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MICRO BIOME POST

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MICROBIOME MODULATION IN MENOPAUSE

A Clinical Guide for Gynecologists

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TABLE OF CONTENTS

Introduction 4

Gut Microbiome Alterations in Menopausal Women 5

Diversity and Composition 5
Estrogen–Microbiome Interactions 6
Metabolic and Immune Implications 6
Bone Health 7
Cardiovascular and Cognitive Aspects 7

Vaginal Microbiome Alterations in Menopausal Women 8

Clinical Consequences 9
Global and Racial Factors 10
Hormone Therapy Effects 10

Microbiome-Targeted Therapies for Menopausal Health 11

Probiotics in Menopausal Women 12
- Probiotics for Gut/Metabolic Health 12
- Probiotics for bone health 13
- Probiotics for Vaginal/Urogenital Health 14

Prebiotics in Menopausal Women 17
- Metabolic Effects and Weight Management 17
- Prebiotics and Estrogen Modulation 17
- Prebiotics for Vaginal Health 18

Synbiotics in Menopausal Women 19
- Metabolic Health 19
- Body Composition 19
- Bone Health 20
- Menopausal Symptoms 20

Postbiotics in Menopausal Women 21

Evidence from Key Clinical Trials 24

Clinical implications 26

Conclusion 29

References 31

INTRODUCTION

Menopause is a natural biological transition defined by the cessation of menses for 12 consecutive months, typically occurring around age 50 (with a range of ~40–59 years). This transition is accompanied by a dramatic **decline in ovarian estrogen and progesterone production**, leading to well-known symptoms and health issues. Common menopausal symptoms include vasomotor symptoms (hot flashes, night sweats), sleep disturbances, mood changes, vaginal dryness, and sexual dysfunction, while longer-term health risks rise for osteoporosis, cardiovascular disease, genitourinary syndrome, and cognitive impairment. **Hormone replacement therapy** (HRT) is an effective treatment for many menopausal symptoms, but not all women are candidates or willing to use hormones long-term due to contraindications or concerns about side effects. Thus, there is growing interest in adjunctive or alternative strategies to support menopausal health.

In recent years, the **human microbiome** – the trillions of microorganisms inhabiting our gut, vagina, skin, and other sites – **has emerged as an important factor in women's health during midlife and aging**. The microbiome and host exist in a symbiotic relationship, and perturbations in this relationship (*dysbiosis*) can influence disease risk. Notably, the gut and vaginal microbiomes are both influenced by female sex hormones. **Estrogen** in particular **has a bidirectional relationship with microbiota**: hormonal changes can alter microbial composition, and conversely the microbiota can metabolize hormones and modulate their levels and effects. The collection of microbial genes capable of metabolizing estrogens – often termed the "**estrobolome**" – can reactivate conjugated estrogens in the gut, affecting systemic estrogen availability. As women enter menopause and endogenous estrogen levels plummet, these host–microbe interactions undergo significant shifts.

Understanding how the gut and vaginal microbiota change during menopause is crucial because such changes may contribute to or exacerbate menopausal symptoms and conditions. For instance, alterations in gut microbes have been linked with inflammation, metabolic dysfunction, and bone density loss in postmenopausal women. Changes in vaginal microbiota underlie the increased incidence of vaginal atrophy, infections, and urinary tract issues in menopausal women. Appreciating these connections opens the door to **microbiome-targeted interventions for menopausal symptom management**. Probiotics (live beneficial microbes), prebiotics (substrates that nourish beneficial microbes), synbiotics (combination products), and postbiotics (beneficial microbial metabolites or components) are being actively researched for their potential to restore microbial equilibrium and improve health outcomes in menopausal and postmenopausal women.

This report provides a detailed review of the current scientific understanding of the gut and vaginal microbiomes in menopause. We outline the known changes in microbial composition and function during the menopausal transition and postmenopause. We then discuss the role of "biotics" – probiotics, prebiotics, synbiotics, and postbiotics – in managing menopausal symptoms or reducing health

risks, highlighting their mechanisms of action and efficacy as reported in recent studies. We incorporate evidence from diverse global populations and include summaries of key clinical trials that are shaping this emerging field.

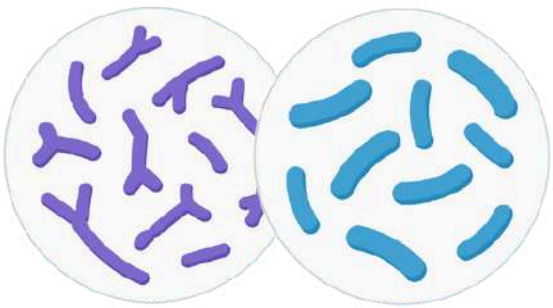
By consolidating these insights, we aim to equip healthcare professionals with up-to-date knowledge of microbiome changes in menopause and to inform on how microbiome-modulating strategies could be integrated into menopausal care.

GUT MICROBIOME ALTERATIONS IN MENOPAUSAL WOMEN

Diversity and Composition

A consistent finding across several studies is that the gut microbiome of women changes significantly after menopause. In general, **microbial diversity** (richness and evenness of species) **tends to decrease postmenopause**, although not all studies agree on the extent of change. A large metagenomic study and other surveys reported that postmenopausal women have a less diverse gut microbiota compared to premenopausal women. Specific compositional shifts have been noted: for example, Firmicutes (a major phylum that includes many beneficial butyrate-producing bacteria like Roseburia) were found to be depleted in postmenopausal women, whereas Bacteroidetes phylum and certain genera (e.g., Tolumonas) were overrepresented. Beneficial genera such as Lactobacillus and Bifidobacterium may decline in relative abundance during perimenopause, while some potentially less favorable groups (e.g., Enterobacteriaceae or other Gram-negative bacteria) become more abundant.

One meta-analysis noted that Lactobacillus and Bifidobacterium counts drop around menopause, concomitant with an increase in Enterobacter counts. **These shifts likely reflect the influence of estrogen loss on the gut ecosystem**.



Intriguingly, the sex-related differences observed in gut microbiota (often termed sexual dimorphism of the microbiome) begin to diminish after menopause. During reproductive age, women typically have higher gut microbiome richness and distinct taxa differences (for instance, lower Prevotella abundance) compared to age-matched men.

After menopause, however, a woman's gut microbiota profile becomes more similar to a man's, as the protective hormonal milieu fades. In other words, some of the female-specific microbiome features are lost, potentially contributing to the convergence in disease risks between older men and women.

Estrogen–Microbiome Interactions

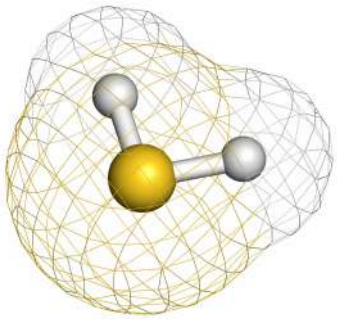
The drop in estrogen at menopause appears to be a key driver of gut microbiome changes, and conversely the gut microbiota can influence circulating estrogen levels.
Many gut bacteria produce the enzyme **β-glucuronidase**, which can deconjugate estrogen metabolites in the intestine, thereby enabling estrogen reabsorption into the bloodstream (part of the enterohepatic circulation).
In premenopausal women, this microbial "***estrobolome***" activity helps maintain estrogen levels.

After menopause, with lower ovarian estrogen production, the role of gut bacteria in hormone metabolism may become even more significant. If the diversity or function of these bacteria is reduced (as suggested by lower microbial gene richness), less estrogen may be reactivated, potentially compounding the estrogen deficiency state. Indeed, research has described the **gut microbiota as an "overall regulator" of estrogen status in menopausal women**.
Lower gut microbial diversity has been associated with lower circulating estrogen and has been linked to various menopause-related disorders.
Encouragingly, one study found that **estrogen replacement therapy can modulate the gut microbiome**, for example by increasing beneficial short-chain fatty acid producers, suggesting a bi-directional feedback.

This interplay is complex: while estrogen shapes the microbiome, the microbiome's composition can also affect how much estrogen (including phytoestrogens from diet) is available to the host.

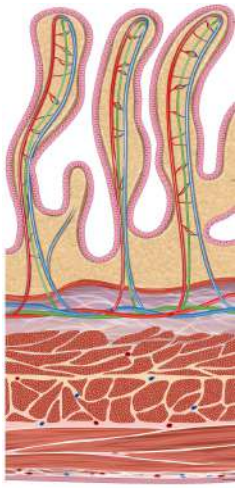
Metabolic and Immune Implications

Changes in the gut microbiome during menopause have been implicated in **metabolic and inflammatory outcomes**. With estrogen loss, women often experience **increases in visceral adiposity, insulin resistance, and unfavorable lipid profiles**.
Gut dysbiosis may exacerbate these trends. For instance, certain bacteria that expand postmenopause (such as some Clostridiales and Bacteroides species) can produce pro-inflammatory metabolites or endotoxins that contribute to systemic inflammation and metabolic dysfunction. A noted example is hydrogen sulfide (H_2S)-producing bacteria (e.g., some Odoribacter species) which were reported to increase in menopausal women alongside higher short-chain fatty acids; moderate increases in SCFAs can be beneficial (supporting energy metabolism, neuronal health, and bone formation), but **excessive H_2S can damage the gut mucosa and promote inflammation**.



Such inflammation is thought to underlie **insulin resistance** and may contribute to a higher risk of conditions like type 2 diabetes in postmenopausal women. Chronic low-grade inflammation ("inflammaging") linked to microbial products (like endotoxins) entering circulation could also affect the

brain and bone. There is speculation that reduced estrogen leads to a **less intact gut epithelial barrier, increasing microbial translocation** (leakage of bacteria or LPS into the bloodstream). This could further drive systemic inflammation, potentially contributing to cognitive decline (through microglial activation in the brain) and bone resorption (through immune activation of osteoclasts).



Bone Health

Emerging evidence connects gut microbiota changes with postmenopausal osteoporosis. The gut microbiome influences calcium and mineral absorption and modulates immune signals that regulate bone turnover. Studies have found that **postmenopausal women with osteoporosis** have a distinct gut microbiome compared to those without osteoporosis. Notably, one genus, Prevotella, particularly Prevotella histicola, was observed at higher abundance in postmenopausal women with healthy bone density versus those with osteoporosis, hinting it may have a bone-protective role. **Prevotella histicola** and other SCFA-producing gut bacteria (like Ruminococcaceae) can promote regulatory immune cells and reduce inflammation, which in turn could limit osteoclastic bone breakdown.
In line with this, **short-chain fatty acids (SCFAs) – especially butyrate – have been identified as important mediators of bone health via the gut**.

Butyrate stimulates regulatory T-cells and directly inhibits osteoclast maturation, thereby protecting bone mass. A reduction in beneficial SCFA producers after menopause might remove this brake on bone loss. This area is under active study, with the goal of manipulating the gut microbiota to prevent osteoporosis in menopausal women.

Cardiovascular and Cognitive Aspects

There are indications that gut microbiome alterations in menopause may also intersect with cardiovascular health and cognitive function. A recent large cohort study of postmenopausal women found correlations between gut microbiome composition, serum sex hormones, and carotid artery plaque, suggesting the microbiome might influence **atherosclerosis risk** in this population. Specifically, higher estrogen levels were associated with greater gut bacterial diversity and with certain taxa (e.g., Alistipes, Collinsella, and class Erysipelotrichia), which in turn correlated with lower plaque burden. However, confounding factors (like underlying health conditions) complicate interpretation.

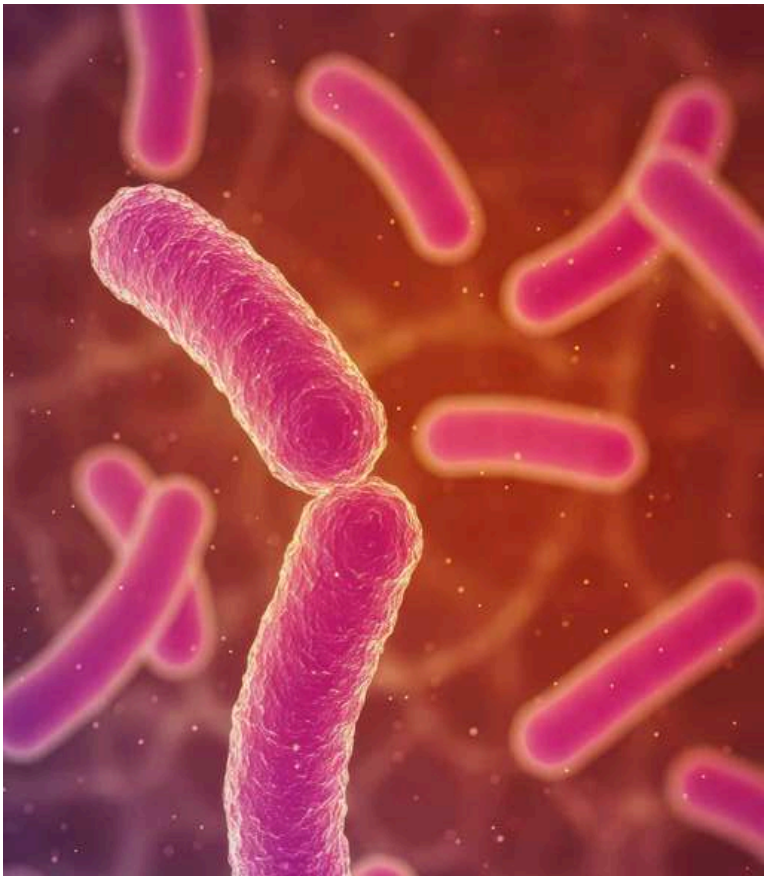
Regarding the brain, menopause is linked to increased **risk of cognitive decline and Alzheimer's disease**. Some researchers propose a **gut-brain connection**: menopausal gut dysbiosis could promote neuroinflammation via circulating microbial metabolites. For example, lower estrogen allows more LPS from gut bacteria into circulation, which can trigger inflammation that affects the brain vasculature and neurons.
While human data are limited, mouse models of menopause (ovariectomized

mice) have shown that manipulating the gut microbiome can **ameliorate menopausal cognitive deficits**.

In summary, the gut microbiome of menopausal women often shows reduced diversity and a shift in composition – potentially less friendly bacteria and more pro-inflammatory species – compared to premenopausal microbiomes. These changes likely result from and contribute to the low-estrogen environment of menopause, forming a feedback loop that can impact metabolism, immunity, and tissue health. However, there is individual variability, and factors such as diet, geography, medication use, and genetics also modulate the gut microbiome.
Notably, diet differences worldwide mean that menopausal microbiome patterns are not uniform globally: e.g., high-fiber diets in some non-Western populations may preserve greater microbial diversity in midlife women than typically seen in Western diets.
Such global insights remind us that context matters when evaluating microbiome changes.

VAGINAL MICROBIOME ALTERATIONS IN MENOPAUSAL WOMEN

The vaginal microbiome undergoes one of the most dramatic microbiological shifts in a woman's life during the transition to menopause.



In **premenopausal** women (especially of reproductive age), the vagina is usually dominated by Lactobacillus species – such as Lactobacillus crispatus, L. iners, L. jensenii, or L. gasseri – which maintain an acidic environment (pH ~3.5–4.5) by producing lactic acid. This acidic, lactobacilli-rich environment protects against pathogenic bacteria, yeast, and sexually transmitted infections.

Estrogen plays a critical role in this ecosystem by promoting thick vaginal epithelium and glycogen deposition; glycogen released from shed epithelial cells is fermented by Lactobacilli into lactic acid.

After menopause, with the steep decline in circulating estrogens (estradiol levels falling from >100 pg/mL in reproductive age to <10 pg/mL postmenopause), the vaginal environment changes markedly. Lactobacillus populations drop in most women. The once-dominant lactobacilli may be partially or almost completely replaced by a more diverse assortment of anaerobic and facultative bacteria. This shift is sometimes termed the **"menopause microbiome paradox": there is a decrease in Lactobacillus dominance but an increase in overall microbial richness in the vagina**. Essentially, no single genus clearly dominates the postmenopausal vaginal microbiome; instead, a variety of organisms co-exist, often at lower levels. Commonly reported genera in postmenopausal vaginal communities include Gardnerella, Prevotella, Atopobium, Sneathia, Peptoniphilus, Anaerococcus, Peptostreptococcus, Dialister, and others, many of which are anaerobes associated with conditions like bacterial vaginosis (BV). Additionally, organisms originating from the skin, gut, or urinary tract (such as Staphylococcus, Streptococcus, Enterococcus, Corynebacterium, and Escherichia coli) are more frequently detected in the vaginal samples of postmenopausal women.

The vaginal pH in these women rises to neutral or slightly alkaline levels (pH 6–7+), largely because of the diminished lactic acid production without abundant lactobacilli. In fact, measurements show that vaginal lactic acid content plummets postmenopause, reflecting the **loss of lactobacillary metabolism** (one study noted vaginal fluid lactic acid composition dropped from ~98% in premenopausal women to ~94% postmenopause, indicating a significant absolute decrease).

Clinical Consequences

The implications of these vaginal microbiome changes are significant for menopausal women's genitourinary health. With thinning of the vaginal epithelium and loss of acidity (a condition often termed vulvovaginal atrophy as part of the genitourinary syndrome of menopause, GSM), women commonly experience symptoms like **vaginal dryness, irritation, and dyspareunia** (painful intercourse). The altered microbiome likely contributes to or exacerbates these symptoms. For instance, studies have found that women with non-Lactobacillus-dominated vaginal microbiota tend to report more severe vaginal dryness and pain.

The presence of anaerobes like Prevotella and Gardnerella in postmenopausal vaginal communities, even at modest levels, can trigger immune responses and low-grade inflammation in vaginal tissues. This can present as **chronic vaginitis or irritation**. Moreover, the loss of Lactobacillus protection predisposes postmenopausal women to **recurrent urogenital infections**. There is an observed increase in incidence of **bacterial vaginosis** (though true BV is somewhat less common in older women than younger due to lower overall bacterial load), **vaginal candidiasis**, and notably **urinary tract infections** (UTIs) after menopause. Without an acidic vaginal environment and Lactobacilli to produce hydrogen peroxide and bacteriocins, pathogens can colonize more easily. Fecal bacteria like E. coli migrating to the vagina and urethra can cause UTIs, and the postmenopausal vagina may serve as a reservoir for such organisms due to the diminished lactobacillar barrier.

Approximately one-third of women over 50 experience some form of GSM-related complications, including UTIs and urinary urgency, which have been linked to the vaginal dysbiosis of menopause. Indeed, studies indicate a correlation between the rise of non-lactobacilli bacteria in the vagina and symptoms like urinary urgency and incontinence in this population.

Another health consideration is the potential link between the menopausal vaginal microbiome and gynecologic cancers. An interesting finding by Walsh et al. noted that postmenopausal women with **endometrial cancer** had significantly more diverse vaginal microbiomes than healthy postmenopausal controls. In particular, the presence of bacteria like Porphyromonas somerae and Atopobium vaginae was higher in women with endometrial cancer, suggesting that the **pro-inflammatory state of a diverse, lactobacillus-poor vaginal microbiome might contribute to carcinogenic processes in the uterus**. While causality is unproven, it underscores how a stable Lactobacillus-dominant microbiome might normally help mitigate some risks, whereas its loss could have systemic implications.

Global and Racial Factors

It is worth noting that vaginal microbiome composition can vary by ethnicity and geography even before menopause, which may influence menopausal patterns. For example, studies have shown that some women of African descent are more likely to have non-Lactobacillus-dominant vaginal microbiota even during reproductive years, which could affect their postmenopausal microbiome trajectory. In contrast, women of East Asian descent more commonly maintain lactobacilli dominance longer. Such differences, along with local hygienic practices and sexual behaviors, mean that the "typical" postmenopausal vaginal microbiome is not identical worldwide. Nonetheless, the loss of estrogen influence universally tends to reduce lactobacilli and increase diversity, albeit the specific taxa filling that void may differ across populations.

Hormone Therapy Effects

Menopausal hormone therapy (systemic or local estrogen) can partially reverse these microbial changes. Estrogen treatment has been shown to lower vaginal pH and increase Lactobacillus colonization in postmenopausal women.

Clinically, **low-dose vaginal estrogen** is a standard treatment for GSM, often restoring a lactobacilli-predominant flora similar to a premenopausal state and thereby improving symptoms of dryness and reducing recurrent UTIs.

In essence, estrogen "re-feeds" the Lactobacillus by providing glycogen substrate and strengthening the mucosal barrier. However, not all women can or choose to use estrogen, which is why **non-hormonal means** of modulating the vaginal microbiome (like probiotics or prebiotic vaginal gels) are being explored.

In summary, menopause leads to a profound shift from a Lactobacillus-rich, acidic vaginal ecosystem to a more diverse, alkaline, and less stable microbial community. This change underlies many of the genitourinary symptoms and risks (atrophic vaginitis, infections, GSM) seen in postmenopausal women. Maintaining or restoring a healthy vaginal microbiome is thus a key goal for menopausal health management. The next sections will discuss how various "biotic" interventions aim to do exactly that – as well as improve gut microbiota health – to support women through menopause.

MICROBIOME-TARGETED THERAPIES FOR MENOPAUSAL HEALTH

Given the connections between the microbiome and menopausal well-being, researchers are actively investigating interventions that can favorably modulate the gut and vaginal microbiota.

These include **probiotics** (beneficial live microorganisms), **prebiotics** (indigestible fibers or substrates that promote growth of beneficial microbes), **synbiotics** (combined probiotic + prebiotic formulations), and **postbiotics** (bioactive metabolites or inactivated microbial products that confer health benefits).

Such therapies are largely non-hormonal and thus appealing as safe complements or alternatives to HRT. Below we summarize the role and mechanisms of each category ("all 'biotics'") in the context of menopause, along with key findings from recent studies.

Probiotics in Menopausal Women

Probiotics can beneficially impact the host by several mechanisms that are relevant to menopause-related conditions. In the gut, probiotic bacteria (commonly Lactobacillus and Bifidobacterium species, among others) can:

- improve gut barrier function
- modulate immune responses (tilting toward anti-inflammatory profiles)
- outcompete pathogenic microbes
- produce helpful metabolites like short-chain fatty acids (SCFAs) and neurotransmitter precursors.

One specific mechanism pertinent to menopausal women is the ability of certain probiotic strains to produce β-glucuronidase or otherwise enhance the **estrobolome** function. By doing so, they help **deconjugate and recycle estrogens in the colon**. A recent randomized controlled trial demonstrated that a probiotic formula containing a high β-glucuronidase-active strain (Levilactobacillus brevis KABP052) was able to maintain serum estrogen levels in peri- and postmenopausal women over 12 weeks, whereas estrogen levels (estradiol and estrone) significantly declined in the placebo group. In that trial, women taking the probiotic ended with higher estradiol levels on average (≈31.6 pg/mL) vs. placebo (≈25.1 pg/mL), indicating that **probiotics can indeed augment systemic estrogen availability during menopause**. This suggests a novel approach to mitigating estrogen deficiency symptoms and risks via manipulating gut microbes.

Probiotics also produce **SCFAs** like butyrate, propionate, and acetate during fermentation of fibers in the colon. SCFAs have far-reaching beneficial effects.

- Butyrate, for example, is known to improve metabolic health by enhancing insulin sensitivity and lipid metabolism, as well as exerting anti-inflammatory effects.
- In postmenopausal models, butyrate supplementation has been shown to activate pathways (like PPARα) that reduce hepatic fat accumulation and inflammation.
- SCFAs also play a role in bone health by **inhibiting bone resorption**; probiotics that increase SCFA production in the gut can indirectly promote bone density.
- Additionally, certain probiotic strains can produce or modulate levels of neurotransmitters (GABA, serotonin) and influence the gut-brain axis – pertinent to mood and cognitive symptoms of menopause.

Probiotics for Gut/Metabolic Health

A number of studies have explored probiotic use to address metabolic and gastrointestinal changes in menopause. In animal models of estrogen deficiency (ovariectomized rodents), probiotics have been found to alleviate weight gain, improve lipid profiles, and reduce systemic inflammation. For instance, supplementation with Bifidobacterium longum 15M1, as well as a combination of Lactobacillus plantarum 30M5 with a soy isoflavone-rich diet, improved cholesterol and triglyceride levels and reduced liver fat accumulation in menopausal model animals.

These findings highlight the synergy of probiotics with diet (here, probiotics plus phytoestrogens) in improving menopausal metabolic disturbances.

In human trials, there is encouraging evidence that probiotics can modestly improve cardiometabolic markers in postmenopausal women.
A **systematic review in 2023** noted some trials where probiotic supplementation led to reduced total cholesterol, LDL cholesterol, and markers of inflammation in postmenopausal participants.
One **triple-blind RCT** in Iran (2023) evaluated a 6-week course of a multi-strain probiotic in 84 postmenopausal women and found significant improvements in physical and psychological menopausal symptoms in the probiotic group compared to placebo. Women taking probiotics reported fewer hot flashes, less fatigue, and better mood (as measured by Menopausal Rating Scale and DASS-21 anxiety/depression scores) by the end of the trial. This suggests that altering gut flora can have rapid effects on well-being, potentially via the gut-brain axis and immune modulation.
Another pilot study observed that probiotic yogurt consumption for 8 weeks in postmenopausal women improved anxiety and perceived stress levels, as well as sleep quality, supporting the idea that gut microbes can influence neuropsychological symptoms during menopause.

Probiotics for bone health

Bone health has been a major focus for probiotic interventions in postmenopausal women. Several RCTs have tested whether probiotics can slow bone loss that accelerates after menopause.

Results have been mixed, but the overall evidence is trending positive. A landmark trial in Sweden (2018) found that Lactobacillus reuteri ATCC PTA 6475 supplementation for 12 months **significantly reduced bone density loss** in older women (75–80 years old) with low bone mass. However, a more recent trial in **early postmenopausal women** (within 5 years of menopause) did not observe a significant benefit of the same probiotic over 2 years, indicating that **efficacy may depend on the population or timing**.

To clarify these findings, a 2024 meta-analysis compiled data from 12 RCTs (1,183 postmenopausal women in total) on probiotics and bone outcomes. The meta-analysis concluded that **probiotic supplementation was associated with a significantly smaller decline in bone mineral density (BMD)** at the lumbar spine and hip, compared to controls. The improvements were more pronounced in women with osteopenia (moderate bone loss) than in those with established osteoporosis. Probiotics also led to **reductions in bone resorption markers** like C-terminal telopeptide (CTX) in these trials. These results are quite promising – they suggest that probiotics (or the shifts in gut microbiota they induce) can create a more **bone-friendly systemic environment**, possibly by enhancing nutrient absorption (calcium, magnesium), producing SCFAs that inhibit osteoclasts, and reducing inflammation that would otherwise accelerate bone turnover.

Probiotics for Vaginal/Urogenital Health

Probiotic approaches to restore a healthy vaginal microbiome have been investigated for decades, primarily in the context of

preventing or treating infections (like BV or UTIs) in younger women. In postmenopausal women, the goal is often to **re-establish Lactobacillus dominance** to protect the vaginal and urinary tract. Direct vaginal administration of probiotics (e.g. Lactobacillus pessaries) has been tried, but oral probiotics may be preferable for ease and regulatory reasons. Remarkably, specific orally administered strains have been shown to colonize the vaginal tract secondarily. A well-known example is the combination of Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14, which has been studied in several trials. In a randomized, placebo-controlled trial involving postmenopausal women, daily oral intake of GR-1/RC-14 for 14 days significantly improved vaginal microbiota composition – 60% of women in the probiotic group achieved a healthier Nugent score (indicative of Lactobacillus predominance) compared to only 16% in the placebo group. This demonstrates that oral probiotics can indeed transit and influence the vaginal niche, likely by gut-vagina migration or by modifying the intestinal reservoir of microbes that eventually reach the vagina. Another study in younger women (ages 18–45) found that an oral Lactobacillus paracasei strain (LPC-S01) significantly reduced vaginal Gardnerella (a BV-associated genus) and increased Lactobacillus gasseri presence, suggesting probiotics can push the vaginal microbiome toward eubiosis (healthy balance). Extrapolated to menopausal women, such shifts could help counteract the postmenopausal rise in pathogenic flora. Indeed, clinicians are considering probiotics as part of managing GSM and recurrent UTIs in menopausal patients. Some trials **combine estrogen therapy with probiotics** to see if dual therapy is superior to estrogen alone in restoring vaginal health; results so far indicate added benefit of probiotics in improving vaginal pH and microflora, though larger studies are ongoing.

Another example concerns supplementation with Lactiplantibacillus plantarum PBS067, Bifidobacterium animalis subsp. lactis BL050, and Lacticaseibacillus rhamnosus LRH020. A 2024 study demonstrated that this supplementation is safe and well tolerated and improves vaginal health in postmenopausal women by reducing inflammation and dysbiosis, lowering pH, and enhancing microbiota balance.

Beyond local effects, **maintaining a Lactobacillus-rich vaginal environment via probiotics could have systemic implications** too. Vaginal lactobacilli have been found to decrease in parallel with estrogen, but when present, they can reduce the risk of urinary infections by producing lactic acid and perhaps even by ascending into the bladder to inhibit uropathogens. Probiotic strains like L. crispatus (available as vaginal capsules in some products) have shown about a **50% reduction in UTI recurrence** in preliminary trials among postmenopausal women, rivaling low-dose antibiotics. Therefore, probiotic therapy offers a promising strategy to manage the urogenital sequelae of menopause, especially for women who cannot use estrogen.
For example, supplementation with L. plantarum KABP™ 051, L. brevis KABP™ 052, and P. acidilactici KABP™ 021 has proven to be safe and effective in supporting hormonal balance and reducing menopausal symptoms. The probiotic acts by modulating the gut–estrogen axis, promoting the recycling of endogenous estrogens, and counteracting inflammation and dysbiosis. Clinical results show tangible benefits on both physical and psychological symptoms, with a positive impact on the quality of life of peri- and postmenopausal women.

The probiotic strains under study for menopausal health are diverse. Lactobacilli (such as L. rhamnosus, L. reuteri, L. casei, L. acidophilus, L. plantarum, L. gasseri) and Bifidobacteria (B. longum, B. lactis, B. bifidum) are common, given their long history of safe use and presence in healthy microbiomes.
Some emerging candidates include next-generation probiotics like Akkermansia muciniphila or Clostridium butyricum, which are being tested for metabolic benefits.

Overall, probiotics are considered safe for most populations, including older adults, with gastrointestinal mild upset being the most noted side effect in some trials. They are generally well-tolerated, and regulatory agencies classify many as GRAS (Generally Recognized as Safe).
One must still exercise caution in immunocompromised individuals, but in the context of menopause, probiotics present a **low-risk intervention**.

The challenge lies in identifying the most effective strains or combinations and optimal dosing regimens for specific goals (be it symptom relief, bone preservation, or infection prevention).

Prebiotics in Menopausal Women

Prebiotics are typically fermentable fibers or other compounds (such as certain oligosaccharides, resistant starches, or polyphenols) that humans cannot digest but our gut bacteria can. **By selectively feeding beneficial microbes, prebiotics can help reshape the microbiome in favorable ways.**

Common prebiotics include inulin and fructooligosaccharides (FOS), galactooligosaccharides (GOS), arabinoxylan, and others. In menopausal women, prebiotics could be used to bolster the growth of health-associated bacteria that may have dwindled with age or hormonal changes.

Metabolic Effects and Weight Management

Prebiotic fiber supplementation has known benefits on metabolism that could counteract menopausal weight gain and dyslipidemia. For example, **inulin-type fructans can promote satiety, improve glycemic control, and alter gut peptide release**. They also increase Bifidobacterium and Lactobacillus numbers in the colon while increasing SCFA production (acetate, propionate, butyrate). These SCFAs, as mentioned, help regulate lipid metabolism and reduce inflammation. An alkaline fermentation environment (due to SCFAs) also improves mineral absorption – critical for **bone health** – and prevents overgrowth of certain harmful bacteria.

Studies in postmenopausal models have shown that inulin supplementation resulted in **enhanced calcium absorption and bone mineralization**, as well as shifts in the gut microbiota that correlate with better metabolic profiles. In an ovariectomized rat model, a diet enriched with inulin not only increased beneficial gut bacteria but also was associated with greater bone density and strength compared to controls, presumably by improving calcium uptake and producing SCFAs that inhibit bone resorption.

Clinically, while specific trials of prebiotics alone in postmenopausal women are somewhat limited, it is well established that high-fiber diets tend to result in **more diverse and resilient gut microbiomes**.

Epidemiologically, menopausal women with higher dietary fiber intake have lower rates of weight gain and possibly fewer hot flashes (one hypothesis is that a high-fiber diet stabilizes blood sugar and insulin, which in turn might reduce vasomotor symptoms).

Prebiotics and Estrogen Modulation

An interesting aspect of prebiotics is their interplay with **phytoestrogens**

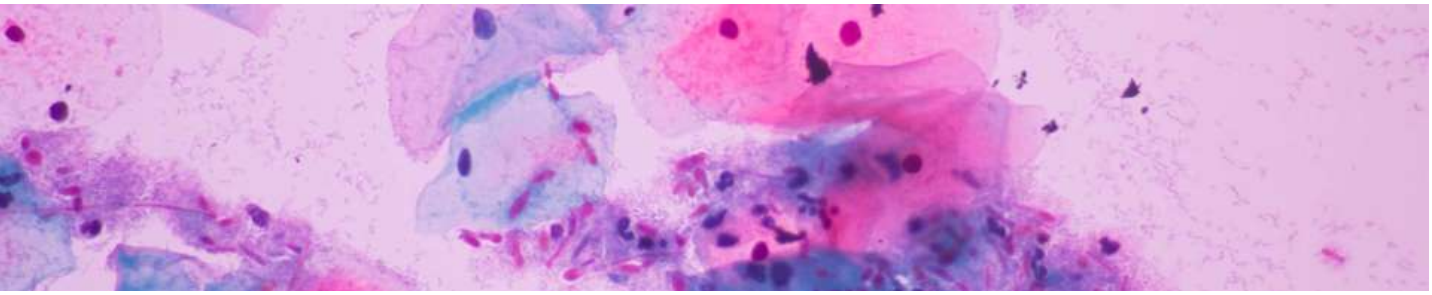
– plant-derived compounds with estrogen-like activity. Many phytoestrogens (such as soy isoflavones, lignans from flaxseed, or red clover isoflavones) **require activation by gut bacteria to exert their effects**. For instance, the isoflavone daidzein (from soy or red clover) can be converted by gut microbes into equol, a metabolite that more potently binds estrogen receptors.

Not all individuals have the gut bacteria capable of this conversion (only ~30–50% of people are "equol-producers"). Prebiotic interventions that **encourage equol-producing bacteria** could enhance the efficacy of dietary phytoestrogens for managing menopausal symptoms.

Research has found that certain fiber types or polyphenols can enrich Slackia and Eggerthella species that are involved in equol production. In animal studies, supplementation with a red clover extract (rich in isoflavones) along with probiotics led to increased equol levels and improved lipid profiles and estrogenic activity in OVX rats. This suggests a synbiotic concept (discussed below) where prebiotics (including phytoestrogens themselves, acting as substrates) can amplify beneficial microbial metabolism of compounds relevant to menopause.

Prebiotics for Vaginal Health

While less studied than probiotics, the concept of prebiotics for the vaginal microbiome exists. These could be substances **applied intravaginally to selectively feed Lactobacilli**. For example, glycogen or specific polysaccharides in gels have been explored as a way to **lower vaginal pH** by fueling lactic acid production. Some over-the-counter products for vaginal health contain FOS or lactulose intended to **promote lactobacillar growth**. There is some evidence that such prebiotic vaginal gels can modestly increase Lactobacillus counts and improve symptoms of **dryness or odor**, but large trials are lacking. Oral prebiotics might indirectly benefit the vaginal flora too, by overall boosting Lactobacillus in the gut which can seed the vagina.



It's important to highlight that natural sources of prebiotics (fruits, vegetables, whole grains, legumes) are a cornerstone of dietary guidelines for midlife and older women.
A global observation is that women in regions with traditionally high-fiber diets (e.g., certain African or Asian diets) tend to maintain more Lactobacilli in both gut and vaginal microbiomes into older age than women on low-fiber Western diets. This implies that part of the microbiome changes we attribute to "menopause" might actually be mitigated by diet. Therefore, recommending a fiber-rich diet (containing natural prebiotics) is a fundamental and low-cost strategy to support a healthy microbiome during menopause.

In summary, **prebiotics act by nourishing beneficial microbes and enhancing their metabolic output**. In menopausal women, prebiotic supplementation (or a high-fiber diet) can improve gut microbiota composition, increase SCFA production (benefiting metabolic and bone health), and possibly assist in maintaining a healthier estrogen balance and vaginal environment. Prebiotics are very safe (they are essentially food components), though gastrointestinal bloating can occur in some individuals when first increasing fiber intake.

Synbiotics in Menopausal Women

Synbiotics are products that **combine probiotics and prebiotics in a synergistic fashion**, ideally such that the prebiotic specifically supports the probiotic strains included.
The goal is to enhance the survival and activity of the probiotic in the gut and to provide an immediate substrate for fermentation.

In the context of menopause, synbiotics can tackle multiple targets – for example, providing a probiotic strain known to perform a desired function (like producing butyrate or β-glucuronidase for estrogen recycling) along with a prebiotic that that strain can readily ferment. This one-two punch may yield greater benefits than either component alone. Additionally, synbiotics may more robustly shift the overall microbial community.

Metabolic Health

A synbiotic yogurt (containing Lactobacillus acidophilus plus inulin) was tested in postmenopausal women with metabolic syndrome in one study, and it significantly **improved insulin resistance and lipid profiles** compared to placebo yogurt. The women saw reductions in fasting insulin and triglycerides after 8 weeks of daily synbiotic yogurt, highlighting a combined effect on metabolism.

Body Composition

Another trial in overweight postmenopausal women found that a synbiotic (multi-strain probiotics with a FOS/inulin blend) led to a significant **reduction in visceral fat mass and a decrease in markers**

of inflammation over 12 weeks, as compared to placebo. This suggests synbiotics might aid weight management and reduce central obesity, a common issue after menopause.

Bone Health

A major ongoing study is the OsteoPreP trial, a 12-month randomized controlled trial in 160 early postmenopausal women, designed specifically to evaluate a synbiotic's effects on bone and metabolic health. The synbiotic being tested (called WBF-038) contains five probiotic strains (Akkermansia muciniphila, Anaerobutyricum hallii, Clostridium butyricum, Clostridium beijerinckii, and Bifidobacterium infantis) along with a prebiotic fiber (chicory inulin). These strains were chosen for their capacity to produce SCFAs (especially butyrate) and influence bone-immune signaling. The primary outcome is the change in distal tibia bone density after 12 months, measured by high-resolution CT, and secondary outcomes include markers of glucose metabolism, inflammation, cognitive function, and the gut microbiota composition itself.
The trial is double-blind and placebo-controlled. While results are pending (the trial is registered as NCT05348694 and expected to complete in 2025), the design reflects the high interest in synbiotics to preserve bone mass and metabolic health post-menopause. The authors note that short-term probiotic or synbiotic trials of 6–12 weeks showed only small effects, which might be why a full 12-month intervention was deemed necessary to observe clinically meaningful bone outcomes. The outcome of OsteoPreP could pave the way for synbiotics as a **preventive strategy against osteoporosis** in postmenopausal women.

Menopausal Symptoms

An industry-sponsored trial in Europe (sponsored by AB-Biotics) is examining a synbiotic formula in peri- and postmenopausal women for improving quality of life. This trial (NCT06604234) uses a multi-strain probiotic blend plus a prebiotic, and measures changes in validated menopause-specific quality of life scales (such as the Cervantes QoL scale and Menopause Rating Scale) over 3 months.
As of early 2025, this study has completed enrollment of ~244 women and results are awaited. The fact that large trials are being conducted signals optimism that

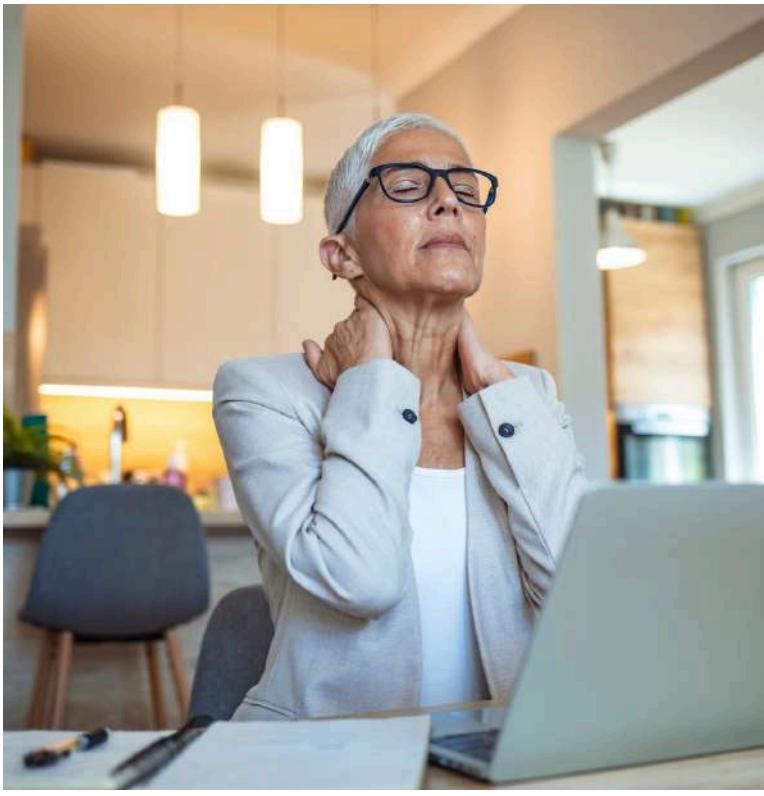
synbiotics could become part of routine menopause care if proven effective.

The hypothesized **advantage of synbiotics** is reflected in subgroup analyses of studies: for instance, a trial that gave L. plantarum with a soy isoflavone prebiotic saw a greater improvement in lipid metabolism than either component alone. Also, in bone studies, combining specific strains that each have different targets (some improving calcium absorption, others reducing inflammation) with a fiber that supports those strains could yield multifaceted benefits.

In terms of safety, synbiotics share the same **safety profile** as their constituent probiotics and prebiotics. Gastrointestinal symptoms (bloating, transient flatulence) can occur initially due to increased fiber fermentation, but these typically subside. Hydration and gradually increasing dose can mitigate discomfort.

Overall, synbiotics represent a **holistic approach** – they attempt to reshape the microbiome environment more comprehensively than single-agent interventions.

For menopausal women dealing with simultaneous issues (weight gain, high cholesterol, bone loss, GI irregularity), synbiotics could offer **broad-spectrum improvements**.
More research is needed to pinpoint optimal combinations and to confirm benefits in large diverse populations, but current trials are an important step in that direction.



Postbiotics in Menopausal Women

Postbiotics are a newer concept, referring to **functional substances generated by microbes that can have direct beneficial effects on the host**.

This term can encompass **metabolites** like SCFAs, vitamins, peptides (e.g., bacteriocins), polysaccharide compounds from bacterial cell walls, or even whole **inactivated microbial cells** (sometimes called paraprobiotics).

The idea is to **harness the beneficial effects of probiotics without needing live organisms** – which can be advantageous in terms of stability, safety in immunocompromised patients, and precise dosing of active molecules.

- **Short-Chain Fatty Acids.** SCFAs such as butyrate, propionate, and acetate are classic postbiotics. As discussed, they play a key role in metabolic health, immunity, and bone metabolism. There is growing interest in developing SCFA-based therapies (like oral butyrate or resistant starch that releases butyrate in the colon) for conditions including osteoporosis and cognitive decline. In one study, supplementing butyric acid in diet was shown to restore certain metabolic pathways and reduce inflammation in a menopause model. However, SCFAs have a strong odor and are tricky to formulate, so stimulating their production via pre/probiotics is often preferred.

- **Equol and Other Phytoestrogen Metabolites.** As mentioned, equol is a microbial metabolite of the soy isoflavone daidzein. Equol selectively binds estrogen receptor β and has been associated with **reduction of menopausal symptoms** (like hot flash frequency) and improved bone markers in some studies. It can be considered a postbiotic since it is produced by gut bacteria. Interestingly, equol itself has been developed as a **supplement** (derived from fermentation processes); a few clinical trials showed that taking equol (produced ex vivo by bacteria and delivered as a pill) can alleviate hot flashes and muscle pain in menopausal women who are not equol-producers naturally. This is a direct use of a postbiotic compound to **mimic a hormonal effect.**

- **Vaginal Postbiotics.** In the vaginal context, lactic acid is a key postbiotic. Some vaginal gels and suppositories contain lactic acid or lactate buffers to lower vaginal pH in women with recurrent BV or after menopause. By acidifying the vagina, these products aim to replicate the natural defense that lactobacilli normally provide. Lactic acid has antimicrobial activity against BV-associated bacteria and pathogens. Another example is hydrogen peroxide (H_2O_2), a chemical produced by some Lactobacillus species; while not typically given exogenously, its presence (or lack thereof) is an important postbiotic factor in vaginal ecology.

- **Heat-Killed Probiotics (Paraprobiotics).** Even non-viable microbes can confer benefits by interacting with the immune system in the gut. Lactobacillus gasseri CP2305 is a notable example: this strain has been studied extensively in Japan for stress and gut health, and recently for menopause. CP2305 is often administered in a heat-killed form (so the cells are dead but intact). In a double-blind trial in middle-aged women, daily ingestion of paraprobiotic CP2305 for 16 weeks significantly relieved menopausal symptoms compared to placebo. Specifically, CP2305 led to **improvements in both psychological symptoms** (anxiety, depressive mood) **and physical/vasomotor symptoms** (hot flashes, dizziness) as measured by standardized scales (SMI and Greene Climacteric Scale). Notably, 75% of women in the CP2305 group experienced overall symptom relief vs. 55% in the placebo group, and improvements in vasomotor scores (hot flashes) were significant. This suggests that even without live colonization, components of L. gasseri (such as its cell wall peptidoglycans or metabolites present in the preparation) can

modulate the gut-brain axis and HPA-HPG axis interplay to ease menopausal complaints.

The exact mechanism is still being unraveled, but CP2305 intake was associated with changes in gut microbiota composition and reduced markers of stress in other studies, indicating an impact on systemic physiology.

- **Other Metabolites.** There are many other microbial metabolites under the umbrella of postbiotics that could be relevant.
  - **Polyamines** (like spermidine) produced by gut bacteria have anti-aging properties and may help cellular health.
  - **Exopolysaccharides** from certain Lactobacilli can have immune-calming effects.
  - **Vitamins** (like vitamin K2, B-vitamins) made by gut microbes are also technically postbiotics that contribute to host health (vitamin K2 is important for bone and cardiovascular health and is produced by some gut bacteria).

Postbiotics offer a **targeted approach** – instead of trying to change the entire microbiome, one can deliver the beneficial molecules directly. This could be useful in patients where probiotics might not colonize effectively or where there's concern about infection risk from live bacteria (for instance, in severely immunosuppressed individuals).
For menopausal women, postbiotic supplements (like equol, SCFAs, or specific bacterial metabolites) could become part of nutraceutical regimens. Some companies are already marketing "menopause supplements" that contain equol or probiotic lysates.

Research is still early, but the proof-of-concept from trials like the CP2305 study is exciting. It hints that microbial products can **influence neuroendocrine pathways** – in this case, likely through the gut-brain axis reducing stress responses and perhaps interacting with estrogen receptor pathways indirectly. Moreover, postbiotics could complement probiotics: for example, one might take a probiotic and also take a postbiotic like butyrate or equol to get immediate effect while waiting for the probiotic to alter the gut environment.

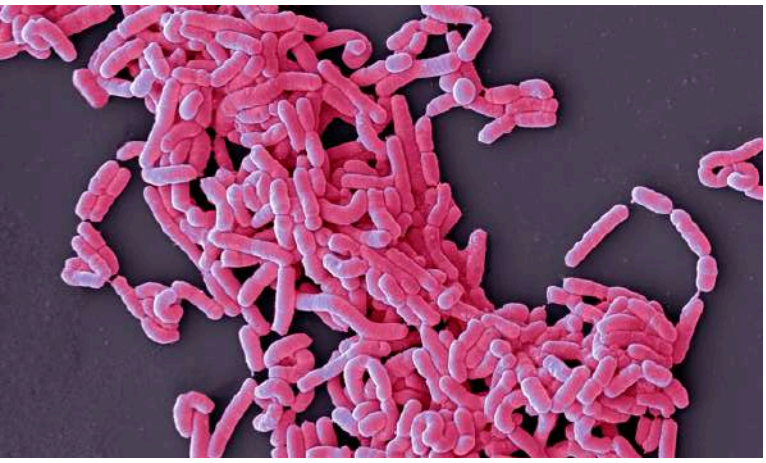
In conclusion, postbiotics represent an emerging frontier in managing menopausal health. They encapsulate the beneficial outputs of a healthy microbiome and can be delivered in a controlled dose. While more human trials are needed to establish efficacy for specific outcomes (be it hot flash frequency, bone density, or vaginal health), the approach is promising.
As our understanding of the microbiome deepens, we may identify novel postbiotic compounds that specifically target menopausal symptom pathways (for instance, a metabolite that could act on thermoregulatory centers to reduce hot flashes).

EVIDENCE FROM KEY CLINICAL TRIALS

To illustrate the therapeutic potential of microbiome modulation in menopause, we summarize below several notable clinical trials (both completed and ongoing) that have investigated probiotics, synbiotics, or related interventions in peri- or postmenopausal women.

Vaginal Microbiome Restoration
(Petricevic et al., 2008)

In a pioneering double-blind RCT, Petricevic and colleagues tested oral Lactobacillus rhamnosus GR-1 and L. reuteri RC-14 in 40 postmenopausal women with disturbed vaginal flora. After 14 days, the probiotic group showed significantly improved Nugent scores (indicative of more Lactobacillus and fewer anaerobes): 60% of women had their vaginal flora grade improve by ≥2 steps, compared to only 16% improvement in the placebo group. This established proof-of-concept that oral probiotics can beneficially alter the vaginal microbiome in menopausal women, reducing the risk of BV and potentially UTIs.



Improvement of vaginal health
(Vicariotto et al., 2024)

The clinical study evaluated the efficacy of an oral supplement containing Lactiplantibacillus plantarum PBS067, Bifidobacterium animalis subsp. lactis BL050, and Lacticaseibacillus rhamnosus LRH020 in postmenopausal women. Administered for 28 days to 50 participants, the treatment led to a significant improvement in vaginal health: the Vaginal Health Index increased by 50%, with greater elasticity, secretions, and hydration. Vaginal pH decreased, reducing the risk of infections, while inflammatory markers (IL-6, TNF-α, IL-1β) showed relevant reductions. Microbiota analysis revealed an increase in lactobacilli and a decrease in pathogens such as Staphylococcus, confirming the safety and efficacy of the probiotic.

Menopausal Symptom Relief
(Ayubi et al., 2025)

This recent triple-blind RCT in Iran enrolled 84 postmenopausal women to receive either a multi-strain probiotic capsule or placebo daily for 6 weeks. Outcomes were measured with the Menopause Rating Scale (MRS) and Depression Anxiety Stress Scales. The probiotic group experienced significantly greater improvements in psychological symptoms (reduced depression, anxiety, stress scores) and in somatic and urogenital symptoms of menopause by week 6. Notably, hot flashes, insomnia, and urinary symptoms all improved more in the probiotic group than placebo, suggesting a broad beneficial impact on quality of life.

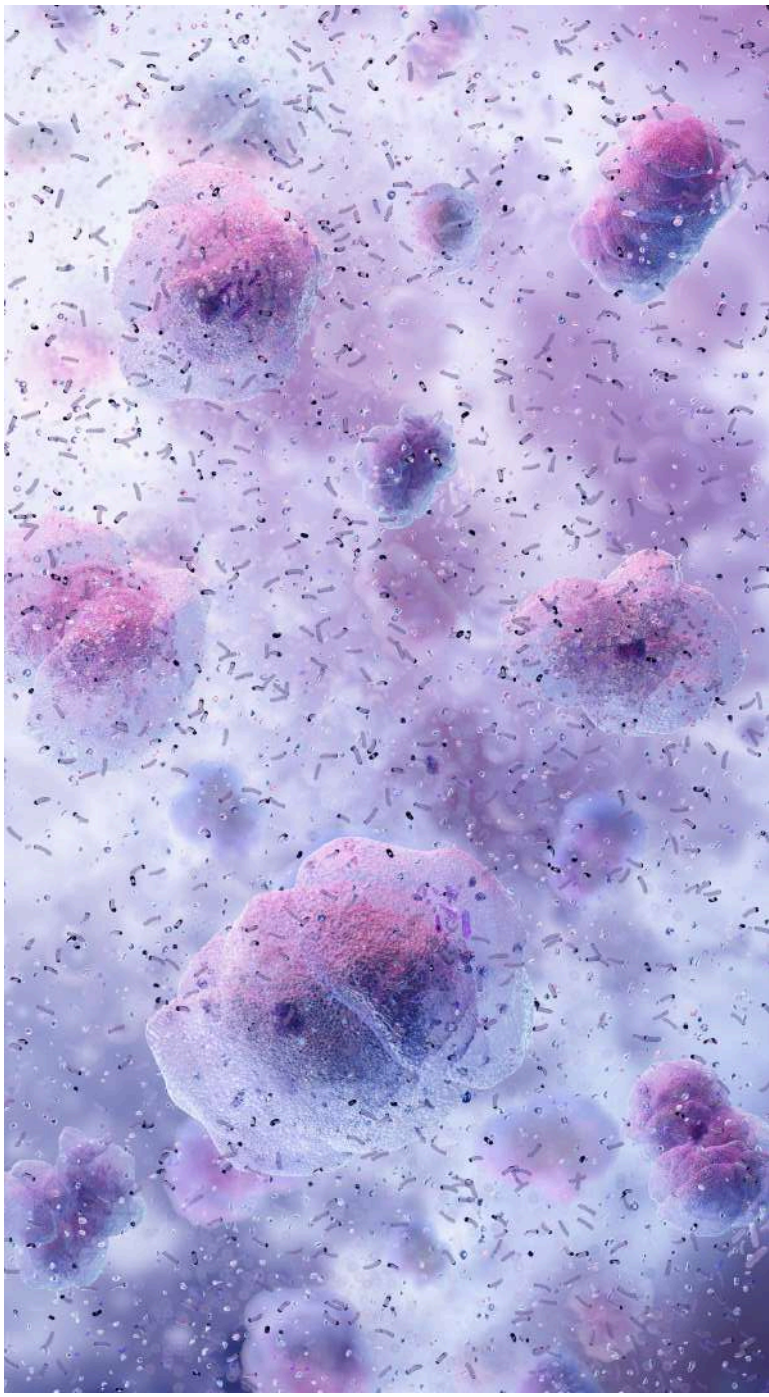
This trial provides level-1 evidence that probiotics can alleviate menopause-related symptoms, complementing hormonal or other therapies.

Estrogen Modulation Trial
(Honda et al., 2024)

As discussed earlier, Honda et al. conducted a randomized placebo-controlled trial in Japan using a probiotic with high β-glucuronidase activity (L. brevis KABP052, combined with 3 other lactobacilli) in peri- and postmenopausal women. Over 12 weeks, the treatment group maintained serum estradiol and estrone levels, whereas the placebo group had a significant decline in these hormones. By study end, estradiol was ~26% higher on average in the probiotic group vs placebo. This was the first clinical demonstration that a probiotic could influence human estrogen levels, highlighting a potential non-hormonal strategy to mitigate estrogen withdrawal effects.

Paraprobiotic for Menopause
(Sawada et al., 2022)

In a placebo-controlled trial, Sawada et al. examined the effects of ingesting heat-killed Lactobacillus gasseri CP2305 (a postbiotic approach) for 6 months in 80 women aged 40–60 who had mild menopausal complaints. The CP2305 group showed statistically significant improvements in multiple domains: the total Simplified Menopausal Index score improved (down by 5.1 points vs 2.5 in placebo), including better vasomotor symptom scores and psychosomatic symptom scores. The proportion of women reporting relief was higher with CP2305 (75% vs 55%). This trial indicates that even non-viable probiotics can effectively reduce menopausal symptoms, likely via gut-brain axis modulation and inflammation reduction. It opens avenues for developing stabilized probiotic derivatives as functional supplements for menopause.



Bone Health and Microbiome
(Meta-Analysis 2024 & ongoing trials)

Fang Wang et al. (2024) performed a meta-analysis pooling 12 RCTs on probiotics and bone outcomes in postmenopausal women. The combined evidence showed that probiotics significantly attenuated bone loss at the spine and hip, and lowered bone resorption markers, particularly in women with osteopenia. Building on such data, the OsteoPreP trial (2024–2025) is now rigorously testing a synbiotic for fracture prevention (as described earlier). Additionally, a "Synbiotic To Attenuate Resorption of the Skeleton (STARS)" trial was launched in the US, focusing on whether a combination of Lactobacillus rhamnosus GG and a prebiotic can reduce bone turnover in postmenopausal women. Results from these studies will clarify how effective microbiome interventions are in preserving bone density and could lead to new recommendations for osteoporosis prevention.

Quality of Life and Metabolic Trials

Apart from the ones above, there are several other noteworthy studies.

- A trial in China (2021) found that a synbiotic (multiple Lactobacillus strains + FOS) given to postmenopausal women with type 2 diabetes led to modest improvements in fasting blood glucose and insulin, hinting at glycemic control benefits.
- An Italian trial (2020) using B. longum and L. reuteri in postmenopausal women reported improvements in bloating and constipation symptoms, showing GI functional benefits.
- The AB-Biotics sponsored trial (Europe) mentioned previously has finished testing a proprietary probiotic blend in ~300 peri/postmenopausal women for 3 months; though results are not yet published, its completion underscores the interest from industry in bringing a menopause-targeted probiotic product to market.

These trials, collectively, demonstrate a range of potential benefits: from subjective symptom relief (hot flashes, mood, vaginal discomfort) to objective clinical outcomes (hormone levels, bone density, infection rates). It's important to note that while many results are positive, not all trials show significant effects – variability in strains, dosages, duration, and participant characteristics can influence outcomes. Some trials have found no major differences versus placebo, highlighting the need to identify which specific interventions work best for which subgroup of women. Nevertheless, the overall trend in the evidence suggests real promise for microbiome-based strategies as part of an integrated approach to menopause management.

Clinical implications

The relationship between the microbiome and menopause is a burgeoning area of research with important implications for women's health. The findings reviewed here illustrate that menopause is not only a hormonal transition but also a microbial one. The **decline in estrogen** and other ovarian hormones triggers **changes in microbial communities**, particularly in the gut and vagina, which in turn can feedback to affect a woman's physiology.

This **bi-directional host-microbe interplay** helps explain why menopausal symptoms and health risks are so multi-faceted – involving not just the endocrine system but also metabolism, immunity, and mucosal health.

One key discussion point is the **causal versus correlative nature** of these changes. While we see strong associations (e.g., low Lactobacillus with high vaginal pH and GSM symptoms, or low gut diversity with higher inflammatory markers and bone loss), it can be challenging to disentangle how much is caused by loss of estrogen directly versus mediated by microbial shifts. Likely, there is a **circular relationship**: estrogen loss creates a less favorable environment for certain beneficial microbes, leading to dysbiosis, which then exacerbates inflammation and tissue degeneration, further worsening menopausal symptoms. This suggests that **interventions at either point – hormonal or microbial** – could potentially break the cycle. Traditional HRT intervenes on the hormonal side (and indeed often improves microbial profiles as a secondary effect). Microbiome-focused therapies intervene on the microbial side, and as we see, can sometimes lead to changes in hormone metabolism or symptom improvement as secondary effects.

The research into "all 'biotics'" provides a hopeful narrative that targeting the microbiome can help manage menopause in a more natural or complementary way. Probiotics, in particular, have moved from the fringe to the mainstream of discussion for menopausal care. The evidence base, while still maturing, is increasingly suggesting that specific probiotic strains or combinations can yield statistically significant benefits for menopausal women – be it improving their quality of life scores, reducing infection rates, or protecting bone density. These benefits, however, can vary widely depending on the strain and outcome of interest. A strain that is excellent for vaginal health (e.g., Lactobacillus GR-1) may not impact bone health, and vice versa. Therefore, one challenge ahead is **personalizing probiotic therapy**: selecting the right strains for the right woman. In the future, we might use microbiome sequencing for a menopausal patient to identify specific deficiencies and then recommend a tailored probiotic/prebiotic regimen.

Another discussion point is the **safety and regulation** of these biotic therapies. Generally, probiotics and prebiotics are available as dietary supplements (with less stringent regulation than pharmaceuticals). This can lead to variability in product quality and dosing. Healthcare professionals should guide patients towards products with clinically validated strains at effective doses, ideally those that have been tested in menopausal populations. Additionally, while probiotics are safe for the vast majority, rare cases of infection (like bacteremia) have been reported in severely ill or immunosuppressed individuals. Menopausal women are typically healthy, but those with underlying conditions (e.g., uncontrolled diabetes or on immune-suppressants) should use probiotics judiciously under medical advice.

Global insights remind us that there is no one-size-fits-all solution. Dietary and cultural practices influence baseline microbiomes; for example, an Indian vegetarian menopausal woman's gut microbiome will differ from that of an American woman on a high-fat diet, and their needs for prebiotic or probiotic support may differ. It underscores the importance of including diverse populations

in clinical trials – encouragingly, we see studies from Asia, Europe, and the Americas all contributing data. Probiotics that work in one region (where perhaps people have certain diets or microbiome profiles) might not have identical effects elsewhere. Therefore, ongoing international research is crucial.

The concept of microbiome interventions as adjuncts to conventional menopause treatments is also worth discussing. None of the "biotics" are meant to be standalone cures for severe menopausal issues. For instance, while probiotics may reduce hot flashes somewhat, they likely will not eliminate moderate-to-severe vasomotor symptoms as effectively as HRT or certain non-hormonal medications. However, they could be used in combination to enhance overall outcomes. A woman on HRT might also take probiotics to support her vaginal flora and gut health, thereby preventing issues like yeast infections or weight gain. On the other hand, for women who cannot take HRT (e.g., cancer survivors or those with contraindications), microbiome-based strategies might offer partial relief and health benefits where few other options exist. This integrative approach aligns with the trend towards holistic management of menopause – addressing diet, lifestyle, microbiome, and hormones together.

We should also consider the **limitations of current research**. Many trials have relatively short follow-up (a few weeks to months). Menopausal health challenges like osteoporosis or cardiovascular disease develop over years. We do not yet have long-term data showing that taking a probiotic for 5+ years through menopause results in fewer fractures or heart attacks – those studies would be expensive and complex but may be warranted if early signals continue to be positive. Additionally, the field of microbiomics is inherently complex: results can vary based on sequencing methods, geographic differences, and the inherent variability of microbiomes between individuals. This means that some studies find "no difference" in gut diversity postmenopause, whereas others find clear differences. Future studies with larger sample sizes and multi-omics approaches (looking at microbial function, not just composition) will help resolve these discrepancies.

It is also worth discussing **educational aspects**: Many healthcare providers and patients are not fully aware of the microbiome's relevance to menopause. Incorporating this knowledge into clinical practice requires disseminating the evidence through professional education. For example, OB/GYNs and endocrinologists might in the future routinely counsel menopausal patients on diet (prebiotics) and possibly recommend a trial of a certain probiotic for those with troubling vaginal or gut symptoms. As evidence solidifies, guidelines may eventually list probiotics or synbiotics as recommended adjunct therapies for specific indications (analogous to how vaginal moisturizers or phytoestrogens are mentioned in some current menopause guidelines).

In summary, the discussion around microbiome and menopause is one of cautious optimism. We now recognize that supporting a healthy microbiome is an integral part of supporting overall health in midlife women. Microbiome-targeted interventions are largely low-risk and can have multiple ancillary benefits (for instance, fiber supplements might improve colon health and regularity while also modulating hormones). However, these interventions should be viewed as part of a comprehensive plan – including diet, exercise, stress management, and conventional medical therapies – tailored to each woman's needs and risk factors.

CONCLUSION

Menopause is a time of profound internal change, extending beyond the endocrine system to the microbial ecosystems that live in and on the human body. The gut and vaginal microbiomes undergo characteristic shifts during menopause, largely driven by the reduction in estrogen and other sex hormones. In the gut, many studies indicate a trend toward reduced microbial diversity and a loss of beneficial SCFA-producing bacteria post-menopause, potentially contributing to inflammation, weight gain, and bone density loss. In the vagina, the menopause transition is marked by the collapse of Lactobacillus dominance and a rise in microbial diversity, leading to a higher vaginal pH and increased susceptibility to genitourinary issues like atrophic vaginitis, infections, and urinary dysfunction. These microbiome changes form an important piece of the puzzle in understanding menopausal symptomatology and health risks.

Encouragingly, the emerging field of menopause and the microbiome offers new strategies to support women through this transition. A range of biotic therapies – probiotics, prebiotics, synbiotics, and postbiotics – are being actively researched and show promise as adjuncts to traditional menopausal care. Probiotics can help tilt the gut and vaginal flora back towards a more youthful, lactobacilli-friendly state, with studies demonstrating improvements in vaginal microbiota composition, mental health and stress in menopause, and even conservation of circulating estrogens and bone density. Prebiotics (from fiber supplements or a plant-rich diet) nourish beneficial microbes and have been linked to better metabolic and bone outcomes in

postmenopausal models. Synbiotics, combining the two, are on the cusp of providing multifaceted benefits, as evidenced by ongoing large trials aiming to reduce osteoporosis and improve quality of life. Postbiotics offer a novel way to deliver the advantageous molecules produced by gut bacteria, such as SCFAs or equol, directly to the host; early clinical use of a postbiotic (L. gasseri CP2305) showed it can safely ease menopausal symptoms.

From a global perspective, research across continents reinforces that while menopause's effects are universal, the context of diet and environment modulates the microbiome response. This underscores the value of personalized and culturally sensitive approaches – what works in one population may need adaptation in another. Nonetheless, a common theme is that supporting the microbiome – through diet, lifestyle, or supplements – contributes to healthier aging in women. Even beyond menopause, fostering a diverse gut microbiota and a Lactobacillus-rich vaginal environment can benefit women's overall health, potentially reducing risks of colorectal cancer, diabetes, and recurrent urogenital infections in older age.

In conclusion, the state-of-the-art evidence suggests that integrating microbiome-focused interventions into menopause management holds considerable promise. While more research is needed to pinpoint optimal protocols, healthcare professionals can begin to consider the microbiome as a therapeutic target when addressing menopausal symptoms and conditions. Practical steps may include dietary counseling to increase natural prebiotics, judicious use of probiotic supplements (especially for women with genitourinary syndrome or those who cannot use hormones), and staying updated on clinical trial developments in this arena. As we move into an era of personalized medicine, microbiome health is poised to become an important pillar of personalized menopausal care, alongside hormonal health, bone health, and cardiovascular health. By restoring microbial balance, we can potentially mitigate some of menopause's challenges and improve quality of life for women globally.

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