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Menopausal Status, Age at Menopause, and Fracture Risk in Women: A Systematic Review of Observational Studies

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Abstract

Early menopause is thought to raise fracture risk, but observational studies define menopause and fracture differently. This systematic review related menopausal status, age at menopause, reproductive span, and surgical menopause to fracture risk in women. PubMed, Europe PMC, and Google Scholar were searched on August 30, 2026, followed by a broadened PubMed search on September 21, 2026, and supplementary PubMed and Europe PMC searches on October 22, 2026, which identified one more report; unsystematic searches outside the databases identified four further reports. The review was not registered, and the eligibility criteria were amended after full-text screening decisions had been made. A total of 17 reports (13 cohort and four case-control studies) from 15 distinct source populations were included; four were extracted from abstracts only. Fragility fracture was the stated outcome in four reports; the rest used any-site, osteoporosis-related, or single-site fracture. Newcastle-Ottawa Scale scores (minimum totals) were 4-8 of 9 for 11 rated cohort studies and 2 and 4 for two rated case-control studies. Synthesis was narrative because of heterogeneity. Earlier natural menopause was associated with higher fracture risk in several analyses, but findings were inconsistent and depended on the exposure definition, comparison group, population, and fracture outcome. Longer reproductive span was associated with lower risk in some analyses. Surgical menopause showed no clear association in two cohorts, although precision was limited for some comparisons; one abstract-only report found more hip fractures after iatrogenic menopause in cancer survivors. Evidence on verified fragility fracture was sparse. The findings are observational; certainty of evidence was not formally graded, and causation cannot be inferred.

Categories: Obstetrics/Gynecology, Epidemiology/Public Health, Endocrinology/Diabetes/Metabolism
Keywords: age at menopause, early menopause, fragility fracture, hip fracture, osteoporosis, premature ovarian insufficiency

Introduction And Background

Fragility fractures, which result from low-energy trauma, are a major cause of morbidity and disability in older women. In the year 2000, an estimated 9.0 million osteoporotic fractures occurred worldwide, including 1.6 million at the hip, and they accounted for 5.8 million disability-adjusted life years lost [1]. Bone loss accelerates around the menopausal transition as estrogen levels fall [2], and women with earlier menopause or a shorter lifetime exposure to endogenous estrogen are therefore expected to reach older age with lower bone mass and a higher fracture risk [3]. Early menopause, usually defined as menopause before age 45 years, and premature ovarian insufficiency, defined as loss of ovarian function before age 40 years, are associated with long-term health consequences including osteoporosis [3,4], and early menopause is commonly listed as a risk factor in clinical guidance on osteoporosis assessment [5]. Three further terms recur in this literature. Reproductive span is the interval between menarche and menopause. Cumulative endogenous estrogen exposure is usually approximated by reproductive span; it is an observational proxy based on reproductive timing, not a measurement of circulating estrogen. Surgical menopause is menopause that follows surgical removal of both ovaries (bilateral oophorectomy), as distinct from natural menopause, and differs in timing and in the reason for surgery.

The epidemiological evidence is less consistent than this mechanism suggests. Cohort studies differ in how they measure menopause (self-reported age, age at the final menstrual period, age at oophorectomy, or a derived reproductive span), whether they separate surgical and natural menopause, and how they define fracture. Some report all clinical fractures, some report only hip or vertebral fractures, and few can verify that a fracture was caused by low-energy trauma. Case-control studies add the problem that fractures may precede the data used to define exposure. These differences make it hard to judge how much of the apparent association reflects the effect of menopause timing and how much reflects the way it was studied. These differences matter for interpretation as follows: self-reported age at menopause is open to recall error, studies that do not separate surgical from natural menopause may attribute an oophorectomy effect to natural timing, and an any-site fracture outcome is not the same as a verified fragility fracture, so estimates that look alike may answer different questions.

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Previous systematic reviews have examined age at menopause and fracture risk directly or as one of several predictors of osteoporotic fracture in postmenopausal women [6,7]. Therefore, this review is not the first to address this question. It provides an updated descriptive synthesis of observational studies published from 2016 onward, examining how menopausal status, menopause timing, reproductive span, and surgical menopause are defined and how they relate to fracture outcomes, with attention to exposure definitions, fracture verification, overlap between source populations and methodological quality. No pooled estimate was calculated.

This review aimed to identify and synthesize observational studies examining the association between menopausal status or timing and fracture risk in women, describe how fracture and menopause were defined, and assess the methodological quality of the evidence. The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [8].

Review

Materials and methods

Protocol and Registration

The review protocol was not registered in the International Prospective Register of Systematic Reviews (PROSPERO) or any other registry, and no protocol was published. The research question, eligibility criteria, and search strategy were set out in a working document that was revised as the review progressed. The eligibility criteria were amended after full-text screening decisions were made, so the amendments were not part of a predetermined protocol, as discussed below.

Eligibility Criteria

Eligibility was structured by population, exposure, comparator, outcome, and study design. The criteria below are the final criteria after amendment.

Population: The study population was adult women in any setting, including postmenopausal women and women with premature ovarian insufficiency, early menopause, or surgical menopause (oophorectomy). Natural menopause was the main focus; surgical menopause was analyzed separately.

Exposure: The exposures were age at menopause (natural and surgical menopause were not always distinguishable); early or premature menopause; time since menopause or menopausal status; reproductive span or cumulative endogenous estrogen exposure (age at menopause minus age at menarche); and surgical or other iatrogenic menopause, including bilateral oophorectomy and treatment-associated early menopause. Studies in which menopause was one of several candidate predictors were retained if the report examined menopausal status or timing as an exposure. An effect estimate was extracted when reported. Chen et al. reported an adjusted odds ratio for age at menopause without specifying its unit or coding; this study is flagged [9]. The study by Katsnelson et al. was excluded because the abstract provided no estimate for menopause and the full text could not be obtained [10].

Comparator: The comparators were later or usual-age menopause, premenopausal women, fewer years since menopause, or women with intact ovaries.

Outcome: The outcome was incident fracture at any site, preferably fragility (low-trauma or osteoporotic) fracture, or fracture at the hip, vertebral, or other specified osteoporotic sites. Studies that reported any clinical or hospitalized fracture without separating low-trauma fractures were retained and flagged as a proxy for fragility fracture rather than excluded. Bone mineral density, osteoporosis diagnosis, Fracture Risk Assessment Tool (FRAX)-estimated risk, and modeled fractures were not eligible outcomes. Incident fracture was preferred; studies in which fractures may have preceded measurement of the exposure were retained and flagged.

Design: Cohort and case-control studies, including trial-derived cohorts and claims-database cohorts analyzed observationally. Reviews, editorials, modeling studies, cross-sectional studies, conference abstracts, and preprints were excluded.

Publication: Peer-reviewed reports in English. The database searches covered 2016 to 2026, a window chosen to prioritize contemporary evidence on the relationship between age at menopause and fracture risk while keeping the evidence base manageable and clinically relevant; older studies that came to the authors' attention outside the formal searches were not assessed. The searches applied no language filter; English was applied at screening.

Post hoc amendments: After full-text screening decisions had been made, the criteria were amended in the following four ways: surgical menopause was retained as a separately analyzed exposure; trial-derived cohorts were allowed when the menopause analysis was observational; studies in which menopause was one

of several predictors were retained; and any-fracture outcomes were retained and flagged instead of requiring verified fragility fracture (Table *1*). Because the amendments followed knowledge of which reports had been retained or excluded, the final criteria may have been influenced by the evidence already seen, and this is a possible source of selection bias. The available screening records do not permit a complete reconstruction of whether every potentially affected report would have been treated differently under the original criteria; the reports listed in Table *1* are those to which each amendment is relevant, not reports reinstated after exclusion.

Amendment	Reason	Reports affected
Retain surgical menopause as a separately analyzed exposure	To capture evidence on oophorectomy-induced menopause while keeping it distinct from natural menopause, because the exposures may differ clinically.	Hueg et al. [11], do Valle et al. [12], and Thong et al. [13]
Allow trial-derived cohorts	To include longitudinal fracture data from trial populations when the menopausal analysis was observational, not based on randomized assignment.	Sullivan et al. [14]
Rule for studies in which menopause was one of several predictors	Allow studies to contribute when menopause-related variables were evaluated alongside other fracture predictors.	Zvekic-Svorcan et al. [15] and Chen et al. [9]
Retain and flag any-fracture outcomes instead of requiring verified fragility fracture	To increase coverage of fracture evidence while flagging outcomes that did not verify low-trauma fracture.	Yoo et al. [16], Shieh et al. [17], Jones et al. [18], Moberg et al. [19], Farahmand et al. [20,21], Sullivan et al. [14], do Valle et al. [12], LeBlanc et al. [22]

TABLE 1: Post hoc amendments to the eligibility criteria.

Definition of abstract-only: In this review, abstract-only means a peer-reviewed journal report whose full text could not be obtained and which was judged and extracted from its published abstract. It does not refer to conference abstracts, which were excluded.

Information Sources and Search Strategy

PubMed, Europe PMC, and Google Scholar were searched on August 30, 2026, with a publication-date limit of 2016 to 2026. The PubMed string combined menopause terms (MeSH and title/abstract terms such as early, premature, and age at menopause), fracture terms (osteoporotic, hip, vertebral, and fragility fracture), and study-design terms (cohort, prospective, longitudinal, and case-control), and excluded review, meta-analysis, and randomized controlled trial publication types. The Europe PMC string used title and abstract fields with the same concept blocks. We ran three Google Scholar searches, screened the first five pages of results for each, and saved 20 plausible records. The exact strings as run, with date filters, are given in appendix 1.

A second, broadened PubMed search was run on September 21, 2026, to improve recall as follows: design terms were removed, exposure terms were widened to reproductive factors, menarche, reproductive span, final menstrual period, and oophorectomy, fracture terms were widened to any fracture, and the date limit of 2016-2026 was retained. Three quoted phrases were not present in the PubMed phrase index and therefore matched no records (appendix 1). The first PubMed search excluded records indexed as randomized controlled trials, so trial-derived cohorts could have been missed; this filter was not used in the second search, and one trial-derived cohort (Sullivan et al.) was found only through unsystematic searching outside the databases [14].

Three supplementary searches were run on October 22, 2026, during revision, and are reported in appendix 1 as new searches, separate from the original record. Two were PubMed searches - the first limited the broadened strategy to records added since September 21, 2026 (one record), and the second covered only the exposure terms that had matched no records in the broadened search (176 records). The third repeated the broadened concepts in Europe PMC (288 records), using title and abstract fields and excluding review publication types, preprints, and records mentioning animal models. The MeSH heading menopause was tested and not used because it returned more than 1,000 records, mostly studies of general postmenopausal osteoporosis. The broadened strategy was therefore run in PubMed and Europe PMC, but not in Google Scholar.

Citation searching was not performed. Older cohort studies that came to the authors' attention but fell

outside the 2016-2026 window (for example, Banks et al., Voort et al., Sullivan et al., and Svejme et al.) were not assessed [23-26]. Four further reports were identified outside the database searches through unsystematic searching and are reported as other methods in Figure *1*. Farahmand et al. and LeBlanc et al. were identified on October 2, 2026, through Google web searches run while looking for the full text of Farahmand et al.; only one query string was saved (appendix 1) [20-22]. Katsnelson et al. and Sullivan et al. were found through other unsystematic searches whose dates and queries were not recorded [10,14]. These searches cannot be reproduced. Farahmand et al. and LeBlanc et al. were later also returned by the supplementary database searches and were counted once, as other-methods reports [21,22]. Embase and Scopus were not searched because of institutional access limitations.

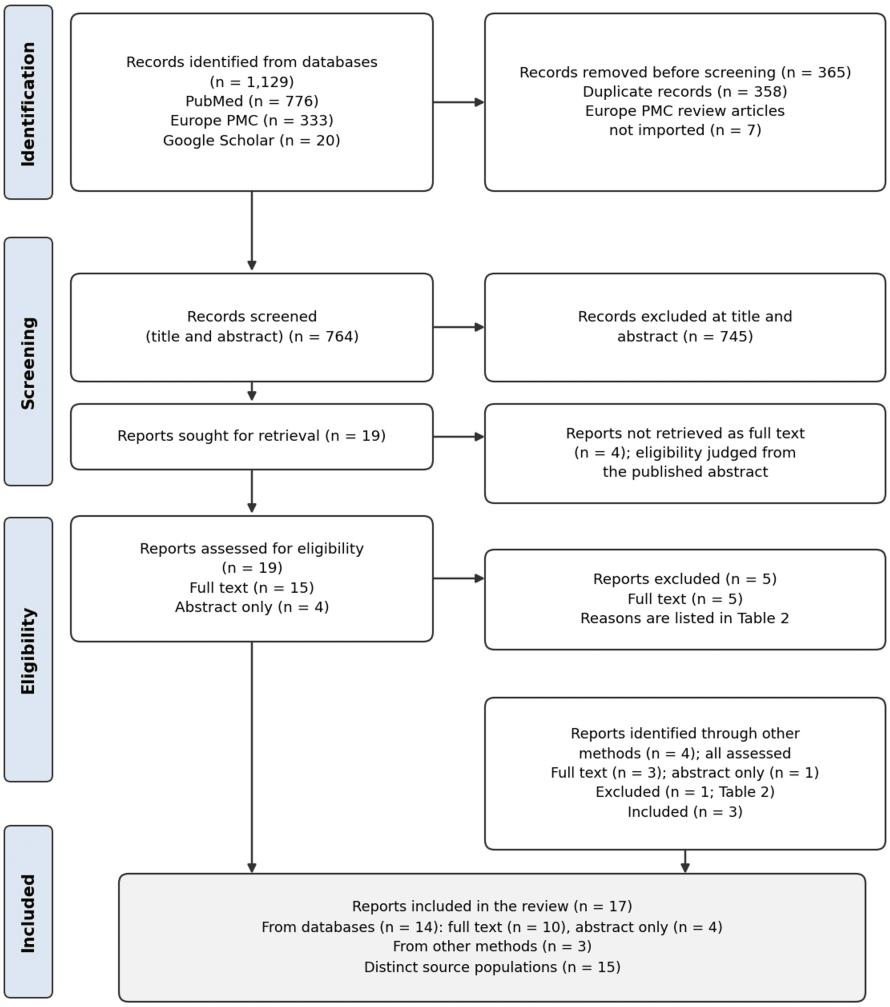


FIGURE 1: PRISMA 2020 flow diagram of study selection.

Study Selection

Records from the database searches were imported into Rayyan (Cambridge, MA: Rayyan Systems Inc.) (seven Europe PMC review articles from the first round were not imported), and duplicates were detected with Rayyan's built-in tools and removed. Screening was done in rounds, one after each set of database searches, including the supplementary searches. In each round, two reviewers independently screened every record at title and abstract level. Both reviewers independently assessed the full texts of all retrieved reports, including the four identified outside the database searches. At both stages, disagreements were resolved by discussion between the two reviewers, and no third reviewer was involved. Where a full text could not be obtained, eligibility was provisionally assessed from the published abstract. This applied to five journal reports; these decisions were not recorded in the full-text screening workbook [10,13,15,27,28]. We obtained the full text of Chen et al., which was also unavailable at that stage, after making the full-text screening decisions; we confirmed its eligibility and extracted its data from the full text [9]. Papers from the same cohort were identified and counted once when describing independent cohorts. Rayyan's AI features were used only for duplicate detection and were not used to decide which records to include or exclude.

Data Extraction

Two reviewers extracted data independently, and disagreements were resolved by discussion; no third reviewer was involved. One row was extracted per study using a standardized sheet as follows: journal and identifiers, cohort and setting, population and number analyzed, follow-up, exposure definition and ascertainment, comparator, fracture outcome and ascertainment, number of events, key results as reported, adjustment, funding, and authors' stated limitations. Values that were not reported were recorded as not reported and were not reconstructed, with two exceptions that are labeled as calculated as follows: the mean difference in age at menopause for Kapetanović et al., and the number of fracture events in Farahmand et al. [21], which was summed from the categories shown in figures of that report (both sums give 143) [21,29]. Where an estimate could be read only from a figure or was derived from supplementary material that was not available, this is stated. Study authors were not contacted for missing or unclear data.

Verification of Extracted Data

For reports with accessible full texts, the extracted population, denominator, event count, comparator, effect measure, confidence interval, adjustment model and outcome definition were checked against the original publication, and cohort provenance was checked for all 17 reports to identify overlapping source populations. For abstract-only reports, extraction was necessarily limited to the information available in the published abstract. Estimates that could not be verified are labeled where they are reported in the Results subsection.

Risk-of-Bias Assessment

Two reviewers assessed methodological quality independently, and disagreements were resolved by discussion; no third reviewer was involved. The Newcastle-Ottawa Scale (NOS) was used for cohort studies and case-control studies [30]. Each scale has nine items (four selection, two comparability, and three outcome or exposure), and each item was recorded as a star (1), no star (0), or not rated (NR) when it could not be judged from the available report. Totals are the number of stars awarded and are therefore minimum scores; they are not a definitive measure of study quality, and studies with more NR items are not directly comparable with those with fewer. Abstract-only studies were not rated. Because the NOS does not capture every concern, additional issues were recorded narratively, for example, exposure definitions that depend on follow-up time.

Synthesis Method

Studies were grouped by exposure (age at natural menopause, early menopause defined by a threshold, reproductive span or cumulative estrogen exposure, and surgical or iatrogenic menopause) and by fracture definition (fragility, any or osteoporosis-related, and single site). Results were synthesized narratively following the Synthesis Without Meta-analysis (SWiM) guideline and are presented as reported by the original authors, using the model with the most complete adjustment [31]. Where reports shared a source cohort (WHI; TLGS), they were described together and treated as one line of evidence, not as independent confirmation. Effect measures (hazard, odds, rate and risk ratios, mean differences) were not converted or compared directly. Estimates missing from an abstract were recorded as not reported and were not interpreted as null findings.

Findings were interpreted in light of study design, sample size and precision, outcome ascertainment, risk of bias, and the extent to which natural and surgical menopause could be distinguished. When results conflicted, prospective cohorts with registry-linked or adjudicated outcomes were given more weight than case-control and abstract-only reports, but no formal evidence hierarchy or numerical weighting was applied, and no single study was taken to establish causation. Reports that shared a source cohort were described together and counted once, so the 15 source populations, not the 17 reports, are the unit used to judge whether findings agree. A statistically non-significant estimate was not read as evidence of no association - precise estimates close to the null were distinguished from imprecise estimates whose confidence intervals were compatible with both no effect and a clinically important effect. Estimates that were not reported were not interpreted as null findings.

Reason for Not Conducting a Meta-Analysis

A pooled estimate was not calculated. The studies used different exposure definitions (continuous age, different category cut-offs and reference groups, reproductive span, surgery), different effect measures (hazard ratios, odds ratios, rate ratios, risk ratios, mean differences), different fracture definitions and different designs, and several included surgical menopause within the exposure group. Four reports describe two overlapping cohorts (Women's Health Initiative {WHI} and the Tehran Lipid and Glucose Study).

Narrower subsets were also considered. Studies of early menopause used different thresholds (before 40, before 45, 40-44 years of age), different comparators, and different outcomes (any fracture, cumulative fracture prevalence, hip fracture). Reproductive-span studies used different contrasts (categories of years, per standard deviation) and one defined exposure partly by follow-up time. Surgical-menopause studies differed in the indication for surgery, the comparison group and the outcome. No subset contained two or

more independent studies that shared exposure definition, comparator, outcome, design and effect measure, so a pooled estimate would not have answered a clinically meaningful question. Funnel plots and tests for small-study effects were therefore not performed. Reporting bias was not formally assessed because the review did not include a meta-analysis and the included studies differed in exposure, comparator, fracture outcome, and design, so a funnel-plot assessment would not have been meaningful.

Certainty of Evidence

The certainty of the body of evidence was not formally graded (for example, with Grading of Recommendations, Assessment, Development and Evaluation {GRADE}). Instead, the Results and Discussion subsections narratively consider study design, risk of bias, consistency, precision, and the directness of the fracture outcome, and list the absence of formal grading as a limitation. NOS ratings were not used as a substitute for an assessment of the certainty of the evidence.

Results

Study Selection

The first-round searches (August 30, 2026) identified 318 records in PubMed (search one), 45 in Europe PMC (38 research articles imported; seven reviews were not imported), and 20 saved records from the first five pages of each of three Google Scholar searches. Rayyan removed duplicates before each round of screening. A second, broader PubMed search on September 21, 2026, retrieved 281 records, and supplementary searches on October 22, 2026, retrieved 465 additional records (PubMed 1 and 176; Europe PMC 288); each set was de-duplicated against records already in Rayyan and screened in a separate round. Across all database searches, 1,129 records were identified (318+45+20+281+465); 365 were removed before screening (358 duplicates and seven unimported Europe PMC reviews), leaving 764 records screened. Of these, 745 were excluded at title and abstract screening, and 19 reports were sought for retrieval. At the time of full-text screening, the full text could not be obtained for Chen et al. [9], Thong et al. [13], Zvekic-Svorcan et al. [15], and Shimizu et al. [27]; the full text of Chen et al. was obtained afterward and is counted as retrieved [9]. We also could not obtain the full text of Adamczyk et al., identified in the supplementary round [28]. We therefore did not retrieve four reports (Thong et al., Zvekic-Svorcan et al., Shimizu et al., and Adamczyk et al.) in full text, and we assessed their eligibility based on the published abstracts [13,15,27,28]. All 19 database reports were assessed for eligibility - 15 at full text and four from the abstract only (Figure *1*). We also identified four reports outside the database searches and reported them as other methods: Farahmand et al. and LeBlanc et al. (October 2, 2026) through unsystematic Google web searches, and Katsnelson et al. and Sullivan et al. through other unsystematic searches whose dates and queries were not recorded [10,14,21,22]. Supplementary database searches also returned Farahmand et al. and LeBlanc et al.; we counted them once as other-methods reports, and marked their Rayyan records as excluded to avoid double counting, so they are among the 745 records excluded at title and abstract screening [21,22]. All four reports were assessed by both reviewers; Katsnelson et al. were assessed from the abstract only [10].

Of the 15 database reports assessed at full text, we excluded five and included 10 (Table *2*). We included all four database reports assessed from the abstract only. Of the four reports from other methods, we included three and excluded one (assessed from the abstract only) (Table *2*) [10,14,21,22]. In total, 23 reports were assessed for eligibility (19 from databases and four from other methods), six were excluded, and 17 were included (14 from databases and three from other methods; 13 assessed at full text and four from abstracts only). These 17 reports drew on 15 distinct source populations, because four reports shared the following two source populations: Sullivan et al. and LeBlanc et al. both used participants of the Women's Health Initiative (WHI), with overlapping but not identical analytic samples, and Farahmand et al. and Farahmand et al. both used the Tehran Lipid and Glucose Study (TLGS) [14,20-22]. We treated the overlapping reports as two lines of evidence rather than four independent confirmations; we compared the cohort names and data sources of the remaining 13 reports and found no further overlap (for the four abstract-only included reports, this rests on the abstracts). The study selection process is shown in the PRISMA 2020 flow diagram (Figure *1*). Table *2* lists the six reports excluded at eligibility assessment (five at full text and one from the abstract only), along with the stage and reason for each exclusion.

Study	Stage	Reason for exclusion
Scholes et al. [32]	Full text	Exposure was oral contraceptive use, not menopause
Logan et al. [33]	Full text	Cross-sectional; bone density outcome, no fracture outcome
Lin et al. [34]	Full text	Exposure was an MRI vertebral bone quality score; menopause only described in the sample
Cui et al. [35]	Full text	Micro-simulation modeling study, not an observational comparison
Minaković et al. [36]	Full text	Cross-sectional; FRAX-estimated probability, not observed fracture (same Novi Sad group as Zvekic-Svorcan et al. [15]; possible overlap)
Katsnelson et al. [10]	Abstract only	Full text not obtained; menopause (claims code) was one of nine predictors and the abstract gave no menopause estimate

TABLE 2: Reports excluded at eligibility assessment.

Study Characteristics

Table 3 summarizes the 17 included reports, and Table 4 gives the principal results of each. There were 13 cohort studies (one trial-derived cohort) and four case-control studies. The studies were conducted in the USA (three), Australia (two), Iran (two), and Sweden (one), and one each in South Korea, China, Japan, Denmark, Canada, Taiwan, Serbia, Bosnia and Herzegovina, and Poland. Sample sizes ranged from 100 to about 1.27 million women. A total of 13 reports were read in full, and four were extracted from abstracts only.

ID	Study	Cohort, country, design	Population (n)	Exposure	Fracture outcome (type)	Source
S01	Yoo et al. [16]	Korean NHIS claims+screening; South Korea; retrospective cohort	1,272,115 postmenopausal women	Self-reported age at menopause (<40 to 55+ years); reproductive span	Vertebral, hip, and other osteoporosis-related sites (ICD-10 claims); any/OP-related	F
S02	Peng et al. [37]	China Kadoorie Biobank; China; prospective cohort	125,336 women, natural menopause	Age at menopause; time since menopause; reproductive years	Hip fracture, fatal or nonfatal (linkage); single site	F
S03	Shieh et al. [17]	SWAN; USA; prospective cohort	1,554 women, natural menopause at 45+ years	Age at final menstrual period (continuous)	Any fracture excluding craniofacial and digital; any	F
S04	Shimizu et al. [27]	JPHC; Japan; prospective cohort	43,652 women aged 40-69 years (menopausal subgroup NR)	Menstrual and reproductive factors including menopause	First vertebral fracture over 10 years, self-reported (implied); single site	A
S05	Jones et al. [18]	ALSWH; Australia; prospective cohort+linkage	8,603 women (610 menopause <45 years)	Self-reported age at menopause <45 vs. 45+ years	Hospital-coded plus self-reported fracture (cumulative prevalence); any	F
S06	Moberg et al. [19]	Malmö Diet and Cancer Study; Sweden; prospective cohort	18,326 women; 12,018 in final model	Self-reported age at menopause (<40, 40-44, 45-54, 55+ years)	First fracture, any site except skull/face (registry); any	F
S07	Farahmand et al. [20]	TLGS; Iran; prospective cohort	6,653 women	Age at menopause; menopausal status; estrogen exposure	Hospitalized extremity fracture (adjudicated); any	F
S08	Kapetanović et al. [29]	Single rehabilitation center; Bosnia and Herzegovina; case-control	50 cases, 50 controls	Mean age at menopause and menarche	Fragility fracture (minimal trauma); fragility	F

S09	Zvekic-Svorcan et al. [15]	National Osteoporosis Registry; Serbia; case-control (retrospective registry data)	217 osteoporotic postmenopausal women (110 with vertebral fracture, 107 without)	Age at menopause (one of several factors)	Verified osteoporotic vertebral fracture; fragility	A
S10	Sullivan et al. [14]	WHI clinical trials; USA; trial-derived cohort	25,499 intact-uterus women	Self-reported age at non-surgical menopause (<40, 40-49, 50+ years)	Any fracture (self-reported; hip adjudicated); any	F
S11	Hueg et al. [11]	Danish Nurse Cohort; Denmark; registry cohort	25,853 nurses (1,938 bilateral oophorectomy)	Bilateral oophorectomy (surgical menopause), time-varying	Fragility fracture by proxy (registry, X-ray/CT confirmed); fragility (proxy)	F
S12	do Valle et al. [12]	British Columbia administrative data; Canada; retrospective cohort	329 BRCA1/2 carriers with RRBSO before 50 years; 6,580 controls	Risk-reducing salpingo-oophorectomy (surgical menopause)	Any-site fracture (billing and ICD codes); any	F
S13	Thong et al. [13]	Western Australia data linkage; retrospective cohort	1,021 exposed (607 cancer, 414 benign oophorectomy); 16,998 controls	Iatrogenic early menopause <45 years (by index event)	Hip fracture hospitalization (secondary outcome); single site	A
S14	Chen et al. [9]	Single hospital; Taiwan; case-control	50 cases, 50 controls	Age at menopause (one of several factors)	First accidental hip fracture; single site	F
S15	Farahmand et al. [21]	TLGS; Iran; prospective cohort	5,269 women	Duration of endogenous estrogen exposure (z-score)	Hospitalized fracture, any site (adjudicated); any	F
S16	LeBlanc et al. [22]	WHI CT+OS; USA; prospective cohort	150,682 women	Years of endogenous estrogen exposure; age at menopause	Clinical fracture by region (self-reported, partly adjudicated); any	F
S17	Adamczyk et al. [28]	RAC-OST-POL; Poland; case-control as labeled by the authors (population sample)	977 postmenopausal women (286 with low-energy fracture)	Age at menopause; reproductive period; early menopause (<45 years)	Low-energy fracture, self-reported and not verified; fragility (self-reported)	A

TABLE 3: Characteristics of the included studies.

F: full text read; A: abstract only (journal report whose full text could not be obtained); OP: osteoporosis; NHIS: National Health Insurance Service; SWAN: Study of Women's Health Across the Nation; JPHC: Japan Public Health Center-based Prospective Study; ALSWH: Australian Longitudinal Study on Women's Health; WHI: Women's Health Initiative; CT: clinical trials; OS: observational study; TLGS: Tehran Lipid and Glucose Study; RRBSO: risk-reducing bilateral salpingo-oophorectomy; NR: not reported

ID	Study	Contrast	Principal result (as reported)	Comment
S03	Shieh et al. [17]	Per year older at FMP	HR: 0.95 (0.91-0.99); 317 fractures. 20-year cumulative probability: 20.2% (FMP: 47 years), 16.1% (52 years), 13.9% (55 years)	Natural menopause at 45+ years only
S02	Peng et al. [37]	Age at menopause 53+ vs. <53 years; time since menopause; reproductive years	Hip fracture HR: 0.78 (0.66-0.92); 1,327 events. Time since menopause 15-19 years vs. <5 years: 2.50 (2.21-2.83). Reproductive years 36+ vs. 30-32: 0.81 (0.72-0.91)	Hip fractures include non-fragility fractures[a]
S10	Sullivan et al. [14]	Age at menopause <40 and 40-49 vs. 50+ years	Adjusted HR: 1.41 (1.15-1.73) and 1.06 (0.99-1.14); unadjusted primary model <40 vs. 50+ years: 1.36 (1.11-1.67); 3,670 fractures	Overlaps S16 (WHI)[b]
		(a) Age at menopause <45 vs. 45-55 years; (b) endogenous estrogen	(a) Total fracture HR: 1.08 (1.05-1.10). (b) Total	Natural and surgical menopause mixed (nearly half of the <30 years

S16	LeBlanc et al. [22]	exposure <30 vs. 36-40 years; (c) region-specific outcomes, exposure <30 years	fracture HR: 1.08 (1.05-1.11). (c) Region-specific outcomes, exposure <30 years only: central body HR: 1.09 (1.04-1.15); lower extremity HR: 1.08	group had bilateral oophorectomy); hip results not seen[c]
S01	Yoo et al. [16]	Age at menopause vs. <40 years; reproductive span 40+ vs. <30 years	Any fracture aHR: 40-44 years 0.97 (0.93-1.01); 45-49 years 0.94 (0.91-0.97); 50-54 years 0.90 (0.88-0.93); 55+ years 0.89 (0.86-0.93). Span 40+ years: 0.86 (0.84-0.88)	Reference group only 1.7% of cohort; 189,883 fractures
S06	Moberg et al. [19]	Age at menopause vs. 45-54 years	Multivariable HR: <40 years 1.06 (0.91-1.24); 40-44 years 1.14 (1.03-1.27); 55+ years 0.97 (0.88-1.07); 6,023 women with fracture	Complete cases (n=12,018); surgical menopause not separable
S05	Jones et al. [18]	Age at menopause <45 vs. 45+ years	OR: 1.45 (1.15-1.81); fracture in 31.2% vs. 22.8%	Cumulative prevalence (GEE), not time to event; natural and surgical mixed
S07	Farahmand et al. [20]	Age at menopause; menopausal status; estrogen exposure	Age at menopause not significant (HR in figure only; value not extracted). Post vs. premenopausal aHR: 3.15 (2.01-4.94). Estrogen exposure aHR: 0.99 (0.95-1.03); 222 fractures	Same TLGS cohort as S15; status strongly age-dependent
S15	Farahmand et al. [21]	Per 1-SD increase in estrogen exposure duration	Adjusted HR: 0.70 (0.58-0.86); 143 fractures (calculated)	Exposure partly determined by follow-up time
S08	Kapetanović et al. [29]	Age at menopause, cases vs. controls	44.70 vs. 51.76 years (difference 7.06 years, calculated), p=0.0001; no OR or CI	Means only; age ranges barely overlapped; fracture timing not reported
S09	Zvekic-Svorcan et al. [15]	Later age at menopause	OR: 0.539 (0.400-0.726) for vertebral fracture; later menopause associated with lower odds; unit not stated, so not interpreted numerically	Abstract only; unstable model (kyphosis OR: 708)
S14	Chen et al. [9]	Age at menopause (years)	Adjusted OR: 1.171 (1.031-1.331), p=0.0155; mean age at menopause 47.6 (SD: 5.6) years in cases vs. 50.2 (SD: 4.8) years in controls, p=0.028	Unit and coding of the OR not stated; direction unclear[d]
S17	Adamczyk et al. [28]	Age at menopause; reproductive period; menopause <45 years vs. later	Age at menopause 48.3 (SD: 5.2) vs. 49.5 (4.7) years in women with vs. without fracture, OR: 0.95 (0.93-0.98). Reproductive period 34.1 (5.5) vs. 35.5 (4.9) years, OR: 0.95 (0.93-0.98). Fracture prevalence 39.1% vs. 27.8% for menopause <45 years vs. later, OR: 1.66 (1.13-2.42); 286 fractures	Abstract only; unit, coding, and adjustment not stated; first two ORs and CIs identical as reported; fracture history may have preceded exposure data; natural and surgical menopause not separated
S04	Shimizu et al. [27]	Reproductive years (menopausal women)	OR: 0.96 (0.92-0.99); estimate for age at menopause not reported in abstract	Abstract only; 250 vertebral fractures
S11	Hueg et al. [11]	Bilateral oophorectomy vs. preserved ovaries	Any fragility fracture HR: 0.98 (0.87-1.11); <51 years 1.12 (0.91-1.39); 51+ years 0.95 (0.83-1.09); hip 1.01 (0.78-1.32)	Surgical only; indication not reported; 6,660 fractures (results text and table of source report; the abstract gives 6,600)
S12	do Valle et al. [12]	RRBSO <50 years in BRCA carriers vs. benign BO/intact ovaries	aHR: 0.80 (0.56-1.14) vs. BO; 1.02 (0.65-1.61) vs. intact; 44 fractures in carriers	Underpowered; unequal follow-up
S13	Thong et al. [13]	Iatrogenic menopause <45 years	Hip fracture IRR: 3.90 (1.83-7.40) in cancer survivors; benign oophorectomy results not reported in abstract	Abstract only; cancer and treatment confound

TABLE 4: Principal results by study.

[a]Fully adjusted values were checked against the report. The abstract gives the same point estimate for age at menopause with a different confidence interval, and describes the reproductive-years comparator as <30 years, whereas the report's table and text use 30-32 years as the reference (used here).

[b]The abstract gives n=21,711; the source article's text, table, and figure give n=25,499 (used here).

[c]The abstract states 11% and 9% higher risk for central body and lower extremity fracture, and the results text states 8-9%; the source article's figure gives HR: 1.09 and 1.08 (figure values used; confidence interval for lower extremity not extracted). Hip results are in a supplement that was not seen.

[d]The direction of the OR is unclear given the lower mean age at menopause in cases; stepwise model (education, total hip BMD, height); hospital outpatient controls matched on age.

Values are as reported by the original authors. Calculated values are labeled. Different effect measures are not directly comparable. Confidence intervals are 95%.

aHR: adjusted hazard ratio; IRR: incidence rate ratio; FMP: final menstrual period; BO: bilateral oophorectomy; GEE: generalized estimating equations; RRBSO: risk-reducing bilateral salpingo-oophorectomy; WHI: Women's Health Initiative; TLGS: Tehran Lipid and Glucose Study

Definitions of Fracture

The following four reports named fragility or osteoporotic fracture as the outcome: Kapetanović et al. (defined as minimal trauma), Zvekic-Svorcan et al. (from abstract), Hueg et al. (fragility approximated from registry fractures after age 50 years, excluding hand, foot, skull, and multiple fractures), and Adamczyk et al. (low-energy fracture, self-reported, from the abstract) [11,15,28,29]. Nine reports used any fracture or a list of osteoporosis-related sites without verifying the trauma level [12,14,16-22]. The following four reports analyzed a single site: hip [9,13,37] or vertebra [27]. Under a strict fragility-only rule, only four of the 17 reports would remain, and none of them verified low-energy trauma in every case. Several authors state explicitly that low-energy trauma could not be distinguished - Peng et al. note that hip fractures in their study included both fragility and non-fragility fractures [37], Sullivan et al. could not assess whether fractures were traumatic or atraumatic [14], and Farahmand et al. could not separate osteoporotic from traumatic fractures [21]. Shieh et al. deliberately included both minimum- and non-minimum-trauma fractures [17].

Age at Natural Menopause

Table *4* gives the principal results with reference groups and confidence intervals. Among cohorts with natural menopause, earlier age at menopause was usually associated with higher fracture risk, but not in every analysis. The largest cohorts (the Korean national cohort [16], the China Kadoorie Biobank [37], and the WHI trial cohort [14]) found lower risk with later menopause, or higher risk with menopause before 40 years of age than with menopause at 50 years of age or older, and a smaller US cohort (Study of Women's Health Across the Nation {SWAN}) found lower risk per year of later menopause [17]. Results were null or inconsistent in the WHI trial cohort for menopause at 40-49 years of age, in the TLGS, where age at menopause was not significantly associated with fracture, in the Malmö Diet and Cancer Study, where only menopause at 40-44 years of age differed from the reference group, and menopause before age 40 years and at 55 years or later did not, and in the Korean cohort for menopause at 40-44 years of age compared with before 40 years of age [19,20]. The four case-control studies also pointed towards higher risk with earlier menopause, but none can be interpreted with confidence as follows: they were small, gave no effect estimate or stated no unit or coding for it, may have measured fractures that preceded the exposure data, or were extracted from abstracts only [9,15,28,29].

Early Menopause Defined by a Threshold

Definitions of early menopause differed - before 45 years of age [18,22,28], before 40 years of age compared with 40-49 years of age [14], and before 40 and 40-44 years of age separately [16,19]. In the Australian cohort, menopause before 45 years of age was associated with higher odds of fracture (OR: 1.45, 1.15-1.81), but fracture was analyzed as cumulative prevalence rather than time to first event; premature ovarian insufficiency and early menopause were combined, and natural and surgical menopause were mixed [18]. In the WHI, menopause before 45 years of age was associated with an 8% higher hazard of total fracture than menopause at 45-55 years of age [22]. The Polish case-control report (abstract only) found a higher fracture prevalence with menopause before 45 years of age (OR: 1.66, 1.13-2.42; adjustment not stated) [28]. These estimates should not be pooled with studies that used different cut-offs.

Reproductive Span and Cumulative Estrogen Exposure

Longer reproductive span or longer exposure to endogenous estrogen was associated with lower fracture risk in four cohorts [16,21,22,37], and the Japanese cohort found lower odds of vertebral fracture with longer reproductive years (abstract only) [27]. The Polish case-control report (abstract only) also found a shorter reproductive period in women with fractures [28]. The TLGS analysis of Farahmand et al. found no association (aHR: 0.99, 0.95-1.03) [20]. Because Farahmand et al. used the same cohort, they are one line of evidence [20,21]. In the Farahmand et al. analysis, exposure time for women who had not reached menopause ended at fracture or at the end of follow-up, meaning exposure is partly determined by observation time and may bias the hazard ratio [21].

Surgical and Iatrogenic Menopause

Three reports addressed surgical or iatrogenic menopause. In the Danish Nurse Cohort, bilateral oophorectomy was not associated with fragility fracture (HR: 0.98, 0.87-1.11), including among women operated on before age 51 (1.12, 0.91-1.39) years; the indication for surgery was not reported [11]. Among BRCA1/2 carriers who had risk-reducing surgery before age 50 years, fracture risk did not differ from that in women with benign oophorectomy or intact ovaries, but the authors state the study was underpowered, follow-up was shorter in carriers (median: 6.9 years) than in controls, and nearly half of carriers had breast cancer [12]. In Western Australia, hip fracture was more common after iatrogenic early menopause in cancer survivors (IRR: 3.90, 1.83-7.40), but this group is also exposed to cancer and its treatment, and the result for benign oophorectomy was not reported in the abstract [13]. Surgical menopause was also mixed into the exposure groups of other cohorts; in the WHI analysis of LeBlanc et al., nearly half of the women with fewer than 30 years of estrogen exposure had bilateral oophorectomy, so the short-exposure category is largely a surgical menopause group [22].

Risk of Bias

Table *5* shows NOS totals; item-level ratings are in appendix 2. Of the 11 cohort studies that could be rated, five scored 8 stars [11,16,19,20,37], one scored 7 [12], three scored 6 [17,18,21], one scored 5, and one scored 4 [14,22]. The WHI-based studies lost stars for representativeness (trial and cohort volunteers), self-reported exposure, and self-reported fracture outcomes [14,22]. Several scores depend on items that could not be rated, mostly adequacy of follow-up, so totals are minimum scores and should not be read as a definitive ranking. The two case-control studies that could be rated scored 2 stars and 4 stars [9,29]. The four abstract-only studies were not rated [13,15,27,28]. Risk of bias due to missing results (reporting bias) was not formally assessed, and selective reporting or non-publication of null results cannot be excluded. Additional concerns not captured by the NOS included self-reported age at menopause (recall bias), a very small reference group in the Korean cohort (menopause before 40 years of age, 1.7%), exclusion of 216,913 Korean women with missing data, complete-case analysis in Moberg et al. [19], and the follow-up-dependent exposure in Farahmand et al. [21].

ID	Study	Design	Stars (of 9)	Items not rated
S01	Yoo et al. [16]	Cohort	8	0
S02	Peng et al. [37]	Cohort	8	1
S03	Shieh et al. [17]	Cohort	6	1
S05	Jones et al. [18]	Cohort	6	1
S06	Moberg et al. [19]	Cohort	8	0
S07	Farahmand et al. [20]	Cohort	8	1
S10	Sullivan et al. [14]	Cohort	4	1
S11	Hueg et al. [11]	Cohort	8	0
S12	do Valle et al. [12]	Cohort	7	0
S15	Farahmand et al. [21]	Cohort	6	3
S16	LeBlanc et al. [22]	Cohort	5	1
S08	Kapetanović et al. [29]	Case-control	2	2
S14	Chen et al. [9]	Case-control	4	2
S04	Shimizu et al. [27]	Prospective cohort (abstract only)	Not assessed	Not applicable
S13	Thong et al. [13]	Retrospective cohort, data linkage (abstract only)	Not assessed	Not applicable
S09	Zvekic-Svorcan et al. [15]	Case-control, registry data (abstract only)	Not assessed	Not applicable
S17	Adamczyk et al. [28]	Case-control, population sample (abstract only)	Not assessed	Not applicable

TABLE 5: Newcastle-Ottawa Scale totals.

Stars are minimum scores; items that could not be judged were scored NR and not counted. Item-level ratings are in appendix 2.

Discussion

Interpretation of Findings

In this review, earlier menopause was generally associated with a higher risk of fracture, but the evidence is heterogeneous, and the size of the association depended on the exposure, comparison group, population, and fracture outcome, so no single summary magnitude is offered. Estimates varied in direction and magnitude as follows: some cohorts reported lower hazards with older age at the final menstrual period or longer reproductive span, others reported higher hazards for specific categorical contrasts, and some reported null results, for example, for menopause at 40-49 years of age in the WHI trial cohort and for age at menopause in the TLGS. In the largest cohort, the gradient arose mainly from comparison of menopause at age 45 years or later with menopause before 40 years of age, not from a contrast between very early and early menopause.

These estimates are not interchangeable - a hazard ratio per year of age at menopause, an odds ratio for cumulative fracture prevalence, and an incidence rate ratio for hip fracture hospitalization answer different questions and cannot be compared directly. All of the evidence is observational, so the associations should not be read as showing that earlier menopause itself causes fracture; age, general health, cancer treatment, indication for surgery, hormone therapy, and other factors may contribute. The large size of the Korean cohort provides precision but does not eliminate bias; its reference group (menopause before 40 years of age) was only 1.7% of the cohort, and many women with missing data were excluded.

Fracture Outcomes

Evidence about fragility fracture specifically is thin. Only four of the 17 reports named fragility fracture as the outcome - one of them by registry proxy and one by self-report. A hip or vertebral fracture is not automatically a verified fragility fracture merely because it is a typical osteoporotic site, and an ICD-coded fracture does not establish low-energy trauma. Several authors state this limitation explicitly [14,21,37]. Therefore, this review's conclusions concern fracture risk broadly and should not be read as estimates of fragility fracture risk.

Case-Control, Abstract-Only, and Surgical Menopause Evidence

The strongest apparent associations came from case-control studies and abstract-only reports (for example, a seven-year difference in mean age at menopause in Kapetanović et al., and OR: 0.539 in Zvekic-Svorcan et al.), which are the studies most vulnerable to selection of controls, prevalent fractures, and unstable models [15,29]. Adamczyk et al., based only on the abstract, pointed in the same direction but analyzed reported fracture history in a population sample, so fractures may have preceded the exposure data, and the units, coding, and adjustments of the odds ratios are unknown [28]. Chen et al. reported an adjusted odds ratio for age at menopause (1.171, 95% CI: 1.031-1.331) whose unit and coding were not stated and whose direction could not be reconciled with the lower mean age at menopause in cases, so it was not interpreted numerically [9]. Findings for surgical menopause were close to null in two studies. The overall Danish cohort estimate was precise (HR: 0.98, 95% CI: 0.87-1.11), whereas the BRCA-carrier study was underpowered, stratified estimates were less precise, and the indication for surgery was unknown or highly selected, and one abstract-only report found more hip fractures after iatrogenic menopause in cancer survivors. The evidence does not support a confident conclusion either way.

Comparison With Previous Reviews

Previous syntheses appear to have reached different conclusions about how strongly earlier menopause predicts fracture [6,7]. The heterogeneity in exposure and fracture definitions may contribute to these differences, although this review was not designed to test that. It is an updated, descriptive review of studies published from 2016 onward and is not the first review of this association. Cohorts published before 2016 were outside our date limit and were not assessed (the search strategies are presented in appendix 1). They include the WHI observational study analysis by Sullivan et al., which reported a higher adjusted fracture hazard for menopause before 40 years of age than for menopause at 50 years of age or older (HR: 1.21, 95% CI: 1.02-1.44) [25]; the Malmö perimenopausal study by Svejme et al., in which menopause before age 47 years was associated with a higher risk of fragility fracture by age 82 years (risk ratio: 1.68, 95% CI: 1.05-2.57) [26]; and other studies that came to our attention [23,24]. Including them could shift the balance of evidence, and we could add them in an update.

Clinical Implications and Research Priorities

Early or premature menopause is reasonably treated as one risk marker among others when assessing fracture risk, but the data here do not support using age at menopause alone to predict fracture. Future studies should record age at menopause prospectively, separate natural from surgical menopause, define fragility fracture explicitly and verify it, report absolute risks, and have enough follow-up and power to examine women with premature ovarian insufficiency.

Strengths and limitations

Strengths include item-level quality assessment with the evidence for each judgment, explicit documentation of discrepancies within source papers (for example, differences between abstracts and tables in sample sizes and confidence intervals), and transparent reporting of how menopause and fracture were defined (appendix 2).

Limitations of the Included Evidence

All evidence is observational, so residual confounding cannot be excluded. Menopause age was mostly self-reported, and most outcomes were any-site fractures; only four reports named fragility fracture and none verified low-energy trauma for every case. Surgical menopause was mixed into the exposure groups of several cohorts (the WHI analysis of LeBlanc et al., Australian Longitudinal Study on Women's Health {ALSWH}, Malmö, and TLGS) and could not be separated [22]. Overlap between WHI reports and between TLGS reports means the number of independent source populations (15) is smaller than the number of reports (17). Case-control and abstract-only reports were small or unstable and could not be fully checked, and some studies did not include supplementary tables, such as the hip fracture results of LeBlanc et al. [22]. Exposures, comparators, outcomes, and effect measures were heterogeneous, which prevented meta-analysis and any assessment of publication bias.

Limitations of the Review Process

The review was not registered, and no protocol was published; the eligibility criteria were amended after full-text screening decisions, so the final criteria may have been influenced by the evidence already seen. Searches covered PubMed, Europe PMC, and Google Scholar from 2016 onward; Embase and Scopus were not accessible. The broadened search was run in PubMed and, as a supplementary search during revision, in Europe PMC, but not in Google Scholar; three phrases in the PubMed version matched no records, the first PubMed search excluded randomized-trial publication types, and Google Scholar screening was limited to the first five pages of each search. Citation searching was not performed. Three included reports (and one excluded report) were found through unsystematic searches whose dates and queries were not fully recorded, so the search is not fully reproducible. Eligibility for five reports was provisionally judged from abstracts and not recorded in the screening workbook, and extraction for the four included abstract-only reports could not be checked against full texts. Certainty of evidence was not formally graded, and NOS totals are minimum scores that should not be read as definitive quality measures.

Conclusions

Earlier menopause was associated with higher fracture risk in several studies, but the associations varied with the exposure definition, comparison group, population, and fracture outcome; they were smaller or null in several analyses (for example, menopause at 40-49 years of age in the WHI trial cohort), and are least reliable in small case-control and abstract-only studies. Evidence specifically for verified fragility fracture and for surgical menopause is limited, and the findings cannot be interpreted causally. Larger prospective studies with verified fragility fractures and clear separation of natural and surgical menopause are needed.

Appendices

Appendix 1: search strategies

Source	Date searched	Filters and limits	Records	Search string as run
PubMed search 1	August 30, 2026	Publication date 2016-2026, applied with the PubMed date filter (not in the string)	318	("Menopause"[MeSH] OR "Menopause, Premature"[MeSH] OR "Primary Ovarian Insufficiency"[MeSH] OR "menopausal status"[tiab] OR "age at menopause"[tiab] OR "early menopause"[tiab] OR "premature menopause"[tiab] OR "time since menopause"[tiab] OR "years since menopause"[tiab]) AND ("Osteoporotic Fractures"[MeSH] OR "Hip Fractures"[MeSH] OR "Spinal Fractures"[MeSH] OR "fragility fracture*"[tiab] OR "osteoporotic fracture*"[tiab] OR "hip fracture*"[tiab] OR "vertebral fracture*"[tiab]) AND ("Cohort Studies"[MeSH] OR cohort[tiab] OR prospective[tiab] OR longitudinal[tiab] OR "case-control"[tiab]) NOT ("Review"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt])
		PUB_YEAR 2016-2026 (in	45 (38 research articles	(TITLE_ABS:"menopausal status" OR TITLE_ABS:"age at menopause" OR TITLE_ABS:"early menopause" OR TITLE_ABS:"premature menopause" OR TITLE_ABS:"time since menopause" OR TITLE_ABS:"years since menopause") AND (TITLE_ABS:"fragility fracture" OR TITLE_ABS:"fragility fractures" OR

Europe PMC	August 30, 2026	the string); title and abstract fields	imported; 7 reviews not imported)	TITLE_ABS:"osteoporotic fracture" OR TITLE_ABS:"osteoporotic fractures" OR TITLE_ABS:"hip fracture" OR TITLE_ABS:"hip fractures" OR TITLE_ABS:"vertebral fracture" OR TITLE_ABS:"vertebral fractures") AND (TITLE_ABS:cohort OR TITLE_ABS:prospective OR TITLE_ABS:longitudinal OR TITLE_ABS:"case-control") AND (PUB_YEAR:[2016 TO 2026])
Google Scholar	August 30, 2026	2016-2026; relevance order; first five pages of each search screened	20 saved	(1) "age at menopause" "fragility fracture" OR "osteoporotic fracture" OR "hip fracture" cohort (2) "early menopause" OR "premature menopause" "fracture risk" cohort OR prospective (3) "menopausal status" OR "time since menopause" "hip fracture" OR "vertebral fracture" cohort
PubMed search 2	September 21, 2026	2016:2026[dp] (in the string); broadened search	281	("Menopause, Premature"[MeSH] OR "Primary Ovarian Insufficiency" [MeSH] OR "Oophorectomy"[MeSH] OR "Reproductive History"[MeSH] OR "age at menopause"[tiab] OR "age at natural menopause"[tiab] OR "age at final menstrual period"[tiab] OR "age of menopause"[tiab] OR "menopausal age"[tiab] OR "age at menarche"[tiab] OR "early menopause"[tiab] OR "late menopause"[tiab] OR "premature menopause" [tiab] OR "premature ovarian insufficiency"[tiab] OR "premature ovarian failure"[tiab] OR "surgical menopause"[tiab] OR "bilateral oophorectomy" [tiab] OR "natural menopause"[tiab] OR "menopausal status"[tiab] OR "menopausal transition"[tiab] OR "time since menopause"[tiab] OR "years since menopause"[tiab] OR "reproductive factors"[tiab] OR "reproductive lifespan"[tiab] OR "reproductive span"[tiab] OR "reproductive years"[tiab] OR "reproductive characteristics"[tiab] OR "menstrual and reproductive" [tiab]) AND ("Fractures, Bone"[MeSH] OR "Osteoporotic Fractures" [MeSH] OR "Hip Fractures"[MeSH] OR "Spinal Fractures"[MeSH] OR fracture*[tiab]) AND (2016:2026[dp]) NOT ("Review"[pt] OR "Meta-Analysis"[pt] OR "Systematic Review"[pt] OR "Case Reports"[pt])
PubMed supplementary search 3a	October 22, 2026	Broadened concepts of search 2 limited to records added since 21 Sep 2026 (entry date 2026/09/21 to 2026/10/22); 2016:2026[dp]; animal-only records excluded	1	("Menopause, Premature"[MeSH] OR "Primary Ovarian Insufficiency" [MeSH] OR "Reproductive History"[MeSH] OR "age at menopause"[tiab] OR "age at natural menopause"[tiab] OR "final menstrual period"[tiab] OR "age of menopause"[tiab] OR "menopausal age"[tiab] OR "age at menarche"[tiab] OR "early menopause"[tiab] OR "late menopause"[tiab] OR "premature menopause"[tiab] OR "premature ovarian insufficiency" [tiab] OR "premature ovarian failure"[tiab] OR "surgical menopause"[tiab] OR "bilateral oophorectomy"[tiab] OR "natural menopause"[tiab] OR "menopausal status"[tiab] OR "menopausal transition"[tiab] OR "time since menopause"[tiab] OR "years since menopause"[tiab] OR "reproductive factors"[tiab] OR "reproductive lifespan"[tiab] OR "reproductive span"[tiab] OR "reproductive years"[tiab] OR "reproductive characteristics"[tiab] OR "menstrual factors"[tiab]) AND ("Fractures, Bone"[MeSH] OR "Osteoporotic Fractures"[MeSH] OR "Hip Fractures" [MeSH] OR "Spinal Fractures"[MeSH] OR fracture*[tiab]) AND (2016:2026[dp]) AND ("2026/09/21"[edat] : "2026/10/22"[edat]) NOT ("Review"[pt] OR "Meta-Analysis"[pt] OR "Systematic Review"[pt] OR "Case Reports"[pt]) NOT ("Animals"[MeSH] NOT "Humans"[MeSH])
PubMed supplementary search 3b	October 22, 2026	Exposure terms that matched no records in search 2 (plus the ovariectomy MeSH heading); all entry dates; 2016:2026[dp]; animal-only records excluded	176	("Ovariectomy"[MeSH] OR "final menstrual period"[tiab] OR "menstrual factors"[tiab]) AND ("Fractures, Bone"[MeSH] OR "Osteoporotic Fractures"[MeSH] OR "Hip Fractures"[MeSH] OR "Spinal Fractures" [MeSH] OR fracture*[tiab]) AND (2016:2026[dp]) NOT ("Review"[pt] OR "Meta-Analysis"[pt] OR "Systematic Review"[pt] OR "Case Reports"[pt]) NOT ("Animals"[MeSH] NOT "Humans"[MeSH])
				(TITLE_ABS:"age at menopause" OR TITLE_ABS:"age at natural menopause" OR TITLE_ABS:"final menstrual period" OR

Europe PMC supplementary search	October 22, 2026	Broadened concepts of search 2; title and abstract fields; PUB_YEAR 2016-2026; review publication types, preprints, and records mentioning animal models excluded	288 (research articles)	TITLE_ABS:"age of menopause" OR TITLE_ABS:"menopausal age" OR TITLE_ABS:"age at menarche" OR TITLE_ABS:"early menopause" OR TITLE_ABS:"late menopause" OR TITLE_ABS:"premature menopause" OR TITLE_ABS:"premature ovarian insufficiency" OR TITLE_ABS:"premature ovarian failure" OR TITLE_ABS:"surgical menopause" OR TITLE_ABS:"bilateral oophorectomy" OR TITLE_ABS:"natural menopause" OR TITLE_ABS:"menopausal status" OR TITLE_ABS:"menopausal transition" OR TITLE_ABS:"time since menopause" OR TITLE_ABS:"years since menopause" OR TITLE_ABS:"reproductive factors" OR TITLE_ABS:"reproductive lifespan" OR TITLE_ABS:"reproductive span" OR TITLE_ABS:"reproductive years" OR TITLE_ABS:"reproductive characteristics" OR TITLE_ABS:"menstrual factors") AND (TITLE_ABS:fracture OR TITLE_ABS:fractures) AND (PUB_YEAR:[2016 TO 2026]) NOT (PUB_TYPE:"Review" OR PUB_TYPE:"Systematic Review" OR PUB_TYPE:"Meta-Analysis" OR PUB_TYPE:"Case Reports") NOT (SRC:PPR) NOT (TITLE_ABS:mice OR TITLE_ABS:mouse OR TITLE_ABS:rats OR TITLE_ABS:rat OR TITLE_ABS:murine)
Registers	-	-	0	Not searched.
Citation searching	-	-	0	Not performed.
Other methods: unsystematic searches	October 2, 2026	Unsystematic; the October 2 searches were run while looking for the full text of Farahmand et al. 2024	4 (reports)	Sullivan et al. 2017 and Katsnelson et al. 2026: found through unsystematic searches; dates and queries not recorded. Farahmand et al. 2022 and LeBlanc et al. 2022 (October 2): only one query string was saved: "Farahmand 2022 J Clin Endocrinol Metab endogenous estrogen exposure fracture incidence Tehran Lipid and Glucose Study menopause type hazard ratio". Farahmand et al. 2022 first appeared as a side result of a free-text query on the title, topic, and cohort of the 2024 paper (query not saved). A direct search then returned a repository copy of the 2022 manuscript and the LeBlanc et al. 2022 article (PMC9283335). Both were also returned by the supplementary database searches (October 22) and counted once, as other methods.
Total	-	-	1,129 from databases; 4 from other methods	318 + 45 + 20 + 281 + 1 + 176 + 288 = 1,129 database records, of which 358 duplicates and 7 unimported Europe PMC reviews were removed before screening, leaving 764 records screened (Figure 1).

TABLE 6: Search strategies and records retrieved by source.

In PubMed search 2, three quoted phrases matched no records: "Oophorectomy"[MeSH] (the MeSH heading is "Ovariectomy"; "Oophorectomy" is only an entry term, so the [MeSH] tag matched nothing), "age at final menstrual period," and "menstrual and reproductive" (not present in the PubMed phrase index). Embase and Scopus were not searched because of institutional access limitations. The MeSH heading "Menopause"[MeSH] was tested and not used in the supplementary searches because it returned more than 1,000 records, mostly general postmenopausal osteoporosis studies. The supplementary searches returned 465 records, which were de-duplicated against the records already in Rayyan; one new report was taken forward and included as an abstract-only report. Two records returned by these searches had already been identified through other methods and were counted once, as in other methods [20,21]. Records mentioning mice, mouse, rats, rat, or murine in the title or abstract were excluded from the Europe PMC supplementary search as a pragmatic filter.

Appendix 2: Newcastle-Ottawa Scale item-level ratings

Item-level ratings for the 11 rated cohort studies are shown below.

ID	Study	1	2	3	4	5	6	7	8	9	Stars
S01	Yoo et al. [16]	1	1	0	1	1	1	1	1	1	8
S02	Peng et al. [37]	1	1	1	1	1	1	1	1	NR	8
S03	Shieh et al. [17]	1	1	1	0	1	1	0	1	NR	6
S05	Jones et al. [18]	1	1	0	0	1	1	1	1	NR	6
S06	Moberg et al. [19]	1	1	0	1	1	1	1	1	1	8
S07	Farahmand et al. [20]	1	1	1	1	1	1	1	1	NR	8
S10	Sullivan et al. [14]	0	1	0	1	1	0	0	1	NR	4
S11	Hueg et al. [11]	0	1	1	1	1	1	1	1	1	8
S12	do Valle et al. [12]	1	1	1	0	1	1	1	0	1	7
S15	Farahmand et al. [21]	1	1	1	NR	1	1	1	NR	NR	6
S16	LeBlanc et al. [22]	0	1	0	1	1	1	0	1	NR	5

TABLE 7: Newcastle-Ottawa Scale item-level ratings for cohort studies.

1 = star, 0 = no star, NR = not rated.

Cohort study items: 1 representativeness of the exposed cohort; 2 selection of the non-exposed; 3 ascertainment of exposure; 4 outcome not present at start; 5 comparability (most important factor); 6 comparability (additional factor); 7 outcome assessment; 8 follow-up long enough; 9 adequacy of follow-up.

Item-level ratings for the two rated case-control studies are shown below.

ID	Study	1	2	3	4	5	6	7	8	9	Stars
S08	Kapetanović et al. [29]	0	0	0	1	0	1	0	NR	NR	2
S14	Chen et al. [9]	NR	0	0	1	1	1	0	1	NR	4

TABLE 8: Newcastle-Ottawa Scale item-level ratings for case-control studies.

1 = star, 0 = no star, NR = not rated

Case-control study items: 1 case definition; 2 representativeness of cases; 3 selection of controls; 4 definition of controls; 5 comparability (most important factor); 6 comparability (additional factor); 7 ascertainment of exposure; 8 same method for cases and controls; 9 non-response rate.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Olisemeka Eboka, Isabella Aghogu

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