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Review Article

Nattokinase (NSK) to Support Cardiovascular Health in Women: A Comprehensive Review

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Abstract

Cardiovascular disease (CVD) is one of the leading causes of death in women. Throughout the lifespan, women experience distinct changes in lipid metabolism, endothelial function, inflammation, and coagulation factors/clotting. Cardiovascular risk rises sharply during midlife and the menopausal transition. These biological shifts contribute to increased susceptibility to hypertension, atherothrombosis, and microvascular dysfunction. These sex-specific biological changes underscore the need for adjunctive strategies that target cardiovascular pathways uniquely relevant to women. Nattokinase (NSK) is a fibrinolytic serine protease derived from the fermentation of soybeans. Emerging mechanistic and clinical evidence indicates that NSK-SD® supports cardiovascular health through multiple pathways, including enhanced fibrinolysis, modulation of coagulation factors, inhibition of platelet aggregation, improvements in endothelial function, reductions in blood pressure, and attenuation of inflammatory signalling. Human studies further suggest beneficial effects on lipid profiles, vascular function, and microcirculation. This review evaluates the potential role of NSK in women's vascular health across the lifespan. NSK may represent a complementary strategy targeting thrombosis, vascular dysfunction, and cardiometabolic risk in women with increased cardiovascular risk. Well-designed, women-focused clinical trials are needed to define optimal dosing, safety, and long-term efficacy.

Keywords: *Nattokinase; Women; Supplement*

Abbreviations

ACE: Angiotensin-Converting Enzyme; aPTT: Activated Partial Thromboplastin Time; BMI: Body Mass Index; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; FDP: Fibrin Degradation Products; FU: Fibrinolysis Units; HDL: High-Density Lipoprotein; HMG-CoA: Hydroxymethylglutaryl Coenzyme A; HSL: Hormone-Sensitive Lipase; LDL-C: Low-Density Lipoprotein Cholesterol; LPL: Lipoprotein Lipase; NSK: Nattokinase; PAI-1: Plasminogen Activator Inhibitor-1; TC: Total Cholesterol; TG: Triglycerides; tPA: Tissue Plasminogen Activator; vWF: Von Willebrand Factor

Introduction

Cardiovascular disease (CVD) encompasses a group of disorders affecting the heart and blood vessels and remains the leading cause of morbidity and mortality worldwide. Despite substantial advances in prevention and treatment, CVD continues to impose a significant public health burden. CVD remains the leading cause of death in women, yet its burden in women is frequently underestimated and underrecognized [1-3]. Women experience unique risk patterns across the lifespan, including increased susceptibility to thrombotic events with oral contraceptive use or hormone therapy, rising cardiovascular risk after menopause, and a higher prevalence of inflammatory and autoimmune conditions that influence vascular function [1]. Although men experience higher absolute CVD event rates earlier in life, the fastest relative increase in CVD mortality occurs in middle-aged women, particularly between 45 and 64 years of age [1,3]. This rise coincides with transitions in cardiometabolic risk that are unique to women, including menopause, pregnancy-related complications, and sex-specific inflammatory and lipid alterations [2,4]. CVD risk in women is shaped by distinct biological mechanisms that evolve across the female life.

Biologically, CVD risk in women is shaped by dynamic changes in lipid metabolism, endothelial function, inflammation, and thrombosis across the life course [1-3]. Menopausal transition is associated with adverse shifts in lipid profiles, including increases in LDL-C, triglycerides, and lipoprotein(a), alongside rising blood pressure, visceral adiposity, and systemic inflammatory markers such as C-reactive protein [4,5]. Women also demonstrate a higher prevalence of endothelial dysfunction and microvascular disease, greater susceptibility to inflammation-driven cardiometabolic risk, and sex-specific differences in coagulation and fibrinolytic balance [1]. Importantly, these processes intersect with pathways implicated in atherothrombosis and vascular ageing, including impaired nitric oxide bioavailability, heightened platelet and coagulation activity, and altered regulation of the renin-angiotensin system. These sex-specific features highlight biological mechanisms that are central to CVD progression in women (Figure 1) and provide a strong rationale for evaluating interventions that target lipid metabolism, endothelial health, inflammation, and fibrinolysis within a women-focused cardiovascular framework.

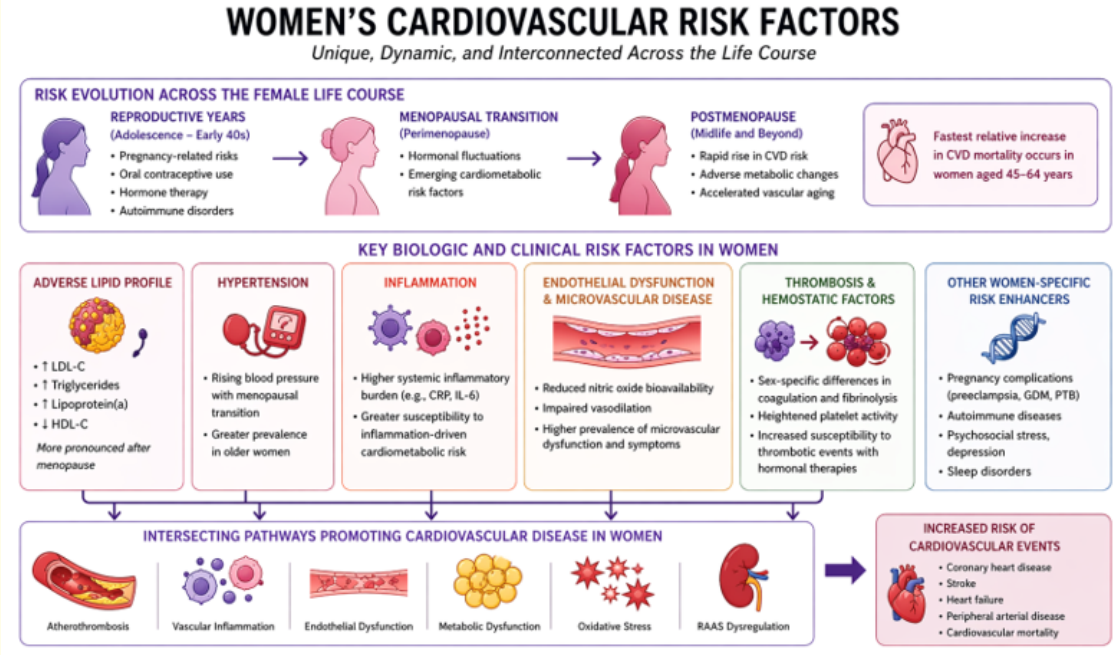

Figure 1: *Women's cardiovascular risk factors.*

Nattokinase (NSK) is a serine protease produced during the fermentation of soybeans with *Bacillus subtilis* var. *natto* to create nattō, a traditional Japanese food consumed for centuries (Graphic 1). Traditionally, natto has been viewed as a dietary contributor to cardiovascular health and longevity in Japanese populations [6]. Accumulating evidence from animal and human studies indicates that NSK possesses a broad range of cardiometabolic activities [7-11]. Epidemiological analyses have associated higher natto intake with lower rates of total cardiovascular disease (CVD) mortality, particularly from ischaemic heart disease. NSK has been reported to exert antihypertensive, anti-atherosclerotic, lipid-lowering, antiplatelet, anticoagulant, and neuroprotective actions [7]. Clinical trials show that NSK supplementation can enhance endogenous fibrinolytic and anticoagulant markers, lower blood pressure, and attenuate measures of atherosclerosis [12-16]. Although the mechanistic and clinical evidence supporting NSK is derived primarily from mixed-sex or general population studies, the pathways influenced by NSK are highly relevant to biological processes that disproportionately impact cardiovascular risk in women.

Graphic 1: *Nattokinase.*

Together, epidemiological findings, mechanistic insights, and early clinical evidence suggest that NSK may hold particular relevance for women's cardiovascular and haemostatic health. Despite clear evidence that traditional risk factors such as dyslipidaemia, hypertension, diabetes, and obesity confer equal or greater relative risk in women compared with men, women are less likely to receive timely diagnosis, risk stratification, or guideline-recommended preventive therapies [1]. As a result, women often accumulate a greater lifetime burden of modifiable cardiovascular risk, contributing to delayed intervention and poorer outcomes later in life. These considerations underscore the need for adjunctive strategies that address thrombosis, vascular dysfunction, and cardiometabolic risk in women. In this context, NSK may be especially well suited to target key pathways implicated in women's cardiovascular risk, including impaired fibrinolysis, endothelial dysfunction, and blood pressure dysregulation. Thus, the purpose of this review is to evaluate the biochemical actions, clinical evidence, and potential role of NSK in women's vascular health. This narrative review was conducted using a targeted literature search of PubMed and Google Scholar to identify relevant preclinical and clinical studies evaluating NSK and cardiovascular outcomes.

Structure and mechanisms of action of NSK

NSK is a single-chain serine protease enzyme composed of 275 amino acids. It belongs to the subtilisin family of proteases and shares high sequence homology with other subtilisins, such as subtilisin E and subtilisin BPN [8-10,17]. This similarity explains NSK's substrate specificity and enzymatic activity. The enzyme's active site contains a catalytic triad of serine, histidine, and aspartic acid residues, which are essential for its proteolytic activity [9,10]. There are multiple mechanisms that make NSK have cardiovascular benefits, and they are broadly categorised into anti-thrombotic, lipid-modulating, and anti-atherosclerotic pathways (Figure 2). These pathways are

particularly relevant in women, who exhibit sex-specific differences in coagulation, inflammatory signalling, endothelial function, and lipid metabolism, especially during the menopausal transition.

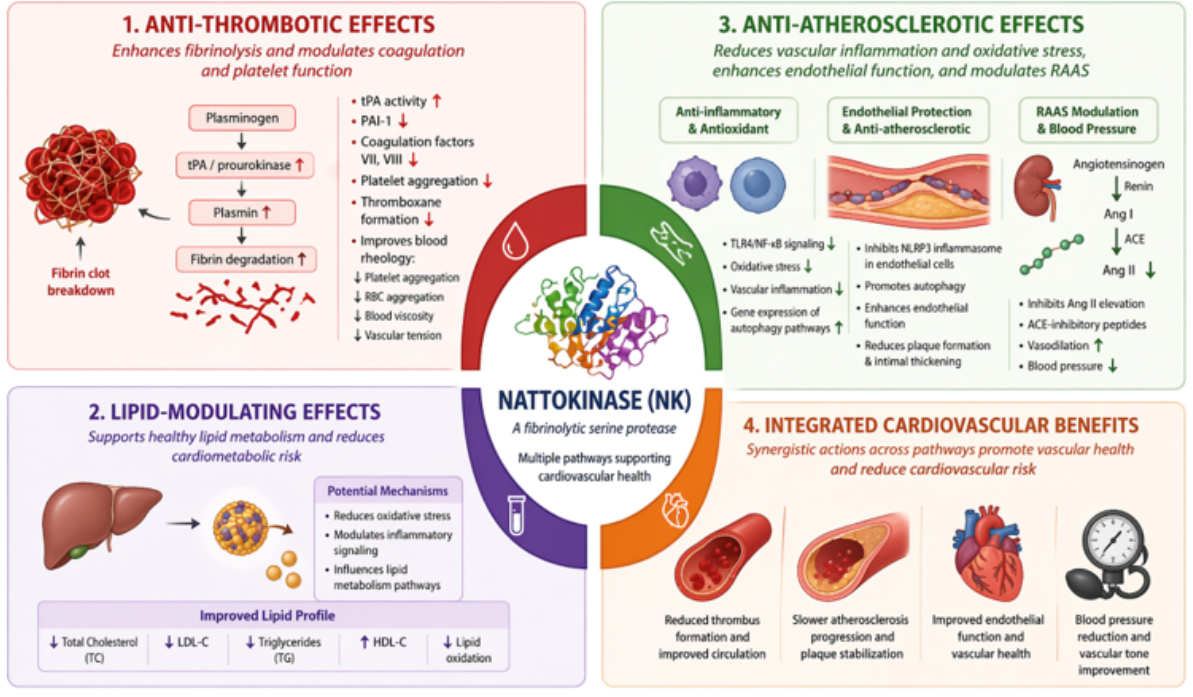

Figure 2: *Nattokinase mechanisms.*

Anti-thrombotic effects

NSK influences components of fibrinolytic and haemostatic regulation through several interrelated mechanisms. Its primary action involves the direct degradation of fibrin, the main structural protein within blood clots, reflecting its similarity to other subtilisin-family serine proteases [8-10]. This direct fibrinolytic effect enhances endogenous fibrinolysis by promoting the conversion of plasminogen to plasmin [18]. This process is further supported by increased activity of tissue plasminogen activator and prourokinase, along with reduced inhibition via degradation of plasminogen activator inhibitor-1 [9,10].

NSK also demonstrates antithrombotic effects through reductions in coagulation factors VII and VIII, inhibition of platelet aggregation, and decreased thromboxane formation [9,19,20]. Experimental and human studies show that NSK enhances fibrinolysis and anticoagulation, even after a single oral dose. In addition, NSK improves key blood rheology parameters, including platelet aggregation, red blood cell aggregation, blood viscosity, and vascular tension, indicating its potential to support healthier circulation and overall blood flow [20,21]. These findings position NSK as a multifaceted modulator of fibrinolytic balance and thrombus resolution. These mechanisms may be important for women, who exhibit sex-specific differences in coagulation and fibrinolytic balance, including oestrogen-mediated regulation of clotting factors and increased thrombotic susceptibility with hormonal fluctuations [22].

Lipid-modulating effects

Emerging evidence suggests that NSK may influence multiple aspects of lipid metabolism, contributing to improvements in circulating lipid profiles. NSK may promote lipolysis through activation of hormone-sensitive lipase (HSL), enhancing the hydrolysis of triglycerides into free fatty acids and glycerol. *In vitro* studies show increased glycerol release and HSL phosphorylation following NSK exposure, supporting this mechanism [23,24].

NSK modulates lipoprotein metabolism by enhancing lipoprotein lipase (LPL) activity, thereby accelerating the breakdown of triglycerides in chylomicrons and very low-density lipoproteins (VLDL) [25]. This may contribute to reductions in circulating triglyceride levels. NSK has been shown to inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in hepatic cholesterol synthesis [25,26]. Inhibition of this enzyme reduces endogenous cholesterol production. Animal studies further report decreases in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) following NSK administration [26]. NSK may also improve lipid profiles by supporting hepatic clearance of LDL and promoting high-density lipoprotein (HDL)-mediated reverse cholesterol transport [27]. In addition, NSK has been shown to exert antioxidant effects that may reduce lipid peroxidation and limit LDL oxidation, a key step in atherogenesis [28].

NSK appears to influence lipid metabolism through pathways involving lipolysis, lipoprotein processing, cholesterol synthesis, and oxidative regulation. Given known sex-specific differences in lipid metabolism and cardiovascular risk across the female lifespan, these mechanisms may have particular relevance for women at elevated cardiometabolic risk.

Anti-atherosclerotic effects

NSK may exert anti-atherosclerotic effects through modulation of vascular inflammation, oxidative stress, endothelial function, and blood pressure regulation. Studies have identified anti-inflammatory and antioxidant properties, including attenuation of TLR4 and NF-κB signalling, reduced oxidative stress, and alterations in gene expression related to vascular inflammation and autophagy [29,30].

NSK's ability to reduce vascular inflammation, promote autophagy, and inhibit NLRP3 inflammasome activation in endothelial cells is thought to enhance endothelial function and reduce atherosclerosis risk [16]. By attenuating these inflammatory pathways, NSK may reduce upstream drivers of endothelial dysfunction and vascular ageing [7,29].

Additionally, fragments of NSK have been shown to inhibit the elevation of angiotensin II, a key vasoconstrictor, through interactions with the renin-angiotensin system, and peptides derived from NSK have demonstrated ACE-inhibitory activity [16,21]. These actions suggest that NSK may contribute to blood pressure regulation and vascular tone, further supporting vascular health. The menopausal transition is characterised by loss of oestrogen-mediated vascular protection, resulting in increased oxidative stress, impaired nitric oxide bioavailability, and heightened inflammatory and thrombotic activity [4]. NSK's effects on inflammation, endothelial function, and vascular tone may align with key sex-specific pathways implicated in atherosclerosis progression and vascular ageing.

NSK, hypertension and women's health

NSK is proposed to lower blood pressure by modulating the fibrinolytic and renin-angiotensin systems [14,15,31]. NSK exhibits angiotensin-converting enzyme (ACE) inhibitory activity, leading to reduced angiotensin II levels and vasodilation [14-16,32]. Effects on plasma renin activity have been observed but are not always statistically significant, suggesting renin suppression is not a primary mechanism [21]. Its high gastrointestinal stability allows absorption and subsequent cleavage of plasma fibrinogen, which may reduce blood viscosity and peripheral vascular resistance [21].

Several studies have observed reductions in blood pressure following supplementation with NSK [14-16,33-35]. In a randomised, double-blind, placebo-controlled trial, participants consumed NSK (2,000 FU/day) or placebo for 8 weeks, resulting in significantly

greater reductions in systolic (-5.55 mmHg) and diastolic (-2.84 mmHg) blood pressure in the NSK group, accompanied by a significant decrease in plasma renin activity [15]. Similarly, Liu., *et al*. [14] (2024) and Jensen., *et al*. [16] (2016) observed greater reductions in blood pressure compared with placebo following 8 weeks of NSK supplementation at the same dose (2,000 FU/day).

Collectively, these findings suggest that the blood pressure-lowering effects of NSK are mediated, at least in part, through modulation of the renin-angiotensin system, including reduced renin activity and potential downstream reductions in angiotensin I and II, as well as possible inhibition of ACE. Given that hypertension prevalence rises sharply in women during the menopausal transition and contributes substantially to cardiovascular risk [36], these results indicate that daily NSK supplementation may represent a useful nutritional strategy to support blood pressure control in women, particularly during perimenopause and postmenopause.

Anti-atherosclerotic, lipid metabolism, and antithrombotic effects

While other nutraceuticals and food-derived compounds have been investigated for cardiovascular benefits, NSK is unique in its direct fibrinolytic activity and dual effects on coagulation and vascular function, supported by both mechanistic and human clinical data. Evidence suggests that NSK influences lipid homeostasis and vascular health through multiple pathways. Proposed mechanisms include regulation of lipid metabolism via activation of hormone-sensitive lipase and lipoprotein lipase, promoting triglyceride hydrolysis and fatty acid mobilisation, and inhibition of key enzymes involved in endogenous cholesterol synthesis [6,37]. NSK's fibrinolytic activity, via activation of plasminogen and direct degradation of cross-linked fibrin, is thought to indirectly support lipid and vascular health by improving blood flow and reducing thrombotic burden [12,13,20]. These mechanisms are particularly relevant to women, who experience sex-specific changes in lipid metabolism, endothelial function, and thrombotic risk across the lifespan, especially during menopause and with hormonal exposures [2-4].

Consistent with these mechanisms, NSK (and natto extracts) are shown to reduce intimal thickening, carotid plaque size, total cholesterol (TC), LDL-C, and triglycerides, while modestly increasing HDL, with effects linked to antioxidant, anti-inflammatory, and hypolipidaemic actions [30,32,38-40]. Jensen., *et al*. [16] (2016) further suggest that NSK's strongest vascular effect may be improvement in endothelial function, demonstrated by a 26% reduction in von Willebrand factor in women, indicating reduced thrombotic risk.

Studies evaluating NSK as an adjunct to lipid-lowering strategies suggest additive benefits rather than standalone efficacy. When combined with lovastatin, a traditional dyslipidaemia medication, NSK significantly reduced total cholesterol (TC), LDL-C, non-HDL-C, and the LDL-C:HDL-C ratio compared with placebo [38]. Similarly, supplementation with NSK and red yeast extract resulted in reductions in TC, LDL-C, triglycerides, and the TC:HDL-C ratio, suggesting that NSK may provide additional fibrinolytic and vascular support when used alongside conventional lipid-lowering therapies [16]. When combined with a low-cholesterol diet, NSK (4,000 FU/day) produced greater reductions in TC, LDL-C, and HDL-C than placebo in adults with primary hypercholesterolaemia [40]. Although these changes did not reach statistical significance, they remain clinically relevant for individuals who may benefit from adjunctive, diet-supported lipid improvement. Women experience disproportionate increases in LDL-C and triglycerides [1] later in life (peri/pre-menopause and menopause); thus the adjunctive lipid effects of NSK may be clinically relevant to women later in life.

Beyond lipid metabolism, NSK consistently enhances endogenous fibrinolytic and anticoagulant pathways. One human trial reported significantly enhanced fibrinolysis following NSK ingestion, demonstrated by shortened euglobulin lysis time, increased fibrinolytic activity, elevated fibrin degradation products, and higher plasma tissue plasminogen activator tPA levels lasting up to 8 - 12 hours [13]. The authors suggest that NSK enhances fibrinolysis primarily by stimulating the release and activity of endogenous tissue plasminogen activator (tPA), leading to increased plasmin formation and accelerated breakdown of fibrin [13]. Following a single oral dose (2,000 FU), NSK significantly increased fibrinolysis, elevating D-dimer, fibrin degradation products (FDP), and antithrombin levels, prolonging activated partial thromboplastin time (aPTT), and reducing factor VIII activity in healthy adults [12]. These coordinated changes suggest a sustained antithrombotic effect mediated by increased plasmin and tPA activity, elevation of antithrombin, and suppression of clot-

promoting factors. In parallel, a single dose of NSK (2,000 FU) significantly increased peripheral blood flow in the middle fingers at 120 and 180 minutes compared with placebo, indicating acute improvements in microcirculation [41].

Notably, response to NSK may depend on metabolic status. One study observed significant reductions in total PAI-1 after 8 weeks of NSK supplementation (4,000 FU/day) only in individuals with BMI > 25, while no effect was observed in those with lower BMI [42]. The authors suggest that lowering PAI-1—a key inhibitor of tPA—may enhance endogenous fibrinolysis in metabolically at-risk individuals, indicating a targeted, BMI-dependent vascular benefit. Similarly, NSK significantly reduced fibrinogen, factor VII, and factor VIII following 8 weeks of supplementation (4,000 FU/day) [43], supporting its role in modulating coagulation pathways and lowering thrombotic risk. Sex-specific vascular responses have also been observed. In a crossover study assessing peripheral blood flow, women exhibited consistently greater increases in finger and hand microcirculation following a single dose of NSK (2,000 FU) compared with men, suggesting heightened vascular responsiveness that may be relevant to female-predominant conditions such as cold sensitivity and microvascular dysfunction [44]. In a clinical setting, NSK administration was well-tolerated and associated with outcomes consistent with enhanced fibrinolysis and reduced thrombotic burden [45]. Participants (n = 153) consumed NSK (100 mg/day; 2,000 FU) as sequential therapy following anticoagulation or as post-surgical treatment. Although not part of the study design, over half the participants were female. NSK administration was associated with significant improvement or complete remission of clinical symptoms and improved Doppler ultrasonography findings. These antithrombotic effects are clinically meaningful in women, who have higher lifetime stroke risk and increased susceptibility to coagulation disturbances related to hormonal contraception, pregnancy history, and menopause [1,2,4,45].

However, NSK does not appear to exert uniform effects across all populations. Hodis., *et al*. [46] (2021) did not observe significant effects of NSK supplementation in healthy adults, suggesting that NSK's benefits may be more pronounced in individuals with elevated cardiovascular risk or pre-existing vascular dysfunction. Supporting this view, a single-dose human study found that NSK reduced C-reactive protein (CRP) levels most prominently in individuals with elevated baseline inflammation, with CRP reaching its lowest point approximately 12 hours post-ingestion [47]. This finding suggests rapid anti-inflammatory and vascular-supportive effects, which may be particularly relevant for women, who disproportionately present with elevated CRP and inflammation-driven cardiovascular risk [4]. This anti-inflammatory response is especially relevant for women, in whom elevated CRP is more strongly associated with cardiovascular events and may reflect underlying microvascular and endothelial dysfunction [4].

Changes in cardiovascular outcomes in response to NSK appear to be dose-dependent. Studies evaluating 2,000 FU/day consistently demonstrate improvements in blood pressure, fibrinolytic activity, and endothelial markers. Higher doses (4,000 - 8,000 FU/day) have been associated with more pronounced effects on lipid parameters and measures related to atherosclerotic burden. While many studies report favourable effects, findings are not entirely consistent across populations, and variability in baseline cardiovascular risk, study duration, and sample size may contribute to differences in observed outcomes. Dose normalisation across trials is limited by heterogeneity in population characteristics, baseline cardiovascular risk, duration of supplementation, and concomitant therapies. Standardised dose-ranging trials are needed to define optimal therapeutic thresholds for specific cardiovascular endpoints, particularly in women.

Safety and future directions

NSK has demonstrated a favourable safety profile in human studies with few reported adverse effects [48-50]; several considerations are particularly relevant for women. Due to its fibrinolytic and anticoagulant properties, theoretical concerns exist regarding heavy menstrual bleeding, and caution may be warranted in women with menorrhagia. NSK use should also be avoided in the perioperative period and in individuals undergoing invasive procedures because of potential bleeding risk [51]. NSK is contraindicated during pregnancy and breastfeeding due to insufficient safety data and the critical role of tightly regulated coagulation during these periods. Addressing these sex-specific safety considerations through targeted clinical research will be essential to inform evidence-based guidance for NSK use in women.

This review is narrative in nature and therefore subject to limitations inherent to heterogeneous study designs, variable dosing regimens, and differences in baseline cardiometabolic risk across trials. Although several randomised controlled trials are included, long-term cohort data in women remain limited. The majority of available NSK studies have been conducted in mixed-sex or general populations, with limited sex-disaggregated analyses. As a result, the ability to draw definitive conclusions regarding women-specific efficacy, optimal dosing, and long-term cardiovascular outcomes remains constrained.

Currently, there are no established sex-specific dosing guidelines, and it remains unclear whether responses differ between premenopausal, perimenopausal, and postmenopausal women. Future research should prioritise clinical trials that specifically evaluate efficacy, optimal dosing, and safety in women across different life stages including perimenopause, menopause, and post-menopause. Studies should compare commonly used doses (e.g. 2,000 FU, 4,000 FU, and higher doses ≥ 6,000 FU/day) to help clarify therapeutic thresholds for blood pressure, lipid modulation, fibrinolytic activity, and atherosclerotic progression. Given the sex-specific differences in lipid metabolism, inflammation, endothelial function, and thrombotic risk, studies powered for sex-stratified analyses are needed to clarify whether women derive differential benefit from NSK supplementation. Additionally, potential interactions between NSK and hormone-based therapies, including oral contraceptives and menopausal hormone therapy, have not been systematically evaluated. Given the known effects of hormonal status on coagulation, vascular function, and lipid metabolism, these factors represent important areas for future investigation.

Longitudinal studies including specific biomarkers (e.g. CRP, PAI-1, fibrinogen, von Willebrand factor) and relevant vascular endpoints (e.g. microvascular function and endothelial markers) would strengthen the mechanistic understanding of NSK supplementation. Additional work should also examine NSK as an adjunct to standard lipid-lowering and antihypertensive therapies, as well as its role in populations with elevated inflammatory burden, metabolic syndrome, or subclinical atherosclerosis. Establishing standardised dosing thresholds, particularly for lipid and atherosclerotic outcomes, and clarifying long-term safety with chronic use remain important.

Study	Preparation/Dose	Subjects	Duration	Outcome
Sumi and Maruyama [33]	6,400 FU	n = 5, hypertensive people	Daily dose for 4 days	Systolic and diastolic blood pressure decreased
Kim., *et al*. [15]	2,000 FU	n = 73, men and women, hypertensive 20-80 yrs	Daily dose for 8 weeks	Reduction in systolic and diastolic blood pressure and renin, all compared to placebo ($p<0.05$)
Liu., *et al*. [14]	2,000 FU	n = 86, men and women, hypertensive, 20-80 yrs	Daily dose for 8 weeks	Significant reductions in systolic and diastolic blood pressure compared to placebo after 8 weeks ($p<0.05$)
Krishnan Medical Association [34]	4,000 FU	n = 50 high BP and normal BP	Daily dose - 4 weeks placebo, 8 weeks NSK	SBP and DBP significantly lowered in high BP group; no significant effect in normal BP group
Jensen., *et al*. [16]	2,000 FU	n = 74, hypertensive adults (men and women, age 18-85)	Daily dose for 8 weeks	Significant reduction in diastolic BP vs placebo; trend toward systolic reduction; 15-26% decrease in von Willebrand factor

Kang [35]	Nattokinase by Lotte: 2,000 FU; by KPX: 2,000 FU	n = 42, men and women with high blood pressure risk	Daily dose for 4 weeks	NSK by Lotte (NSK-SD) had drastic reduction in blood pressure compared to competitor NSK by KPX
Liu., *et al*. [38]	2,500 FU combined with 7 mg red yeast, split in 2 doses	n = 113 adults with dyslipidaemia (TC ≥5.2 mmol/L, TG ≥1.7 mmol/L)	2×/day for 120 days	Significantly reduced TC, LDL-C, non-HDL-C, and LDL:HDL ratio vs placebo; no significant effects on BP or CIMT
Hodis., *et al*. [46]	2,000 FU	n = 265 adults (median age 65), healthy individuals without clinical CVD	36 months	No effects
Gallelli., *et al*. [45]	100 mg/day (~2,000 FU)	—	30 days	Significant improvement or complete remission of clinical symptoms and Doppler findings; no new thrombotic events or adverse drug reactions reported
Wu., *et al*. [40]	8,000 FU/day	n = 30, hypercholesterolaemia patients	8 weeks, single dose per day	Slight reduction in HDL-C and LDL-C
Yang., *et al*. [39]	1,750 FU NSK + 300 mg red yeast rice per capsule or 1,750 FU per capsule (50 mg)	n = 47 adults ≥40 years with untreated hyperlipidaemia	4 capsules/day for 6 months	NSK alone produced minimal lipid changes; NSK + red yeast rice significantly reduced TC (25%), LDL-C (41%), TG (15%), TC:HDL-C ratio (29.5%) and increased HDL-C (7.5%) vs placebo
Jeske [47]	2,000 FU	n = 18, men and women, 3+ cardiovascular risk factors	Single dose	CRP levels decreased more significantly in those with higher CRP levels at baseline
Sumi., *et al*. [13]	3,900 FU	n = 7 healthy volunteers, 21-55 years old	Daily supplementation for 8 days	NSK significantly enhanced fibrinolytic activity: shortened euglobulin lysis time, increased fibrinolytic activity, elevated fibrin degradation products, higher plasma tPA levels
Kurosawa., *et al*. [12]	2,000 FU	12 young males	Single dose; blood samples at 2, 4, 6, 8 hrs post-administration	D-dimer and fibrin/fibrinogen degradation products elevated significantly; factor VIII activity declined; antithrombin concentration higher; aPTT prolonged
Hsia., *et al*. [43]	4,000 FU	n = 45, healthy or with cardiovascular risk factors or on dialysis	8 weeks, daily dose	Decrease in plasma levels of fibrinogen, factor VII and factor VIII (coagulation factors)

Miruzzi., *et al*. [42]	4,000 FU	n = 45, slightly overweight individuals (BMI: 23-28)	8 weeks, daily dose	Fibrinolytic effect vs placebo not significant overall; significant decrease in PAI-1 when limited to participants with BMI >25
Iuchi., *et al*. [44]	2,000 FU	n = 15, healthy men and women, 30-49 years old	Single dose	Increased blood flow in fingers and backs of hands vs baseline at 80, 120, and 180 minutes after consumption
Watanabe., *et al*. [41]	2,000 FU	n = 15 healthy adults (7 men, 8 women), aged 30-49 years	Single dose	Significantly increased peripheral blood flow in the middle fingers vs placebo at 120 and 180 minutes post-ingestion

Table 1: *Summary of human clinical studies evaluating NSK supplementation.*

Conclusion

NSK exhibits a unique combination of fibrinolytic, antithrombotic, lipid-modulating, antihypertensive, and anti-inflammatory actions that align closely with pathways related to cardiovascular disease in women. Throughout life, women experience changes in lipid metabolism, endothelial function, inflammation, and coagulation that contribute to rising cardiovascular risk, particularly during the menopausal transition and in the presence of hormone-related or inflammatory conditions. Emerging evidence suggests that NSK may support vascular health through improvements in blood pressure, lipid profiles, fibrinolytic balance, endothelial function, and microcirculation, with several studies indicating heightened or clinically meaningful effects in women.

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