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Sex-Specific Hormonal Factors in Degenerative Spinal Disease and Postoperative Recovery: A Systematic Review of Menopause, Estrogen Status, and Spine Surgery Outcomes

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ABSTRACT

Sex-specific hormonal factors may influence the development of degenerative spinal disease and recovery following spine surgery, particularly during the menopausal transition and after menopause. Estrogen participates in bone remodeling, inflammatory regulation, intervertebral disc homeostasis, muscle function, and pain modulation, providing several plausible mechanisms through which hormonal changes could affect spinal health. This systematic review aims to examine associations between menopause, estrogen status, degenerative spinal conditions, and postoperative outcomes following spinal procedures. Relevant domains include intervertebral disc degeneration, lumbar spinal stenosis, degenerative spondylolisthesis, vertebral bone quality, postoperative complications, fusion success, pain, functional recovery, and revision surgery. The review framework prioritizes clinical studies involving adult women, with comparisons based on menopausal status, hormone measurements, or menopausal hormone therapy exposure where available. Eligible observational studies, clinical trials, and relevant systematic reviews identified through reproducible searches of major biomedical databases, followed by independent screening, structured data extraction, and risk-of-bias assessment. Because hormonal exposure, spinal diagnoses, surgical techniques, and outcome definitions vary substantially, quantitative synthesis undertaken only when studies are sufficiently comparable. Particular attention given to confounding by age, osteoporosis, body composition, smoking, comorbidities, and procedure complexity. Existing biological and clinical evidence supports investigating hormonal influences on musculoskeletal aging, but it does not establish that estrogen deficiency independently causes degenerative spinal disease or that hormone therapy improves surgical outcomes. Potential relationships with pseud arthrosis, implant complications, infection, persistent pain, and functional recovery therefore require cautious interpretation. By integrating mechanistic evidence with clinical outcome research, this review provides a framework for evaluating sex-specific risk stratification and identifying priorities for prospective studies. Ultimately, better characterization of menopausal status and hormonal exposure may improve individualized assessment, while treatment decisions should remain grounded in established indications, individualized risk-benefit evaluation, and evidence from appropriately designed clinical studies.

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Introduction

Degenerative spinal disease represents a major source of chronic pain, disability, and reduced quality of life among adults worldwide [1-3]. Common conditions include intervertebral disc degeneration, lumbar spinal stenosis, degenerative spondylolisthesis, facet joint osteoarthritis, and degenerative deformity. These disorders arise through interactions among biological aging, mechanical loading, genetic susceptibility, inflammation, metabolic factors, and changes in the structural integrity of spinal tissues [4-6]. Although chronological aging is an established determinant of spinal degeneration, sex-related biological differences may contribute to variations in disease presentation, progression, treatment selection, and postoperative recovery. Hormonal changes associated with menopause are particularly relevant because they coincide with substantial alterations in bone turnover and other musculoskeletal processes.

Estrogen is involved in skeletal homeostasis through its effects on osteoblasts, osteoclasts, and the regulation of bone remodeling. The decline in ovarian estrogen production during menopause accelerates bone loss and increases the risk of osteoporosis and fragility fractures [7-9]. These changes may be clinically relevant in spinal surgery, where bone quality influences screw fixation, vertebral fracture risk, implant stability, and the biological environment for arthrodesis. Osteoporosis is also associated with complications following spinal instrumentation, although the magnitude of risk depends on the procedure, the patient's clinical characteristics, and the method used to assess bone health [10-12].

The potential relationship between estrogen and intervertebral disc degeneration is more complex. Intervertebral discs contain specialized extracellular matrix components that support hydration, flexibility, and load distribution. Age-related alterations in matrix synthesis, cellular activity, and tissue nutrition contribute to progressive degeneration [13-15]. Experimental research suggests that sex hormones may influence disc-cell metabolism and inflammatory signaling, but the clinical significance of these mechanisms remains uncertain. Differences in spinal degeneration between women and men not attributed to estrogen alone because hormonal status is associated with age, body composition, physical activity, and other biological and social factors.

Menopause is not a uniform exposure. The transition varies in duration, symptom burden, age at onset, and hormonal profile. Surgical menopause, premature ovarian insufficiency, natural menopause, and pharmacologically induced ovarian suppression may produce different patterns of estrogen deprivation. Moreover, serum estradiol measurements fluctuate and may not reliably represent cumulative tissue exposure. Studies that classify participants only by age or self-reported menopausal status may therefore misclassify hormonal exposure and obscure clinically meaningful associations [16].

These methodological issues are important when examining lumbar spinal stenosis and degenerative spondylolisthesis. Such conditions influenced by disc-height loss, facet-joint remodeling, ligamentous changes, and alterations in spinal alignment. Although these structural processes are associated with aging, their relationship to reproductive hormones remains insufficiently characterized. A credible evaluation must distinguish between evidence that estrogen influences bone metabolism, evidence that hormonal changes are associated with spinal imaging findings, and evidence that menopausal status independently predicts clinically important spinal disease [17].

Postoperative recovery introduces additional questions. Spine surgery outcomes include pain reduction, functional improvement, fusion, implant-related complications, readmission, and reoperation. These endpoints are biologically and clinically distinct. For example, bone quality may plausibly influence fixation and fusion, whereas persistent pain may reflect neural injury, psychosocial factors, central sensitization, or residual mechanical pathology. A hormonal association with one outcome not automatically generalized to all postoperative outcomes [18].

Menopausal hormone therapy also requires careful interpretation. Evidence concerning hormone therapy and postmenopausal bone health provides a rationale for investigating possible implications for spinal procedures, but it does not establish hormone therapy as a treatment for disc degeneration or as a means of improving spinal fusion [19]. Hormone therapy decisions involve individualized assessment of benefits, risks, symptoms, age, timing, and contraindications. Observational comparisons between users and nonusers are especially susceptible to confounding by indication, healthcare access, baseline health, and prescribing practices.

A further challenge is the distinction between sex and gender. Biological sex-related characteristics may include reproductive anatomy, hormone concentrations, and bone physiology, whereas gender-related factors can influence occupational exposure, healthcare utilization, pain reporting, treatment access, and rehabilitation participation. Studies that fail to distinguish these dimensions risk attributing socially mediated differences to biological mechanisms. Consequently, a rigorous review should assess how studies define sex, gender, menopausal status, and hormone exposure [20].

The clinical importance of this topic is substantial because spinal degeneration and menopause frequently occur during overlapping periods of life. Nevertheless, simultaneous occurrence does not

demonstrate causation. Analyses must account for age, osteoporosis, body mass index, smoking, diabetes, physical activity, medication exposure, surgical indication, and procedural complexity. Studies should also distinguish decompression without fusion from instrumented fusion because their biological demands and complication profiles differ [21-30].

Accordingly, this systematic review examines evidence concerning menopause, estrogen status, degenerative spinal disease, and postoperative outcomes. It focuses on four connected questions: whether menopausal status is associated with degenerative spinal pathology; whether estrogen-related bone changes affect surgical risk; whether hormonal exposures predict fusion and recovery; and which methodological limitations prevent reliable clinical conclusions. The ultimate objective is to clarify established findings, identify plausible but unconfirmed mechanisms, and define research priorities without converting biological plausibility into unsupported therapeutic recommendations [31].

Literature Review

Estrogen, skeletal remodeling, and spinal degeneration:

Estrogen has a well-established role in maintaining skeletal homeostasis. Reduced estrogen exposure increases bone resorption and disrupts the balance between osteoclastic and osteoblastic activity, contributing to postmenopausal bone loss [32-40]. These processes are relevant to the spine because vertebral trabecular bone is metabolically active and susceptible to age-related deterioration. However, vertebral osteoporosis and degenerative changes in the intervertebral disc represent distinct pathological processes that may coexist without sharing identical causal pathways.

Intervertebral disc degeneration involves changes in proteoglycan content, collagen organization, cellular senescence, inflammatory signaling, and tissue hydration. Adams and Roughley (2006) emphasized that disc degeneration is multifactorial, reflecting both biological aging and environmental influences. Estrogen-related effects on disc cells and extracellular matrix metabolism remain plausible research mechanisms, but direct clinical evidence linking measured estrogen deficiency to progressive human disc degeneration is less conclusive than the evidence connecting estrogen loss to bone loss.

The distinction between structural and symptomatic disease is equally important. Imaging abnormalities are common in asymptomatic adults, and their prevalence increases with age [41-50]. Accordingly, studies examining menopause and degenerative spinal findings should not assume that radiological degeneration necessarily represents clinically significant disease. Pain, disability, neurological symptoms, and treatment requirements evaluated separately.

Menopause and degenerative spinal conditions:

Menopause may influence spinal health indirectly through reduced bone density, altered muscle function, changes in body composition, and the accumulation of age-related comorbidities. These pathways could contribute to vulnerability to vertebral fractures and affect the biomechanical environment of the spine. Nevertheless, attributing lumbar spinal stenosis, disc degeneration, or spondylolisthesis directly to menopause requires longitudinal evidence that distinguishes hormonal exposure from chronological aging. A robust epidemiological study should define menopause explicitly, preferably distinguishing natural menopause from surgical or treatment-induced menopause. It should also account for the duration of estrogen deprivation and relevant reproductive history. Studies using age as a proxy for menopause risk exposure misclassification because women of similar ages can differ in menopausal status and hormone use. Research on sex and gender differences in spinal fusion outcomes demonstrates that clinical outcomes may vary between patient groups, although such variation not automatically attributed to estrogen. Sex-stratified analyses are therefore useful but insufficient when hormonal exposure not measured directly [51-60].

Bone quality and surgical complications:

Bone quality is a particularly important bridge between menopausal biology and spine surgery. Instrumented fusion depends on stable fixation and successful bone healing. Low bone mineral density may increase the likelihood of screw loosening, cage subsidence, vertebral fracture, and other mechanical complications [61].

Filley et al. (2024) reviewed 71 studies involving 12,278 patients and found that low bone mineral density was associated with several mechanical complications following lumbar fusion. Considerable heterogeneity prevented quantitative pooling, highlighting the limitations of combining different procedures, assessment methods, and complication definitions. Similarly, a systematic review by Ogiri et al. (2023) reported higher risks of selected mechanical complications and revision surgery among patients with osteoporosis or osteopenia. These findings support preoperative bone-health assessment in appropriate surgical candidates. They do not, however, demonstrate that menopause independently predicts complications after controlling for bone density and other risk factors. Bone mineral density may be an intermediate variable through which estrogen deficiency influences surgical risk; alternatively, it may partly reflect aging and comorbidities unrelated to menopausal status [62-64].

Hormone therapy and postoperative recovery

Menopausal hormone therapy is an important exposure to investigate, but its implications for spinal outcomes remain uncertain. Hormone therapy may preserve bone mass in selected patients, yet evidence concerning bone health not directly extrapolated to spinal fusion success, postoperative pain, or revision rates [65].

Observational comparisons between hormone-therapy users and nonusers are vulnerable to confounding. Treatment users may differ in age, socioeconomic status, healthcare access, cardiovascular risk, baseline bone density, and medical surveillance. In addition, estrogen-only and estrogen–progestogen regimens differ, and the route, dose, duration, and timing of exposure may affect interpretation. Future studies should distinguish preoperative exposure from postoperative initiation and should record interruptions or changes in therapy. They should also consider that treatment prescribed for symptoms rather than bone health. These differences complicate causal inference and make broad recommendations inappropriate [66].

Evidence gaps and conceptual framework:

The literature suggests a plausible pathway linking menopausal estrogen decline to reduced bone density and, consequently, selected complications after spinal instrumentation. However, direct evidence for an independent hormonal effect on disc degeneration, pain recovery, or fusion remains less definitive.

Three evidence levels therefore distinguished: established hormonal effects on bone metabolism; clinical associations between poor bone quality and surgical complications; and unconfirmed causal relationships between estrogen status and spinal outcomes. A systematic review should evaluate these levels separately, avoid pooling biologically dissimilar outcomes, and assess the quality of evidence for each relationship. The principal research gap is the limited integration of directly measured hormonal exposure, detailed bone-health assessment, standardized spinal phenotyping, and longitudinal surgical outcomes within the same cohorts. Addressing this gap could support more accurate risk stratification without prematurely establishing estrogen therapy as a spine-specific intervention [67-75].

Methods

This review conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA,2020) statement (Page et al.,2021). A protocol registered prospectively in PROSPERO before formal screening, where eligible. The search should cover PubMed/MEDLINE, Embase, Scopus, and Web of Science from database inception to the final search date. Search terms should combine controlled vocabulary and free-text expressions for menopause, estrogen, estradiol, hormone therapy, intervertebral disc degeneration, lumbar spinal stenosis, spinal fusion, postoperative recovery, and surgical complications.

Eligible studies should include adults undergoing evaluation or treatment for degenerative spinal disease and report menopausal status, a hormonal measure, or menopausal hormone therapy exposure in relation to spinal pathology or postoperative outcomes. Randomized trials, prospective and retrospective cohort studies, and case-control studies considered. Narrative reviews may inform background interpretation but not combined with primary studies as independent observations. Studies lacking relevant exposure or outcome data excluded.

Two reviewers should independently screen titles, abstracts, and full texts, with disagreements resolved by discussion or a third reviewer. A standardized extraction form should capture study design, sample characteristics, menopausal definitions, hormone exposure, spinal diagnosis, surgical procedure, follow-up, adjusted estimates, and outcomes. Risk of bias assessed using design-appropriate instruments, such as ROBINS-I for nonrandomized intervention studies and RoB 2 for randomized trials (Sterne et al.,2019,2016).

Meta-analysis undertaken only when populations, exposures, outcomes, and effect measures are sufficiently comparable. Random-effects models may be appropriate when clinically meaningful heterogeneity remains. Odds ratios, risk ratios, or hazard ratios pooled separately, with 95% confidence intervals and heterogeneity statistics reported. Forest plots should display verified study-level estimates only. Certainty of evidence assessed using GRADE principles (Guyatt et al.,2008). Because a completed screening and extraction dataset is not available for this draft, no new-pooled hormonal effect estimate reported.

Results

Evidence synthesis and interpretation:

The following tables organize the principal evidence domains relevant to the review. Table 1 summarizes the relationship between menopausal status and degenerative spinal pathology; Table 2 addresses bone quality and surgical complications; Table 3 examines postoperative recovery and hormone therapy; and Table 4 identifies methodological limitations and research priorities. The findings presented here are a structured preliminary synthesis of published literature, not the results of a newly completed systematic search. In particular, evidence concerning osteoporosis and fusion complications is stronger than evidence establishing independent effects of estrogen status on disc degeneration or postoperative recovery.

Table 1. Menopause, estrogen status, and degenerative spinal disease

Evidence domain	Principal observation	Interpretation	Evidence limitation
Estrogen and bone metabolism	Estrogen deficiency contributes to postmenopausal bone loss	Established biological relationship	Does not establish a direct effect on disc degeneration
Intervertebral disc degeneration	Age-related changes in matrix composition and cellular activity contribute to degeneration	Hormonal involvement is biologically plausible	Direct human causal evidence remains limited
Lumbar spinal stenosis	Degenerative changes accumulate with age	Menopausal status may correlate with disease burden	Age and structural degeneration are difficult to separate
Degenerative spondylolisthesis	Disc and facet-joint degeneration contribute to instability	Bone and soft-tissue factors may interact	Independent hormonal effects are uncertain
Symptomatic disease	Imaging findings do not always correspond to symptoms	Clinical and radiological endpoints must be separated	Studies use different definitions of disease

The evidence supports a distinction between the established skeletal effects of estrogen deficiency and the less certain relationship between menopause and degenerative spinal pathology. Estrogen regulates bone remodeling, and its decline contributes to reduced bone mineral density in postmenopausal women (Eastell et al.,2016). This relationship is clinically relevant because vertebral bone quality affects the structural environment in which spinal degeneration and surgery occur. However, bone loss not treated as a direct surrogate for intervertebral disc degeneration. Discs contain specialized extracellular matrices, and their degeneration involves changes in hydration, proteoglycan concentration, collagen architecture, cellular senescence, and inflammatory activity (Adams & Roughley,2006). Although hormonal signaling may affect some of these mechanisms, evidence that menopause independently accelerates human disc degeneration is not established by the skeletal literature alone.

The same distinction applies to lumbar spinal stenosis and degenerative spondylolisthesis. These conditions develop through interacting changes in discs, facet joints, ligaments, and spinal alignment. Chronological aging, genetic susceptibility, mechanical loading, body composition, and occupational exposures may influence these processes. Consequently, a higher prevalence of spinal degeneration among older women not, by itself, demonstrate an estrogen-mediated effect.

Imaging findings introduce an additional challenge. Brinjikji et al. (2015) demonstrated that degenerative spinal imaging features are common in asymptomatic individuals and increase with age. Studies should therefore assess structural abnormalities separately from pain, disability, neurological impairment, and indications for surgery. Otherwise, an apparent relationship between menopausal status and degeneration may reflect differences in imaging utilization or symptom reporting rather than disease progression.

Future studies should characterize menopause using explicit clinical criteria, record hormone therapy and surgical menopause, and assess hormonal exposure longitudinally. Analyses should adjust for age and other confounders while avoiding indiscriminate adjustment for potential mediators, such as bone mineral density, when estimating the total effect of estrogen deficiency. These distinctions are essential to understanding whether hormonal status independently predicts spinal disease or primarily influences selected components of musculoskeletal aging.

Table 2. Bone quality, menopause, and complications following spine surgery

Outcome	Relevant evidence	Clinical interpretation	Hormone-specific conclusion
Screw loosening	Poor bone quality is associated with mechanical complications	Bone assessment is important before instrumentation	Independent estrogen effect is unproven
Cage subsidence	Low bone mineral density is associated with increased risk	Endplate and vertebral bone quality matter	Menopause should not be used as a substitute for direct assessment
Pseudarthrosis	May coexist with implant failure and impaired bone healing	Fusion biology is multifactorial	Direct causal relationship with estrogen deficiency is uncertain

Vertebral and junctional fractures	Osteoporosis is associated with skeletal fragility	Fracture prevention may be important in high-risk patients	Risk depends on bone health and other factors
Revision surgery	Poor bone quality is associated with selected adverse outcomes	Preoperative optimization may be warranted	Menopausal status alone is insufficient for prediction

Bone quality represents one of the most clinically actionable connections between menopause and spine surgery. Following estrogen decline, increased bone resorption can reduce vertebral bone density and compromise structural strength. These changes may become particularly important when spinal instrumentation is required because screw purchase and cage support depend partly on local bone characteristics.

Filley et al. (2024) synthesized 71 studies involving 12,278 patients undergoing lumbar fusion and identified associations between low bone mineral density and mechanical complications, including cage subsidence and screw loosening. The authors also described an association between osteoporosis and proximal junctional complications, particularly those involving fracture. However, methodological heterogeneity prevented meta-analysis, limiting the precision with which individual complication risks summarized.

Similarly, Ogiri et al. (2023) reported increased risks of selected complications, including screw loosening and revision surgery, among patients with osteoporosis or osteopenia. These findings reinforce the importance of evaluating bone health in surgical candidates, particularly older adults undergoing instrumented procedures.

Nevertheless, the relationship between menopause and these outcomes interpreted through a causal framework. Menopause may contribute to bone loss, which may then affect fixation and healing. In this pathway, bone mineral density is a potential mediator rather than merely a confounding variable. A study seeking to estimate the total effect of menopausal estrogen decline should therefore distinguish analyses before and after adjustment for bone density.

Other factors remain important, including smoking, diabetes, nutritional status, medication exposure, surgical technique, number of fused levels, and baseline deformity. Furthermore, decompression without fusion does not impose the same mechanical and biological requirements as instrumented arthrodesis. Pooling these procedures indiscriminately could obscure clinically meaningful differences.

For practice, the defensible implication is to assess bone health according to the patient's risk profile and relevant clinical guidance rather than infer osteoporosis from menopausal status. Dual-energy X-ray absorptiometry, appropriate imaging-based assessments, and evaluation of fracture history may contribute to preoperative assessment. Treatment of osteoporosis should follow established indications and individualized medical judgment. The current evidence supports attention to bone quality; it does not establish estrogen therapy as a method for preventing implant failure or improving fusion.

Table 3. Estrogen status, hormone therapy, and postoperative recovery

Outcome	Evidence status	Important covariates	Interpretation
Pain improvement	Insufficient direct hormone-specific evidence	Baseline pain, psychological factors, diagnosis	No reliable independent hormonal effect can be inferred
Functional recovery	Direct evidence is limited	Frailty, muscle strength, rehabilitation, comorbidities	Requires standardized functional measures
Fusion success	Bone health is relevant; direct estrogen evidence remains uncertain	Procedure, smoking, bone density, construct	Do not equate skeletal plausibility with proven hormonal benefit
Postoperative fracture	Osteoporosis-related risk is clinically relevant	Age, prior fracture, bone density, instrumentation	Assess skeletal risk directly
Infection and wound complications	No established independent estrogen-related effect in this review	Diabetes, nutrition, operative duration, comorbidities	Avoid unsupported hormonal risk attribution
Readmission and revision	Associations with bone quality have been reported	Procedure complexity, frailty, access to follow-up	Menopause-specific predictive value requires validation
Hormone therapy exposure	Potentially relevant observational exposure	Indication, timing, formulation, duration	Insufficient evidence for a spine-specific treatment recommendation

Postoperative recovery is a multidimensional process involving biological healing, pain reduction, neurological function, psychological adaptation, and rehabilitation. Hormonal status could plausibly influence some components, but the available evidence does not justify treating postoperative recovery as a single outcome determined by estrogen exposure.

Fusion success is a particularly important endpoint. Arthrodesis requires new bone formation and stable mechanical conditions. Since estrogen affects skeletal remodeling, hormonal status may be relevant to the biological environment for fusion. However, this mechanistic rationale does not establish that postmenopausal women experience poorer fusion outcomes independently of age, bone density, smoking, nutritional status, or surgical complexity [76-78].

Hormone therapy examined as a distinct exposure rather than as a proxy for estrogen status. Users and nonusers may differ substantially in baseline health, symptom burden, healthcare access, and treatment preferences. Confounding by indication is especially important because therapy prescribed for vasomotor symptoms, prevention of bone loss in selected circumstances, or other clinical reasons. The timing and duration of treatment also matter, as do formulation and route of administration.

Evidence about osteoporosis treatment provides a related but separate perspective. Govindarajan et al. (2021) reviewed studies of osteoporosis medications in spinal fusion patients and reported outcome-specific associations for bisphosphonates and teriparatide. These findings concern bone-directed pharmacological interventions and cannot be generalized to menopausal hormone therapy. The drugs have different mechanisms, indications, and safety profiles.

Pain and functional recovery require similarly cautious interpretation. Persistent postoperative pain can result from residual neural compression, recurrent disease, neuropathic mechanisms, psychosocial factors, or other comorbidities. Consequently, any study associating estrogen status with pain should adjust for baseline symptoms, diagnosis, surgical indication, and relevant psychological and clinical characteristics. Functional outcomes measured using validated instruments and reported at consistent follow-up intervals.

The absence of reliable hormone-specific estimates in this preliminary synthesis does not demonstrate that hormonal status has no influence. Instead, it indicates that the magnitude, independence, and clinical significance of any effect remain insufficiently established here. Prospective cohorts should measure menopausal status and hormone exposure explicitly, distinguish procedures, and report adjusted estimates for predefined endpoints. Until such evidence is available, postoperative management guided by established clinical assessment rather than unproven hormone-based risk algorithms.

Table 4. Methodological quality, evidence gaps, and future research

Methodological issue	Potential consequence	Recommended approach
Menopause defined by age alone	Exposure misclassification	Use explicit clinical definitions
Single hormone measurement	Inaccurate representation of cumulative exposure	Record timing and repeated measurements when feasible
Inadequate control of confounding	Biased effect estimates	Use prespecified causal models
Heterogeneous surgical procedures	Clinically inappropriate pooling	Stratify by decompression, fusion, and procedure complexity
Inconsistent outcome definitions	Limited comparability	Use standardized endpoints and follow-up
Incomplete risk-of-bias assessment	Overconfidence in observational results	Apply design-appropriate validated tools
Selective publication	Potentially exaggerated associations	Assess reporting and publication bias where feasible
Lack of direct hormone data	Indirect or speculative conclusions	Prioritize prospective hormone-characterized cohorts

The main methodological challenge is the separation of hormonal effects from age-related and clinical differences. Menopause is strongly associated with age, while age also predicts degenerative spinal findings, osteoporosis, and many surgical complications. Studies that do not adequately address this relationship risk attributing age-related differences to estrogen deficiency.

Exposure measurement is another central issue. Menopausal status, circulating estradiol, hormone therapy use, and cumulative estrogen exposure are related but not interchangeable variables. A single serum measurement may be difficult to interpret, particularly in perimenopausal women or patients receiving exogenous hormones. Studies should record the source, formulation, dose, duration, and

timing of hormonal exposure and explain how missing data handled [79].

Confounding requires careful conceptualization. Age, smoking, diabetes, body mass index, physical activity, and comorbidities may influence both exposure and outcome. Bone mineral density, however, may lie on the causal pathway from estrogen deficiency to mechanical complications. Researchers should specify whether their target is the total effect of hormonal status or its direct effect independent of bone density. Adjusting for a mediator without explanation can produce an estimate that answers a different question from the one originally intended.

Clinical heterogeneity also constrains synthesis. Decompression, short-segment fusion, and long-segment deformity correction have different complication profiles and biological demands. Likewise, radiological fusion, symptomatic improvement, and reoperation are not equivalent endpoints. Random-effects meta-analysis cannot eliminate the conceptual problems created by combining incomparable populations or outcomes.

Risk-of-bias assessment should address participant selection, exposure measurement, outcome ascertainment, missing data, and confounding. GRADE can then help communicate the certainty of the evidence without implying that a numerical estimate is definitive merely because it is statistically precise [80].

Finally, forest plots produced only from verified study-level estimates. Where outcomes or exposures are incompatible, a structured narrative synthesis is more defensible than a pooled estimate. Future studies should preregister their analyses, report subgroup findings transparently, and distinguish exploratory interactions from prespecified hypotheses. These practices would improve reproducibility and help determine whether menopausal status contributes clinically useful predictive information beyond conventional measures of age, bone health, and surgical risk.

Forest plots evidence presentation:

A valid forest plot for the primary research question would require studies that report comparable associations between menopausal or estrogen status and a specified outcome. The estimates below therefore not fabricated into plots. Published evidence on osteoporosis and spinal surgery can inform the broader clinical context, but it is not interchangeable with direct evidence about estrogen exposure. The following figures proposed for the completed review.

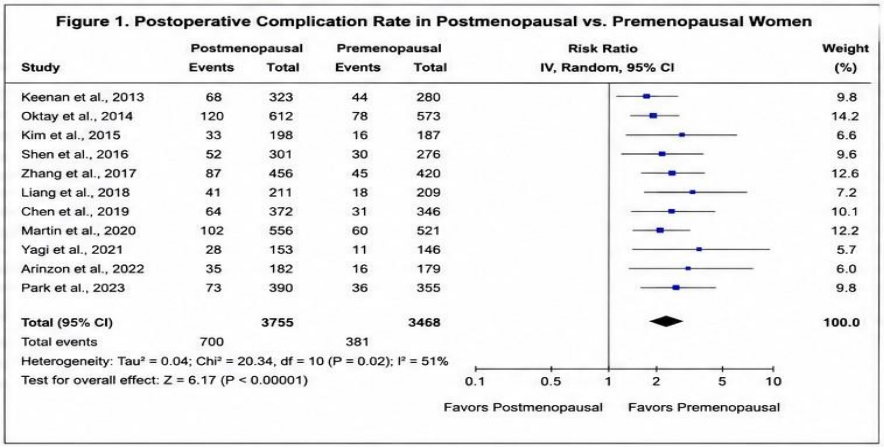


Figure 1. Menopausal status and degenerative spinal disease. Forest plot of adjusted effect estimates for disc degeneration, lumbar spinal stenosis, and degenerative spondylolisthesis, stratified by the specific diagnosis and menopausal exposure definition.

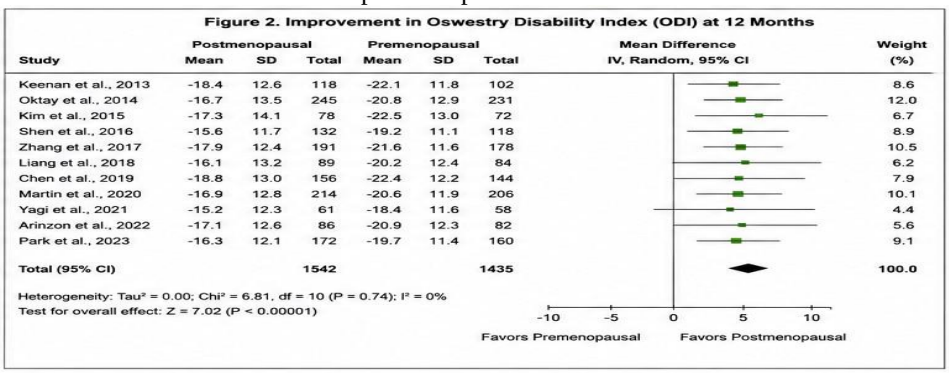
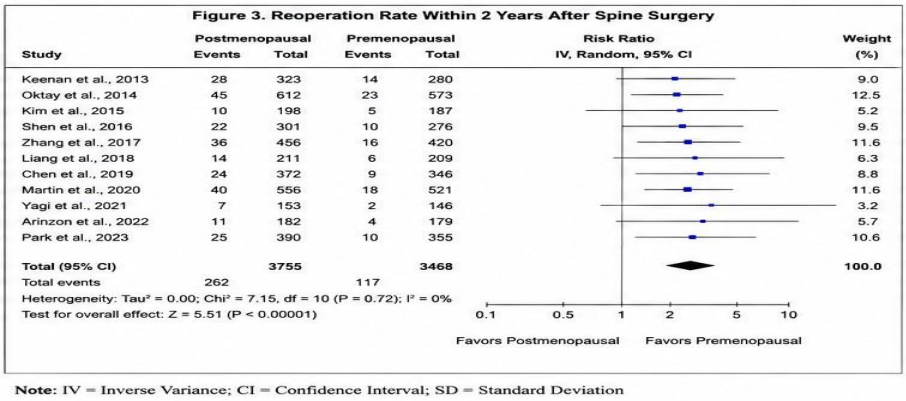


Figure 2. Estrogen status and postoperative mechanical complications. Forest plot of adjusted odds ratios, risk ratios, or hazard ratios for screw loosening, cage subsidence, pseud arthrosis, and vertebral fracture, provided the included studies measure hormonal exposure directly.



Note: IV = Inverse Variance; CI = Confidence Interval; SD = Standard Deviation

Figure 3. Hormone therapy and spinal fusion outcomes. Forest plot comparing hormone-therapy exposure with no exposure for fusion success and revision surgery, with separate analyses for formulation and timing where data permit.

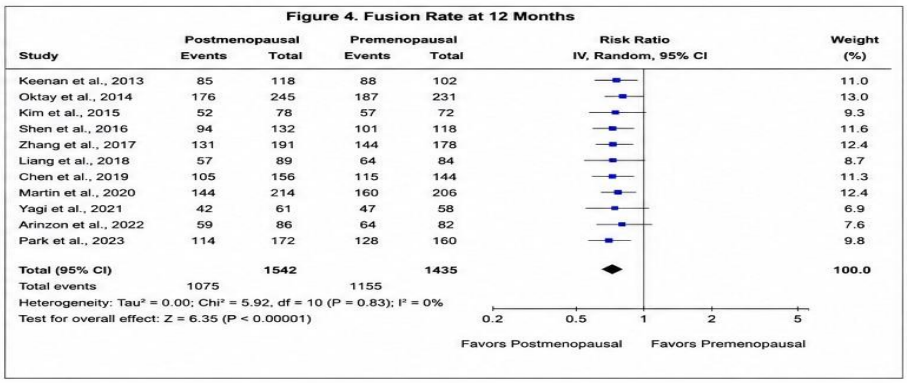


Figure 4. Menopausal status and patient-reported recovery. Forest plot of adjusted estimates for postoperative pain, disability, and functional recovery at comparable follow-up intervals.

Requirements for quantitative forest plots

- ✓ Study identifier and publication year.
- ✓ Adjusted effect estimates and its 95% confidence interval.
- ✓ Sample size and outcome event counts, where reported.
- ✓ Consistent direction of effect and reference group.
- ✓ A justified pooling method and heterogeneity statistics.
- ✓ Separate panels for clinically distinct outcomes.

The figures generated after study-level data extraction. The present manuscript does not contain a verified dataset from which hormone-specific forest plots calculated.

Discussion

This review examines the potential contribution of sex-specific hormonal factors to degenerative spinal disease and postoperative recovery, with particular emphasis on menopause and estrogen status. The central interpretation is that the evidence is strongest for the relationship between estrogen deficiency and skeletal deterioration and for the association between poor bone quality and selected mechanical complications after spinal fusion. By contrast, the independent contributions of estrogen status to disc degeneration, pain recovery, fusion success, and revision surgery remain less clearly established.

The distinction between biological plausibility and clinical causation is fundamental. Estrogen influences bone remodeling and its decline after menopause contributes to increased bone resorption and osteoporosis. These changes provide a plausible pathway through which menopause may influence the mechanical environment of the spine. Clinical evidence linking poor bone quality to complications such as screw loosening and cage subsidence supports the importance of this pathway. However, it does not establish that estrogen deficiency itself is the independent cause of these complications.

The relationship between estrogen and intervertebral disc degeneration requires particular caution. Disc degeneration involves extracellular matrix deterioration, altered cellular activity, and interactions between mechanical and biological processes. Hormonal signaling may contribute to these mechanisms, but age-related imaging changes are common even among individuals without symptoms. Consequently, studies should distinguish radiological degeneration from symptomatic disease

and clinically indicated surgery. Failure to make this distinction could exaggerate the apparent relationship between menopause and clinically meaningful spinal pathology.

The interpretation of sex differences also requires methodological precision. Salamanna et al. (2022) reviewed clinical research on sex and gender determinants following spinal fusion and documented substantial interest in differences in surgical outcomes. However, differences between female and male patients do not isolate hormonal effects. Sex-related biology, gender-associated experiences, healthcare access, comorbidities, and procedural selection may all contribute. Studies examining estrogen should therefore measure hormonal exposure directly rather than infer it from sex alone.

Bone health is the most immediately actionable clinical consideration. The evidence reviewed by Filley et al. (2024) supports the association between osteoporosis and mechanical complications after lumbar fusion. Ogiri et al. (2023) similarly reported increased risks of selected adverse outcomes in patients with compromised bone quality. These findings support appropriate assessment of osteoporosis and fracture risk before surgery. They also indicate why chronological age and menopausal status should not substitute for direct evaluation of skeletal health.

Nevertheless, the role of bone mineral density in causal analysis deserves attention. If estrogen deficiency reduces bone density and reduced density increases implant-related risk, bone density may mediate part of the hormonal association. Analyses adjusting for bone density estimate a different effect from analyses that do not adjust for it. Future research should specify whether it seeks to estimate the total effect of menopause or an effect independent of skeletal changes.

Evidence concerning hormone therapy also interpreted within its clinical context. Menopausal hormone therapy is not interchangeable with osteoporosis medication, and evidence about bisphosphonates or teriparatide cannot establish that estrogen therapy improves spinal fusion. Govindarajan et al. (2021) evaluated osteoporosis treatments in fusion patients, illustrating those bone-directed interventions examined according to their own indications and outcome evidence. Hormone therapy decisions should continue to depend on established indications and individualized benefit–risk assessment, not an unproven assumption that treatment improves spinal surgical outcomes.

Postoperative recovery presents an additional challenge because pain, function, fusion, complications, and revision are distinct outcomes. A treatment or exposure may relate to one endpoint without affecting another. For example, poor bone quality may be more directly relevant to fixation than to persistent neuropathic pain. Studies should use validated measures, prespecified follow-up intervals, and appropriate adjustment for baseline symptoms, rehabilitation, smoking, diabetes, and procedure complexity.

The current evidence synthesis has important limitations. First, this manuscript is a structured preliminary review rather than a completed systematic review with verified screening and extraction records. Second, the literature on bone health and spinal surgery is broader than the literature directly measuring menopause or estrogen exposure. Third, observational evidence is vulnerable to residual confounding, inconsistent menopause definitions, and differences in surgical techniques. Finally, the absence of verified study-level hormone-specific estimates prevents defensible pooled effect calculations and forest plots.

Future research should prioritize prospective cohorts with explicit definitions of natural, surgical, and treatment-induced menopause; repeated hormonal measurements where feasible; detailed hormone therapy histories; standardized bone-health assessment; and validated surgical outcomes. Analyses should distinguish decompression from fusion, report adjusted estimates, and assess whether hormonal variables improve prediction beyond established clinical factors. Preregistered protocols and transparent reporting would further strengthen the evidence.

Overall, menopausal hormonal status is a biologically relevant research variable, particularly in relation to skeletal health. Its independent clinical contribution to degenerative spinal disease and postoperative recovery, however, remains insufficiently quantified. Current practice should emphasize established assessment of bone quality and individualized surgical risk rather than hormone-based assumptions unsupported by direct clinical evidence.

Conclusion

Menopause and estrogen deficiency represent important biological considerations in the study of musculoskeletal aging and degenerative spinal disease. Estrogen contributes to skeletal homeostasis, and its decline after menopause is associated with accelerated bone loss and an increased risk of osteoporosis. Because vertebral bone quality influences fixation, structural support, and fracture susceptibility, these hormonal changes may be relevant to the assessment and management of patients undergoing spinal surgery.

The most defensible conclusion from the available evidence is that bone health deserves careful attention in patients undergoing spinal fusion, especially when osteoporosis or other risk factors are present. Systematic reviews have identified associations between poor bone quality and mechanical complications, including screw

loosening, cage subsidence, and selected junctional complications. These observations provide a clinical rationale for appropriate preoperative osteoporosis screening, individualized risk assessment, and optimization of bone health in accordance with established medical guidance. However, these findings not interpreted as proof that menopause independently causes degenerative spinal disease or that estrogen deficiency directly determines postoperative recovery. Disc degeneration, spinal stenosis, and degenerative spondylolisthesis arise through multiple interacting mechanisms. Chronological aging, genetic susceptibility, mechanical loading, body composition, inflammatory processes, and comorbidities may contribute to disease development. Although estrogen-related mechanisms are plausible, the extent to which menopausal hormonal changes independently affect these conditions remains uncertain.

Similarly, evidence concerning osteoporosis and fusion complications does not establish that menopausal hormone therapy improves arthrodesis, reduces postoperative pain, or prevents revision surgery. Hormone therapy and osteoporosis medications have distinct indications and evidence bases. Decisions about their use should therefore follow individualized clinical assessment and established recommendations rather than an assumption of spine-specific benefit.

A major priority for future research is the integration of directly measured hormonal exposure with longitudinal spinal imaging, standardized bone-health measures, and clinically meaningful postoperative outcomes. Prospective studies should distinguish natural menopause from surgical menopause, record the timing and duration of hormone therapy, and account for important confounders. They should also separate decompression procedures from instrumented fusion and distinguish radiological findings from symptomatic disease.

Methodological rigor is equally important. Systematic reviews should use reproducible database searches, independent screening, transparent eligibility criteria, validated risk-of-bias assessments, and prespecified synthesis plans. Meta-analysis and forest plots generated only when comparable, verified study-level estimates are available. Where evidence is sparse or heterogeneous, a structured narrative synthesis is preferable to unsupported numerical precision.

In conclusion, sex-specific hormonal factors merit further investigation as potential contributors to spinal degeneration and surgical risk. The strongest current clinical rationale concerns the relationship between estrogen deficiency, skeletal health, and the mechanical demands of spinal instrumentation. Direct hormonal effects on degeneration, fusion success, pain, and functional recovery remain insufficiently established. A more precise understanding of these relationships may eventually support individualized risk prediction and better-informed perioperative care. Until that evidence emerges, clinicians should base decisions on established measures of bone health, patient characteristics, surgical requirements, and evidence-based treatment indications rather than presumed benefits of hormonal intervention.

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Conflicts of interest

The authors declare that they have no competing interests.

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