranged from 45-71 years, with a mean age of 53.6 ± 3.6 years; All subjects were recruited from menopause clinics at Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB).	Calcaneal BMD was measured by QUS and was expressed in BUA as well as T-score.	• Non-osteoporotic (n=144) • Osteoporotic (n=57)	Comparison analysis: NA Correlation analysis: NA Hierarchical regression analysis: • YSM was not a predictor of BUA. • Step 1: (B=1.116; SEB 0.735; $\beta=0.227$; $p>0.05$) • Step 2: (B= 0.935; SEB 0.654; $\beta=0.190$; $p>0.05$)	Absent

Abbreviations: ANOVA (Analysis of variance), Bone mineral density (BMD), Broadband ultrasound attenuation (BUA), C-telopeptide (CTx), Not applicable (NA), N-telopeptide (NTx), Quantitative ultra-sonography (QUS), Speed of Sound (SOS), years-since-menopause (YSM).

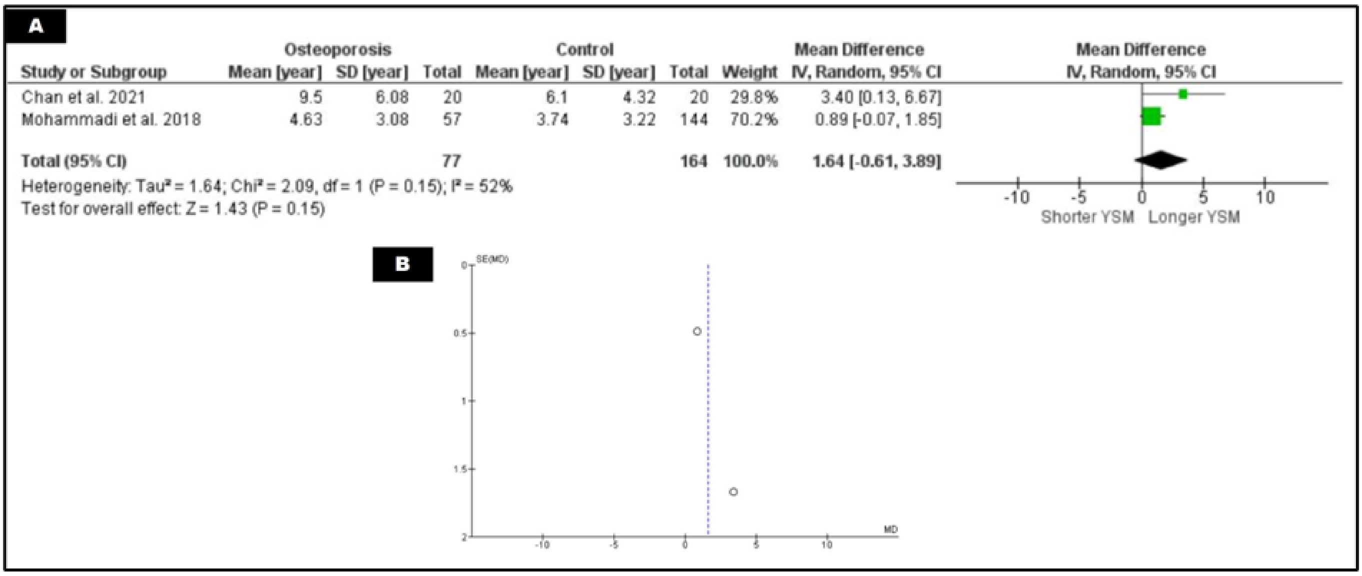

Figure 2: Comparison of YSM between postmenopausal women with and without osteoporosis. (A) Forest plot illustrating the mean difference in YSM, and (B) funnel plot assessing publication bias.

Several studies consistently found a significant negative correlation between YSM and BMD (measured by BUA or DXA), although the correlation strength was weak ($r=-0.284$, $r=-0.176$, $r=-0.439$, respectively; $p<0.01$).[11,22,34] In contrast, another study reported a positive correlation between YSM and the Fracture Risk Assessment Tool (FRAX®) major osteoporotic fracture risk score ($r=0.581$; $p < 0.001$) and FRAX® hip fracture probability ($r=0.495$; $p<0.001$).[33] One study found no significant correlation between YSM and serum CTx ($r=0.109$; $p > 0.05$).[8] The forest plot in Figure 3(A) summarizes the correlation results, with each study's bone indices indicated. Five studies were included in the meta-analysis, pooling data from 1134 postmenopausal women. The fixed effect model yielded a pooled effect size of -0.251 ($p<0.001$), while the random effect model resulted in -0.0677 ($p=0.712$). The heterogeneity I^2 was 96.99%, and the symmetrical funnel plot suggested no publication bias (Figure 3(B)).

Two studies indicate that YSM can predict osteoporosis. Based on multiple linear regression, one study found that YSM was not a predictor of BUA ($B=0.935$; $\beta=0.190$; $p>0.05$),[35] while another reported that YSM predicted BUA ($B=-0.018$), SI (-0.562), and T score ($B=-0.054$) ($p<0.001$), but not SOS.[24] Another study found YSM to be a significant positive predictor of CTx ($B=0.007$; $\beta=-0.265$; $p<0.05$) and NTx ($B=0.013$; $\beta=0.211$) bone resorption markers ($n=150$; $p<0.05$).[32] Conversely, one study reported that YSM was not a predictor of CTx (B=NA; β 0.053; $p=0.624$).[8]

Relationship between parity and osteoporosis

Table III summarizes five studies on the association between parity and osteoporosis in postmenopausal women in Malaysia. Only one study examined the relationship, and two studies measured the association between parity and osteoporosis. One study found no significant difference in the number of pregnancies between osteoporotic (2.85 ± 2.06) and non-osteoporotic women (3.10±2.27).[31] However, another study reported that osteoporotic women had significantly more pregnancies (5.43±1.89) than non-osteoporotic women (4.77±2.05, $p=0.027$).[22] Another study found that middle-aged and elderly women with more than three pregnancies had lower BUA than those with fewer pregnancies or nulliparous women ($p=0.010$).[24]

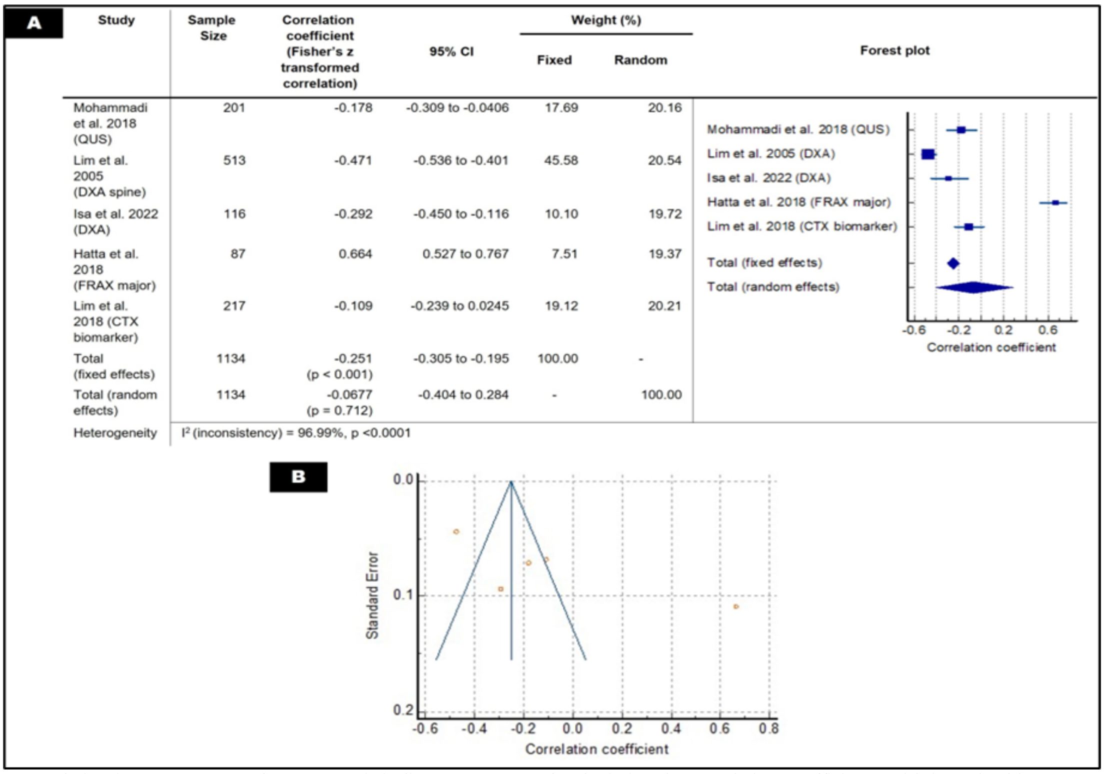

Figure 3: Correlation between YSM and osteoporosis indices. (A) Forest plot depicting the correlation coefficients, with bone health assessment methods indicated for each study, and (B) funnel plot evaluating publication bias.

The pooled results for parity in postmenopausal women with and without osteoporosis are shown in Figure 4(A). The meta-analysis included data from 77 postmenopausal women with osteoporosis and 164 controls from two studies,[22,31] excluding other studies with unavailable parity data.[24,32,35] Notably, one study divided groups based on menopausal years without specifying osteoporosis status, so it was not included in the meta-analysis of comparison.[32] The overall result did not significantly favour osteoporosis in either direction, with no clear association between parity and osteoporosis (Overall Mean Difference=0.41; 95% CI: −0.38 to 1.21; P=0.31). The heterogeneity test (p=0.22, I^2=32%) showed acceptable variability, and the symmetrical funnel plot indicated no publication bias (Figure 4(B)).

In terms of the strength of this relationship, only one study measured the correlation between parity and bone status. One study found that parity was negatively correlated with BUA (r=-0.162; p<0.005).[22] However, based on multiple linear regression, another study found that parity was not a predictor of BUA (B=-0.152 β=-0.020; p>0.05),[35] which contrasts with findings from another study that reported parity as a predictor of BMD measured using BUA (B=-0.040; β=-0.133; p=0.011) and stiffness index (B=-0.888; β=-0.112; p=0.033).[24] Other studies did not perform multiple linear regression, making it difficult to definitively confirm the relationship or predictive value of parity in osteoporosis.

Relationship between lactation and osteoporosis

Table IV presents three studies on lactation and osteoporosis in postmenopausal women in Malaysia. Of these, two studies measured the relationship or association. One study found that osteoporotic women had a significantly longer lactation period (46.30±19.75 months) than non-osteoporotic women (39.07±23.16 months).[22] In the same study, lactation was inversely correlated with BUA (r=-0.159; p<0.05). However, the relationship between lactation and BUA remains unclear. Stepwise multiple regression showed lactation as a positive predictor of BUA (B=0.036; p=0.015),[22] while hierarchical multiple regression indicated it as a negative predictor (B=-0.111; β=-0.158; p<0.01) for the same population.[35] This inconsistency highlights the need for further studies to confirm whether lactation can reliably predict osteoporosis.

DISCUSSION

This systematic review highlights that most studies on osteoporosis in Malaysia are cross-sectional. While cross-sectional studies are adept at determining prevalence and identifying potential associations, they are often preliminary and require further investigation through cohort or randomized controlled studies. Case-control studies on osteoporosis risk factors in Malaysian postmenopausal women are limited, often with small sample sizes.[31] There is also a dearth of cohort studies

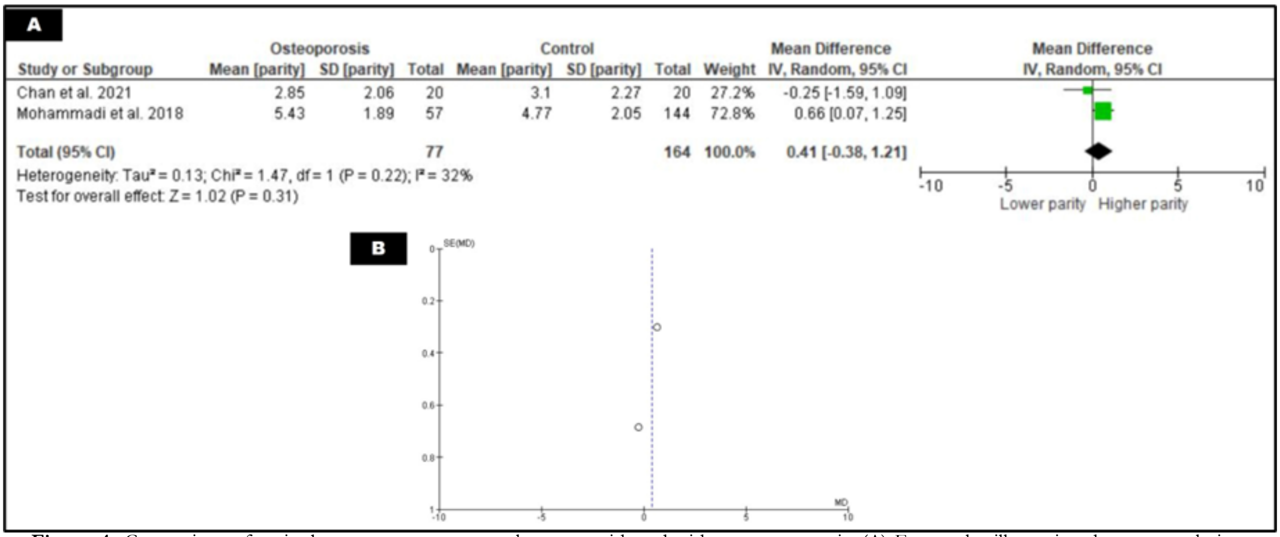

Figure 4: Comparison of parity between postmenopausal women with and without osteoporosis. (A) Forest plot illustrating the meta-analysis results, and (B) funnel plot assessing publication bias.

specifically focused on this population.[36] A group of researchers conducted a cohort study on osteoporosis risk factors for osteoporosis in the Malaysian population, but it included participants of mixed gender.[37] While randomized controlled trials are the gold standard for establishing causality, practical and ethical constraints often preclude their implementation. In these cases, observational research, such as case-control studies, provides valuable insights and is cost-effective.[38] More studies in this direction were anticipated.[31,39] This review offers an overview of the research trends in Malaysia, highlighting a pronounced bias towards cross-sectional studies. It emphasizes the heavy reliance on cross-sectional designs and underscores the scarcity of case-control, cohort, and randomized controlled trials. This indicates a pressing need for more robust research methodologies to enhance the quality and depth of findings in the field.

A significant portion of the cross-sectional studies in this review used purposive sampling, which, although lacking statistical representativeness,[40] allows for the selection of participants expected to provide valuable insights.[41] In contrast, convenient sampling, as used in some studies,[24,32] is less representative but was still included in this systematic review due to its overall moderate quality score. Given Malaysia's ethnically diverse population, studies focused on a single ethnicity may not adequately represent the entire population. Therefore, factors beyond sampling methods, such as ethnicity and whether the study was conducted at single or multiple centres, must also be considered.

Table IV: Evidence table - Lactation

First author	Type of study and population (sample size and source)	Bone-related parameters	Categorization of population	Comparison/ correlation/ regression analysis	Relationship/ Association (Presence or absence)
Mohammadi et al.[22]	Cross-sectional study. 201 post-menopausal women. aged ranged from 45 to 71 years, with a mean age of 53.6 ± 3.6 years; All subjects were recruited from menopause clinics at Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB).	Calcaneal QUS The mean BMD defined as BUA and T-score ≤ 1.8 at calcaneus was the threshold to determine osteoporosis and normal density.	• Non-osteoporotic (n=144) • Osteoporotic (n=57)	Comparison using Student's t-test: • Osteoporotic subjects had longer lactation period (46.30±19.75 months) than the normal subjects (39.07±23.16 months) (p=0.028). Pearson's correlation: • Total lactation period negatively correlated with BUA (*r*= -0.15, *p*<0.005). Stepwise regression: • Lactation period was a predictor of BMD (B=0.036, SEB=-0.126; p=0.015).	Present
Hapidin et al.[32]	Cross-sectional study. A total of 51 healthy premenopausal women and 99 healthy postmenopausal women were recruited. Mean age for all subjects was 55.8 ± 7.11 years; All subjects were recruited from lower income family, based on Pendapatan Garis Kemiskinan (PGK) 2009 by Economic Planning Unit, Prime Minister's Department Malaysia.	Biochemical markers of bone resorption can be used clinically to predict future bone loss. CTx and NTx of type 1 collagen	• Healthy pre-menopausal group (n=51). • Postmeno-pausal A group (n=65) who had been in menopausal state for less than 10 years. • Postmeno-pausal B groups (n=34) who had been in menopausal state for more than 10 years.	Comparison: There was no significant difference in duration of breastfeeding among the groups: Data presented in percentage, no standard deviation or mean. ANOVA: NA Correlation analysis: NA Regression: NA	Maybe absent
Mohammadi et al.[35]	Cross-sectional study. A total of 201 postmenopausal, disease -free women. Their ages ranged from 45-71 years, with a mean age of 53.6 ± 3.6 years. All subjects were recruited from menopause clinics at Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB).	Calcaneal BMD was measured by QUS and was expressed in BUA as well as T-score.	• Non-osteoporotic (n=144) • Osteoporotic (n=57)	Hierarchical regression analysis: Lactation negative predictor of BUA (N=201) Step 1: (B= -0.082; SEB 0.050; β = -0.116; p<0.001) Step 2: (B= -0.111; SEB 0.045; β= -0.158; p<0.01)	Present

Abbreviations: ANOVA (Analysis of variance), Bone mineral density (BMD), Broadband ultrasound attenuation (BUA), C-telopeptide (CTx), Not applicable (NA), N-telopeptide (NTx), Quantitative ultra-sonography (QUS).

Epidemiological evidence indicates that reduced lifetime oestrogen exposure, such as that resulting from early menopause and late menarche, is linked to lower BMD and a higher incidence of fractures.[12,13,42] Research involving women from other ASEAN countries has demonstrated that early menopause reduces oestrogen exposure and is consistently associated with an increased risk of osteoporosis.[12,13] While lactation induces a temporary hypoestrogenic state that can lead to transient bone loss, the long-term effects of this phenomenon remain a subject of debate.[19,21] Furthermore, parity introduces repeated hormonal fluctuations, with high parity showing mixed associations with BMD.[43,44] The differences in oestrogen decline, transient during pregnancy and lactation versus continuous after menopause, may explain why our findings revealed a relationship between young maternal age and osteoporosis, while parity and lactation did not show the same connection.

The meta-analysis on the impact of YSM on bone health indicates a tendency towards osteoporosis or compromised bone health with increased menopausal age, though this effect was not statistically significant due to the limited number of studies and the use of cross-sectional study designs. The meta-analysis of the correlation between YSM and bone health indices suggests a negative relationship, indicating lower bone density with an extended duration of postmenopausal state. However, the correlation was weak, regardless of whether a fixed or random effects model was used. Due to significant heterogeneity among studies, the random effects model was deemed more appropriate.[45] Variations in methods for assessing bone health, such as DXA, QUS, FRAX®, and biomarkers, likely contributed to this heterogeneity. While DXA is the gold standard, its limited availability must be considered.[46] Additionally, confounding factors like age may influence results, highlighting the need to consider both menopausal and age-related factors when assessing osteoporosis risk and deciding on hormone treatments for prevention.[47] Studies in this review that found YSM as a non-significant predictor of bone indices reflect the complexities associated with the temporal sequence of osteoporotic fractures,[8,35] which are influenced by bone type and age.

The association between parity and osteoporosis remains inconclusive, as only one study measured the relationship, and two studies assessed the association with contradictory findings. Similarly, there is a lack of studies to confirm the relationship between lactation and osteoporosis among postmenopausal women.

This systematic review highlights the heterogeneity in assessing bone health, with varying methods such as DXA, QUS, and biomarkers. Beyond summarizing current evidence and suggesting avenues for future research, this review emphasizes the challenges in using reproductive factors as reliable risk assessment measures for osteoporosis screening. Key issues include the lack of standardization in bone health assessments, with varying methods such as DXA, QUS, and biomarkers, as well as potential recall bias in the studies reviewed. A significant limitation of our review is the small number of studies and their observational design. Therefore, further research is essential to validate the association between reproductive factors, particularly young maternal age, before integrating them into a robust risk assessment tool for Malaysia. Identifying women needing DXA and implementing preventive measures necessitates a comprehensive understanding of these factors. This initiative aims to enhance screening and prevention efforts, particularly in primary care and community health settings.

CONCLUSION

Years-since-menopause (YSM) is a key reproductive factor associated with osteoporosis in postmenopausal women in Malaysia, though the relationship remains weak and warrants further study. Qualitative analysis revealed that five out of nine studies indicated a relationship between YSM and osteoporosis, while two out of four studies showed a connection between parity and osteoporosis, and two out of three studies indicated a link between lactation and osteoporosis. Quantitatively, a significant negative correlation was found between YSM and osteoporosis indices; however, the available data on parity and lactation were insufficient for a thorough quantitative analysis. These findings suggest that future research should prioritize YSM when developing risk assessment models to enhance osteoporosis screening and prevention in this population.

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