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Review

Integration of Precision Nutrition, Digital Health, and Functional Foods in Postmenopausal Women: A Comprehensive Review and a Novel Tiered Framework for Clinical Implementation

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Abstract

The postmenopausal period is associated with a significantly increased risk of metabolic disorders, osteoporosis, and cardiovascular disease, highlighting the need for innovative nutritional approaches. This comprehensive review summarizes data from 187 selected publications across three major databases (PubMed/MEDLINE, Scopus, and Web of Science), with a specific focus on systematic reviews, meta-analyses, and randomized controlled trials (RCTs). We critically assessed precision nutrition strategies that integrate omics technologies, including nutrigenomics, metabolomics, and microbiome analysis, and digital health tools, such as artificial intelligence (AI)-based apps, continuous glucose monitoring systems, and wearable biosensors, to address postmenopausal health challenges. Moreover, we evaluated the evidence for the effectiveness of functional foods and nutraceuticals, focusing on dietary patterns (Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and plant-based diets); key bioactive compounds (phytoestrogens such as soy isoflavones and lignans, plant sterols/stanols, marine-derived omega-3 fatty acids, and antioxidants/polyphenols); baseline calcium/vitamin D supplementation; microbiome-targeted interventions (probiotics, postbiotics, and prebiotics); novel nutraceuticals (collagen peptides, coenzyme Q10, and myo-inositol). Finally, we distinguished approaches supported by robust clinical evidence from those requiring further validation. As a key new contribution, we propose a tiered implementation framework (basic, advanced, and detailed) to facilitate clinical integration from phenotype-based approaches to multi-omics personalization, with clear biomarker cutoff values and multidisciplinary engagement. This review highlights the promising, yet still evolving, potential of a systematic approach to precision nutrition to improve long-term health outcomes for a growing number of postmenopausal women, while emphasizing the need for further research to address gaps in the evidence base.

Keywords: postmenopause; personalized nutrition; digital health; nutrigenomics; metabolomics; functional foods; precision medicine

1. Introduction

The transition to menopause represents a critical physiological milestone that profoundly impacts women's health trajectories. The postmenopausal period, characterized by the cessation of ovarian function and a sharp decline in endogenous estrogen production, is associated with accelerated metabolic dysfunction, increased risk of cardiovascular disease (CVD), progressive bone loss, and debilitating vasomotor symptoms [1]. Many women currently spend 50% of their lives in a postmenopausal state, and given the global aging population, more than one billion women worldwide are expected to be perimenopausal or postmenopausal by 2025, highlighting the urgent need for effective preventive public health strategies [2].

Traditional approaches to postmenopausal health management rely primarily on hormone replacement therapy (HRT) and general dietary recommendations emphasizing calcium, vitamin D, and balanced macronutrient intake [3]. However, significant limitations of universal dietary recommendations have been identified due to the heterogeneity of individual responses to interventions and the complex interactions between genetics, metabolism, and gut microbiota [4,5,6]. Moreover, concerns about the long-term safety of HRT have led to a paradigm shift toward non-pharmacological, nutrition-based strategies [7].

Recent advances in omics technologies, including nutrigenomics, metabolomics, and microbiome profiling, have opened unprecedented opportunities for precision nutrition interventions tailored to individual biological profiles [8]. Concurrently, the proliferation of digital health technologies, artificial intelligence (AI)-based applications, and wearable biosensors has created new platforms for real-time monitoring and personalized dietary counseling [9]. These innovations promise to transform postmenopausal health management from reactive symptom treatment to proactive data-driven prevention. However, translating this promise into routine clinical practice depends on robust

validation, demonstration of cost-effectiveness, and the removal of significant barriers to implementation, including access and equity in healthcare.

In this review, we employ the following definitions: 'personalized nutrition' refers to dietary recommendations tailored to a person's individual characteristics (e.g., phenotype or lifestyle), while 'precision nutrition' specifically denotes approaches based on quantitative biological data, including genomics, metabolomics, and microbiome profiling.

This comprehensive review summarizes the available evidence on innovative dietary and nutritional strategies for postmenopausal women, with a particular focus on:

(1) Personalized nutrition approaches based on nutrigenomics, metabolomics, and microbiome analysis;

(2) Digital health technologies for dietary monitoring, symptom tracking, and AI-based dietary recommendations;

(3) Evidence-based dietary models and targeted functional foods/nutraceuticals;

(4) A practical, multi-tiered framework for implementing precision nutrition into clinical practice, including clinically established biomarker cutoff value and a multidisciplinary approach.

2. Materials and Methods

This paper is a comprehensive narrative review designed to summarize and critically evaluate the available evidence on innovative dietary and nutritional strategies for postmenopausal women. The primary objective was to integrate knowledge from various fields, including precision nutrition, omics technologies, digital health, and nutritional science, to develop a new practical model for clinical application. Given the conceptual and interdisciplinary nature of this task, a formal systematic review methodology with strict inclusion criteria and meta-analysis was not employed, as it would have been unsuitable for answering such a broad, integrative research question.

2.1 Literature Search Strategy

Relevant publications were identified through a targeted search of three major scientific databases: PubMed/MEDLINE, Scopus, and Web of Science. The search covered the period from January 1, 2000, to November 20, 2025, with the final search conducted on November 23, 2025. While the focus was on the sources published over the period of 2000–2025, earlier seminal works (e.g., early studies in nutrigenomics) were also included in the search if they were identified through reference lists or author information.

The search strategies used a combination of keywords and Medical Subject Headings (MeSH) terms related to the main topics of the review as follows: *"postmenopause", "menopausal transition", "precision nutrition", "personalized nutrition", "nutrigenomics", "metabolomics", "microbiome", "estrobolome", "digital health", "mobile health", "artificial intelligence", "continuous glucose monitoring", "wearable sensors", "functional foods", "nutraceuticals", "phytoestrogens", "soy isoflavones", "omega-3 fatty acids", "plant sterols", "probiotics", "Mediterranean diet", "DASH diet", "plant-based diet", "ketogenic diet", "intermittent fasting", "time-restricted eating", "bone health", "cardiovascular risk", and "vasomotor symptoms"*. The search was limited to articles and reviews published in English. In PubMed, this was achieved using the filters article[pt] OR review[pt]; in Scopus and Web of Science, the document type was limited to "article" or "review" (see **Supplementary Material 1** for the full search strings).

Given the narrative and integrative nature of this review, a formal, systematic selection process using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was not employed. Instead, a purposive sampling approach was used: after an initial broad search, the authors iteratively selected publications based on their relevance to the conceptual framework, scientific impact (e.g., number of citations, journal prestige, impact on the field), and contribution to understanding mechanisms or clinical applications. This approach is consistent with established methodologies for narrative and integrative reviews, which prioritize conceptual synthesis over exhaustive enumeration.

2.2 Study Selection and Prioritization

During the selection process, the following types of evidence were prioritized:

(1) High-level evidence. Systematic reviews, meta-analyses, and large randomized controlled trials (RCTs) with a sample size of over 100 participants were given the highest weight. They served as the primary basis for conclusions regarding intervention effectiveness;

(2) Fundamental and impactful research. Seminal original research articles that shaped understanding of menopause-related pathophysiology or introduced key concepts in the field of precision nutrition were included, regardless of publication date, if they provided the necessary context;

(3) Recent advances. Publications within the last 5–10 years were prioritized to ensure that the review reflected the current state of rapidly evolving fields such as digital health and omics technologies;

(4) Mechanistic evidence. Selected preclinical (animal or *in vitro*) studies and small observational studies in humans were included only when they provided the necessary mechanistic explanations for clinical observations and when human intervention data were absent or insufficient. Their inclusion is clearly noted in the text as preliminary or mechanistic.

Ultimately, 187 publications were included in the review. This final set was obtained through an iterative process: after removing duplicates, the authors screened the titles and abstracts of 3488 records, of which 1843 were

deemed potentially relevant. Full texts were retrieved for 412 articles that met preliminary relevance criteria, and 187 of these were ultimately included in the synthesis.

2.3 Data Synthesis and Evidence Assessment

A narrative thematic approach to the synthesis was adopted. The identified evidence was organized into coherent thematic sections (pathophysiological foundations, omics technologies, digital health, intervention strategies) to facilitate logical and critical discussion.

To enhance transparency and clinical utility, we qualitatively assessed the strength of evidence for key interventions using clear terminology throughout the text:

(1) Strong evidence (consistent results from multiple high-quality RCTs and/or meta-analyses demonstrating clinically meaningful effects);

(2) Promising evidence (limited RCTs, often with small samples or short duration, but with consistent observational data or mechanistic support implying the necessity of further investigation);

(3) Preliminary/emerging evidence (results from small pilot studies, uncontrolled trials, or preclinical studies; such evidence is insufficient for clinical recommendations but noted for future guidelines).

Whenever possible, quantitative data (effect sizes, confidence intervals, sample sizes, study durations) are provided to provide specificity. The synthesis concludes with a proposed structured tiered implementation framework (Section 7), which represents the main new contribution of this review.

2.4 Scope and Limitations

This review provides a critical state-of-the-art perspective rather than an exhaustive quantitative summary of all available publications. The following limitations are inherent to the narrative review format and are openly acknowledged:

(1) Selection bias. Although we prioritized high-level evidence, our purposive selection process may have missed some relevant studies. We mitigated this by including comprehensive search strings in **Supplementary Materials** and cross-referencing bibliographies of key articles;

(2) Lack of formal bias assessment. Unlike systematic reviews, we did not conduct a formal risk of bias assessment (e.g., Cochrane RoB 2) for individual studies. However, the qualitative assessment framework (Section 2.3) provided a transparent indication of the strength of the evidence;

(3) Temporal asymmetry. Rapidly evolving fields (digital health, microbiome) rely heavily on recent publications, while some nutrigenomic concepts are supported by older, but still valid, mechanistic studies;

(4) Population representativeness. As discussed in Section 8.3.1, the evidence base is drawn largely from trials in which racial and ethnic minorities are underrepresented, thereby limiting generalizability of the results to different populations.

These limitations are offset by the broad scope of integration and critical analysis achieved across disciplines and emphasize that precision nutrition should currently complement rather than replace standard, evidence-based nutrition recommendations for most postmenopausal women.

3. Pathophysiological Basis: Metabolic Transitions During Menopause

3.1 Hormonal Changes and Metabolic Consequences

The transition to menopause is primarily driven by progressive depletion of ovarian follicles, leading to a noteworthy decrease in circulating levels of estradiol (E2) and progesterone [10]. These hormonal shifts trigger a cascade of the following metabolic changes that significantly increase disease risk:

(1) Cardiometabolic dysfunction. Estrogen deficiency disrupts insulin signaling, promotes visceral fat accumulation, and negatively impacts lipid metabolism via increasing total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides while decreasing high-density lipoprotein cholesterol (HDL-C) [11]. Postmenopausal women have a 2-3-fold higher risk of developing metabolic syndrome than premenopausal women [5,6,12].

(2) Impaired bone remodeling. The loss of estrogen's protective effect on osteoblast function and osteoclast apoptosis leads to accelerated bone resorption, with trabecular bone loss reaching 2–3% per year in the first 5–7 years after menopause [13]. This dramatically increases the risk of osteoporosis and fractures, with the lifetime fracture rate exceeding 40% in postmenopausal women [14];

(3) Cardiovascular vulnerability. Decreased estrogen levels impair endothelial function, increase arterial stiffness, promote an atherogenic lipid profile, and elevate inflammatory markers, e.g., C-reactive protein and interleukin 6 (IL-6). All of these collectively contribute to the dramatic increase in CVD incidence after menopause [15];

(4) Vasomotor symptoms (including hot flashes and night sweats) that occur in 70–80% of postmenopausal women and significantly impair quality of life, potentially serving as markers of underlying cardiovascular dysfunction [16].

3.2 Gut Microbiome Changes

Emerging evidence suggests that menopause-associated hormonal changes profoundly influence the composition and function of the gut microbiome, with significant implications for metabolic health, bone homeostasis, and systemic inflammation [17,18,19].

Key microbiome changes include:

• Decreased microbial diversity. Postmenopausal women exhibit reduced gut microbial diversity compared with premenopausal women, together with compositional shifts including depletion of butyrate-producing taxa such as *Roseburia spp.*; findings across cohorts are not fully consistent, and larger studies are required [20];

• Estrobolome dysfunction. The estrobolome, a collection of gut bacterial genes encoding enzymes capable of metabolizing estrogens, is disrupted during menopause, potentially affecting estrogen bioavailability and contributing to the development of estrogen deficiency symptoms [18,21];

• Short-chain fatty acid (SCFA) alterations. Decreased SCFA production (especially butyrate) disrupts the integrity of the gut barrier, promotes systemic inflammation, and negatively impacts bone metabolism by affecting osteoclast and osteoblast activity [22,23,24];

• Gut-bone axis dysregulation. Microbiome-mediated modulation of immune function (particularly T cell and B cell responses) directly impacts bone remodeling, with dysbiosis promoting osteoclastogenesis and bone loss [25].

3.3 Metabolomic Signatures

Metabolomic profiling has revealed distinct metabolic signatures of the postmenopausal period, characterized by disrupted glucose homeostasis, lipid metabolism, and amino acid profiles [8,26].

Postmenopausal women experience the following:

• Postprandial dysmetabolism: excessive postprandial fluctuations in glucose and lipid levels, reflecting insulin resistance and altered incretin responses [5,6,27];

• Altered bile acid metabolism: shifts in primary and secondary bile acid profiles affecting lipid absorption, glucose metabolism, and gut microbiome composition [8,28];

• Oxidative stress markers: elevated markers of lipid peroxidation and decreased antioxidant capacity, contributing to accelerated aging and disease progression [29].

These pathophysiological underpinnings provide critical targets for precision nutrition-based interventions aimed at restoring metabolic homeostasis and reducing disease risk.

4. Personalized Nutrition: Omics-Based Approaches

4.1 Nutrigenomics: The Genetic Basis of Response to Dieting

Nutrigenomics investigates how genetic variation modulates individual responses to dietary components, forming the scientific basis for genotype-based nutritional strategies [4,30]. In postmenopausal women, several polymorphisms influence nutrient metabolism, disease risk, and the effectiveness of dietary interventions, suggesting potential avenues for personalization. To enhance clinical applicability, we distinguish between variants with established clinical evidence and those that remain under investigation.

4.1.1 Lipid Metabolism

Established clinical evidence indicates that the ε4 allele of apolipoprotein E (*APOE*) is associated with elevated LDL-C levels, and that ε4 carriers, including postmenopausal women, show greater improvement in LDL-C in response to reductions in dietary saturated fat and cholesterol [31].

Further research is needed (FRIN): polymorphisms in the cholesteryl ester transfer protein (*CETP*) gene, such as *TaqIB* (*rs708272*), modulate the HDL-C response to dietary fat, but the effect sizes are small, population-specific, and inconsistently reproduced, so a clinical benefit has not yet been established [32].

4.1.2 Bone Metabolism

Established clinical benefit: vitamin D pathway (vitamin D receptor (*VDR*), cytochrome P450 family 2 subfamily R member 1 (*CYP2R1*), group-specific component (*GC*)): polymorphisms in genes critical for vitamin D metabolism significantly impact bone health. Variants in *CYP2R1* (encoding vitamin D 25-hydroxylase) and in *GC* (encoding vitamin D-binding protein, DBP) affect serum 25-hydroxyvitamin D [25(OH)D] levels and may influence vitamin D dosage [33]. Variants in the *VDR* gene (e.g., BsmI, TaqI) affect calcium absorption and bone mineral density (BMD) response; carriers may require higher vitamin D intake [33].

FRIN: variants in the collagen type I alpha 1 (*COL1A1*) and estrogen receptor alpha (*ESR1*) genes are associated with altered fracture risk and may influence skeletal response to dietary phytoestrogens, but are insufficient for gene-targeted therapy [34].

4.1.3 Carbohydrate Metabolism and Insulin Sensitivity

Established clinical evidence: The T allele of transcription factor 7-like 2 (*TCF7L2*) *rs7903146* is the strongest common genetic risk factor for type 2 diabetes, influencing postprandial glucose regulation. The adverse cardiometabolic effects associated with this variant appear to be attenuated by a Mediterranean diet, but not by a conventional low-fat diet [4,35].

FRIN: Insulin receptor substrate 1 (*IRS1*) variants may exacerbate the risk of insulin resistance, but dietary interactions are poorly understood [36]. Women carrying multiple risk alleles may particularly benefit from a low-glycemic index diet combined with physical activity [37].

4.1.4 Energy Metabolism and Body Composition

FRIN: obesity susceptibility genes (fat mass and obesity-associated gene (*FTO*), melanocortin-4 receptor (*MC4R*), peroxisome proliferator-activated receptor gamma (*PPARG*)) are associated with obesity risk, but data on genotype-specific dietary recommendations for postmenopausal women are conflicting [38,39]. Variants in the *FTO* (e.g., *rs9939609*) influence energy homeostasis and may predict differential weight loss in response to caloric restriction in postmenopausal women [38]. The effect of FTO may be enhanced during the menopausal transition due to decreased estrogen levels. Polymorphisms in the *MC4R* and *PPARG* genes additionally influence satiety signals and

adipose tissue distribution, although their interaction with menopausal status requires further investigation [39].

4.1.5 Micronutrient Metabolism

Established clinical evidence: the *MTHFR C677T* polymorphism (methylenetetrahydrofolate reductase, *MTHFR*) reduces enzyme activity, increasing homocysteine levels, a modifiable risk factor for CVD [4,10,40]. Although general folate supplementation is beneficial, specific nutrigenomic interactions have been observed; for example, carriers of the TT genotype demonstrate a significant reduction in blood pressure in response to riboflavin (vitamin B2) supplementation (~1.6 mg/day) [4].

FRIN: *SLC30A8* acts as a zinc transporter; there is also preliminary evidence of glucose homeostasis, but clinical benefit has not been established yet [4]. The *SLC30A8 rs11558471* variant allele of the zinc transporter gene may require additional zinc to maintain optimal glucose homeostasis [4]. Polymorphisms in glutathione-S-transferase (*GST*) genes affect detoxification capacity. Although theoretically relevant for managing oxidative stress during menopause, there is currently a lack of compelling clinical data supporting genotype-specific antioxidant supplementation in this population [29].

4.1.6 Estrogen Metabolism and Detoxification

FRIN: polymorphisms in phase I (cytochrome P450 1A1 (*CYP1A1*) and 1B1 (*CYP1B1*)) and phase II (catechol-O-methyltransferase, *COMT*) enzymes determine the estrogen metabolite profile [41]. Dietary components such as indole-3-carbinol (from cruciferous vegetables) and soy isoflavones may modulate these enzymatic pathways, but genotype-based phytoestrogen recommendations lack robust clinical trial data [41,42,43].

4.1.7 Taste Perception and Eating Behavior

FRIN: variants in fat (*CD36*) and sweet taste receptors (*TAS1R*) may influence food preference and intake, while genetic variation (*TAS2R38*) in bitter taste receptors (*TAS2R*) may influence the perception and intake of cruciferous vegetables, which are sources of glucosinolates and phytoestrogens, but evidence linking them to meaningful clinical outcomes is insufficient [39].

To summarize these findings in a clinically relevant format, Table 1 (Ref. [4,29,31,32,33,34,35,36,38,39,40,41,42,43]) presents key nutrigenomic interactions by major clinical concerns in postmenopausal women, highlighting personalized strategies and expected benefits.

4.1.8 Current Limitations and Future Directions

Despite promising mechanistic data, the clinical application of nutrigenomics faces several challenges as follows [44]:

• Limited number of intervention studies. Few RCTs have demonstrated superior clinical outcomes with genotype-based recommendations vs. standard dietary guidelines;

• Polygenic complexity. Most traits require polygenic risk assessments rather than single-gene approaches [45];

• Gene-environment interactions. Genetic effects often vary with underlying diet and lifestyle [46,47].

It is crucial to recognize that, with the exception of a few treatable polymorphisms (APOE, TCF7L2, MTHFR, VDR), genotype-specific dietary recommendations are not yet ready for widespread clinical application and should currently be reserved for research purposes or specialized clinics.

4.2 Metabolomics: Real-Time Metabolic Phenotyping

Metabolomics offers a dynamic assessment of metabolic status, enabling personalized dietary interventions in real time based on individual metabolic responses [48]. Key applications in postmenopausal nutrition are listed in Sections 4.2.1 and 4.2.2.

4.2.1 Postprandial Metabolic Profiling

Large-scale studies, such as the PREDICT consortium, have demonstrated substantial interindividual variability in postprandial glucose, lipid, and insulin responses to identical test meals, with menopausal status significantly influencing these responses [27,49].

Postmenopausal women exhibit:

• Greater postprandial glucose fluctuations: in the ZOE PREDICT 1 cohort, postmenopausal women showed a 42% higher 2-h incremental area under the curve (iAUC) for glucose than premenopausal women after standardized test meals, together with unfavourable continuous glucose monitoring measures (glycaemic variability and time in range); in an age-matched subgroup this difference was attenuated but persisted (4% higher 0–2 h glucose peak), indicating that age contributes substantially to the observed effect [5];

• Long-term lipid reduction: sustained elevation of postprandial triglyceride levels reflecting impaired lipoprotein lipase activity and insulin resistance [50];

• Altered metabolic profiles: distinct patterns of amino acids (especially branched-chain amino acids), acylcarnitines, and inflammatory lipid mediators [8,51].

Machine learning algorithms trained on metabolomics data can predict individual postprandial responses and generate personalized dietary recommendations to minimize glycemic and lipid fluctuations [27,52]. Preliminary studies suggest that these approaches can improve glycemic control and lipid profiles more effectively than standard dietary recommendations, although large-scale validation studies are needed [27,53].

Table 1. Key nutrigenomic interactions and personalized nutrition strategies for addressing key clinical issues in postmenopausal women.

Clinical problem	Key genes/Polymorphisms	Clinical evidence	Personalized nutrition strategy	Expected benefit/Goal	Ref
Weight and body composition management	*FTO* (*rs9939609*), *MC4R*, *PPARG*, *TAS2R38*, *CD36*, *TAS1R*	FRIN	Intensive calorie control, high-protein diet (to increase satiety). Combined with resistance training to optimize body composition.	Enhanced fat loss, overcoming genetic predisposition to weight gain in the context of estrogen deficiency. Impact on food preferences and food intake.	[38,39]
Bone health support	*VDR* (*BsmI*, *TaqI*), GC, *CYP2R1*, *COL1A1*	*VDR*, *CYP2R1*, GC: established clinical evidence. *COL1A1*: FRIN.	Vitamin D dosage and choice of calcium form depend on genotype. Emphasis on vitamin K2 (natto, fermented foods) and magnesium.	Achieving target 25(OH)D levels and optimal calcium absorption to maximize BMD.	[33,34]
Cardiometabolic risk reduction	*APOE* (ε4 allele), *CETP* TaqIB, *TCF7L2* (rs7903146 T allele), *MTHFR* (C677T)	*APOE*, *TCF7L2*, *MTHFR*: established clinical evidence. *CETP*: FRIN.	For *APOE* ε4: strict restriction of saturated fat (<7% of calories). For *CETP* TaqIB: targeted use of omega-3 fatty acid supplements to modulate the HDL-C response. For *TCF7L2* T allele: A Mediterranean diet as a mandatory regimen. For *MTHFR* TT: folate from greens combined with riboflavin (vitamin B2) supplements (~1.6 mg/day).	Targeted reduction of LDL-C, glucose, and homocysteine; reduction of specific genetic risk for CVD and type 2 diabetes.	[4,31,32,35,36,40]
Management of vasomotor symptoms and mood	*COMT* (Val158Met), *CYP1B1*, *ESR1*	FRIN	Personalized approach to phytoestrogens: for the *COMT* Met/Met genotype: cautious administration of soy isoflavones. Cofactors: ensuring adequate levels of vitamins B6, B12, and magnesium to support neurotransmitter metabolism.	Enhancement of the effects of phytoestrogens while reducing the risk of intolerance; improvement of mood stability.	[39,43]
Prevention of cancer risks (breast cancer, endometrial cancer)	*CYP1A1*, *CYP1B1*, *COMT*, *GST*	FRIN	Research focus on dietary detoxification modulators: Regular consumption of cruciferous vegetables (indole-3-carbinol). High dietary fiber intake (≥30 g/day) for metabolite excretion. Strict alcohol restrictions.	Shifting estrogen metabolism toward less genotoxic metabolites; reducing chronic inflammation.	[29,41,42]

APOE, apolipoprotein E; BMD, bone mineral density; COMT, catechol-O-methyltransferase; CD36, cluster of differentiation 36 (fatty acid translocase); CETP, cholesteryl ester transfer protein; COL1A1, collagen type I alpha 1; CVD, cardiovascular disease; CYP1A1, cytochrome P450 1A1; CYP1B1, cytochrome P450 1B1; CYP2R1, cytochrome P450 family 2 subfamily R member 1; ESR1, estrogen receptor alpha; FTO, fat mass and obesity-associated gene; GC, group-specific component; FRIN, further research is needed; GST, glutathione S-transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MC4R, melanocortin-4 receptor; MTHFR, methylenetetrahydrofolate reductase; PPARG, peroxisome proliferator-activated receptor gamma; TAS1R, type 1 taste receptor; TAS2R38, type 2 taste receptor member 38; TAS2Rs, type 2 taste receptors; TCF7L2, transcription factor 7-like 2; VDR, vitamin D receptor; 25(OH)D, 25-hydroxyvitamin D.

4.2.2 Biomarker Panels for Precision Nutrition

Currently, the following minimal metabolomic marker panels to manage personalized nutrition interventions are proposed [8,54]:

(1) Carbohydrate metabolism panel: fasting glucose and insulin, glycated hemoglobin (HbA1c), postprandial glucose iAUC, insulin sensitivity indices, such as Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index and Matsuda index;

(2) Lipid metabolism profile: comprehensive lipoprotein profiling (LDL-C, HDL-C, very-low-density lipoprotein (VLDL), apolipoprotein B), postprandial triglyceride response, LDL particle size and count, oxidized LDL;

(3) Inflammation and oxidative stress analysis package: high-sensitivity C-reactive protein (hs-CRP), IL-6, tumor necrosis factor-alpha (TNF-α), malondialdehyde (MDA), other lipid peroxidation markers, and total antioxidant capacity;

(4) Bone turnover markers (including bone formation markers and bone resorption markers). The former category includes bone-specific alkaline phosphatase (BSAP), osteocalcin, and procollagen type I N-terminal propeptide (P1NP). The latter category includes C-terminal telopeptide of type I collagen (CTX) and N-terminal telopeptide (NTX).

Integration of these panels with dietary intervention allows for iterative optimization of nutrition plans based on objective metabolic responses [55].

4.3 Microbiome Analysis: The Gut Health Axis

The gut microbiome is a critical mediator of the impact of diet on health in postmenopausal women, with microbiome-targeted nutrition emerging as a promising approach in precision medicine [56].

4.3.1 Microbiome Profiling Approaches

Three microbiome profiling approaches can be specified:

(1) 16S ribosomal RNA (rRNA) gene sequencing. Cost-effective taxonomic profiling that determines bacterial composition at the genus/species level; it is useful for assessing overall microbial diversity and identifying key patterns of dysbiosis [57];

(2) Shotgun metagenomics. Comprehensive functional profiling that identifies microbial genes, metabolic pathways, and strain-level resolution and enables the identification of specific metabolic capabilities (e.g., SCFA production, estrogen metabolism) [58];

(3) Metabolome integration. Combined analysis of microbiome and metabolome; it links microbial composition to functional outcomes (SCFAs, bile acids, tryptophan metabolites), providing mechanistic insights [59].

4.3.2 Interactions Between Diet, Microbiome, and Health During Menopause

These interactions can be categorized as follows:

• Vasomotor symptoms. A pioneering randomized controlled trial revealed that a low-fat vegan diet supplemented with cooked soy (86 g/day) significantly reduced the frequency and severity of hot flashes in postmenopausal women, with parallel changes in gut microbiome composition [60]. Respondents showed an increase in *Porphyromonas* and *Prevotella* species, suggesting microbiome-mediated mechanisms for diet-mediated symptom relief;

• Bone health. Epidemiological analyses from the National Health and Nutrition Examination Survey (NHANES) demonstrated that dietary patterns that promote microbiome diversity (high fiber, fermented foods, polyphenols) were associated with a reduced risk of osteoporosis in postmenopausal women [61]. Mechanistic studies showed that microbiome-derived SCFAs (particularly butyrate) enhanced calcium absorption, reduced bone resorption through immunomodulation, and promoted osteoblast differentiation [62];

• Cardiometabolic outcomes. According to some studies [63], microbiome diversity and specific taxa (e.g., *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*) correlate with improved insulin sensitivity, lipid profiles, and reduced systemic inflammation in postmenopausal women [63]. The Mediterranean diet increases the abundance of these beneficial taxa while reducing proinflammatory species [64].

4.3.3 Dietary Strategies Targeting the Microbiome

Dietary strategies targeting the microbiome are as follows:

• Prebiotic interventions: inulin, fructooligosaccharides (FOS), and resistant starch selectively promote the development of beneficial bacteria and increase SCFA production. Doses of 10–20 g per day have been shown to improve calcium absorption and bone metabolism in postmenopausal women [65];

• Probiotic and postbiotic supplements: specific strains (*Lactobacillus reuteri*, *Lactobacillus helveticus*, *Bifidobacterium longum*) demonstrate bone-protective effects in animal experiments and preliminary human studies [66,67,68]. Postbiotics (heat-inactivated bacteria, bacterial metabolites) offer stability advantages and show promise for bone health [69];

• Polyphenol-rich foods: dietary polyphenols (from berries, tea, cocoa, olive oil) serve as prebiotic substrates and are metabolized by gut bacteria into bioactive metabolites with anti-inflammatory and antioxidant properties [70,71,72];

• Fermented foods: regular consumption of fermented foods (yogurt, kefir, kimchi, sauerkraut) increases microbiome diversity and may improve immune function and metabolic health in postmenopausal women [73].

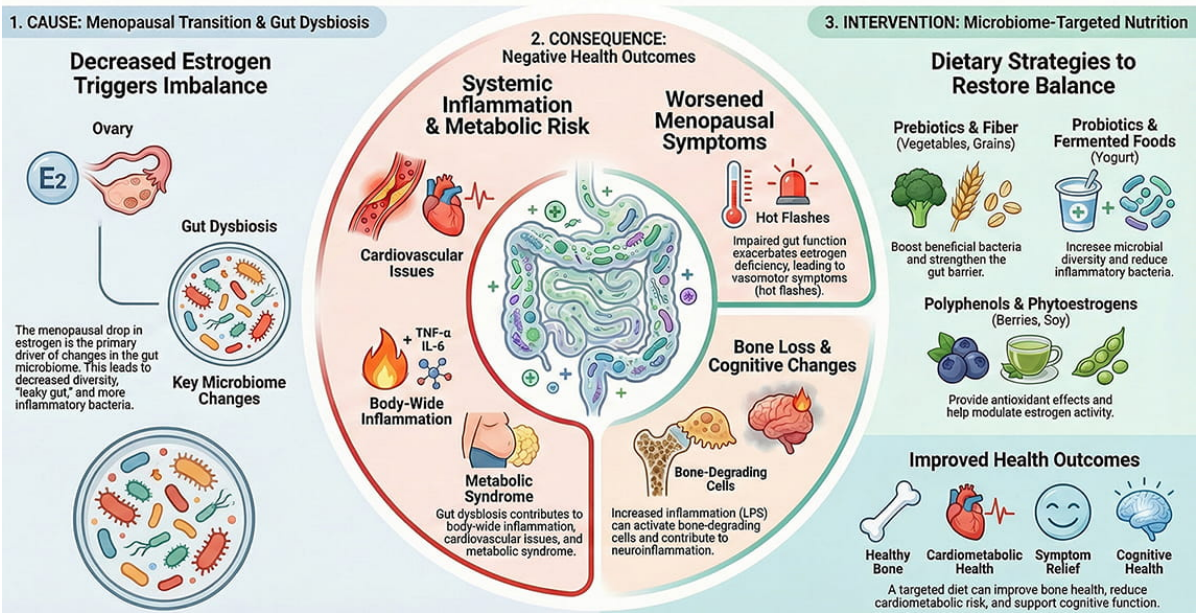

Fig. 1. The gut microbiome as a central mediator of menopause: A dysbiosis-intervention model. The figure illustrates the bidirectional nature of the gut-bone and gut-metabolism axes and highlights the potential of nutritional strategies to mitigate menopause-related health decline by modulating the gut microbiome. LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-alpha.

Taken together, these data suggest a model in which the gut microbiome serves as a key link between hormonal changes during menopause and systemic health. This integrative pathophysiological and interventional model is presented in Fig. 1.

4.3.4 Issues of Clinical Implementation

While personalized microbiome-based nutrition is promising, several challenges still remain:

(1) Interindividual variability (the underlying microbiome composition varies significantly, requiring personalized prebiotic/probiotic selection [67,68,74]);

(2) Temporal stability (the microbiome fluctuates, requiring long-term monitoring [75]);

(3) Gaps in standardization (the lack of standardized protocols, which limits clinical application [76]);

(4) Cost considerations (comprehensive profiling remains expensive [77]).

Practical recommendations include starting with evidence-based dietary patterns known to promote healthy microbiome composition (Mediterranean diet, high fiber intake), while detailed microbiome profiling should be reserved for research or specialized clinics [78].

4.4 Integration of Multi-Omics Layers: A Holistic View

The three main omics fields (genomics, metabolomics, and microbiome analysis) are not independent data streams but rather complementary layers that together form a comprehensive biological portrait of an individual. Understanding their interactions is essential for translating multi-omics data into precision nutrition strategies, but the clinical application of such integration is still in its infancy.

4.4.1 Complementary Information of Layers

Each omics layer contributes a distinct type of information. Genomics reveals inherent predispositions: fixed genetic blueprints that influence nutrient metabolism and disease risk (e.g., *VDR* polymorphisms affecting vitamin D utilization, *APOE* variants modulating lipid response). Metabolomics captures functional indicators in real time: a dynamic metabolic state reflecting genetics, diet, and the environment (e.g., serum 25(OH)D levels, branched-chain amino acid profiles).

Microbiome analysis identifies a modifiable mediator (the gut microbial ecosystem) that interacts with host genetics and diet to produce bioactive metabolites (e.g., SCFAs, equol from soy isoflavones).

4.4.2 Temporal Dynamics

These levels operate on different time scales that are clinically relevant: genomics is static (a single assessment provides ongoing risk stratification), the microbiome is moderately dynamic (it changes over days or weeks in response to dietary changes, thus requiring periodic reassessment), and metabolomics is highly dynamic (it reflects daily changes and is ideal for monitoring treatment adherence and efficacy).

4.4.3 Illustrative Integrative Concepts

The value of multi-omics integration is best understood through the examples demonstrating how the layers influence each other:

• Bone health. A patient with a *VDR* polymorphism (genomics) may have reduced calcium absorption efficiency, but this predisposition only becomes clinically significant if metabolomics reveals insufficient serum 25(OH)D levels. Microbiome analysis showing low levels of butyrate-producing bacteria adds another dimension, as butyrate enhances calcium absorption. Together, these layers point to the need for higher vitamin D intake (based on genomics), confirmation of sufficiency through metabolomics, and potential prebiotic support for the microbiome (each of these aspects is discussed below in Section 7);

• Cardiometabolic risk. *APOE ε4* carriers (genomics) may require more stringent saturated fat restriction, but the urgency and intensity of intervention are determined by metabolomics (e.g., elevated LDL cholesterol, triglycerides). Microbiome characteristics, such as low *Akkermansia muciniphila* levels, may indicate metabolic vulnerability and suggest potential benefit from polyphenol-rich foods (the specific implementation strategies are outlined in Section 7);

• Vasomotor symptoms. A patient's ability to benefit from soy isoflavones depends not only on their consumption but also on the presence of equol-producing gut bacteria (microbiome). Genomics (e.g., *COMT* variants) may influence estrogen metabolism, but this is still under investigation. The clinical approach (whether to recommend soy, consider fermented foods, or explore equol supplementation) is determined by the integration of these levels, with options stratified by level of evidence, as described in Section 7.

4.4.4 From Integration to Implementation

These examples illustrate that the integration of multi-omics data enables a coherent, hypothesis-driven approach: genomics reveals long-term predispositions, metabolomics reveals current metabolic state, and the microbiome suggests targets for modification. The practical translation of this integrated approach into clinical practice, including determining which assessments are appropriate for different resource levels and how to act on the results, is implemented in the tiered framework presented in Section 7. This division ensures that the conceptual integration (Section 4.4) does not extend beyond prescriptive clinical guidelines, which are more appropriately considered within an implementation framework.

5. Digital Health Technologies for Precision Nutrition

5.1 AI-Based Dietary Applications

AI and machine learning algorithms are revolutionizing personalized nutrition delivery through smartphone apps that integrate multidimensional data to generate customized dietary recommendations [4,9,79].

5.1.1 Predictive Algorithms

Postprandial response prediction. AI models trained on continuous glucose monitoring data, food composition, physical activity, sleep, and gut microbiome profiles can accurately predict individual glycemic responses to foods (R^2 = 0.68–0.76) [49,80]. These predictions enable proactive meal planning to minimize glucose fluctuations in postmenopausal women at risk for diabetes [5,27].

Lipid response modeling. Machine learning approaches incorporating genetic variants, baseline lipid profiles, and food intake patterns can predict individual responses to changes in dietary fat intake, enabling personalized fat intake recommendations [81].

Weight management algorithms. AI-based applications utilizing behavioral data, food intake data, physical activity tracking, and psychometric assessments demonstrate superior weight loss outcomes vs. standard calorie-counting apps in postmenopausal women [82].

5.1.2 Nutrigenomic Decision Support Systems

The PREVENTOMICS project (personalized nutrition for disease prevention based on omics technologies) aims to empower consumers to prevent diet-related diseases through an integrated system. This system assesses the state of five key biological processes (oxidative stress, systemic inflammation, carbohydrate and lipid metabolism, and microbiota-produced metabolites) using metabolomics, proteomics, and genetic data. To facilitate the system's implementation in various information and communications technology (ICT) applications, a separate score is calculated for each process to provide personalized recommendations [83]. Platforms such as PREVENTOMICS are integrated frameworks that collect multi-omics data (genomics, metabolomics, microbiome), apply dimensionality reduction and machine learning algorithms, generate personalized nutrition recommendations, and provide practical advice through mobile apps [8,83,84].

5.1.3 Chatbots and Virtual Nutritionists

AI-based conversational agents provide real-time nutrition recommendations, answer nutrition-related questions, and offer behavioral support. A systematic review and meta-analysis of 19 trials demonstrated modest but significant effects of chatbot interventions on lifestyle behaviours, including fruit and vegetable consumption (standardized mean difference = 0.59; 95% confidence interval: 0.25–0.93), together with advantages in accessibility and scalability; however, most of the included trials were of low methodological quality, and head-to-head comparisons with dietitian-delivered counseling are lacking [85].

5.1.4 Evidence Base and Limitations

While pilot studies support the operational feasibility of AI-based nutrition tools, evidence from large-scale studies demonstrating the superiority of dietary counselling

over standard care for major clinical outcomes (e.g., cardiovascular disease, fractures) remains limited. Existing studies have shown only modest additional benefits [86]. Given their high cost and complexity, these platforms require rigorous validation of cost-effectiveness and clinical utility before widespread adoption. These considerations generally apply to AI-based nutrition tools and are discussed in more detail in Section 5.4.2.

5.2 Wearable Biosensors and Continuous Monitoring

5.2.1 Continuous Glucose Monitors (CGMs)

CGMs track glucose levels in real time, identifying individual glycemic responses to specific foods, meals, and lifestyle factors [87]. They are employed in postmenopausal women for the following purposes:

• Glycemic variability assessment. CGMs detect glucose fluctuations not captured by HbA1c or fasting glucose, thereby identifying individuals at risk of diabetes progression [88];

• Diet optimization. Real-time feedback allows for rapid dietary adjustments to minimize glucose fluctuations, with studies showing improved glycemic control and weight loss [89];

• Behavioral reinforcement. Immediate visualization of glucose responses to food choices increases dietary adherence and motivation [90].

5.2.2 Activity Trackers and Energy Expenditure Monitoring

Wearable activity monitors (accelerometers, heart rate sensors) provide objective assessment of physical activity and energy expenditure, enabling:

• Energy balance optimization (integrating food intake and energy expenditure data for precise calorie management) [91];

• Sedentary behavior detection (identifying prolonged periods of sitting that are independently associated with cardiometabolic risk in postmenopausal women) [92];

• Exercise prescription (Personalized physical activity recommendations based on fitness level and health goals) [93].

5.2.3 Novel Biosensors

Among novel biosensors, we should mention continuous lactate monitors detecting metabolic responses to exercise and dietary interventions [94]; sweat sensors providing noninvasive monitoring of electrolytes, cortisol, and metabolites [95]; and breath analyzers ensuring real-time assessment of ketone bodies and volatile organic compounds indicative of metabolic status [96].

While these new technologies are promising, they require further validation before routine clinical implementation [97].

5.3 Digital Symptom Tracking

5.3.1 Vasomotor Symptom Monitoring

Mobile apps enable real-time recording of hot flash frequency and severity, providing objective outcome data for dietary intervention trials. In the Women's Study for the Alleviation of Vasomotor Symptoms (WAVS) - a randomized controlled trial of a low-fat plant-based diet with soybeans in postmenopausal women - participants recorded hot flashes via a mobile application continuously across the 12-week intervention, demonstrating the feasibility of app-based continuous symptom tracking in this population [98].

5.3.2 Quality of Life and Mood Assessment

Digital tools for ecological momentary assessment (EMA) record mood, sleep quality, energy levels, and quality of life measures in real time, enabling the identification of the impact of dietary interventions on subjective well-being [99].

5.4 Integration Issues and Security Considerations

5.4.1 Data Privacy and Security

Collection of sensitive medical data raises significant privacy concerns. Implementation requires Health Insurance Portability and Accountability Act (HIPAA)-compliant data storage and transmission, a transparent data use policy, and patient control over data sharing [100].

5.4.2 Clinical Validation

Despite the proliferation of digital health tools, their clinical validity varies widely. Most commercially available nutrition apps have not undergone rigorous peer-reviewed validation; the accuracy of food intake estimates can be low, and AI algorithms are often opaque (black box), raising concerns about reproducibility [101]. CGMs are well-validated for diabetes management, but their usefulness in non-diabetic postmenopausal women for primary prevention remains a topic of research. Similarly, new sensors (lactate, sweat) are in early stages of development and require further validation before routine use [97]. Clinicians should recommend only those tools for which there is published evidence of accuracy and clinical utility, and be mindful of the risk of overreliance on unvalidated results.

5.4.3 Monitoring Drug-Nutrient Interactions

Digital platforms should integrate drug-nutrient interaction databases to prevent adverse events, particularly in postmenopausal women who often take multiple medications (statins, antihypertensives, bisphosphonates, hormone therapy) [102].

5.4.4 Digital Inequality

To ensure equal access to digital health technologies, the following challenges must be addressed: barriers related to technological literacy, affordability, language and

cultural adaptation [103]. Moreover, older adults and members of minority groups are disproportionately affected by the digital inequality. Targeted outreach, simplified interfaces, and inclusion of these groups in validation studies are essential to ensure prevention of worsening inequalities in health care [104,105,106,107,108].

6. Evidence-Based Intervention Strategies

This section discusses dietary considerations and targeted nutraceuticals, reflecting the reality of clinical practice, in which supplements are typically added to the basic diet. We first discuss the established dietary patterns (strong evidence), then additional functional foods/nutraceuticals, organized by target outcome, with the strength of evidence clearly indicated (Table 2, Ref. [65,67,68,70,73,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129]).

6.1 Main Dietary Patterns

6.1.1 Mediterranean Diet (Strong Evidence)

The Mediterranean diet, characterized by high intakes of vegetables, fruits, whole grains, legumes, nuts, olive oil, and moderate fish consumption, is the most widely studied and evidence-supported approach to postmenopausal health [130].

6.1.1.1 Cardiovascular Benefits. The PREvencion con DIeta MEDiterranea (PREDIMED): this landmark study demonstrated that a Mediterranean diet supplemented with extra virgin olive oil or mixed nuts significantly reduces cardiovascular events by approximately 30% in high-risk individuals, with a significant proportion occurring in postmenopausal women [131].

Regarding its effect on lipid profile, a Mediterranean diet consistently reduces LDL cholesterol, triglycerides, and inflammatory markers, while improving HDL function [132].

As for blood pressure: systematic reviews show its modest but significant reduction (2–3 mmHg systolic) with adherence to a Mediterranean diet [133].

6.1.1.2 Metabolic Health. A Mediterranean diet improves insulin sensitivity, reduces the incidence of diabetes by 20–30%, and promotes healthy weight management in postmenopausal women [134].

6.1.1.3 Bone Health. Adherence to the Mediterranean diet has been associated with higher BMD and a reduced risk of fractures in observational studies, likely due to its anti-inflammatory effects, antioxidant content, and beneficial effects on the gut microbiome [135].

6.1.1.4 Cognitive Function. The Mediterranean diet has been associated with reduced cognitive impairment and dementia risk in aging adults, including postmenopausal women [136].

6.1.1.5 Implementation. Key components of this diet include daily consumption of vegetables (≥3 servings), fruit (≥2 servings), whole grains and olive oil (main source of fat), and weekly intake of fish (≥2 servings), legumes (≥3 servings) and nuts (daily handful). This diet also includes moderate consumption of poultry, eggs and dairy (preferably fermented) products, along with limited intake of red meat, processed foods, and added sugars [137].

6.1.2 DASH Diet (Strong Evidence)

The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes fruit, vegetables, low-fat dairy products, whole grains, lean proteins, while limiting sodium, saturated fat, and added sugars [138].

6.1.2.1 Blood Pressure Management. The DASH diet reduces systolic blood pressure by 8–14 mmHg in hypertensive individuals, with effects particularly pronounced in postmenopausal women [139].

6.1.2.2 Cardiometabolic Benefits. In addition to lowering blood pressure, the DASH diet improves lipid profiles, insulin sensitivity, and reduces inflammation [140].

6.1.2.3 Bone Health. The DASH diet's emphasis on calcium-rich dairy products, potassium, magnesium, and reduced sodium supports bone health in postmenopausal women [141].

6.1.3 Plant-Based Diets (Strong Evidence for Cardiometabolic Effect, Promising Evidence for Vasomotor Effect)

6.1.3.1 Management of Vasomotor Symptoms. A low-fat vegan diet supplemented with soy (86 g cooked soybeans daily) resulted in a significant reduction in hot flash frequency (79%) and severity (84%) in a recent RCT [60]. The intervention was well tolerated and associated with beneficial microbiome changes.

6.1.3.2 Cardiometabolic Benefits. A plant-based diet reduces LDL-cholesterol, body weight, and diabetes risk, with benefits comparable to or greater than other dietary patterns [142].

6.1.3.3 Bone Health Considerations. Bone health concerns with plant-based diets have been addressed in studies showing adequate BMD with adequate calcium, vitamin D, vitamin B12, and protein [121,122,143].

6.1.3.4 Implementation. A well-planned plant-based diet should include a variety of protein sources (legumes, soy, whole grains, nuts), calcium-fortified plant milks and calcium-rich vegetables, vitamin B12 supplements (essential for vegans), adequate intake of vitamin D (supplements often needed), and sources of omega-3 (flaxseed, chia, walnuts, algae-based eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA)) [144].

Table 2. Summary of targeted nutraceuticals and functional foods for postmenopausal women.

Clinical goal	Intervention	Level of evidence	Typical dose	Effect size/Outcome	Human-based vs. Preclinical data	Ref
Vasomotor symptoms	Soy isoflavones	Strong	40–110 mg/day	↓ Hot flash frequency (by 25–50%)	Human-based (multiple RCTs, meta-analyses)	[111]
	Flaxseed (lignans)	Promising	40 g/day	Modest ↓ of hot flashes	Human-based (limited RCTs)	[113,114]
	Curcumin	Preliminary	500–1500 mg/day (with piperine)	Symptom improvement in one small-sample RCT	Human-based (one small RCT); preclinical supporting evidence	[126]
Cardiovascular risk	Omega-3 (EPA/DHA)	Strong	2–4 g/day (for hypertriglyceridemia); 1–2 g/day (general use)	↓ Triglycerides by 25–30%	Human-based (large RCTs, meta-analyses)	[115,117,118]
	Plant sterols/stanols	Strong	2–3 g/day with meals	↓ LDL-C by 8–10%	Human-based (multiple RCTs, meta-analyses)	[119,120]
	Phytosterols + omega-3 + MedDiet	Promising	Same as above, in combination	Significant improvement in lipid profile parameters compared with diet alone (pilot study)	Human-based (one pilot RCT)	[116]
Bone health	Calcium + vitamin D	Strong	Calcium 1200 mg/day (dietary preferred); vitamin D 800–2000 IU/day	↓ Fracture risk (combined)	Human-based (large RCTs, meta-analyses)	[121,122]
	Vitamin K2 (menaquinone)	Promising	45–90 mcg/day	↑ Osteocalcin activation, ↑ BMD in some studies	Human-based (limited RCTs); mechanistic supporting evidence	[109,110]
	Lactobacillus reuteri (probiotic)	Promising	10^{10} CFU/day	↓ Bone loss in women with osteopenia (one RCT)	Human-based (one RCT); animal models	[123]
	L. helveticus + *B. longum* (probiotics)	Preliminary	10^{9}–10^{10} CFU/day	Improved bone turnover markers	Human-based (small trials); animal models	[124]
	Collagen peptides	Preliminary	5–10 g/day	↑ Spine BMD in women with osteopenia (small-sample RCTs)	Human-based (small RCTs); preclinical	[127]
	Soy isoflavones (effect on bones)	Strong	40–110 mg isoflavones/day	Modest ↑ of lumbar spine BMD (by 0.01–0.02 g/cm^2)	Human-based (meta-analyses)	[112]

Table 2. Continued.

Clinical goal	Intervention	Level of evidence	Typical dose	Effect size/Outcome	Human-based vs. Preclinical data	Ref
Metabolic health	Myo-inositol	Preliminary	2–4 g/day	May improve metabolic syndrome parameters	Human-based (limited, not specific to postmenopause); preclinical	[129]
	Coenzyme Q10	Preliminary	100–300 mg/day	Improved endothelial function (↑ flow-mediated dilation; SMD 1.70, 95% CI: 1.00–2.40)	Human-based (meta-analysis of 5 small RCTs, n = 194; not specific to postmenopausal women)	[128]
	Resveratrol	Preliminary	150–500 mg/day	Mixed results; preclinical evidence for benefits for bone tissue and metabolism	Mostly preclinical data; Human-based studies are small and inconsistent	[125]
Microbiome support	Prebiotics (inulin, FOS, resistant starch)	Promising	10–20 g/day	↑ Calcium absorption, ↑ SCFA production	Human-based (some RCTs); mechanistic supporting evidence	[65,67,68]
	Polyphenol-rich foods (berries, tea, cocoa)	Promising	Dietary intake (no specific dose)	Prebiotic effects, anti-inflammatory	Human-based (observational, some trials)	[70]
	Fermented foods (yogurt, kefir, kimchi)	Promising	Regular dietary intake	↑ Microbiome diversity	Human-based (observational, some trials)	[73]

Note: Strong evidence: consistent results from multiple, high-quality RCTs and/or meta-analyses. Promising evidence: a limited number of RCTs, but with consistent observational data or mechanistic support. Preliminary evidence: small pilot studies, uncontrolled trials, or primarily preclinical studies; insufficient for clinical recommendations but noted for future directions. Dosage ranges are consistent with those used in published studies; individual patient factors may require adjustment. Arrows indicate the direction of change in the corresponding parameter following the intervention: ↑, increase; ↓, decrease. BMD, bone mineral density; CFU, colony-forming unit; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FOS, fructooligosaccharides; LDL-C, low-density lipoprotein cholesterol; MedDiet, Mediterranean diet; SCFA, short-chain fatty acid; RCTs, randomized controlled trials.

6.1.4 Low-Carbohydrate and Ketogenic Diets (Promising for Weight/Glucose, but With Caution)

6.1.4.1 Weight Loss and Metabolic Effects. Low-carbohydrate diets (≤130 g carbohydrate/day) and very-low-carbohydrate ketogenic diets (VLCKD; ≤50 g carbohydrate/day) demonstrate superior short-term weight loss and improvements in insulin sensitivity, triglyceride levels, and HDL-C compared with low-fat diets in postmenopausal women [145]. A recent study showed that VLCKD reduced left ventricular mass and epicardial adipose tissue in obese postmenopausal women with hypertension, suggesting cardiovascular benefits [146].

6.1.4.2 Potential Concerns. In terms of LDL-C variability, some individuals experience significant elevations in LDL-C levels, necessitating lipid profile monitoring [147].

Regarding bone health, long-term implications in postmenopausal women require careful consideration. Although short-term studies showed no adverse effects, theoretical concerns remain regarding acid-base balance and weight loss-induced bone loss [148]. For postmenopausal women on a long-term or very low-carbohydrate diet, we strongly recommend monitoring bone turnover markers (P1NP, CTX) and BMD with dual-energy X-ray absorptiometry (DXA) every 1–2 years, and ensuring adequate calcium (1200 mg/day) and vitamin D (800–2000 international units (IU)/day) intake.

Sustainability: Dietary adherence challenges and social restrictions limit its long-term feasibility for many individuals [149].

6.1.4.3 Personalized Application. Low-carbohydrate dietary approaches may be particularly beneficial for postmenopausal women with metabolic syndrome or type 2 diabetes, elevated triglycerides, significant obesity, and a preference for this dietary pattern [150]. Close monitoring of lipid profiles, bone health, and nutritional adequacy is recommended [151].

6.1.5 Intermittent Fasting and Time-Restricted Eating (Emerging Evidence)

6.1.5.1 Metabolic Benefits. Time-restricted eating (TRE; restricting food intake to a consistent daily eating window) and intermittent fasting protocols show promise for weight management, insulin sensitivity, and metabolic health in postmenopausal women [152].

6.1.5.2 Gaps in the Existing Data. Most studies are short-term and do not provide data on long-term outcomes in postmenopausal populations. Concerns regarding potential impacts on bone health and muscle mass require further investigation [153].

6.1.5.3 Practical Considerations. TRE may be easier to implement than calorie restriction for some individuals, but it should be combined with attention to dietary adequacy and protein intake to preserve muscle mass [154].

6.2 Targeted Nutraceuticals and Functional Foods

In addition to mainstream dietary patterns, specific nutraceuticals and functional foods may serve as complementary interventions to address the specific clinical needs of postmenopausal women. Table 2 provides a summary of key nutraceuticals grouped by primary clinical use, indicating the strength of evidence, dosage, effect size, and differences between preclinical data and human-based data. This organization is intended to help clinicians prioritize interventions based on individual patient profiles and the robustness of the underlying evidence.

6.2.1 Clinical Application Considerations

6.2.1.1 Equol Production and Personalized Response. Only 30–50% of the Western population has gut bacteria capable of converting the soy isoflavone daidzein to equol, a more bioactive metabolite [155]. Equol producers demonstrate greater benefit from soy consumption effects on vasomotor symptoms and bone health, suggesting potential for stratifying phytoestrogen recommendations based on the microbiome [155,156]. For those who do not produce equol, alternative phytoestrogen sources (e.g., flaxseed lignans) or a longer period of soy consumption may be considered, although evidence is limited. Direct supplementation with S-equol is available in some regions and may benefit those who do not produce equol, but large-scale studies of the kind in postmenopausal women are lacking.

6.2.1.2 Combination Strategies. In clinical practice, nutraceuticals are often used in combination rather than individually. A recent pilot study showed that omega-3 supplements combined with phytosterols and a Mediterranean diet had a synergistic lipid-lowering effect, superior to the effect of individual interventions in menopausal women [116]. Such combinations may provide enhanced effects but require further confirmation. Similarly, the combined use of calcium, vitamin D, vitamin K2, with magnesium and omega-3 fatty acids as potential adjuncts may have additive effects on bone health, although comparative studies are limited [157,158].

6.2.1.3 Safety Considerations. Most of the nutraceuticals discussed have a favorable safety profile at recommended doses, but caution should be exercised in certain populations and situations as follows:

(1) Soy isoflavones. Generally safe up to 150 mg/day based on long-term observational data and clinical studies [159]. However, women with hormone-dependent cancers (breast, endometrial) should consult with their oncologist before starting high-dose isoflavone supplementation, as safety in this population remains controversial [160]. The cardiovascular benefits of soy protein are supported by a Food and Drug Administration (FDA) health claim [161]

and a scientific opinion from the American Heart Association [162];

(2) Omega-3 fatty acids. Well tolerated up to 5 g/day, but may increase the risk of bleeding at very high doses or in combination with anticoagulants (e.g., warfarin, aspirin) [163]. Patients taking anticoagulants should be monitored when initiating high-dose omega-3 therapy.

(3) Plant sterols/stanols. Generally recognized as safe, but may reduce the absorption of fat-soluble vitamins (A, D, E, K) [164]. Patients should be advised to maintain adequate intake of these vitamins through diet or supplements and to take plant sterols with meals rather than on an empty stomach.

(4) Calcium supplements. Recent debate about the potential link between high-dose calcium supplements and cardiovascular disease has led to recommendations to prioritize dietary sources of calcium whenever possible [165]. Supplemental calcium, if needed, should be taken in divided doses ($\leq$500 mg per serving) and with meals to optimize absorption and minimize risks [122].

(5) Probiotics. Generally safe for healthy individuals, but caution should be exercised in immunocompromised patients where there is a theoretical risk of infection. The safety profiles of specific strains should be reviewed.

(6) Curcumin. Its low bioavailability limits efficacy; piperine-containing formulations or liposomal delivery systems may improve absorption but also increase cost [126].

6.2.2 Integration With Dietary Models

Nutraceuticals should be considered as a complement to, not a replacement for, evidence-based dietary patterns. There are several important synergies:

• Soy isoflavones are most effective when consumed as part of a whole-grain, plant-based diet, as shown in a recent RCT where combining cooked soy with a low-fat vegan diet resulted in a significant reduction in hot flashes [60];

• Omega-3 supplements provide the greatest cardiovascular benefits when combined with a Mediterranean diet, which itself has anti-inflammatory and lipid-lowering effects [116];

• Prebiotic fibers (inulin, FOS) are naturally present in many foods that are an integral part of healthy diets (onions, garlic, bananas, whole grains), but their supplementation may be considered if dietary intake is inadequate;

• Polyphenol-rich foods (berries, tea, cocoa, extra virgin olive oil) are key components of the Mediterranean diet and provide synergistic effects through their prebiotic and anti-inflammatory properties [70].

Therefore, clinicians should first establish a baseline dietary regimen that matches the patient's clinical profile and preferences and then consider the use of targeted nutraceuticals as adjunctive therapy when specific goals are not achieved or when certain risk factors require additional intervention.

7. Integrative Framework for Implementing Precision Nutrition Into Clinical Practice

7.1 Conceptual Framework and Principles of Implementation

The evidence synthesis presented in the previous sections highlights the complexity and multifactorial nature of personalized nutrition approaches for postmenopausal women. Structured, evidence-based models are needed to translate the theoretical perspectives of precision nutrition into practical clinical application. This section proposes a comprehensive implementation model based on a sequential, phenotype-based approach that systematically integrates evidence-based nutrition models, targeted nutraceuticals, and digital health technologies. The overall structure of the proposed model, integrating a sequential clinical protocol with a resource-adaptive tiered model, is presented in Fig. 2.

The conceptual framework of this model is built on several key principles:

(1) Phased implementation (stepwise approach). The process begins with basic, widely available diagnostic assessments and interventions, increasing complexity only when warranted by lack of efficacy or when advanced resources are available;

(2) Iterative optimization. Nutritional prescription is not a static event, but a dynamic process requiring continuous refinement based on long-term monitoring of objective biomarkers and patient-reported outcomes;

(3) Risk-based prioritization. The selection of primary intervention targets is determined by the individual's dominant risk profile (e.g., cardiometabolic, osteoporotic, symptomatic).

(4) Multidisciplinary integration. Optimal effectiveness is achieved through the collaborative work of the physician coordinator, registered dietitian, exercise physiologist, and other relevant healthcare professionals.

7.2 Structured Protocol for Clinical Implementation

Guided by the above principles, the following structured protocol, consisting of five sequential phases, is proposed for clinical implementation.

7.2.1 Phase 1: Comprehensive Baseline Phenotyping

Goal: To create a comprehensive clinical, metabolic, and lifestyle profile for the individual.

Methodology includes the following components:

• Clinical phenotyping: detailed medical history, anthropometric measurements (body mass index, BMI; waist circumference), and body composition analysis;

• Essential laboratory assessment: standard biochemical panel (fasting lipid profile, glucose, HbA1c), inflammatory markers (e.g., high-sensitivity C-reactive protein), and vitamin D status (25-hydroxyvitamin D); specific cutoff values for these biomarkers and for bone mineral density assessed by DXA

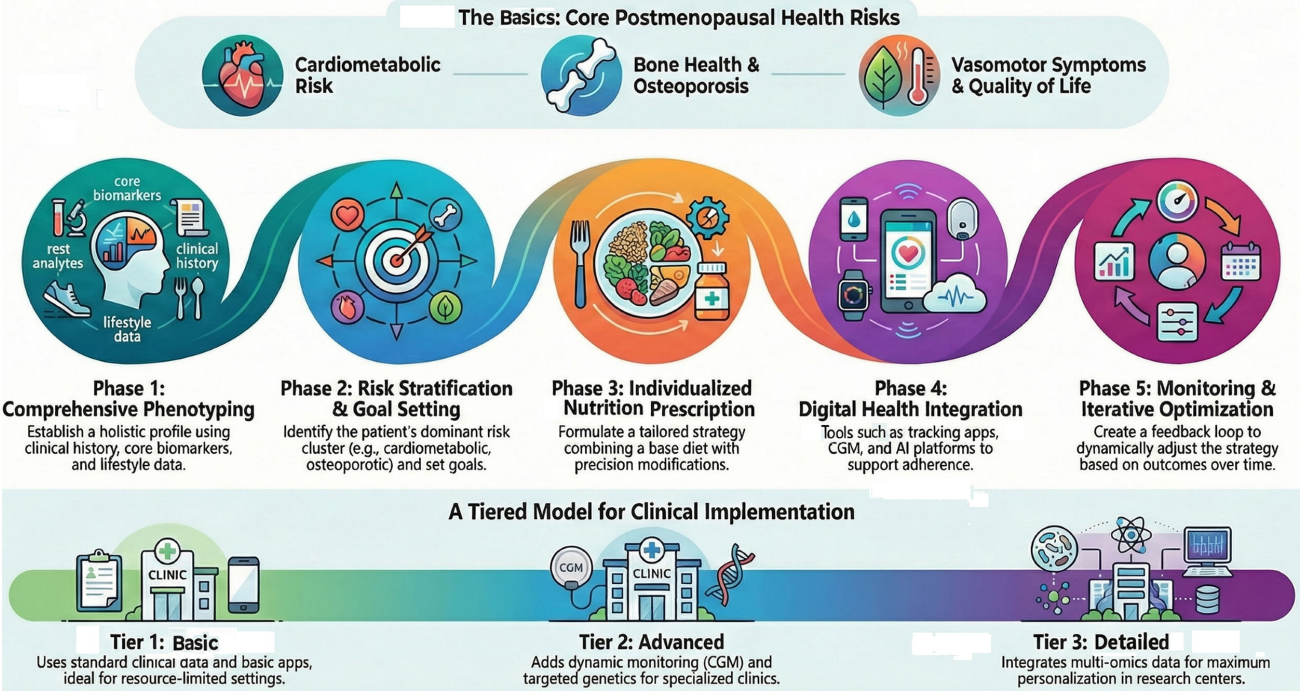

Fig. 2. A structured five-phase protocol and a tiered model for implementing precision nutrition in postmenopausal women. The flowchart describes the sequential steps (phenotyping → stratification → prescription → integration → optimization) for clinical application. The tiered model (bottom) correlates the intensity of diagnostic and interventional tools with available clinical resources, from basic (Tier 1) to detailed (Tier 3) approaches. Thus, the figure provides clinicians with a roadmap for implementing precision nutrition principles into practice, taking into account resource constraints. AI, artificial intelligence; CGM, continuous glucose monitoring.

are provided for risk stratification (Table 3, Ref. [166,167,168,169,170,171,172,173,174,175,176,177]);

• Extended phenotyping (if needed): postprandial responses, targeted genetic testing (*APOE*, *VDR*, *MTHFR*), metabolomics, microbiome;

• Diet and lifestyle assessment.

7.2.2 Phase 2: Risk Stratification and Target Identification

Goal: To identify priority intervention targets based on an individualized risk taxonomy.

Regarding the methodology, based on the data collected during Phase 1, patients are stratified according to their predominant risk groups (cardiovascular, metabolic, bone health, symptom severity). Subsequent goals are set jointly using the SMART (Specific, Measurable, Achievable, Relevant, Time-bound) criteria.

7.2.3 Phase 3: Developing a Personalized Nutritional Strategy

Goal: To develop a personalized nutrition program.

Methodology includes the following:

• Choosing a baseline dietary pattern. The baseline diet is selected based on the primary risk group (e.g., a Mediterranean diet for multifactorial risk, the DASH diet for hypertension, a soy-rich plant-based diet for severe vasomotor symptoms, or a low-carbohydrate approach for metabolic syndrome);

• Precision modification. The basic dietary pattern is subsequently adjusted to address specific phenotypic manifestations (e.g., enrichment with plant sterols and soluble fiber for hypercholesterolemia, inclusion of prebiotic products to address signs of intestinal dysbiosis);

• Integration of functional foods and nutraceuticals. Scientifically validated supplements and functional foods are additionally included to address specific needs (e.g., soy isoflavones to alleviate vasomotor symptoms, omega-3 fatty acids to treat hypertriglyceridemia, specific probiotic strains for bone health).

7.2.4 Phase 4: Integration of Digital Health Technologies

Goal: To improve treatment adherence, ensure objective monitoring, and provide personalized support.

Methodology: A tailored set of digital tools is recommended, ranging from basic apps (diet tracking, physical activity monitoring) to advanced systems (CGMs, AI-based nutrition platforms), depending on individual needs, level of technological literacy, and resource availability.

7.2.5 Phase 5: Dynamic Monitoring and Iterative Optimization

Goal: To evaluate the effectiveness of the intervention and facilitate the refinement of the long-term strategy.

Methodology: A structured monitoring schedule is implemented with assessments in the short-term (4–12

Table 3. Clinical cutoff values for key biomarkers and clinical measures used for risk stratification.

Biomarker/Clinical measure	Clinical cutoff values	Interpretation/Proposed action	Ref
25-Hydroxyvitamin D (25(OH)D)	<20 ng/mL (50 nmol/L) 20–30 ng/mL (50–75 nmol/L) >30 ng/mL (>75 nmol/L) >60 ng/mL (>150 nmol/L)	Deficiency: High-dose vitamin D treatment (e.g., 50,000 IU/week for 8 weeks), then maintenance dose of 1500–2000 IU/day Insufficiency: Supplementation dose of 1500–2000 IU/day Sufficient content: Maintenance dose of 800–2000 IU/day Potential toxicity: Avoid long-term unmonitored use of high doses	[166,167]
hs-CRP	<1.0 mg/L 1.0–3.0 mg/L >3.0 mg/L >2.0 mg/L	Low cardiovascular risk Moderate risk: Consider lifestyle modifications and omega-3 fatty acid supplementation High cardiovascular risk: Implement a Mediterranean diet, consider omega-3 supplementation, and evaluate for other causes of inflammation Alternative risk stratification cutoff values according to AHA/ACC	[168,169]
LDL-C	<100 mg/dL (2.6 mmol/L) 100–129 mg/dL (2.6–3.3 mmol/L) 130–159 mg/dL (3.4–4.1 mmol/L) ≥160 mg/dL (4.1 mmol/L) ≥190 mg/dL (4.9 mmol/L)	Optimal Near optimal: Reinforce dietary pattern (Mediterranean, DASH) Borderline high: Consider plant sterols (2–3 g/day), increase soluble fiber High: Intensify dietary therapy, consider statin if elevated global risk Very high: Initiate statin therapy regardless of calculated risk	[169,170,171]
Fasting glucose	<100 mg/dL (5.6 mmol/L) 100–125 mg/dL (5.6–6.9 mmol/L) ≥126 mg/dL (7.0 mmol/L)	Normal Prediabetes: Implement a low glycemic index diet, consider using a CGM, increase physical activity Diabetes: Refer to a doctor	[172]
HbA1c	<5.7% (<39 mmol/mol) 5.7–6.4% (39–47 mmol/mol) ≥6.5% (≥48 mmol/mol)	Normal Prediabetes: Intensive lifestyle changes Diabetes: Refer to a doctor	[172]
Triglycerides	<150 mg/dL (1.7 mmol/L) 150–199 mg/dL (1.7–2.2 mmol/L) 200–499 mg/dL (2.3–5.6 mmol/L) ≥500 mg/dL (≥5.7 mmol/L)	Normal (optimal level <100 mg/dL) Borderline high: Reduce consumption of refined carbohydrates, alcohol, and added sugar High: Consider taking omega-3 fatty acids 2–4 g/day, intensify lifestyle changes Very high: Risk of pancreatitis; Initiate pharmacotherapy (fibrates, high-dose omega-3)	[169,170,171]
CTX	<0.573 ng/mL (573 pg/mL) >0.573 ng/mL Varies by assay	Normal range for postmenopausal women (may vary by laboratory) Increased bone resorption: Ensure adequate calcium/vitamin D intake, consider antiresorptive therapy for osteoporosis or high fracture risk Clinical context: Used to monitor response to antiresorptive therapy	[173,174,175,176]

Table 3. Continued.

Biomarker/Clinical measure	Clinical cutoff values	Interpretation/Proposed action	Ref
P1NP	16–96 ng/mL (mcg/L) >96 ng/mL (depends on the analysis)	Normal range for postmenopausal women (reference intervals vary by test and laboratory) Increased bone formation: May indicate high bone turnover rate; monitor response to osteoporosis therapy Clinical context: Used to monitor response to anabolic therapy	[173,174,175,176]
BMD assessed via DXA	T-score ≥ –1.0 T-score –1.0 to –2.5 T-score ≤–2.5 Fracture history + T-score ≤–2.5	Normal Osteopenia (low bone mass): Ensure adequate calcium/vitamin D intake, weight-bearing exercise Osteoporosis: Initiate pharmacotherapy unless contraindicated Severe osteoporosis: Initiate pharmacotherapy	[175,176,177]

Note: 25(OH)D, 25-hydroxyvitamin D; AHA, American Heart Association; ACC, American College of Cardiology; BMD, bone mineral density; CGM, continuous glucose monitoring; CTX, C-terminal telopeptide of type I collagen; DASH, Dietary Approaches to Stop Hypertension; DXA, dual-energy X-ray absorptiometry; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; ISCD, International Society for Clinical Densitometry; LDL-C, low-density lipoprotein cholesterol; P1NP, procollagen type I N-terminal propeptide; All cutoff values should be interpreted in the context of each patient's complete clinical profile, including age, comorbidities, medication use, and overall risk assessment. Reference ranges for bone metabolism markers (CTX, P1NP) can vary significantly between laboratories and assays; the values above represent standardized reference intervals for postmenopausal women, but local laboratory reference ranges should be considered when making clinical decisions. For 25(OH)D, levels >60 ng/mL (>150 nmol/L) are generally not associated with additional benefits and may increase the risk of toxicity with long-term supplementation; routine monitoring is recommended when using high doses of vitamin D. In the case of hs-CRP, the 2019 AHA/ACC guidelines recommend a cutoff value of ≥2.0 mg/L for cardiovascular risk stratification in intermediate-risk patients; the traditional three-category classification is used for clinical context. LDL-cholesterol cutoff values are derived from the 2018 AHA/ACC guidelines, which emphasize decision-making based on absolute risk; the values provided are for general purposes and do not replace a comprehensive risk assessment. Interpretation of BMD values should be consistent with the official ISCD position papers, which recommend using the lowest T-score at the lumbar spine, hip, or femoral neck, and, where available, considering ethnicity-specific reference databases.

weeks: symptoms, treatment adherence), medium-term (3–6 months: key biomarkers), and long-term (annually: comprehensive metabolic assay panel; BMD, if indicated). The nutrition strategy is iteratively refined based on these results.

7.3 Multidisciplinary Team Approach and Implementation Considerations

Successful implementation of this model requires coordinated interdisciplinary efforts. To operationalize the model, we define specific roles for each team member:

• Physician (general practitioner, gynecologist, or endocrinologist): provides medical care, interprets laboratory results, identifies drug-food interactions, prescribes medications, and makes referrals;

• Registered dietitian (nutritionist): conducts an in-depth dietary assessment (e.g., a 3-day food diary), educates about nutritional needs, develops individualized meal plans, monitors adherence, and adjusts nutraceutical intake;

• Exercise physiologist: assesses physical function (e.g., gait speed, grip strength), prescribes individualized exercises (aerobic, strength, balance), and monitors changes in body composition;

• Behavioral health specialist (psychologist, health counselor, or social worker): addresses psychological barriers (stress, mood swings, eating disorders), conducts motivational interviewing, and supports behavior change;

• Clinical pharmacist (if available): analyzes medication profiles for potential nutrient interactions and provides advice on supplement safety.

Several critical barriers to implementation must be recognized and addressed:

(1) Cost and affordability. This concept advocates a tiered approach to alleviate financial constraints, prioritizing highly effective and affordable interventions (e.g., dietary modification) and reserving advanced phenotyping for conducting research or specialized trial settings;

(2) Knowledge gaps. Continuous professional education and the development of tools for clinical decision support are necessary to address knowledge gaps about precision nutrition among practicing clinicians;

(3) Healthcare equity. Concerted efforts are needed to ensure that these advanced strategies do not exacerbate health inequities, requiring the use of culturally appropriate resources and advocacy for broader insurance coverage as evidence accumulates;

(4) Standardization and quality control. Variability in laboratory methods, genetic testing platforms and digital health apps may lead to inconsistent results. Mitigation strategies include using certified laboratories and validated tests, counseling on reference ranges specific to postmenopausal women, and preferring digital health tools supported by published validation studies.

This structured framework provides a pragmatic, evidence-based path for clinicians to implement personalized nutrition principles, thereby translating scientific innovations into improved outcomes for postmenopausal women.

7.4 A Tiered Implementation Strategy for Different Clinical Settings

Given the heterogeneity in resource availability and technological infrastructure across healthcare systems, a pragmatic tiered implementation strategy is proposed. This approach allows for the gradual integration of precision nutrition principles, maximizing accessibility and feasibility.

7.4.1 Tier 1: Basic Precision Nutrition (Low-Resource Settings)

Focus: Phenotype-based personalization using readily available clinical data.

Components:

• Deep phenotyping. Comprehensive clinical history, anthropometric measurements (BMI, waist circumference), and standard biochemical analysis including lipid profile, fasting glucose, HbA1c, hs-CRP, and 25-hydroxyvitamin D. Bone turnover markers (CTX, P1NP) may be added if indicated based on risk factors (see Table 3 for clinical cut-off values);

• Intervention. Evidence-based dietary patterns (Mediterranean, DASH, or plant-based) tailored to the predominant risk profile (cardiometabolic, osteoporotic, or symptomatic). Inclusion of targeted functional foods and nutraceuticals with strong evidence of efficacy, such as soy isoflavones for vasomotor symptoms or plant sterols for hypercholesterolemia (see Table 2 for dosage and effect size);

• Technology. Use of simple, low-cost mobile apps for self-monitoring of diet, tracking physical activity, and recording symptoms (e.g., hot flash diaries). Plain-language patient information materials;

• Indications. Suitable as first-line therapy for all postmenopausal women seeking preventive care or for the treatment of mild to moderate symptoms.

Transition to Tier 2 should be considered after 3–6 months of adequate adherence in case of:

(1) Insufficient response (e.g., lack of clinically significant improvement in target parameters: LDL-C reduction <10%, persistent severe vasomotor symptoms impairing quality of life, failure to lose weight if indicated);

(2) Presence of high-risk factors (metabolic syndrome, type 2 diabetes, osteoporosis with fragility fractures, or high cardiovascular risk score);

(3) Patient preference for further testing (either self-pay or through insurance coverage).

7.4.2 Tier 2: Advanced Precision Nutrition (Specialized Clinics)

Focus: Integration of dynamic monitoring and targeted genetic analysis.

Components:

• Advanced phenotyping. Addition of CGM for 7–14 days to assess glycemic variability and postprandial responses; validated genetic testing for high-impact, treatable variants, including *APOE ε4*, *TCF7L2 rs7903146*, *MTHFR C677T*, and *VDR* polymorphisms (Table 1). Targeted metabolomic profiling (e.g., branched-chain amino acids, acylcarnitines) may be considered, where available;

• Intervention. Dynamic dietary adjustment based on CGM data (e.g., personalized meal timing and composition to minimize glucose fluctuations). More precise nutraceutical prescriptions based on genetic and metabolic data, such as higher vitamin D dosage for *VDR* variants, riboflavin supplementation for the *MTHFR TT* genotype, or targeted probiotic strains for bone health (Table 2). Integration of the obtained data into a personalized meal plan developed by a registered dietitian;

• Technology. AI-based dietary planning apps that incorporate recorded data (food logs, CGM, symptoms) to provide real-time feedback and nutrition recommendations. Wearable activity monitoring devices with heart rate tracking to assess energy expenditure and sedentary behavior. Secure platforms for sharing data with the clinical team;

• Indications. Suitable for patients with an inadequate response to Tier 1 treatment, patients with complex or high-risk diseases, and individuals motivated by deeper personalization.

Transition to Tier 3 should be considered in case of:

(1) Persistent poor response despite optimized Tier 2 interventions;

(2) Complex multiple comorbidities requiring the integration of multiple data streams;

(3) Participation in research protocols;

(4) The patient requesting the highest level of personalization (given he/she can afford associated costs).

7.4.3 Tier 3: Detailed Precision Nutrition (Research and Highly Specialized Centers)

Focus: Integration of multi-omics data for maximum personalization.

Components:

• Comprehensive phenotyping. Gut microbiome sequencing (shotgun metagenomics for functional profiling), broad metabolomics panels (including lipidomics, amino acids, and inflammatory mediators), and comprehensive genomic analysis (polygenic risk scores for cardiometabolic and bone disorders). Integration of data from wearable sensors (continuous monitoring of lactate, ketones, etc.), where available;

• Intervention. Highly individualized nutrition plans based on integration of the multi-omics data, including personalized prebiotic/probiotic recommendations based on baseline microbiome composition and food choices tailored to predicted metabolic responses (e.g., using machine learning algorithms). Regular iterative adjustments based on longitudinal multi-omics monitoring;

• Technology. Advanced digital platforms integrating multi-omics data with AI-based decision support, enabling dynamic, data-driven dietary optimization. Secure, research-grade data management systems;

• Indications. Primarily intended for research settings, specialized academic medical centers, or exceptional clinical cases where standard approaches have proven ineffective and the potential benefits justify the complexity and cost.

The progressive expansion of capabilities across all five phases of the protocol, from Tier 1 to Tier 3, is summarized in the implementation matrix shown in Fig. 3.

7.5 Cost-Effectiveness and Implementation Considerations

While formal cost-effectiveness data for Tier 2 and Tier 3 interventions remains limited, preliminary recommendations can be made:

Tier 1 interventions (dietary modification, basic laboratory testing, simple apps) are highly cost-effective and should be widely available as first-line treatment.

Tier 2 adds moderate additional costs. It may be justified for high-risk patients (e.g., those with metabolic syndrome, diabetes, or osteoporosis), where targeted interventions have the potential to reduce the cost of treating long-term complications. Reimbursement models are evolving; some insurance companies may cover CGM for prediabetes or genetic testing if their clinical utility is demonstrated.

Tier 3 remains largely experimental. Its use should be limited to research protocols or exceptional cases where funding is available, as evidence of improvement in key outcomes (fractures, cardiovascular events) is currently insufficient to justify its routine clinical use.

Healthcare systems and clinicians should prioritize the widespread implementation of Tier 1 strategies while advocating for research and policy development to establish cost-effectiveness and ensure equitable access to higher-level tiers as evidence accumulates.

8. Research Outlook and Priorities

8.1 Critical Knowledge Gaps

Despite significant progress, several key questions remain:

(1) Genotype-guided dietary intervention studies: large-scale RCTs comparing genotype-guided dietary recommendations vs. standard dietary recommendations with hard clinical endpoints (fractures, cardiovascular events) in postmenopausal women;

(2) Microbiome-targeted interventions: controlled trials testing personalized prebiotic/probiotic selection based on baseline microbiome composition vs. standardized approaches;

(3) Superiority of AI-based nutrition: head-to-head comparisons of personalized nutrition using AI and expert dietary guidance on clinical outcomes and cost-effectiveness;

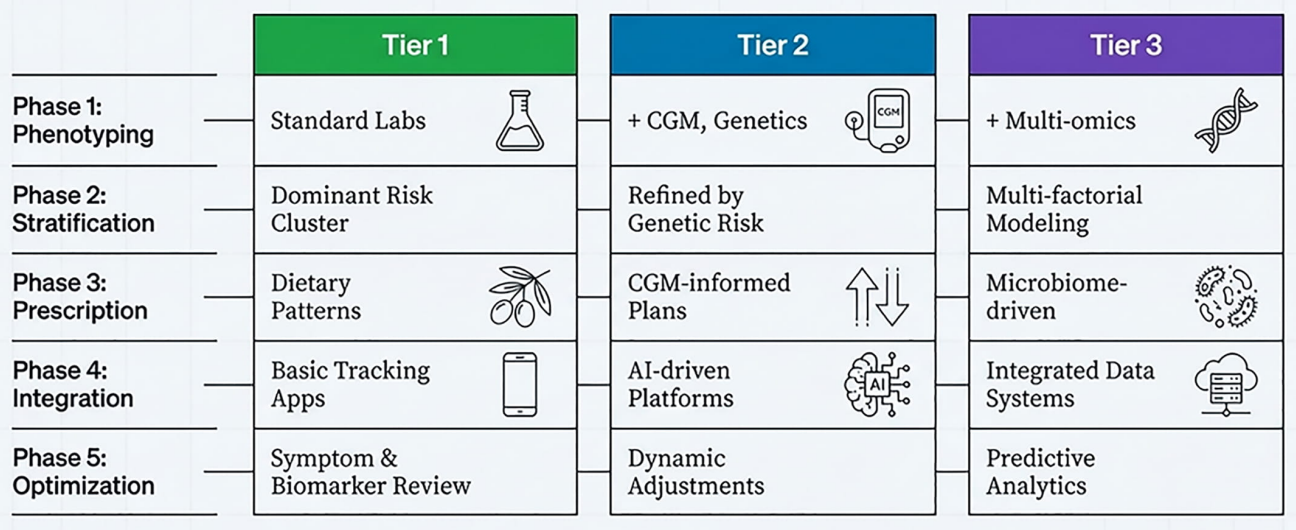

Fig. 3. Evolution of clinical actions at different tiers of precision nutrition protocol implementation. The matrix details how specific components of phenotyping, risk stratification, prescription, technology integration, and monitoring evolve in complexity and specificity from Tier 1 (basic) to Tier 3 (detailed) precision nutrition, providing a clear visual guide for clinical application. The matrix serves as a quick reference for clinicians to determine what level of precision is feasible and appropriate for a specific patient, emphasizing the incremental nature of precision nutrition implementation. CGM, continuous glucose monitoring; Labs, standard laboratory biomarkers; AI, artificial intelligence.

(4) Long-term safety and efficacy: long-term monitoring of new dietary patterns (ketogenic diet, TRE) in terms of bone health, cognitive function, and longevity in postmenopausal women;

(5) Optimal biomarker panels: validation of minimal marker sets that maximize predictive value while minimizing cost and burden;

(6) Implementation science: pragmatic studies evaluating the real-world implementation of precision nutrition in diverse healthcare settings and populations.

8.2 Technological Innovations of Today and the Near Future

These technological innovations include:

• Multi-omics integration platforms. Seamless integration of genomics, transcriptomics, proteomics, metabolomics, and microbiome data into unified predictive models [178];

• Wearable metabolic sensors. Noninvasive continuous monitoring of glucose, ketones, lactate, and other metabolites [179];

• Advances in AI. Deep learning models incorporating longitudinal data, environmental factors, and real-time feedback for dynamic nutrition optimization [4,180];

• Personalized foods. Functional foods (3D printed or custom-made) tailored to individual dietary needs and preferences [181];

• Pharmacomicrobiomics. Integrating drug-microbiome interactions into personalized nutrition recommendations for women taking multiple medications [182].

8.3 Healthcare Policy and Transformation

Reimbursement models include development of value-based care models that incentivize precision nutrition interventions with proven cost-effectiveness [183].

Regulatory frameworks establish appropriate oversight for direct-to-consumer testing of omics technologies and AI applications in nutrition [184].

Professional education integrates nutrigenomics, microbiome science, and digital health into medical and nutrition curricula [185].

Health equity ensures that advances in precision nutrition benefit all populations, not just the wealthy with access to expensive research [186]. Future strategies should include developing affordable diagnostic tools, advocating for public funding or insurance coverage for proven interventions, and creating culturally appropriate resources to prevent exacerbation of existing health inequalities.

8.3.1 Health Inequalities and Future Research

A major limitation of the current evidence base is the lack of racial and ethnic diversity. We did not formally quantify the demographic composition of participants across the studies reviewed; however, the underrepresentation of racial and ethnic minorities in the trial literature is well documented: among US trials with reported results, fewer than half disclose race or ethnicity data, and, where such data are reported, the median proportion of White participants approaches 80%, with combined minority enrollment falling below census-based expectations [187]. This limits the generalizability of the findings to Black, His-

panic, Asian, and Indigenous postmenopausal women, who bear a disproportionate burden of menopause-related cardiometabolic and bone diseases [11,188].

8.4 Critical Appraisal: Strengths and Limitations

This review has several methodological and conceptual strengths that support the credibility and utility of its findings. First, its interdisciplinary synthesis brings together disparate fields (nutrigenomics, metabolomics, microbiome science, digital health, and clinical nutrition) into a coherent framework specifically designed for postmenopausal physiology. This fills a significant gap in the existing literature, which has largely addressed these fields separately. Second, throughout the synthesis, we used a hierarchical evidence prioritization framework, clearly distinguishing between interventions with strong, promising, or preliminary evidence (Section 2.3, Table 2).

This approach provides clinicians with clear guidance in terms of which strategies are ready for implementation and which remain in the research phase. Third, the new tiered implementation framework (Section 7) represents a key conceptual contribution, translating the theoretical principles of precision nutrition into a pragmatic, resource-stratified clinical protocol that takes into account real-world constraints (a feature absent from previous reviews). Fourth, we maintained methodological transparency by explicitly disclosing the narrative review format and its inherent limitations (Sections 2.1–2.3) while ensuring quantitative specificity (dose ranges, effect sizes, biomarker cut-off values) to improve efficacy, reproducibility, and clinical utility (Tables 1,2,3). Fifth, the review uniquely focuses on equity in health care, explicitly addressing the digital divide and lack of diversity in existing research (Section 8.3.1) and proposing tiers of access to mitigate inequalities.

However, several limitations should be noted. The narrative review methodology, while appropriate for this integrative purpose, precluded an exhaustive systematic search, formal assessment of bias, or meta-analytic quantitative evaluation. As detailed in Section 2.1, the purposive selection process may have introduced selection bias, despite efforts to prioritize high-level evidence and provide transparent search queries. The evidence base exhibits a temporal asymmetry: sections on the microbiome and digital health rely heavily on data from 2000–2025, reflecting the rapid evolution in these fields, while some nutrigenomic concepts necessarily reference older mechanistic studies, as large-scale RCTs on postmenopausal women with hard endpoints remain rare. Clinical outcome heterogeneity is another limitation because most digital health and omics interventions report surrogate endpoints (blood glucose changes, microbiome alpha diversity) rather than specific clinical outcomes (fracture rates, cardiovascular events), thereby limiting the ability to draw firm conclusions about effectiveness. Cost-effectiveness data are largely absent in available publications: we did not identify any RCTs that included formal cost-effectiveness analyses of Tier 2–3 interventions, limiting implementation recommendations to qualitative assessments. Population representativeness is limited: although we did not quantify participant demographics, racial and ethnic minorities remain underrepresented in the trial literature (Section 8.3.1), which constrains the generalizability of the findings to these groups, even though they bear a disproportionate burden of menopause-related cardiometabolic and bone disease. Finally, the lack of original data precludes validation of the proposed design; its effectiveness requires prospective testing in pragmatic clinical trials.

These limitations highlight that precision nutrition, while being promising, should currently complement (rather than replace) standard, evidence-based dietary counseling for most postmenopausal women. The framework proposed in Section 7 should not be considered as a definitive clinical guideline, but rather as a hypothesis-generating tool that requires empirical testing.

9. Conclusion

The postmenopausal period presents significant health challenges that require innovative approaches. This review summarizes the available evidence and proposes a structured, tiered framework for implementing personalized nutrition into clinical practice. Our key findings are as follows:

(1) Dietary patterns (the Mediterranean diet, DASH, and well-planned plant-based diets) provide the strongest foundation for promoting health (strong evidence);

(2) Targeted nutraceuticals (soy isoflavones, omega-3s, plant sterols, and specific probiotics) offer additional benefits for symptom management and risk reduction (strong and promising evidence). New nutraceuticals (collagen, CoQ10) require further evaluation;

(3) Omics technologies (genomics, metabolomics, and microbiome profiling) provide mechanistic data and potential for personalization, but routine clinical use is currently limited to a few actionable markers (*APOE*, *TCF7L2*, *MTHFR*, *VDR*) in specialized settings;

(4) Digital health (AI-based apps, wearables, and CGMs) can improve treatment monitoring and adherence, but many tools have not been rigorously validated; their use should be based on evidence and patient awareness;

(5) Implementation framework. The proposed phased protocol (phenotyping → stratification → prescription → technology → monitoring) and tiered model (basic → advanced → detailed) offer a pragmatic roadmap. Clearly defined cutoff values for biomarkers and clinical measures (Table 3) and multidisciplinary approach (Section 7.3) enhance clinical applicability;

(6) Significant barriers to implementation remain, including the cost and availability of advanced diagnostics, knowledge gaps among practitioners, standardization issues, and equity concerns. Future studies should include diverse populations to ensure equitable benefits.

Hence, precision nutrition offers a promising complement to conventional care for postmenopausal women. A prudent, evidence-based approach is needed: mainstreaming basic strategies and reserving advanced technologies for complex cases or research. As the evidence base evolves, this paradigm has the potential to significantly improve healthy life expectancy and quality of life in postmenopausal women.

Abbreviations

ACC, American College of Cardiology; AHA, American Heart Association; AI, artificial intelligence; APOE, apolipoprotein E; BMD, bone mineral density; BMI, body mass index; BSAP, bone-specific alkaline phosphatase; COMT, catechol-O-methyltransferase; CD36, cluster of differentiation 36 (fatty acid translocase); CETP, cholesteryl ester transfer protein; CFU, colony-forming unit; CGM, continuous glucose monitoring; COL1A1, collagen type I alpha 1; CTX, C-terminal telopeptide of type I collagen; CVD, cardiovascular disease; CYP1A1, cytochrome P450 1A1; CYP1B1, cytochrome P450 1B1; CYP2R1, cytochrome P450 family 2 subfamily R member 1; DASH, Dietary Approaches to Stop Hypertension; DBP, vitamin D-binding protein; DHA, docosahexaenoic acid; DXA, dual-energy X-ray absorptiometry; E2, estradiol; EMA, ecological momentary assessment; EPA, eicosapentaenoic acid; ESR1, estrogen receptor alpha; FDA, Food and Drug Administration; FOS, fructooligosaccharides; FTO, fat mass and obesity-associated gene; GC, group-specific component; GST, glutathione S-transferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HIPAA, Health Insurance Portability and Accountability Act; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HRT, hormone replacement therapy; hs-CRP, high-sensitivity C-reactive protein; iAUC, incremental area under the curve; ICT, information and communication technology; IL-6, interleukin 6; IRS1, insulin receptor substrate1; ISCD, International Society for Clinical Densitometry; IU, international units; LDL-C, low-density lipoprotein cholesterol; LPS, lipopolysaccharide; MDA, malondialdehyde; MedDiet, Mediterranean diet; MeSH, Medical Subject Headings; MC4R, melanocortin-4 receptor; MTHFR, methylenetetrahydrofolate reductase; NHANES, National Health and Nutrition Examination Survey; NTX, N-terminal telopeptide; P1NP, procollagen type I N-terminal propeptide; PPARG, peroxisome proliferator-activated receptor gamma; PREDICT, Personalized REsponses to Dietary Composition Trial; PREDIMED, PREvencion con DIeta MEDiterranea Study; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized controlled trials; rRNA, ribosomal RNA; SCFA, short-chain fatty acid; SMART, specific, measurable, achievable, relevant, time-bound; TAS1R, type 1 taste receptor; TAS2R38, type 2 taste receptor member 38; TAS2Rs, type 2 taste receptors; TCF7L2, transcription factor 7-like 2; TNF-α, tumor necrosis factor-alpha; TRE, time-restricted eating; VDR, vitamin D receptor; VLDL, very-low-density lipoprotein; VLCKD, very low-carbohydrate ketogenic diet; WAVS, Women's Study for the Alleviation of Vasomotor Symptoms; 25(OH)D, 25-hydroxyvitamin D.

Author Contributions

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Ethics Approval and Consent to Participate

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The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

In the writing process, AI and AI-assisted technologies were used only for language proofreading of the initial draft. No generative AI tools were employed to generate the substantive scientific content. Furthermore, the final version of this article underwent language editing by a professional editor who is a native English speaker.

Supplementary Material

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