Clinical Nutrition ESPEN 69 (2025) 241–256

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Meta-analysis

Investigating the effects of probiotics during the menopause transition: A systematic review & meta-analysis

Robin A.F. Andrews [a,*], Arron Lacey [b], Helen Roach [c], Rebeccah Tomlinson [d], Emma J. Kidd [a], Kate Bache [c]

[a] Cardiff University, Health & Her, Welsh School of Pharmacy, King Edward VII Ave, Cardiff, UK
[b] Swansea University, The Alan Turing Institute, Swansea Medical School. Institute of Life Science 2, Sketty, Swansea SA2 8QA, UK
[c] Health & Her, Unit D, Tramshed Tech, Pendyris St, Cardiff CF11 6BH, UK
[d] Health & Her, The National Health Service (NHS), Unit D, Tramshed Tech, Pendyris St, Cardiff CF11 6BH, UK

ARTICLE INFO

Article history:
Received 10 March 2025
Accepted 6 July 2025

Keywords:
Probiotics
Menopausal symptoms
Menopause
Osteoporosis
Hormone replacement therapy
Urogenital health
Hot flushes
Lactobacillus
Estriol
Oestrogen

SUMMARY

This review investigated the impact of probiotics during the menopause transition and explored their potential to enhance the effectiveness of estrogenic substances in perimenopausal or recently post-menopausal women.

A thorough literature search of EMBASE, MEDLINE, Cochrane Library, Scopus, and Web of Science was conducted, identifying 39 studies involving 3187 women. Quality assessments were conducted using the relevant Cochrane Risk of Bias tools.

The results demonstrated that probiotics had positive effects on menopausal symptoms, urogenital health, bone health, and the efficacy and safety of estriol and isoflavones. Meta analysis of 7 studies comparing probiotics versus placebo demonstrated large effects of probiotics on menopausal symptoms (total score) [standardized mean difference (SMD) = 0.82, 95 % CI -0.52 to −1.09], vasomotor symptoms (SMD = −0.96, 95 % CI -1.25 to −0.68), psychological symptoms (SMD = −0.51, 95 % CI -0.95 to −0.08), vaginal dryness (SMD = 0.95, 95 % CI -1.40 to −0.49), and vaginal microbiome health (Nugent score) (SMD = −0.91, 95 % CI -1.32 to −0.49). Meta-analysis results were nonsignificant for reducing somatic and sexual symptoms.

Probiotics hold promise in addressing symptoms related to low estrogen levels and may enhance the effects of estriol and isoflavones, offering potential benefits as part of the management of menopausal women. It's important to note that the included studies had a high risk of bias, emphasising the need for further rigorous research in this area. Should findings continue to show promise, clinicians should consider incorporating probiotics into their strategies for managing menopausal symptoms.

Systematic Review Registration Number: CRD42019146270.

Practice Points:

- Findings suggest that probiotics can be beneficial option for women during the menopause transition by reducing menopausal symptoms and improving cardiovascular, urogenital, and bone health.
- Some evidence indicated that probiotics may enhance the effects of estriol and isoflavones, which may suggest probiotics could be a beneficial adjunct to these treatments.
- Findings are limited by high risks of bias and heterogeneity between included studies.
- It is recommended that high quality studies be conducted to rigorously evaluate the effects of probiotics on health outcomes during menopause.
- Should beneficial outcomes persist probiotics may be an ideal candidate for treatment or inclusion in existing treatment regimens for menopause.

* Corresponding author.
E-mail addresses: AndrewsR16@cardiff.ac.uk (R.A.F. Andrews), a.s.lacey@swansea.ac.uk (A. Lacey), Helen@healthandher.com (H. Roach), DrRTomlinson@healthandher.com (R. Tomlinson), KiddEJ@cardiff.ac.uk (E.J. Kidd), Kate@healthandher.com (K. Bache).

https://doi.org/10.1016/j.clnesp.2025.07.009

1. Introduction

Recent studies have demonstrated the beneficial effects of probiotics on osteoporosis [1], vaginal health [2], menopausal symptoms [3], and biomarkers of cardiovascular disease [4]. Given that these conditions are commonly associated with oestrogen declines which occur during the menopause transition [5], this suggests that probiotics can benefit peri- and postmenopausal women.

The estrobolome, consisting of gut microbes involved in oestrogen metabolism, plays a crucial role in maintaining oestrogen homeostasis [6]. An unhealthy gut microbiome can lead to imbalances in circulating oestrogen levels, contributing to the development of oestrogen related pathologies [6]. Menopausal symptoms arise from both deficiencies and fluctuations in oestrogen and commonly include vasomotor symptoms (e.g. hot flushes and night sweats), sleeping problems, mood changes, and urogenital issues [3]. Therefore, therapies which target oestrogen balance may reduce these types of symptoms.

While several studies have assessed the effects of probiotics on menopausal symptoms, to date, no meta-analytic quantification of the effects of probiotics on menopausal symptoms (such as hot flushes and night sweats) have been presented [3].

Chen et al. suggested that combining Hormone Replacement Therapy (HRT) with probiotics might enhance treatment outcomes [7]. Long-term oestrogen supplementation was found to decrease β-glucuronidase activity, which affects the half-life and efficacy of HRT [7].

Probiotics with oestrogen reactivating properties can modulate β-glucuronidase activity [8–11], leading to the hypothesis that probiotics could increase HRT's half-life and reduce the required dosage, thereby enhancing safety, particularly in women susceptible to oestrogen-dependent cancers [7]. Additionally, probiotics have been shown to enhance the estrogenic effects of isoflavones [12], further supporting their potential as beneficial adjuvants [13]. Given that combining probiotics with estrogenic substances could potentially enhance the effects of oestrogen, it is important to evaluate the safety of this combination in relation to oestrogen-related pathologies such as breast and endometrial cancer. These findings suggest that probiotics may influence circulating oestrogen levels by optimizing the estrobolome's efficiency, presenting a plausible mechanism for how probiotics could improve health conditions known to be exacerbated in the oestrogen-deficient state. In this systematic review, we aim to comprehensively examine the effects of probiotics on peri- and postmenopausal women. By analysing available evidence, including potential interactions with HRT and isoflavones, this review will provide valuable insights into the use of probiotics as a therapeutic approach for managing menopausal symptoms and related health conditions. The findings could have significant implications for clinical practice and public health strategies aimed at improving menopausal women's overall well-being and quality of life.

1.1. Objectives

The aim of this review was to evaluate whether probiotics could improve health during the menopause transition in relation to menopausal symptoms and cardiovascular, bone, and vaginal health. Due to the lack of existing meta-analyses on this topic, this review included a meta-analysis of seven studies which investigated the effects of probiotics on menopausal symptoms versus placebo. A secondary enquiry assessed whether probiotics could enhance the efficacy and safety of estrogenic substances such as HRT and isoflavones.

2. Methods

This systematic review was reported according to PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions [14]. The PROSPERO protocol provides further details on the search strategy: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=364811.

2.1. Inclusion criteria

Criteria for inclusion were perimenopausal or recently postmenopausal participants, assessment of probiotics' influence (alone or combined with estrogenic substances such as HRT or isoflavones), and measurement of health outcomes known to be impacted by the menopause transition such as cardiovascular health, urogenital health, bone health, and menopausal symptoms. Perimenopause defines woman who are experiencing menopausal symptoms and still having menstrual periods, recent postmenopause defines women who are no longer menstruating and still experiencing menopausal symptoms. Search terms focused on the top 15 most commonly reported menopausal symptoms as indexed by the British Menopause Society [15]: hot flushes, night sweats, sleeping problems, weight gain, cognitive changes, mood changes, vaginal dryness, painful sex, urinary changes, loss of libido, low energy, joint aches, period changes, palpitations, and headaches.

2.2. Exclusion criteria

- Studies which do not assess the health impact of probiotics.
- Studies assessing probiotics combined with nutraceuticals (e.g., calcium, vitamin D) without comparing the effect of probiotics independently.
- Conference abstracts and proceedings.
- Studies focusing on populations who are not peri- or postmenopausal.
- Studies assessing older populations (70+ years), to target outcomes that are relevant to the effects of the menopause transition, and populations who are still experiencing menopausal symptoms.

2.3. Literature search

The following databases were searched: EMBASE, MEDLINE, Cochrane Library, Scopus, Web of Science, and Google Scholar, searches were updated in March 2023. Any studies which measured the impact of oral or vaginal probiotics among a peri- or postmenopausal population were included, ideal studies included randomised controlled trials, however nonrandomised trials and cross-sectional studies were also included to capture the breadth of research conducted on this topic. English-language systematic reviews were included if they summarised any studies which were not captured by our systematic searches in cases where the original articles met all eligibility criteria but were not translated into English. Full-text screening, independently conducted by two authors, reached an acceptable agreement level [16] after calibration (Kappa statistic $\kappa = 0.692$, $\rho < 0.001$). A PRISMA flowchart (Fig. 1) displays study selection and exclusions.

2.3.1. Data extraction

Supplementary Table S1 includes all extracted data from selected studies. Abstraction included the following data: Authors (year), Country, Design, Sample size (mean age), Symptoms, Menopausal status, Comorbidities, Sponsors, Type/species/strain,

CFU content, Formulation, Details of probiotic administration and dosage (i.e., oral/vaginal), Alongside other medications (i.e., HRT/phytoestrogens), Assessment of health outcomes (how were symptoms/health measured?), Main Results (what were the findings?).

2.4. Data synthesis

Narrative synthesis was predominantly used as studies were heterogenous in terms of health outcomes, probiotic formulations, and populations. However, meta-analysis was conducted on comparable RCT data where possible. The narrative synthesis grouped studies thematically based on the outcomes assessed, and studies are summarised in terms of risk of bias in relation to each outcome. Outcomes are presented starting with higher quality evidence (i.e., more studies with "Low" risks of bias) to lower quality evidence (i.e., more studies with "High" risks of bias).

2.4.1. Quality evaluation

Risk of bias assessment used ROB-2 for Randomized Controlled Trials (RCTs) and revised ROB-2 for crossover RCTs, ROBINS for non-randomized studies, and ROBIS for review studies [17–19].

Heterogeneity among studies included in the meta-analysis was assessed using I^2 and Tau^2 tests. Publication bias was not evaluated due to limited number of studies suitable for meta-analysis [22].

2.5. Statistical methods

Meta-analysis (RStudio version 2022.7.2.576) of comparable studies with continuous data provided standardized mean differences and 95 % CIs for menopausal and vaginal symptom scores post-placebo and post-probiotic treatment. Cohen's effect size convention guided classifications: 0.20 = small effect size, 0.40 = medium effect size, and 0.60 = large effect size. Significance was set at $p < 0.05$ [20,21]. Only data from RCTs were meta-analysed. Seven studies described comparable study designs, and menopause and vaginal symptom/health scores post-placebo and post-probiotic treatment were compared, and the standardised mean difference and 95 % confidence intervals (CIs) were computed. Random-effects models were used to compensate for variations within the selected studies. Heterogeneity was tested using the I^2 value and Tau^2 tests of significance. The interpretation of the observed I^2 value was determined by The Cochrane Handbook of Systematic Reviews [14] guidance which indicated that I^2 <30 % was considered mild heterogeneity, I^2 >30 % as moderate heterogeneity, I^2 >50 % as substantial heterogeneity and I^2 >75 % as considerable heterogeneity.

3. Results

3.1. Study characteristics

Searches returned 39 studies which met the eligibility criteria and contributed data from 3187 participants (mean age = 55.7, age

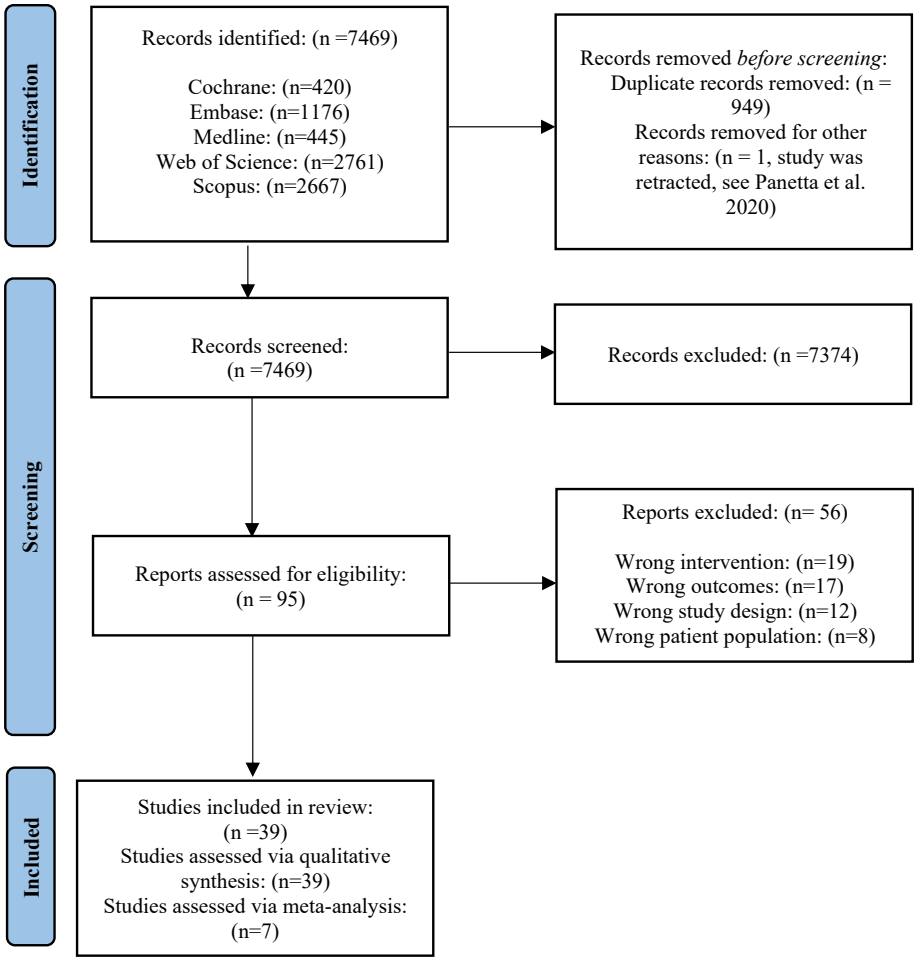

Fig. 1. PRISMA Flow Chart adapted from Page et al. [63].

range = 45 to 65), 72 % were recently postmenopausal, 18 % entered menopause due to medical treatment or surgery, and 10 % were perimenopausal. Figure 1 outlines the study selection process.

3.1.1. Outcomes

Table 1 summarises the outcomes in relation to key findings. See supplementary file to view comprehensive details for each included study. Eight studies evaluated the effects of probiotics on menopausal symptoms [23–30]. Fifteen studies explored probiotics and urogenital health including genitourinary syndrome of menopause [31,32,34–36], bacterial vaginosis [37], urinary tract infections [38,39], and vaginal atrophy [40–46]. Seven studies examined the effects of probiotics on bone health [47–53] and 9 assessed cardiovascular risk factors [54–62].

3.1.2. Risk of bias assessment

As shown in Table 2, few studies were judged to have "Low" risks of bias (N = 13, 33 %). Ten studies (26 %) had "Moderate" or "Some Concerns" relating to risk of bias, and 16 (41 %) were deemed to have "Critical" or "High" risks of bias.

3.1.3. Bone health

Four studies demonstrated that probiotics were superior to placebo in preventing lumbar spine, total hip, vertebra, femoral neck, and trochanter bone mineral density loss (BMD) [47,48,50,52]. Jafarnejad et al. [49] and Zhao et al. [53] reported that probiotics significantly reduced parameters relating to bone turnover including serum parathyroid hormone, tumour necrosis factor, and bone-specific alkaline phosphatase and C-telopeptide levels [49,53]. Likewise, a study by Narva et al. [51] demonstrated that *L. helveticus* fermented milk reduced serum parathyroid hormone and increased serum calcium, compared to a control milk, albeit this study was judged to have high risks of bias. The majority of these studies were judged to have "Low" risks of bias [48–50,52,53], one had "Some concerns" [47], and one was judged to have "High" risks of bias [51].

3.1.4. Menopausal symptoms

Studies examining this outcome reported statistically significant reductions in menopausal symptoms (total score) following administration of probiotics [22–24,26,29,40], including specific symptoms such as hot flushes [28] and facial wrinkles [27]. Placebo controlled RCTs, which were deemed to have low risks of bias, demonstrated probiotics could significantly reduce menopausal symptoms [24,26,29]. For example, Lim et al. [26] examined the effects of L. acidophilus and demonstrated that menopausal symptoms improved relative to placebo along with quality of life in all four domains (i.e., physical, psychosocial, vasomotor, and sexual). Moreover, this study did not report significant differences in blood follicle-stimulating hormone, oestradiol levels or endometrial thickness [26]. In terms of bias, three studies were judged as having "Low" risks [24,26,29], two studies had "Some concerns" [22,28], three had "High" risks of bias [23,27,40].

3.1.5. Cardiovascular risk factors

Barreto et al. [57] did not find evidence that L. plantarum use resulted in beneficial changes to body composition, and Szydłowska et al. [55] demonstrated that probiotics were no more efficacious than a placebo in reducing body weight after 5 weeks. However, Kaczmarczyk [54] and Szulinska et al. [59] reported that probiotics were beneficial for reducing body weight and waist circumference. Szulinska et al. [59] demonstrated that both high (1×1010 CFU per day) and low (2.5×109 CFU per day) doses of probiotics were associated with reduced waist, fat mass, and subcutaneous fat, although higher probiotic doses were associated with greater benefits, suggesting dose-dependent effects.

Szulinska et al. [59] also demonstrated that probiotics could reduce cholesterol as assessed via total and low-density lipoprotein. These results are in line with two other studies which also found evidence that probiotics could reduce cholesterol [22,61]. Conversely, one study examined soy isoflavones + probiotics, probiotics alone, isoflavones alone, and a control preparation, and did not find evidence that probiotics could lower cholesterol levels or enhance the effects of soy isoflavones [62].

A second analysis of the sample in Szulinska et al. [59] explored functional and biochemical markers of vascular dysfunction [60]. This study demonstrated that, when compared with placebo, probiotic supplementation for 12 weeks decreased metabolic risk markers including systolic blood pressure, interleukin 6, and tumour necrosis factor alpha [60]. Likewise, Barreto et al. [57] found that L. plantarum fermented milk decreased glucose and homocysteine levels. Skrypnik et al. [56] concluded that multistrain probiotic supplementation improved iron metabolism in obese postmenopausal patients. In contrast, Brahe et al. [58] investigated the effect of interventions with L. paracasei or a prebiotic, flaxseed mucilage, on gut microbiota and metabolic risk markers and did not find evidence that probiotics were more efficacious than placebo or prebiotics in reducing insulin sensitivity and glucose tolerance.

In terms of bias, the majority of these studies had "Some Concerns" [22,55,58–60], two studies had "High" or "Critical" risks of bias [61,62], and three studies were deemed to have "Low" bias [54,56,57].

3.1.6. Vaginal health

Results favoured the effects of both vaginally and orally administered probiotics on improved vaginal health outcomes, including improvements in the vaginal microbiome, bacterial vaginosis, and vaginal atrophy [32,37,40,42,44]. In three studies, probiotics were also beneficial for reducing reoccurrences of urinary tract conditions [35,39,40]. Conversely, Jongjakapun et al. [38] and Beerepoot et al. [39] concluded that in postmenopausal women with recurrent UTIs, probiotics were not superior to antibiotics or placebo. However, all of these studies were judged to have "High" or "Critical" risks of bias [32,37,40,42,44].

3.1.7. Probiotics combined with estriol

Most studies which examined the effects of combining intravaginal estriol with *L. acidophilus* on urogenital conditions reported positive findings relating to vaginal atrophy, sexual functioning, and urinary symptoms [33–35,41,43,45]. However, Jongjakapun et al. [38] did not demonstrate that this combination was superior to placebo in reducing lower urinary tract symptoms. Notably this study [38] was the only one which was deemed to have "Low" risks of bias.

Two studies suggested that probiotics could enhance the effects of estriol [35,41]. Capobianco et al. [35] found evidence that combining 0.03 mg of estriol with L. acidophilus was more efficacious than 1 mg of estriol alone in relieving urogenital atrophy, stress incontinence, and UTIs. A clinical review [41] of estriol plus L. acidophilus vaginal tablets reported two German language studies which assessed the efficacy of this combination.

These studies each reported that vaginal 0.03 mg estriol combined with L. acidophilus led to similar efficacy in relieving vulvovaginal symptoms compared to the 16-fold higher standard dose of 0.5 mg estriol [64,65].

The safety of estriol + L. acidophilus was also evaluated among postmenopausal breast cancer patients. Donders et al. [33] found that low dose estriol + L. acidophilus led to transient increases in

Table 1
Probiotic formulations and key outcomes.

Reference(s)	Probiotic formulation(s)	Administration	Outcomes Assessed	Key Findings
Jahnsson et al. [48]	L. paracasei & L. plantarum	Oral	• Bone mineral density (BMD).	Probiotics protected against lumbar spine bone loss in healthy, early postmenopausal women.
Jafarnejad et al. [49]	L. casei, Bifidobacterium (B.). longum, L. acidophilus, L. rhamnosus, L. bulgaricus, B. breve, & S. thermophilus.	Oral	• Bone mineral density. • Biomarkers of bone health.	Consumption of a multispecies probiotic supplement for 6 months had significant effects on serum BALP, CTX, PTH and TNF-α among postmenopausal women with osteopenia; however, effects were non-significant on bone density compared to the control group.
Takimoto et al. [50]	Bacillus subtilis	Oral	• Bone mineral density. • Gut microbiome Diversity.	When compared with a placebo, the probiotic significantly increased total hip BMD. There was a significant group-by-time interaction effect for urinary type I collagen cross-linked N-telopeptide (uNTx), a marker of bone resorption. The probiotic group showed significantly lower uNTx when compared with the placebo group at 12 weeks of treatment. The relative abundance of genus Bifidobacterium significantly increased at 12 weeks of treatment compared with the baseline in the probiotic group. The relative abundance of genus Fusobacterium was significantly decreased in the probiotic group at 12 and 24 weeks of treatment compared with the baseline.
Lambert et al. [28,47]	Proprietary culture of probiotic lactic acid bacteria + isoflavones	Oral	• Bone mineral density. • Vasomotor symptoms (VMS).	Probiotic formulations attenuated BMD loss caused by oestrogen deficiency, improved bone turnover, promoted a favourable oestrogen metabolite profile, and stimulated equol production in postmenopausal women with osteopenia. Was more effective and superior to placebo in reducing physiological and self-reported VMS.
Narva et al. [51]	*L. helveticus*	Fermented milk	• Calcium metabolism.	The results suggest that milk fermented with *L. helveticus* increased serum calcium and reduced serum PTH versus a control beverage, suggesting the probiotic had beneficial effects on calcium metabolism.
Szydłowska et al. [55] Szulinska et al. [60] Szulinska et al. [59] Skrypnik et al. [56] Kaczmarczyk et al. [54]	B. bifidum, B. lactis, L. acidophilus, L. brevis, L. casei, L. salivarius & L. lactis	Oral	• Cardiovascular disease risk markers. • Iron metabolism. • Weight gain.	Probiotics were associated with reduced waist circumference and body weight, and favourably modified functional and biochemical markers of vascular dysfunction in obese postmenopausal women. Probiotics also influenced iron metabolism in obese postmenopausal patients with obesity-related iron deficiency.
Barreto et al. [57]	L. plantarum	Fermented milk	• Cardiovascular disease risk markers.	Fermented milk with L. plantarum decreased two cardiovascular risk factors: Glucose and homocysteine levels. These findings were obtained without changes in body composition.
Brahe et al. [58]	L. paracasei	Oral	• Metabolic risk markers.	Intake of L. paracasei did not modulate metabolic markers compared with placebo or flaxseed.
Greany et al. [62]	L. acidophilus & B. longum + isoflavones	Oral	• Cholesterol	Confirmed a beneficial effect of soy on plasma cholesterol in mildly hypercholesterolemic postmenopausal women but did not support an independent or additive effect of particular probiotic bacteria.
Desfita et al. [61]	L. casei + soymilk + honey (Treatment group 1) L. plantarums+ Soymilkh+ Honey (Treatmegt Group 2)	Soymilk beverage	• Random blood glucose. • Uric Acid. • Cholesterol. • Serum Osteocalcin levels.	Fermented soymilk-honey with Lactobacillus plantarum significantly decreased osteocalcin levels. Soymilk-honey with Lactobacillus casei subsp. casei significantly lowered cholesterol levels. No significant differences in

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Table 1 (*continued*)

Reference(s)	Probiotic formulation(s)	Administration	Outcomes Assessed	Key Findings
				random blood glucose, uric acid, cholesterol, and serum osteocalcin levels were observed before and after the intervention in the soymilk-only group.
Tedeschi et al. [46] Colacurci et al. [23]	L. sporogenes + isoflavones + calcium + vitamin D	Assessed both oral and topical probiotic formulations.	• Endometrial, breast, and liver safety. • Menopausal symptoms. • Vaginal dystrophy.	The combination of oral and topical formulations was shown to be more effective than oral treatment alone in reducing the symptoms of postmenopausal vaginal dystrophy. Formulations were found to be safe for endometrium and mammary tissue and hepatic function at the recommended daily dose. Demonstrated effectiveness for reducing menopausal symptoms.
Kano et al. [27]	B. breve & L. mali + soymilk	Soymilk (Yakult)	• Facial Wrinkles. • Bioavailability of isoflavones.	The probiotic group demonstrated significant improvements in the maximum depth and average depth of wrinkles, and significantly elevated urinary isoflavones (daidzein, genistein, and glycitein) compared with the no-treatment control during the consumption period.
Lim et al. [26]	L. acidophilus	Oral	• Menopausal symptoms. • Menopause-related Quality of life	Kupperman index (KMI) scores revealed a ~66 % reduction after 12 weeks of probiotic treatment relative to baseline levels, whereas a 37 % reduction was observed in the placebo group. Regarding specific symptoms, probiotic treatment alleviated hot flushes, paresthesia, nervousness, melancholia, fatigue, arthralgia, headache, heart palpitation, formication, and vaginal dryness according to KMI scores. Physical, psychosocial, vasomotor, and sexual symptoms showed significant reductions via the menopause-specific quality of life questionnaire (MENQOL), relative to the placebo group.
Trimarco et al. [22]	B. breve + isoflavones (intervention period), B. breve onlc (Control period)	Oral	• Menopausal symptoms. • Cholesterol. • Blood Pressure.	Probiotics were associated with a significant reduction in menopausal symptoms in comparison to baseline and the placebo period. Probiotics were associated with a significant reduction in triglycerides, total and low-density lipoprotein cholesterol plasma levels, and an increase in high-density lipoprotein cholesterol plasma concentration versus baseline and versus placebo. During the intervention period, there was a significant reduction in diastolic blood pressure in comparison to baseline, but not in comparison to the placebo period.
Sawada et al. [24]	L. Gasseri	Oral	• Menopausal symptoms. • Hormone levels.	Analyses suggested that daily administration of probiotics significantly improved psychological and vasomotor menopausal symptoms, with no effect on the follicular phase levels of reproductive hormones
Yoshikata et al. [40]	L. rhamnosus & L. plantarum	Probiotic vaginal soap + probiotic vaginal cream (Treatment group 1), or probiotic vaginal gel + probiotic soap + probiotic cream (Treatment group 2).	• Menopausal symptoms. • Vaginal and urinary symptoms. • Vaginal microbiome health.	Genitourinary symptoms significantly improved. Pathogenic flora population significantly reduced in both perimenopausal and postmenopausal women. Menopausal symptoms were significantly improved in perimenopausal participants only. Using probiotic vaginal gel, alongside probiotic soap, and cream, was associated with larger improvements.
Shafie et al. [29]	L. acidophilus & B. lactis	Oral	• Psychological symptoms. • Sleep Quality	Mean anxiety score, mean stress score, and mean quality of life score in the group receiving probiotic yogurt were

Table 1 (*continued*)

Reference(s)	Probiotic formulation(s)	Administration	Outcomes Assessed	Key Findings
				significantly lower than those in the placebo- control group. There were no statistically significant differences between groups in terms of mean scores on measures of depression and sleep quality.
Parma et al. [37]	L. rhamnosus	Vaginal tablets	• Bacterial vaginosis (BV) reoccurrence	Observed a population at high-risk of recurrent BV receiving L. rhamnosus for six months. Fifty-seven percent of patients treated with probiotics did not recur in the follow-up period, while 43 % presented with one or more episodes of BV. Results demonstrated a positive prevention efficacy with a long-term maintenance treatment.
Ribeiro et al. [31]	L. acidophilus, L. casei, L. lactis, B. bifidum & B. lactisi+ Isoflavones	Oral	• Genitourinary syndrome of menopause.	The vaginal health score improved in the isoflavone and hormone therapy groups. Probiotics improved the metabolism of isoflavones after 16 weeks of treatment as indicated by an increase in the content of daidzein, glycitein, equol intermediate, and O-DMA. However, the increase in the levels of isoflavones and their metabolites failed to yield an estrogenic effect on the urogenital tract and relieve the vulvovaginal symptoms.
Buchholz et al. [43] Donders et al. [33] Donders et al. [34] Mueck et al. [41] Capobianco et al. [35] Jaisamrarn et al. [45] Jongjakapun et at. [38]	L. acidophilus + estriol	Vaginal Tablets.	• Urogenital and sexual symptoms. • Effects on the efficacy of Ultra-low dose estriol.	This combination led to improvements in vaginal atrophy, urinary tract, and sexual symptoms, and improved vaginal microbiome health. Probiotics enhanced the effects of ultra-low dose estriol (0.03 mg) on urogenital symptoms, showing similar efficacy to higher doses (0.5 mg). Furthermore, this formulation was not associated with increases in serum E1 or E2 and was found to be tolerable and safe among postmenopausal breast cancer patients on aromatase inhibitors. However, was not more efficacious versus placebo among women with lower urinary tract symptoms.
Kwak et al. [42]	L. Gasseri, L. fermentum & L. rhamnosus	Topical ointment	• Vaginal atrophy. • Vaginal biome health	Vaginal atrophy symptoms were significantly reduced. Vaginal biome health was improved as demonstrated by increased colonisation of probiotic bacteria in the intervention group.
Petricevic et al. [36] Beerepoot et al. [39] Bisanz et al. [44]	L. rhamnosus & L. reuteri	Oral ([35]; [38]). Vaginal ([43]).	• Vaginal microbiome health. • Efficacy of Probiotics on UTI reoccurrence Rates versus antibiotics.	Vaginal probiotic administration resulted in a temporary increase in the relative proportion of beneficial Lactobacillus in the vagina. Oral probiotics improved vaginal health (as assessed via Nugent scores) above that of placebo. Oral probiotics also reduced UTI symptoms, but not to a greater extent than antibiotics; however, unlike antibiotics, probiotics were not associated with developing antibiotic resistance.
Marschalek et al. [32]	L. crispatus, L. rhamnosus, L. jensenii & L. gasseri + chemotherapy for breast cancer	Oral	• Vaginal microbiome health (assessed via Nugent score).	When analysing the difference between the Nugent score at baseline and after treatment among women in the probiotic intervention group, this study observed a mean reduction of −1.3 at follow-up visit 1, and –0.57 at follow-up visit 2. Women in the control group presented with an increase in Nugent score from baseline to follow-up visit 1 by +0.45. At follow-up visit 2, the smears of the women in the control group revealed a significant increase of +2.5. These findings suggest that

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Table 1 (*continued*)

Reference(s)	Probiotic formulation(s)	Administration	Outcomes Assessed	Key Findings
				probiotic supplementation was associated with a beneficial reduction in Nugent scores indicating changes towards normal vaginal microbiota health (i.e., a Nugent score of 0–3).
Han et al. [52]	L. fermentum	Oral	• Bone mineral density. • Osteocalcin levels.	Femur neck BMD showed a significant increase at 6 months post-trial in the study group ($P = 0.030$) but not in the control group. The control group showed a decrease in osteocalcin (OC) levels ($P = 0.028$), whereas the levels in the study group were maintained during the trial period. The change in L. fermentum concentration was significantly correlated with that in OC levels ($r = 0.386$, $P = 0.047$) in the study group at 3 months post-trial.
Zhao et al. [53]	Bifdobacterium animalis subsp. Lactis + Ca and calcitriol	Oral	• Effect of probiotics as adjunctive treatment for postmenopausal osteoporosis	No significant change was observed in the bone mineral density of patients at 3 months. Co-administering Probio-M8 improved the bone metabolism, reflected by an increased vitamin D3 level and decreased PTH and procalcitonin levels in

L. = Lactobacillus.
B. = Bifidobacterium.
BMD = Bone Mineral Density.
OC = Osteocalcin.
UTI = Urinary Tract Infection.
E1 = Estrone.
E2 = Oestradiol.
O-DMA.
BV = Bacterial Vaginosis.
KMI = Kupperman Index.
MENQOL = Menopause-specific quality of life questionnaire.
VMS = Vasomotor Symptoms.
BALP = Serum bone-specific isoenzyme of alkaline phosphatase.
CTX = Serum cross-linked C-telopeptide of type I collagen.
PTH = Parathyroid hormone.
TNF-α = Tumour necrosis factor-α
uNTx = Urinary type I collagen cross-linked N-telopeptide.

serum estriol (E3), but not estrone (E1) or oestradiol (E2), relevant as E1 and E2 can be a potential danger to women with breast cancer. These findings suggest that, in contrast to the standard dose of 0.5 mg estriol, 0.03 mg estriol + L. acidophilus neither produces significant absorption nor triggers a relevant increase in systemic oestrogen levels [41]. Notably, the majority of studies exploring estriol and probiotics were nonrandomised, controlled studies. Most of these studies had "High" or "Critical" risks of bias [35,41,43,45], two had "Moderate" risks [33,34], and as stated only one had "Low" risks of bias [38].

3.1.8. Probiotics combined with isoflavones

Studies which examined isoflavones combined with probiotics demonstrated that this combination was efficacious for reducing menopausal symptoms and enhancing bone and vaginal health. For example, Trimarco et al. [22] demonstrated that the probiotic strain B. breve combined with soy isoflavones led to greater improvements in menopausal symptoms than probiotics plus placebo alone. Likewise, Lambert [47] demonstrated that red clover isoflavones combined with probiotics were associated with improvements in bone status and oestrogen metabolism.

However, Greany et al. [62] demonstrated that adding probiotics to soy isoflavones did not significantly lower cholesterol levels or enhance the effects of soy.

The safety of combining soy isoflavones with L. sporogenes was demonstrated by Colacurci et al. [23] and Tedeschi et al. [46]. These studies reported that mammographic density, endometrial thickness, and hepatic function did not show significant differences between treatment and placebo control groups, suggesting that soy isoflavones plus probiotics did not negatively influence these parameters [23,46]. Three of these studies were judged to have "High" risks of bias [23,46,62], and the other two had "Some Concerns" relating to risks of bias.

3.2. Meta-analysis

Seven RCTs were evaluated via quantitative synthesis [24,26,28,29,32,36,42]. Of these studies four were judged to have "Low" risks of bias [24,26,29,36], one had "Some Concerns" [28], and two had "High" risks of bias [32,42]. These studies included continuous data measuring the independent effects of probiotics, versus a placebo control group, on menopausal symptoms (total score), psychological symptoms, vasomotor symptoms, vaginal symptoms, sexual symptoms, and vaginal biome health (as assessed via Nugent scores). Six additional studies measured the independent effects of probiotics versus placebo on menopausal symptoms and vaginal health however were excluded from the meta-analysis due to missing outcome data, or lacking placebo control groups [22,23,40,44–46].

3.2.1. Probiotics & total menopausal symptom scores

A meta-analysis of 4 studies was conducted to quantify the effects of probiotic supplementation relative to placebo [24,26,28,29].

Table 2
Risk of bias across all studies.

ROBINS-I

Study:	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	**Overall**
Buchholz et al. [43]	Critical	Low	Moderate	Low	Low	Moderate	Low	Critical
Donders et al. [33]	Low	Low	Moderate	Moderate	Low	Low	Low	Moderate
Donders et al. [34]	Low	Low	Moderate	Moderate	Low	Low	Low	Moderate
Desfita et al. [61]	Serious	Critical	Moderate	Low	Moderate	Low	Low	Critical
Barreto et al. [57]	Low	Low	Low	Low	Low	Low	Low	Low
Parma et al. [37]	Critical	Low	Low	Low	Low	Serious	Critical	Critical

ROB-2 (crossover RCTs)

Study:	Randomisation process	Risk of bias arising from carryover effects	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	**Overall**
Narva et al. [51]	Low	High	Low	Low	Low	Low	High
Greany et al. [62]	Low	Low	Low	Low	High	Low	High
Trimarco et al. [22]	Low	Low	Low	Low	Low	Some concerns	Some concerns
Bisanz et al. [44]	Low	Low	Low	High	Low	Low	High

ROB-2 (other RCTs)

Study:	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	**Overall**
Takimoto et al. [50]	Low	Low	Low	Low	Low	Low
Marschalek et al. [32]	Some concerns	Some concerns	Low	High	Low	High
Ribeiro et al. [31]	High	Low	Low	High	Low	High
Jaisamrarn et al. [45]	Low	Low	High	Low	Low	High
Capobianco et al. [35]	Low	Low	Low	High	Some concerns	High
Kaczmarczyk et al. [54]	Low	Low	Low	Low	Low	Low
Skrypnik et al. [56]	Low	Low	Low	Low	Low	Low
Szulinska et al. [59]	Low	Low	Low	Low	Some concerns	Some concerns
Szulinska et al. [60]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Brahe et al. [58]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Kano et al. [27]	High	Low	Low	Low	Low	High
Kwak et al. [42]	Low	Low	Low	High	Some concerns	High
Lim et al. [26]	Low	Low	Low	Low	Low	Low
Szydłowska et al. [55]	Low	Low	Low	Low	Some concerns	Some concerns
Sawada et al. [24]	Low	Low	Low	Low	Low	Low
Beerepoot et al. [39]	Some concerns	Low	Low	Low	Low	Some concerns
Yoshikata et al. [40]	Some concerns	Low	High	Low	Low	High
Colacurci et al. [23]	Some concerns	Some concerns	High	High	Some concerns	High
Jafarnejad et al. [49]	Low	Low	Low	Low	Low	Low
Jongjakapun et al. [38]	Low	Low	Low	Low	Low	Low
Han et al. [52]	Low	Low	Low	Low	Low	Low
Zhao et al. [53]	Low	Low	Low	Low	Low	Low
Jahnsson et al. [48]	Low	Low	Low	Low	Low	Low
Lambert et al. [28]	Some concerns	Low	Low	Low	Low	Some concerns

(*continued on next page*)

Table 2 (*continued*)

ROB-2 (other RCTs)						
Study:	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	**Overall**
Lambert et al. [47]	Low	Some concerns	Low	Low	Low	Some concerns
Petricevic et al. [36]	Low	Low	Low	Low	Low	Low
Shafie et al. [29]	Low	Low	Low	Low	Low	Low
Tedeschi et al. [46]	Some concerns	Some concerns	Low	High	Some concerns	High

ROBIS					
Study:	Study eligibility criteria	Identification & selection of studies	Data collection & study appraisal	Synthesis & findings	**Overall**
Mueck et al. [41]	High	High	High	No information	High

A shown in Fig. 2, the standardised mean difference for menopausal symptom frequency suggested a large effect size (−0.63, 95 % CI -0.26 to −0.99) and the difference was in favour of probiotic use (Z = 3.36, p < 0.001). Heterogeneity was substantial (I^2 = 55 %), albeit non-significant (Tau2 = 0.08, 95 % CI 0.00 to 1.9).

Heterogeneity was a result of the large standard deviations in the study by Shafie et al. [29]. Removal of this study removed all heterogeneity (I^2 = 0 %, Tau2 = 0.00 95 % CI 0.00; 0.74), this amended analysis still suggested a large effect size (−0.82, 95 % CI -0.52 to −1.09). Figure 2 shows the forest plot with the removal of the Shafie et al. [29] study.

3.2.2. Probiotics & vasomotor symptoms

Sawada et al. [24], Lambert et al. [28], and Lim et al. [26] provided outcome data on vasomotor symptoms (VMS) subscales. Figure 2 shows the standardised mean difference for VMS frequency suggested a large effect size (−0.96, 95 % CI -1.25 to −0.68) and the difference was in favour of probiotic use (Z = 6.54, p < 0.001). Heterogeneity was absent (I^2 = 0 %, Tau2 = 0.00, 95 % CI 0.00 to 1.72).

3.2.3. Probiotics & psychological symptoms

Sawada et al. [24], Lambert et al. [28], Shafie et al. [29], and Lim et al. [26] provided outcome data on psychological symptoms of menopause. Figure 2 shows the standardised mean difference for psychological symptom frequency suggested a moderate effect size (−0.51, 95 % CI -0.95 to 0.08) and the difference was in favour of probiotic use (Z = 2.32, p = 0.02). Heterogeneity was substantial (I2 = 68 %, Tau2 = 0.13, 95 % CI 0.01 to 1.64).

3.2.4. Probiotics & vaginal health

Marschalek et al. [32] and Petricevic et al. [36] provided complete outcome data on Nugent scores. Figure 2 shows the standardised mean difference suggested a large effect size (−0.91, 95 % CI -1.32 to −0.49) and the difference was in favour of probiotic use (Z = 4.29, p < 0.001). Heterogeneity was absent (I2 = 0 %, Tau2 = 0.00).

3.2.5. Probiotics & vaginal dryness

Kwak et al. [42] and Lim et al. [26] examined the effects of probiotics versus placebo on vaginal dryness. Figure 2 shows the standardised mean difference suggested a large effect size (−0.95, 95 % CI -1.40 to −0.49) and the difference was in favour of probiotic use (Z = 4.09, p < 0.001). Heterogeneity was absent (I2 = 0 %, Tau2 = 0.00).

3.2.6. Probiotics & sexual symptoms

Sawada et al. [24] and Lim et al. [26] provided outcome data on the effects of probiotics on sexual symptoms versus placebo. Figure 2 shows this analysis suggested a non-significant effect (−0.30 95 % CI -0.91 to 0.31) for probiotic use versus placebo on sexual menopausal symptoms (Z = 0.97, p = 0.33). Moreover, heterogeneity was substantial (I2 = 71 %, Tau2 = 0.138).

3.2.7. Probiotics & somatic symptoms

Sawada et al. [24], Lambert et al. [28], and Lim et al. [26] provided outcome data on somatic menopausal symptoms. Figure 2 shows this analysis showed a non-significant effect (−0.31 95 % CI -1.32 to 0.69) for probiotic use versus placebo on somatic menopausal symptoms (Z = 0.61, p = 0.54).

Moreover, heterogeneity was substantial (I2 = 92 %, Tau2 = 0.72, 95 % CI 0.15 to 31.33).

4. Discussion

4.1. Main findings

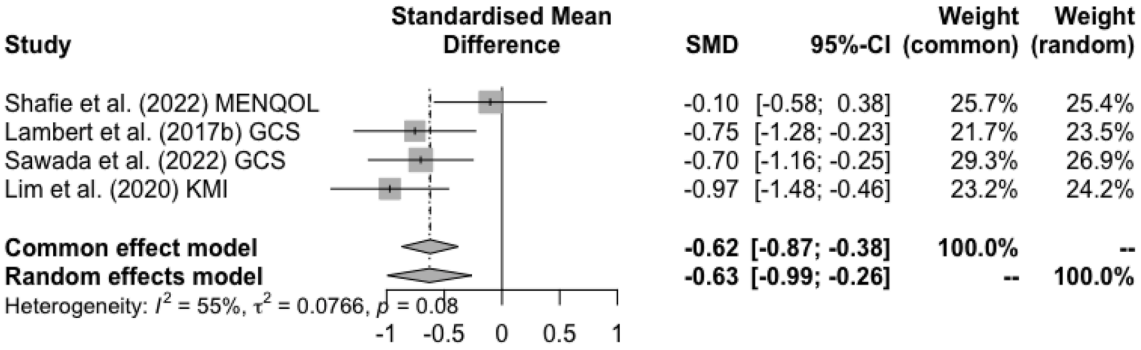
This review provides evidence that probiotics could improve health outcomes relating to menopausal symptoms, and cardiovascular, bone, and vaginal health during the menopause transition. Key benefits were related to reduced menopausal symptoms and improved vaginal and bone health. Some evidence, albeit of low quality, suggested that probiotics could safely enhance the effects of estriol and isoflavones. Meta-analysis suggested large effects favoring probiotics versus placebo in improving vaginal biome health and reducing menopausal symptoms, with vasomotor symptoms, vaginal dryness and psychological symptoms showing significantly greater improvements than placebo.

4.2. Interpretation

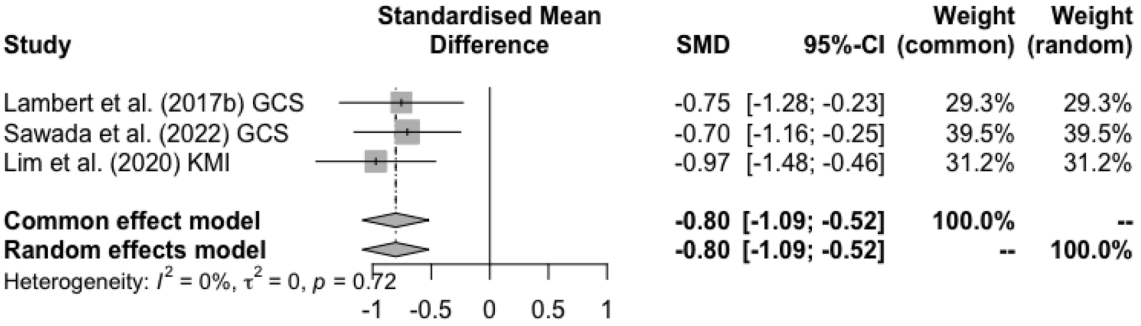
These outcomes might suggest that the estrobolome can be harnessed to enhance health outcomes among peri- and postmenopausal women [7,10]. Meta-analysis indicated that vasomotor and vaginal symptoms were reduced by probiotics to a large effect. These symptoms are highly characteristic of estrogen deficiency; therefore, probiotics may improve the efficiency of the estrobolome in metabolizing estrogen to its unconjugated, bioavailable form, thus increasing circulating estrogen levels and therefore decreasing VMS and vaginal dryness [66].

This review also supports prior research which found evidence that probiotics could improve bone health among postmenopausal women. A meta-analysis by Yu et al. [2] demonstrated that probiotic supplementation could improve bone mineral density. Oestrogen deficiency is a risk factor for osteoporosis; therefore, probiotics may support bone health by improving bioavailability of exogenous and remaining endogenous estrogens.

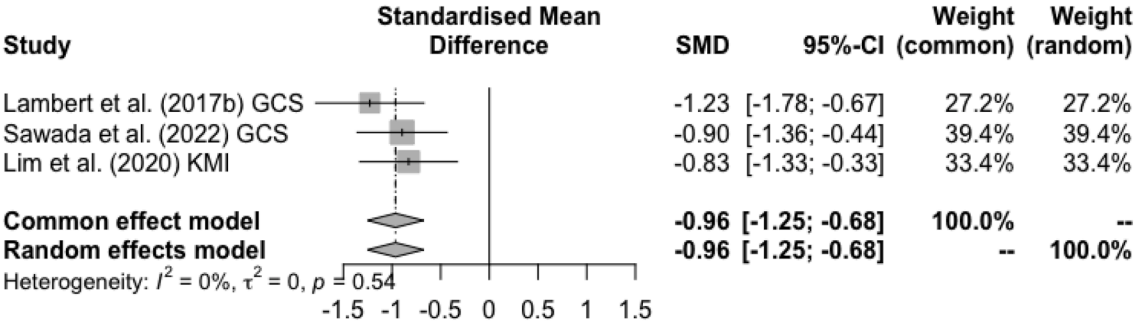
Total Menopausal Symptoms:



Total Menopausal Symptoms (with Shafie et al. omitted):



Vasomotor Symptoms:



Psychological Symptoms:

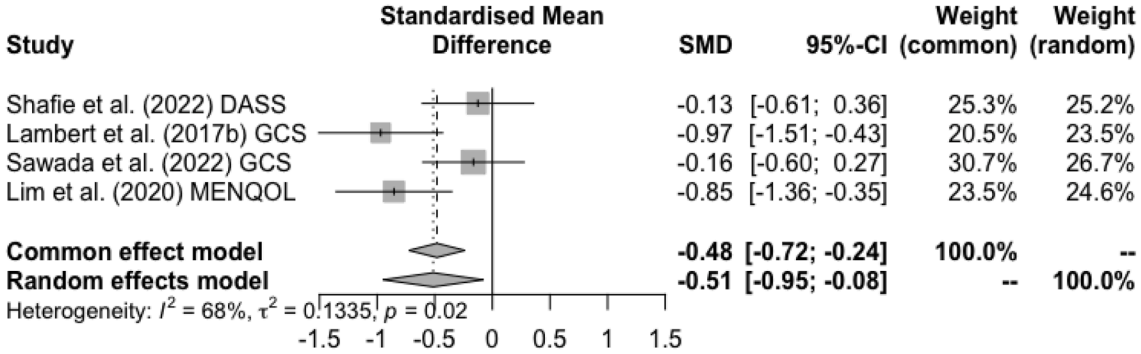
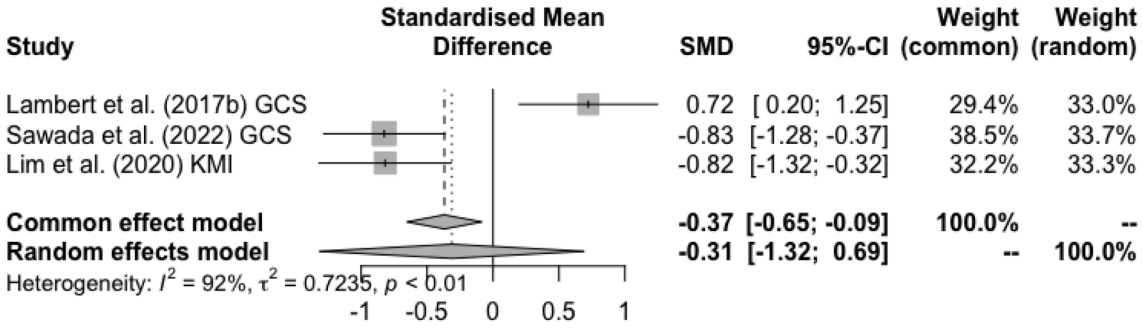
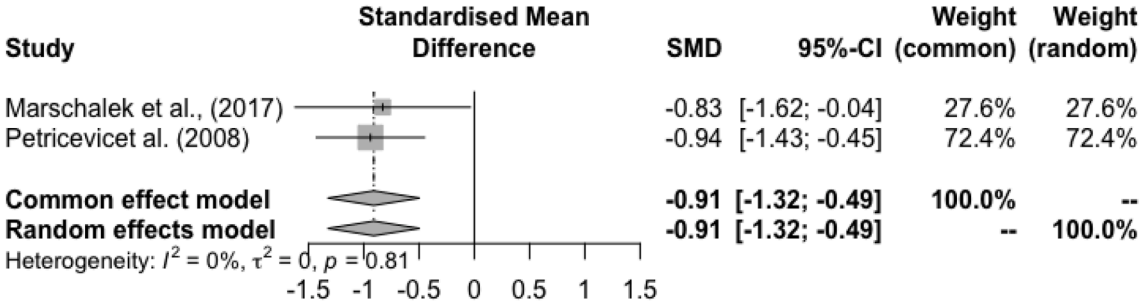


Fig. 2. Forest plot showing the effect of probiotics versus placebo on menopausal symptoms.

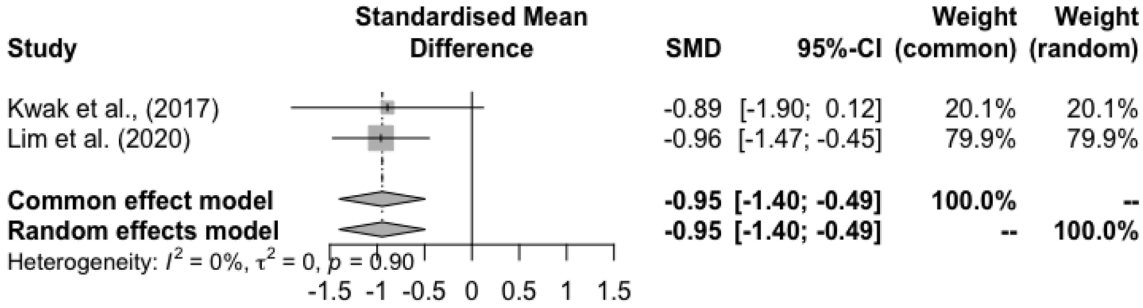
Somatic Symptoms:



Vaginal Biome Health:



Vaginal Dryness:



Sexual Symptoms:

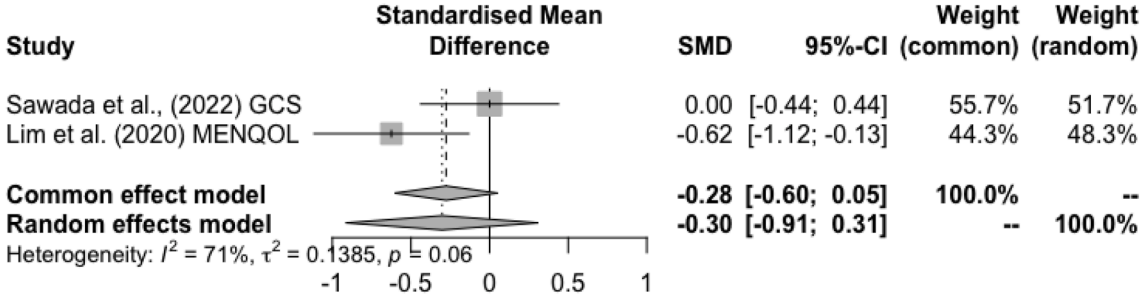


Fig. 2. (*continued*).

Other evidence suggested that probiotics could enhance the absorption of calcium and iron [51,56]. Therefore, another mechanism by which probiotics may improve health is by increasing absorption of general health-promoting nutrients.

Six studies found evidence that probiotics could enhance the effects of estriol when applied vaginally and combined with probiotics [33–35,41,43,45]. Ultra-low dose (0.03 mg) estriol when combined with L. acidophilus was associated with a similar

efficacy in reducing vulvovaginal symptoms to 0.5 mg estriol; however, unlike the higher 0.5 mg dose, estriol plus L. acidophilus neither produced significant absorption nor triggered a relevant increase in systemic estrogen levels [40]. This supports preclinical research by Chen et al. [7] which suggested that probiotic supplementation could enhance the effects of exogenous estrogens, without the need to increase the dosage, thus enhancing both the safety and efficacy of HRT. Thus, vaginal estriol preparations alongside probiotics may be a beneficial alternative treatment for women with estrogen-sensitive cancers. Albeit one study which explored estriol plus L. acidophilus did not report increased efficacy relative to placebo in reducing lower urinary tract symptoms [38]. Therefore, further research is needed to clarify the efficacy of this combination.

Several studies suggested that mammographic density, endometrial thickness, and hepatic function did not show significant differences after supplementation with isoflavones plus probiotics [23,46]. These findings suggest that probiotics combined with estrogenic substances can alleviate symptoms resulting from estrogen deficiencies, without enhancing risks of pathologies relating to excess estrogen levels. Furthermore, the majority of studies examined probiotics without the addition of estriol and isoflavones and improvements were found in vasomotor, psychological, and vaginal symptoms, as well as cardiovascular and bone health. This suggests that the use of probiotics alone is associated with beneficial effects.

Of all the studies evaluated, L. acidophilus was the most frequently examined probiotic strain and was explored in 44 % of the included studies. This strain was related to improvements in menopausal symptoms, bone health, genitourinary symptoms, and metabolic risk markers, and was shown to improve the efficacy of estriol. Moreover, the beneficial effects of topical L. acidophilus were demonstrated even at extremely low doses (CFU = 10^8). This might suggest that this strain is particularly beneficial for improving the health of midlife women, therefore it is recommended that future research explores this strain among menopausal populations. Less frequently explored strains such as L. plantarum and L. casei were also associated with improved health outcomes, particularly in relation to bone health and vaginal symptoms [31,40,48,61]. Therefore these strains may also be particularly beneficial for symptoms which emerge during a low-oestrogen state, including vasomotor symptoms, however more studies investigating these strains are needed.

4.3. Safety & adverse effects

Probiotic interventions were generally well-tolerated across studies, with no significant adverse effects reported in most trials. For instance, studies examining bone health found no notable safety concerns, even when reductions in bone turnover markers were achieved [49,53]. Similarly, research into menopausal symptom management demonstrated improvements in quality of life without adverse effects, with no significant changes observed in blood follicle-stimulating hormone, oestradiol levels, or endometrial thickness [26]. Notably, in studies which used the highest dosages of probiotics [22,58], gastrointestinal issues (which are the most reported side effect of probiotics) and other adverse effects were not significantly increased in those using high dose probiotics, exemplifying the safety profile of high-dose probiotics. In vaginal health studies, probiotics combined with low-dose estriol were evaluated among postmenopausal breast cancer patients. While transient increases in serum estriol were observed, systemic oestrogen levels remained within safe ranges, suggesting minimal systemic absorption [33,41]. In interventions combining probiotics with isoflavones, no adverse effects were observed on mammographic density, endometrial thickness, or hepatic function, further supporting their safety profile [23,46]. This suggests that the estrobolome can be harnessed to improve health outcomes without increasing risks of oestrogen dependent cancers, however, to date no research has been conducted with has investigated this hypothesis indicating a need for further research. Overall, while some studies had methodological concerns regarding bias, no substantial evidence emerged indicating safety risks across the evaluated outcomes. These findings support prior suggestions that probiotics are a safe and well-tolerated alternative therapy.

4.4. Strengths, limitations & future directions

A key strength of this review is that it enhances work conducted by Sivamaruthi et al. [3] who conducted literature searches using the keywords “probiotics” and “menopause” across Google Scholar, Scopus, and PubMed. The present review used a wider variety of key words and terms relating to probiotics, menopause, and menopausal symptoms, and a wider range of databases. Another strength is the inclusion of the first reported meta-analysis quantifying the impact of probiotics on menopausal health metrics, using high quality placebo-controlled studies.

A limitation is the low number of studies eligible for inclusion in the meta-analysis, hence why assessments of publication bias and meta-regressions identifying sources of heterogeneity could not be conducted [14]. To enhance the precision of these outcomes, there is a need for more RCT studies examining probiotics so this analysis can be repeated in the future to further clarify these outcomes.

Another limitation is that many studies were of poor quality. In several cases studies did not fully report outcome values, and therefore could not be included in meta-analyses [22,23,40,44–46]. Moreover, many studies had clear conflicts of interest. For example, five out of the seven studies exploring estriol + L. acidophilus were commissioned by the same sponsors (Medinova) who developed the estriol + L. acidophilus treatment (Gynoflor; 43, 33, 34, 45, 41). Nonetheless, outcomes relating to the effects of probiotics on reducing estrogen-related pathologies were promising and suggest that probiotics may influence estrogen. Therefore, future research within the field of probiotics, HRT, and menopause should focus on conducting high quality RCTs to build upon these findings. This is especially pertinent to women at risk of estrogen-dependent cancers, and other pathologies that negate the use of higher doses of HRT, as probiotics may offer a suitable remedy for menopausal symptoms and a potential pathway to improve the efficacy of low-dose exogenous estrogens. Another limitation was the high heterogeneity between studies in terms of menopausal populations examined, probiotic preparations, types and CFU contents, and delivery alongside additional substances. This was a likely outcome given that it was deemed important to capture all research relating to probiotics and menopausal health, and the vast number of available probiotic species and strains, especially given that probiotics are generally thought to be safe when combined with medications and other nutritional preparations. Currently, comparative health effects of probiotic strains, frequency, dosage and duration of probiotic therapy are not well established [67]. However, there is evidence that higher dosages of probiotics are associated with greater improvements in metabolic risk markers than lower dosages [59], which might suggest that higher probiotic CFU contents are more likely to result in greater improvements in menopause-specific health outcomes. Regardless of the variability between studies, most findings indicated that probiotics could lead to benefits, with all but three included studies [38,58,62] finding statistically

significant beneficial effects. Thus, further research should delve deeper into these findings and aim to conduct high quality RCTs, with clear parameters in terms of probiotic type and dosage, to identify the ideal formulations needed to effectively enhance health during the menopause transition.

5. Conclusions

This review found evidence that probiotics could lead to improvements in menopausal symptoms, cardiovascular, vaginal and bone health, and enhancing the effects of low dose estriol and isoflavones. Findings are limited by the high risks of bias relating to the studies included here, and the high heterogeneity between studies in relation to the menopausal populations and interventions being explored. It is recommended that future research should aim to establish and quantify the ideal probiotic dosages needed to achieve the most benefits among menopausal women. Additionally, comprehensive analyses of specific probiotic strains are needed to identify the most effective types and combinations for maximising these benefits. Should findings continue to show benefits, probiotics should be considered an alternative or complementary treatment for women experiencing menopausal symptoms, or for women with contraindications for using high-dose HRT formulations. Based on the available evidence, probiotics show promise as a potential intervention for improving the health and well-being of menopausal women. Probiotics demonstrate potential clinical significance for reducing menopausal symptoms and increasing bone health. However, higher-quality trials are needed to confirm the clinical significance of cardiovascular and vaginal health outcomes. Probiotics combined with other therapies (e.g., estriol or isoflavones) may offer enhanced benefits. Should more high-quality studies demonstrating benefits emerge, clinical practice guidelines can be updated to incorporate probiotics as a potential adjunct therapy for managing menopausal symptoms and promoting overall health during the menopause transition.

Author contribution statement

RA prepared the manuscript and devised the study design and hypotheses and conducted the meta-analysis. RA & HR conducted the searches, study extractions, and quality assessments. AL consulted on the statistical analyses. EJK, AL, HR, RT and KB revised and reviewed the manuscript. KB contributed to the study design and hypotheses and revised and reviewed the manuscript.

Ethical approval

Ethical approval was not required, as this is a systematic review of published studies.

Industry funded research

This study was sponsored by industry (Health & Her). Health & Her was involved in the study design, execution, analysis, and interpretation of these findings. The involvement of Health & Her funding was transparent, acknowledged, and appropriately recognized throughout all stages of design, implementation, and reporting. Project design, implementation, analysis, and interpretation had been performed with efforts to maximize academic independence in each of these areas through the engagement of an academic co-author who does not have financial ties to Health & Her. All raw data (e.g. study extraction tables, meta-analyses calculations, and quality assessment check lists) will be made available to interested scientists if requested.

Declaration of competing interest

RA, HR, AL, and RT are engaged with Health & Her on a contractual or employment basis. KB is the CEO and co-founder of Health & Her. EJK has no financial conflicts of interest to declare but collaborates with Health & Her on an externally grant funded research project.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2025.07.009.

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