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Review Article

The Estrobolome-Epigenetic Inflammatory Axis in Menopause: A Multisystem Mechanistic Link to Chronic Disease

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ABSTRACT

Menopause is characterized by a progressive decline in ovarian estrogen production, resulting in immune dysregulation and a chronic low-grade inflammatory state known as inflammaging. Beyond hormonal deficiency, emerging evidence highlights the role of the Estrobolome-the collection of gut microbial genes involved in estrogen metabolism-in regulating estrogen homeostasis and inflammatory responses. Disruption of the estrobolome may further exacerbate systemic inflammation and contribute to the development of multiple chronic diseases in postmenopausal women. To comprehensively review the molecular mechanisms linking estrogen deficiency, the estrobolome, immune dysregulation, and chronic inflammation during menopause, and to summarize their multisystem effects, current therapeutic strategies, and emerging directions for precision medicine. A comprehensive narrative review of the recent literature was conducted using peer-reviewed publications retrieved from major biomedical databases. Studies investigating estrogen deficiency, inflammatory signaling pathways, immune regulation, oxidative stress, gut microbiota and the estrobolome, menopause-associated diseases, and therapeutic interventions were critically evaluated and synthesized to provide an integrated overview of current evidence. Estrogen deficiency promotes persistent activation of inflammatory pathways, including NF-κB, MAPK, Toll-like receptor signaling, and the NLRP3 inflammasome, resulting in increased production of pro-inflammatory cytokines, oxidative stress, endothelial dysfunction, mitochondrial impairment, and immune dysregulation. Alterations in the estrobolome further disrupt estrogen metabolism, increase intestinal permeability, and amplify systemic inflammation through microbiota-immune interactions. These interconnected mechanisms contribute to cardiovascular disease, osteoporosis, metabolic syndrome, neurodegeneration, hormone-sensitive cancers, and other menopause-associated disorders. Emerging therapeutic approaches-including menopausal hormone therapy, anti-inflammatory lifestyle interventions, microbiome-targeted strategies, and precision medicine based on multi-omics, pharmacogenomics, and artificial intelligence-offer promising opportunities for individualized management. Menopause-associated inflammation is a complex multisystem process driven by interactions among estrogen deficiency, immune dysfunction, oxidative stress, and estrobolome dysregulation. A deeper understanding of these interconnected mechanisms will facilitate the development of personalized preventive and therapeutic strategies that improve healthy aging and long-term outcomes in postmenopausal women.

Keywords: Chronic Inflammation, Estrobolome, Estrogen Deficiency, Gut Microbiota, Immune Dysregulation, Menopause, Precision Medicine.

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INTRODUCTION

Menopause is the permanent cessation of menstrual cycles, diagnosed after 12 consecutive months without menstruation, not explained by other medical causes (Yang *et al*., 2024). The central event in menopause is a significant decline in ovarian production of estrogen, progesterone, and androgens. Concurrently, there is a reduction in the production of estrogen and progesterone. Estrogen deficiency during menopause leads to an increase in inflammation throughout the body. As estrogen levels decline, especially the potent estradiol form, the body's natural ability to regulate inflammation weakens. Systemic inflammation in menopause refers to a persistent, poor-grade inflammatory state that happens during the menopausal transition and persists into post menopause. Elevated levels of circulating inflammatory markers are its defining feature and activate immune pathways

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beyond local tissue inflammation. In recent years, increasing attention has been directed toward the estrobolome, a collection of gut microbial genes capable of metabolizing estrogens through enzymes such as β-glucuronidase. By regulating the deconjugation and enterohepatic recirculation of estrogens, the estrobolome plays a critical role in maintaining estrogen homeostasis. Alterations in gut microbial composition during menopause may disrupt estrobolome function, resulting in reduced estrogen bioavailability, impaired intestinal barrier integrity, and enhanced systemic inflammation. Consequently, the bidirectional interaction between the gut microbiota, estrogen metabolism, and immune regulation has emerged as an important mechanism linking menopause with chronic inflammatory disorders and represents a promising target for future therapeutic interventions (Baker *et al*., 2017; Kumari *et al*., 2024a). Elevated systemic inflammation correlates with an elevated risks in age-related illness in females following menopause, comprising osteoporosis, neurodegenerative diseases like Alzheimer's, cardiovascular diseases, and periodontal disease (McCarthy & Raval, 2020). Premenopausal women's physiological estrogen levels inhibit the generation of cytokines that promote inflammation, such as interleukins IL6 and IL8, Factor α for Tumor Necrosis (TNFα). Postmenopausal women's low physiological estrogen levels do not prevent the release of cytokines that promote inflammation (Averyanova *et al*., 2022).

Hormonal Transition and Immune Dysregulation

It acts through its receptors Estrogen receptor alpha (Erα) and Estrogen Receptor beta (Erβ) expressed by monocytes, along with T and B lymphocytes and dendritic cells. Decrease in estrogen levels after menopause brings about immunosenescence which impacts the innate as well as the adaptive immunity. The result is that the ability to control inflammatory response through estrogen is lost, with pro-inflammatory cytokine production rising to increase inflammation, senescence of immune cells, and apoptosis leading to impaired coordination of the immune response. The net effect is that infection rate goes up, response to vaccination decreases, and autoimmunity becomes the order of the day (Engelmann *et al*., 2016). Immune diseases like Rheumatoid Arthritis (RA) may become worse because of lowered estrogen levels, as demonstrated by Cutolo and Gotelli (2023) and Motta *et al*. (2025) and the hormonal transition together with its immunological consequences is illustrated in Figure 1.

Mechanisms associating inflammation and estrogen decline

Decline of estrogen during menopause increases inflammation via altered immune response signaling and oxidative-reduction imbalance. Decreased activity of ERα, ERβ, and G Protein-coupled Estrogen Receptor (GPER) leads to the dysregulation of immune responses, causing upregulation of Nuclear Factor Kappa B (NF-κB) and NLRP3 inflammasome signaling, leading to increased levels of pro-inflammatory cytokines such as Interlukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and IL-1β (McCarthy and Raval 2020; Zhang *et al*., 2024). Increased activity of pattern recognition receptors maintains chronic inflammation in different organs, including the Central Nervous System (CNS) (McCarthy & Raval 2020b). At the same time, estrogen deficiency causes an increase in oxidative stress by diminishing antioxidant activity, activating other redox-sensitive signaling pathways (Wood *et al*., 2025).

Inflammaging and Menopause

Inflammaging is a persistent low-grade inflammatory condition linked to aging and decreased estrogen levels, which disturbs immune regulation and increases cytokines including IL-6, TNF-α, and CRP (Franceschi *et al*., 2020). Lower estrogen levels make the NF-κB and NLRP3 pathways more active, which leads to more cytokine release and oxidative stress. When resolution doesn't happen, inflammation stays high (Ryczkowska *et al*., 2023). Elevated visceral adiposity further exacerbates metabolic inflammation, contributing to the systemic effects of estrogen deficiency during menopause (Figure 2).

Multiple-Organ Impact of Menopause-Associated Inflammatory Reprogramming

Decreased estrogen levels during menopause cause a long-lasting pro-inflammatory state that affects many organ systems through molecular pathways that are linked to each other. In the cardiovascular system, oxidative imbalance coupled with NF-κB activation diminish nitric oxide bioavailability, thereby facilitating endothelial dysfunction and atherogenesis (Sena *et al*., 2018). Estrogen deficiency in bone and muscle hastens bone resorption, elevates fracture risk, and fosters sarcopenia (Mou *et al*., 2025; Suvvari *et al*., 2023). In the central nervous system, diminished estrogen levels stimulate microglia, leading to increased pro-inflammatory cytokines, neuroinflammation, and cognitive decline, this increases the susceptibility to neurodegenerative and metabolic disorders (Zhu *et al*., 2023). Epigenetic changes including DNA methylation and histone remodeling, maintain the expression of inflammatory genes. Estrogen depletion alters immune regulation via ERα, ERβ, and GPER, activating NLRP3 and NF-κB pathways, resulting in blood-brain barrier disruption, impaired neuroplasticity, and mood disorders, including menopausal depression (Zhang *et al*., 2024b; Yang *et al*., 2022). Visceral adiposity exacerbates inflammation via adipocyte hypertrophy, macrophage infiltration, and fibrosis, which increases the secretion of TNF-α, IL-6, and Monocyte Chemoattractant Protein-1 (MCP-1), consequently worsening insulin resistance, metabolic syndrome, and cardiovascular risk (Smith *et al*., 2012; Mori *et al*., 2022; Sinatora *et al*., 2022; Milani *et al*., 2025). The loss of estrogen increases circulating inflammatory markers including IL-6, TNF-α, and CRP (El Khoudary *et al*., 2023). Mucosal immunity is compromised

due to impaired barrier integrity, diminished antimicrobial peptides, and alterations in the microbiome, thereby increasing susceptibility to chronic inflammation and infections (Ahrend *et al.*, 2025a; Feng *et al.*, 2023; Hu *et al.*, 2021; Pressi *et al.*, 2023; Liu *et al.*, 2024). Chronic inflammation promotes hormone-sensitive cancers through NF-κB signaling, cytokine-mediated activation, Signal Transducer and Activator of Transcription 3 (STAT3) signaling, senescence-associated secretory phenotype, tumor microenvironment remodeling, and Reactive Oxygen Species/ Reactive Nitrogen Species (ROS/RNS)-induced genomic instability (Figure 3).

Post-menopausal women display high levels of inflammation and oxidative stress that correlate highly with the onset and worse outcome of ER+ breast cancer. The adipose aromatase maintains estrogen synthesis within the tissue despite low estradiol levels (Carleton *et al.*, 2024). Cytokines involved in inflammation, notably IL-6 and TNF-α, ROS, and immune infiltration contribute to tumor progression and escape from immune detection (Thoene *et al.*, 2025). Estrone supports the induction of pro-inflammatory genes, Epithelial-Mesenchymal Transition (EMT), and tumor initiation (Diaz-Ruano *et al.*, 2023).

Pro-inflammatory cytokines and tumor microenvironment

Recent evidence has further strengthened the link between menopause-associated chronic inflammation and the progression of hormone-sensitive malignancies through alterations in the Tumor Microenvironment (TME). Persistent low-grade inflammation promotes the recruitment of tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells, creating an immunosuppressive microenvironment that facilitates tumor initiation, angiogenesis, immune evasion, and metastatic dissemination. Pro-inflammatory cytokines, particularly Interleukin-6 (IL-6), Tumor Necrosis Factor-Alpha (TNF-α), and Interleukin-1β (IL-1β), activate key signaling pathways including Nuclear Factor-Kappa B (NF-κB), Signal Transducer and Activator of Transcription 3 (STAT3), and Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/Akt), thereby enhancing cancer cell proliferation, epithelial-mesenchymal transition, and resistance to apoptosis. Moreover, recent studies have highlighted that Senescence-Associated Secretory Phenotype (SASP) factors released during cellular senescence amplify inflammatory signaling and reshape the TME, further accelerating tumor progression. These findings suggest that targeting inflammatory mediators and the TME may represent a promising therapeutic strategy for preventing and managing hormone-sensitive cancers in postmenopausal women (Abdul-Rahman *et al.*, 2024; Dong *et al.*, 2024; Wang *et al.*, 2024).

Estrobolome-Epigenetic Memory Axis in Menopause: Macrophage Reprogramming and Mitotic Heritability of Inflammation

Menopause-induced estrogen decline disrupts estrobolome-mediated estrogen recycling, resulting in microbial dysbiosis and increased endotoxin burden. These signals activate inflammatory pathways such as TLR4/NF-κB, driving epigenetic remodeling in macrophages through DNA methylation and histone modifications. This reprogramming promotes a sustained M1 phenotype and establishes trained immunity, wherein inflammatory responses are amplified and mitotically inherited, ultimately leading to persistent low-grade inflammation and increased susceptibility to chronic diseases (Figure 4).

Therapeutic and Lifestyle Interventions

Therapeutic interventions for menopause are medical and psychological strategies aimed at relieving the physical and emotional symptoms that result from hormonal changes during menopause.

Hormone Replacement Therapy (HRT)

Recent evidence supports a more individualized approach to Hormone Replacement Therapy (HRT), taking into account the patient's age, time since menopause, cardiovascular risk profile, metabolic status, and symptom burden. Current recommendations favor initiating HRT in women younger than 60 years or within 10 years of menopause onset, provided no contraindications exist. Transdermal estrogen formulations are increasingly preferred over oral preparations in women at elevated cardiovascular or thromboembolic risk because they avoid first-pass hepatic metabolism and exert less influence on coagulation factors and inflammatory biomarkers. Emerging clinical and mechanistic studies further demonstrate that appropriately selected HRT improves endothelial function, reduces vascular inflammation, preserves bone health, and may attenuate menopause-associated low-grade inflammatory responses. These findings reinforce the importance of personalized HRT strategies that maximize therapeutic benefits while minimizing adverse outcomes through individualized risk assessment and continuous clinical monitoring (Yang *et al.*, 2024b).

Anti-inflammatory diet, exercise, and pharmacological options

Lifestyle interventions remain fundamental for reducing menopause-associated chronic inflammation. Recent evidence indicates that adherence to the Mediterranean diet, characterized by abundant fruits, vegetables, whole grains, legumes, olive oil, and omega-3 fatty acids, significantly improves inflammatory biomarkers, metabolic health, and overall quality of life in postmenopausal women. Furthermore, modulation of the gut microbiota through dietary fiber, probiotics, and prebiotics has emerged as a promising strategy to restore estrobolome

function, enhance estrogen metabolism, and reduce systemic inflammation. Regular resistance and aerobic exercise further suppress pro-inflammatory cytokine production while improving insulin sensitivity, muscle mass, and bone integrity. In women with obesity or metabolic syndrome, Glucagon-Like Peptide-1 (GLP-1) receptor agonists have demonstrated additional anti-inflammatory and cardiometabolic benefits, suggesting their potential role as adjunctive therapies in carefully selected menopausal women (Kumari *et al.*, 2024b).

Herbal Approaches in managing menopausal inflammation

Growing evidence supports the complementary role of selected phytochemicals in mitigating menopausal inflammation and improving symptom control. Phytoestrogens, particularly soy isoflavones, exert selective estrogen receptor-modulating effects that may alleviate vasomotor symptoms while reducing oxidative stress and inflammatory cytokine production. Polyphenolic compounds such as curcumin and resveratrol have also attracted considerable attention because of their antioxidant and anti-inflammatory activities, primarily through modulation of the NF-κB and NLRP3 inflammasome pathways. Although current clinical trials demonstrate encouraging improvements in inflammatory biomarkers, endothelial function, and quality of life, substantial heterogeneity exists regarding dosage, formulation, and treatment duration. Consequently, larger well-designed randomized controlled trials are required before these agents can be routinely recommended as stand-alone therapies for menopause-associated inflammatory disorders (Chavda *et al.*, 2024; Mad Azli *et al.*, 2024; Portella *et al.*, 2024).

FUTURE DIRECTIONS AND RESEARCH GAPS

Personalized medicine in managing menopausal inflammation

Personalized medicine is rapidly transforming the management of menopause-associated inflammation by integrating genomic, transcriptomic, proteomic, metabolomic, and microbiome-derived information into individualized clinical decision-making. Multi-omics approaches enable comprehensive characterization of inflammatory pathways and estrogen-responsive molecular networks, allowing identification of women at increased risk for cardiovascular disease, osteoporosis, metabolic dysfunction, and cognitive decline. Artificial Intelligence (AI)-assisted predictive models further enhance precision medicine by integrating clinical variables with biomarker profiles to improve early risk stratification and optimize therapeutic selection. Pharmacogenomic testing may also facilitate individualized Menopausal Hormone Therapy (MHT) by identifying genetic variants affecting estrogen metabolism, receptor signaling, and thromboembolic risk, thereby maximizing therapeutic efficacy while minimizing adverse effects. In parallel, microbiome-guided interventions targeting the estrobolome may enable personalized dietary and probiotic strategies that restore estrogen homeostasis and attenuate chronic inflammation. Together, these emerging technologies support a transition from symptom-based management toward precision medicine that addresses the biological heterogeneity of menopause and promotes healthier aging (Dong *et al.*, 2023a; Lim *et al.*, 2026).

The Key Personalized Strategies in Managing Menopausal Inflammation are

Personalized management strategies are increasingly focusing on interventions tailored to an individual's inflammatory and microbial profile. Modulation of the estrobolome through

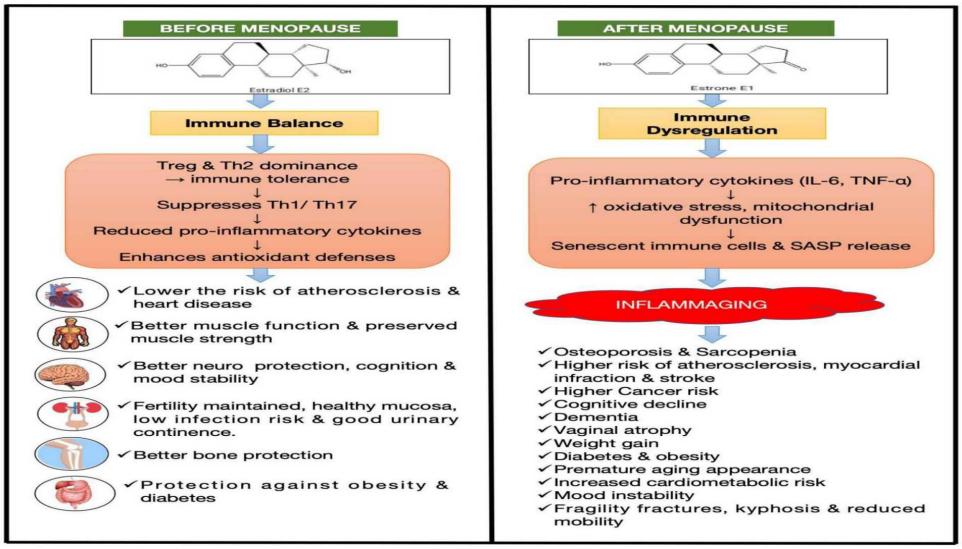


Figure 1: Hormonal transition during menopause and its systemic consequences. Declining estrogen levels promote chronic inflammation, oxidative stress, immune dysregulation, and increased susceptibility to age-related diseases

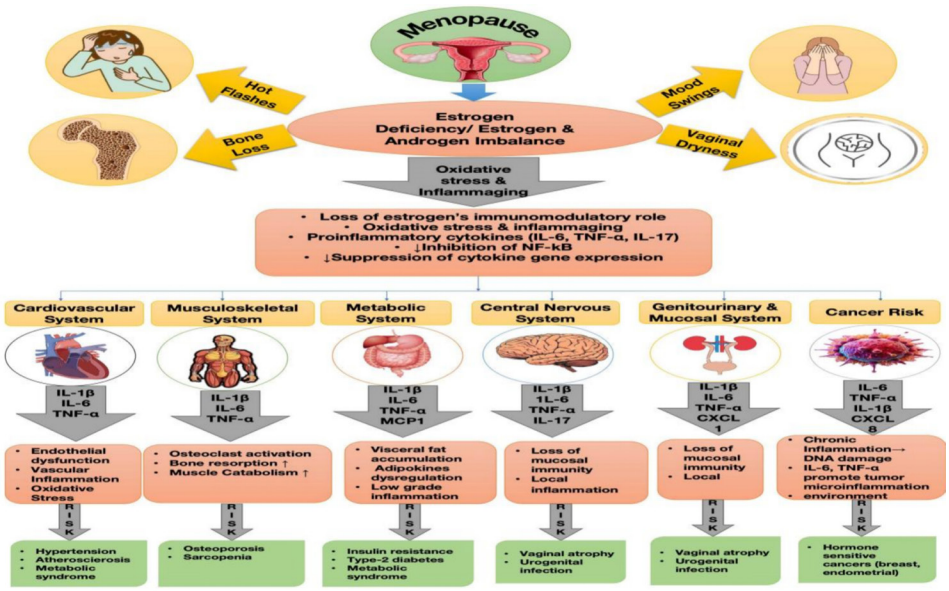


Figure 2: Systemic inflammatory pathways associated with estrogen deficiency. Estrogen loss activates inflammatory mediators, including NF-κB and pro-inflammatory cytokines, contributing to cardiovascular, metabolic, skeletal, and neurological disorders.

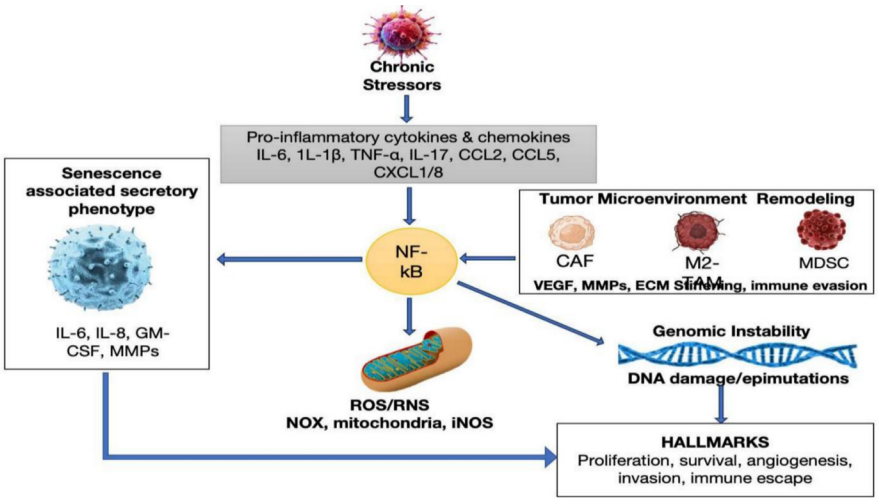


Figure 3: Inflammatory mechanisms underlying hormone-sensitive cancers. Chronic inflammation promotes oxidative stress, immune dysregulation, and signaling pathways that facilitate tumor initiation and progression.

strain-specific probiotics and prebiotics has emerged as a promising approach for improving estrogen metabolism, intestinal barrier integrity, and immune homeostasis. Personalized nutritional interventions emphasizing dietary fiber, phytoestrogens, omega-3 fatty acids, and polyphenol-rich foods may further reduce chronic low-grade inflammation while supporting microbial diversity. In addition, wearable devices and digital health platforms facilitate continuous monitoring of sleep quality, physical activity, heart-rate variability, and vasomotor symptoms, enabling real-time assessment of therapeutic response and individualized lifestyle modification. Integrated multidisciplinary care involving gynecologists, endocrinologists, nutritionists, and mental health specialists can further optimize long-term outcomes. Emerging immunomodulatory therapies targeting inflammasome activation, cytokine signaling, and immune cell function may complement conventional hormone therapy in selected high-risk patients, although further clinical validation remains necessary (Liaquat *et al.*, 2025; Lin *et al.*, 2025).

Need for system-based inflammatory biomarkers

Future research should prioritize the identification of integrated biomarker panels that accurately reflect the complex inflammatory landscape of menopause. Beyond traditional inflammatory markers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Tumor Necrosis Factor-α (TNF-α), emerging biomarkers including Interleukin-18 (IL-18), activation of the NLRP3 inflammasome, circulating microRNAs, metabolomic and proteomic signatures, and gut microbiome-derived profiles may provide greater diagnostic and prognostic value. Multi-omics integration combined with AI-based analytical platforms can identify complex biomarker patterns that predict disease

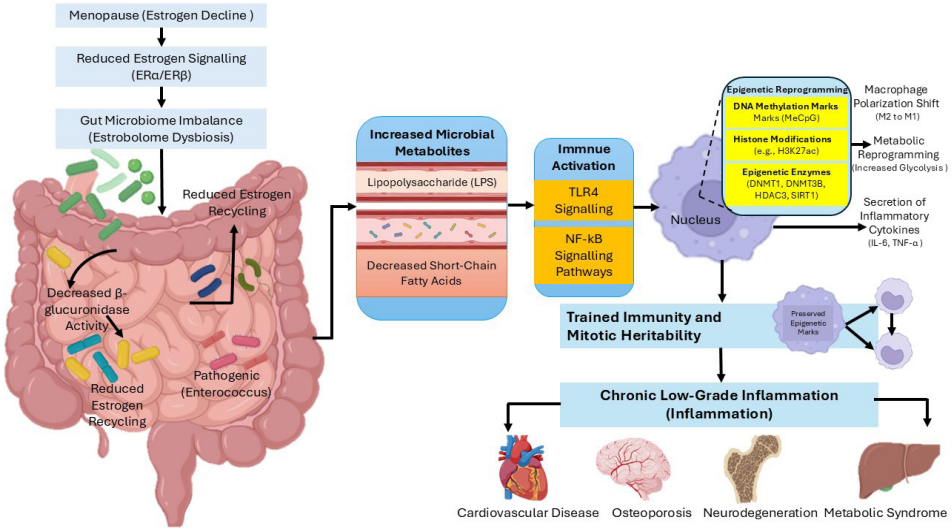


Figure 4: The Estrobolome-epigenetic memory axis in menopause. Altered gut microbiota and impaired estrogen metabolism contribute to persistent inflammation and age-related diseases, highlighting potential targets for microbiome-based interventions.

progression, treatment response, and long-term health outcomes with greater accuracy than individual biomarkers. Such systems biology approaches are expected to facilitate early diagnosis, individualized therapeutic selection, and continuous monitoring of inflammatory status throughout the menopausal transition, ultimately advancing precision medicine in women's health (Dong *et al.*, 2023b; Tahtouh Zaatar *et al.*, 2026).

CONCLUSION

Menopause is accompanied by a profound decline in estrogen levels that extends beyond reproductive aging to influence immune regulation, metabolic homeostasis, and systemic inflammatory processes. The resulting chronic low-grade inflammation contributes significantly to the development of cardiovascular disease, osteoporosis, metabolic dysfunction, neurodegenerative disorders, and other age-related conditions that adversely affect women's health and quality of life. Growing evidence further highlights the critical role of the estrobolome in regulating estrogen metabolism through the gut microbiota, thereby linking intestinal microbial composition with estrogen homeostasis and inflammatory responses during menopause. Advances in understanding the molecular mechanisms underlying menopause-associated inflammation-including oxidative stress, inflammasome activation, immune dysregulation, and alterations in the gut microbiome-have created new opportunities for targeted therapeutic interventions. Current management strategies combine menopausal hormone therapy, anti-inflammatory lifestyle modifications, dietary interventions, regular physical activity, and selected complementary therapies, while emerging precision medicine approaches incorporating multi-omics technologies, pharmacogenomics, artificial intelligence, and microbiome-based interventions hold promise for individualized patient care.

Future research should prioritize large, well-designed longitudinal studies to validate novel inflammatory biomarkers, clarify the mechanistic role of the estrobolome, and evaluate personalized therapeutic strategies that integrate hormonal, immunological, metabolic, and microbial factors. A comprehensive understanding of the complex interactions between estrogen deficiency, chronic inflammation, and the gut microbiota will facilitate the development of more effective preventive and therapeutic approaches, ultimately promoting healthy aging and improving long-term health outcomes in postmenopausal women.

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ABBREVIATIONS

NF-κB: Nuclear Factor kappa-Light-Chain-Enhancer of Activated B cells; **NLRP3:** NOD-, LRR-, and pyrin domain-containing protein 3; **RANKL:** Receptor activator of nuclear factor κB ligand; **RANK:** Receptor Activator of Nuclear Factor κB; **HPO axis:** Hypothalamic–Pituitary–Ovarian axis; **IL-6:** Interleukin-6; **IL-8:** Interleukin-8; **ER-α:** Estrogen receptor alpha; **ER-β:** Estrogen receptor beta; **GPER:** G protein-coupled Estrogen receptor; **TNF-α:** Tumor Necrosis Factor-alpha; **MCP-1:** Monocyte Chemoattractant Protein-1; **STAT3:** Signal Transducer and Activator of Transcription 3; **ROS/RNS:** Reactive Oxygen Species/ Reactive Nitrogen Species; **EMT:** Epithelial–Mesenchymal Transition; **IFN-γ:** Interferon-gamma; **TLR4:** Toll-like receptor 4.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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