Received: 26 January 2025 | Revised: 23 April 2025 | Accepted: 23 April 2025

DOI: 10.1111/dom.16442

SPECIAL ISSUE ARTICLE

WILEY

Metformin use in prediabetes: A review of evidence and a focus on metabolic features among peri-menopausal women

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Abstract

The prevalence of prediabetes has more than doubled over the past two decades. Although hormones associated with the menstrual cycle may offer some protection against diabetes by enhancing insulin sensitivity and suppressing gluconeogenesis, the prevalence of diabetes among women remains high at 10.5%. Notably, among the perimenopausal population, the prevalence catches up to—and even surpasses—that of men starting from the 70–74 age group, according to the 2021 International Diabetes Federation (IDF) report. This narrative review examines the benefits and potential risks of metformin across diverse populations, with a particular emphasis on women in the perimenopausal phase. Metformin's interaction with hormonal regulation significantly influences both its therapeutic efficacy and long-term side effect profile, contributing to sex-specific differences in treatment response. Consequently, its effectiveness varies among women at different stages of menopause, potentially due to differential impacts on inflammatory markers and modulation of the hypothalamic–pituitary-ovarian (HPO) and hypothalamic–pituitary-thyroid (HPT) axes. Emerging evidence also highlights metformin's potential in managing conditions such as polycystic ovary syndrome (PCOS), breast tissue inflammation and endometrial disorders within this demographic. Given these potential and multifaceted benefits, this review highlights the need for further randomized controlled trials (RCTs) to investigate metformin's role among perimenopausal and menopausal women and to better understand how menopausal status may influence its efficacy.

Plain language summary

The number of people with prediabetes has more than doubled in the last 20 years. By 2021, about 720 million people worldwide were living with this condition, and that number is expected to reach 1 billion by 2045. While hormones that fluctuate

Beth Shi Yu Lim and Muzi Chen contribute to the first authorship equally.

with the menstrual cycle might help protect against diabetes, the overall rate of diabetes among women is still concerning, at 10.5%. For women going through menopause, the situation is even more serious. From the age of 70 to 74, the rates of diabetes in women surpass those in men. This may be because menopause reduces levels of protective hormones like estrogen and progesterone, which help guard against type 2 diabetes (T2D). Despite this growing issue, there hasn't been much research focused on prediabetes in women going through menopause and how the changes in hormones might affect treatment guidelines. To address this lack of information, our review focused on the use of metformin for women in the perimenopausal stage with prediabetes, aiming to help prevent them from developing T2D in the future. We gathered insights from recent clinical trials to summarize the benefits and risks of metformin for various groups, particularly perimenopausal women. Our findings indicate that metformin can be effective for managing prediabetes, although opinions vary. It's currently the only diabetes medication recommended for prediabetes by the American Diabetes Association (ADA), supported by significant studies like the Diabetes Prevention Program (DPP) and the Coronary Endothelial Dysfunction Multicentre Prospective Study (CODYCE study). Metformin's effectiveness seems to increase when combined with lifestyle changes, such as diet and exercise. Some challenges exist, though, like concerns that it might only work for those at a high risk of developing T2D, potential side effects, and the availability of other options, such as lifestyle adjustments or a new medication called tirzepatide. Still, many experts argue that metformin remains valuable because it allows for early intervention, particularly when lifestyle changes alone may not be enough. We also found that metformin might work differently for men and women due to variations in hormone interactions, differing gut bacteria, and weight-related factors that can influence its effectiveness. Interestingly, metformin seems to work better for women who have not yet gone through menopause. This might be because it helps with weight loss and reduces inflammation, which are important for postmenopausal health. Moreover, metformin has shown promise in addressing other health issues that postmenopausal women may face, such as inflammation in breast tissue, certain types of cancer, endometrial problems (as an alternative to hormone therapy), and polycystic ovarian syndrome (PCOS). In conclusion, our review stresses the importance of creating specific guidelines for managing prediabetes (e.g., metformin therapy) in the perimenopausal population. Understanding how sex hormones interact with blood sugar control is crucial for developing effective treatments tailored to women at different stages of menopause.

KEYWORDS
prediabetes, female populations with prediabetes, metformin, perimenopausal, women

1 | UNDERSTANDING PREDIABETES AND METFORMIN IN WOMEN AROUND MENOPAUSE

Prediabetes is a warning stage where blood sugar levels are higher than normal but not yet high enough to be called type 2 diabetes (T2D).[1,2] As of 2021, about 720 million people worldwide had prediabetes, and this number is expected to reach 1 billion by 2045.[1,2] People with prediabetes are at a higher risk of developing T2D, so it's important to catch and manage it early. However, there's still not enough research on how prediabetes affects women—especially those going through the hormonal changes of

perimenopause (the time around menopause). This is a crucial gap, as a better understanding could help prevent many future cases of T2D in women.

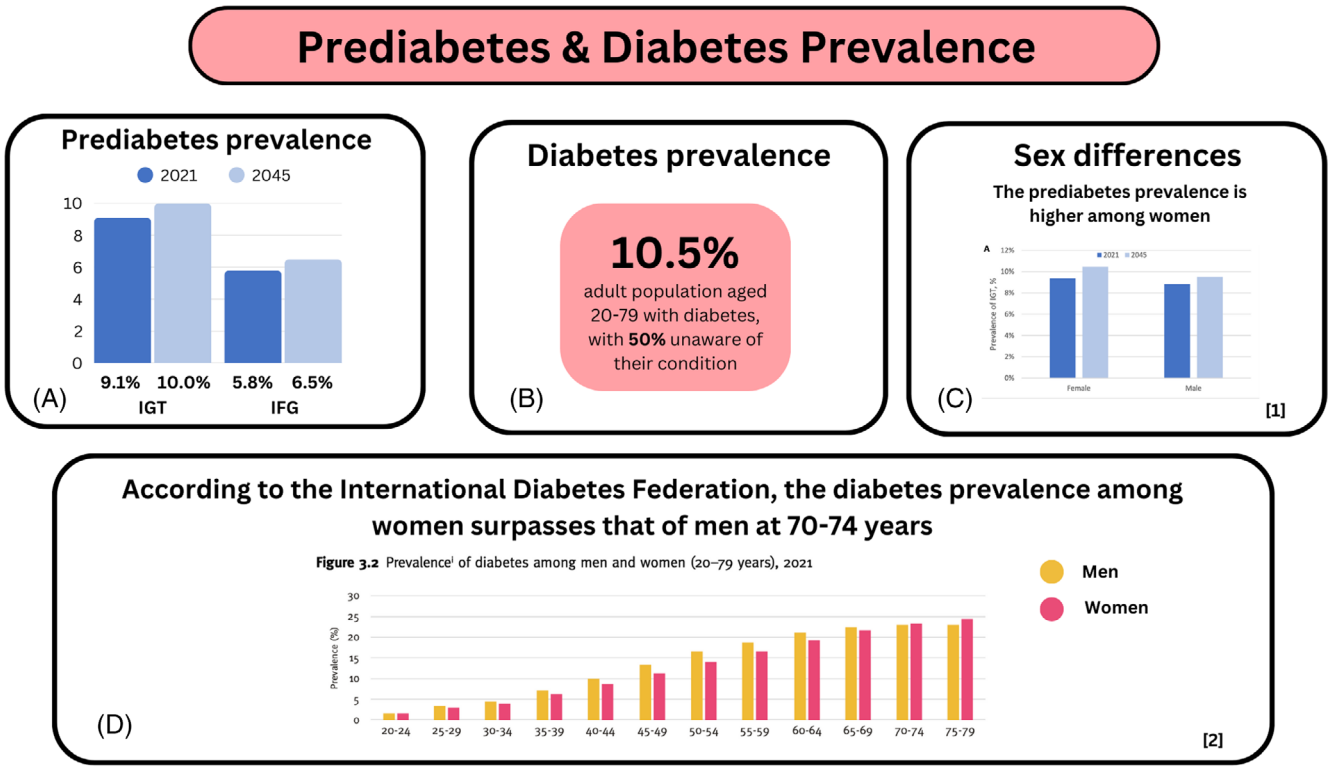
One commonly used medication for T2D is metformin. While it is mainly used to lower blood sugar, it has shown other helpful effects for women in their midlife. For example, metformin can reduce testosterone levels in women with Polycystic Ovary Syndrome (PCOS),[3] improve body weight and fat distribution[4] and reduce inflammation in breast tissue.[5] It may also help treat some conditions affecting the lining of the uterus, offering a potential alternative to hormone treatments like progesterone.[6]

This narrative review explores four key areas—epidemiology, pharmacology, clinical practice and future perspectives—centred on the use of metformin in preventing T2D among prediabetic women during the perimenopausal period. It provides an updated summary of metformin's pharmacological mechanisms of action and examines sex-based differences in treatment efficacy, with a particular focus on how hormonal fluctuations across different stages of perimenopause may influence therapeutic outcomes. Finally, the review highlights future research directions for metformin use in prediabetic perimenopausal women, grounded in the current unmet needs and knowledge gaps identified throughout the article.

2 | TOPIC 1: CURRENT PRACTICE OF METFORMIN IN THE POPULATION WITH DIABETES

2.1 | Prediabetes and type 2 diabetes (T2D): An escalating global concern

Prediabetes and Type 2 diabetes (T2D) are two rapidly increasing metabolic disorders that significantly impact the global population.[1,2] The prevalence of impaired glucose tolerance (IGT) was estimated at 9.1% worldwide in 2021 and is projected to increase to 10.0% by 2045.[2] Similarly, impaired fasting glucose (IFG) was estimated to affect 5.8% of the global population in 2021, with a projected rise to 6.5% in 2045. These projections are based on a comprehensive analysis of 7014 publications, providing high-quality estimates for IGT and IFG prevalence. Notably, women showed a higher prevalence than men in both IGT and IFG (Figure 1).[2] Meanwhile, T2D has emerged as the biggest epidemic of the 21st century. According to the International Diabetes Foundation (IDF) Diabetes Atlas, 10.5% of the adults aged 20–79 have diabetes, with nearly half unaware of their condition[7] (Figure 1). The progression from prediabetes to T2D is concerning. An expert panel from the American Diabetes



[1] Rooney MR, Fang M, Ogurtsova K, et al. Global Prevalence of Prediabetes. Diabetes Care. 2023;46(7):1388-1394
[2] International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: International Diabetes Federation, 2021. http://www.diabetesatlas.org

FIGURE 1 Global Prediabetes and Diabetes Prevalence. (A) represents the estimated increase in prevalence of impaired glucose tolerance (IGT) from 9.1% in 2021 to 10.0% by 2045 and impaired fasting glucose (IFG) from 5.8% in 2021 to 6.5% in 2045. (B) shows the global prevalence of diabetes at 10.5%. (C) illustrates that women showed a higher prevalence than men in both IGT and IFG. (D) shows that the prevalence of diabetes in the perimenopausal population surpasses that of men from the 70–74 age group.

Association (ADA) proposed that up to 70% of individuals with prediabetes will eventually develop diabetes.[8] Similarly, a Chinese diabetes prevention trial reported that the 20-year cumulative incidence of diabetes exceeded 90% among individuals with IGT at baseline, as assessed by repeated oral glucose tolerance tests (OGTTs).[9] Given the global burden of T2D, public health initiatives are increasingly focused on the early detection of prediabetes to prevent its progression.

Currently, several definitions of prediabetes are employed in current practice, based on various cut-off points for HbA1c, fasting glucose and 2-h glucose levels.[10] Even though emerging techniques such as continuous glucose monitoring (CGM) and the use of glycated albumin (GA) – a biomarker that reflects short-term glycaemic variability[11] – have been explored by researchers in the search for optimal management strategies, their complementary value in prediabetes diagnostic criteria remains inconclusive. Moreover, treatment guidelines for prediabetes and T2D continue to evolve, driven by ongoing clinical trials. Beyond lifestyle modifications and weight loss, metformin has remained a recommended pharmacological intervention for decades, demonstrating efficacy both as monotherapy and in combination with other glucose-lowering agents.[12]

2.2 | Metformin: Pharmacokinetics, mechanism of action and therapeutic effects in metabolic disorders

Metformin is not metabolized and is excreted unchanged in the urine, with a half-life of about 5 hours. The drug is widely distributed into body tissues, including the intestine, liver and kidney by organic cation transporters.[13] Metformin's role as the common therapy for the treatment of T2D is well established in various guidelines from the IDF,[14] American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD),[15] as well as Kidney Disease: Improving Global Outcomes (KDIGO)[16] guidelines.

Despite its widespread clinical adoption, the precise mechanism of action of metformin remains incompletely understood. However, metformin is clinically hypothesized to function through several key mechanisms (Figure 2). Its primary metabolic effects are proposed to occur via the activation of AMP-activated protein kinase (AMPK), a key cellular regulator of lipid and glucose metabolism in the liver. Metformin-induced AMPK activation occurs via AMP-dependent and AMP-independent pathways, influenced by metformin concentration and target organelles, such as the mitochondria or lysosome.[17] By activating AMPK in hepatocytes, metformin reduces acetyl-CoA carboxylase (ACC) activity, induces fatty acid oxidation and suppresses the expression of lipogenic enzymes, thereby lowering the levels of hepatic lipids.[18,19] Chronic AMPK activation is also proposed to increase the mRNA expression of genes encoding GLUT-4 glucose transporters and enhance glucokinase activity, resembling the periodic AMPK activation observed during endurance exercise, which facilitates glucose uptake.[20,21] Emerging evidence also highlights metformin's cardioprotective benefits, particularly in the context of ischaemia–reperfusion (I/R) injury. Through AMPK activation, metformin reduces inflammatory responses and mitigates myocardial tissue damage.[22] Additionally, AMPK lowers intercellular cAMP levels,

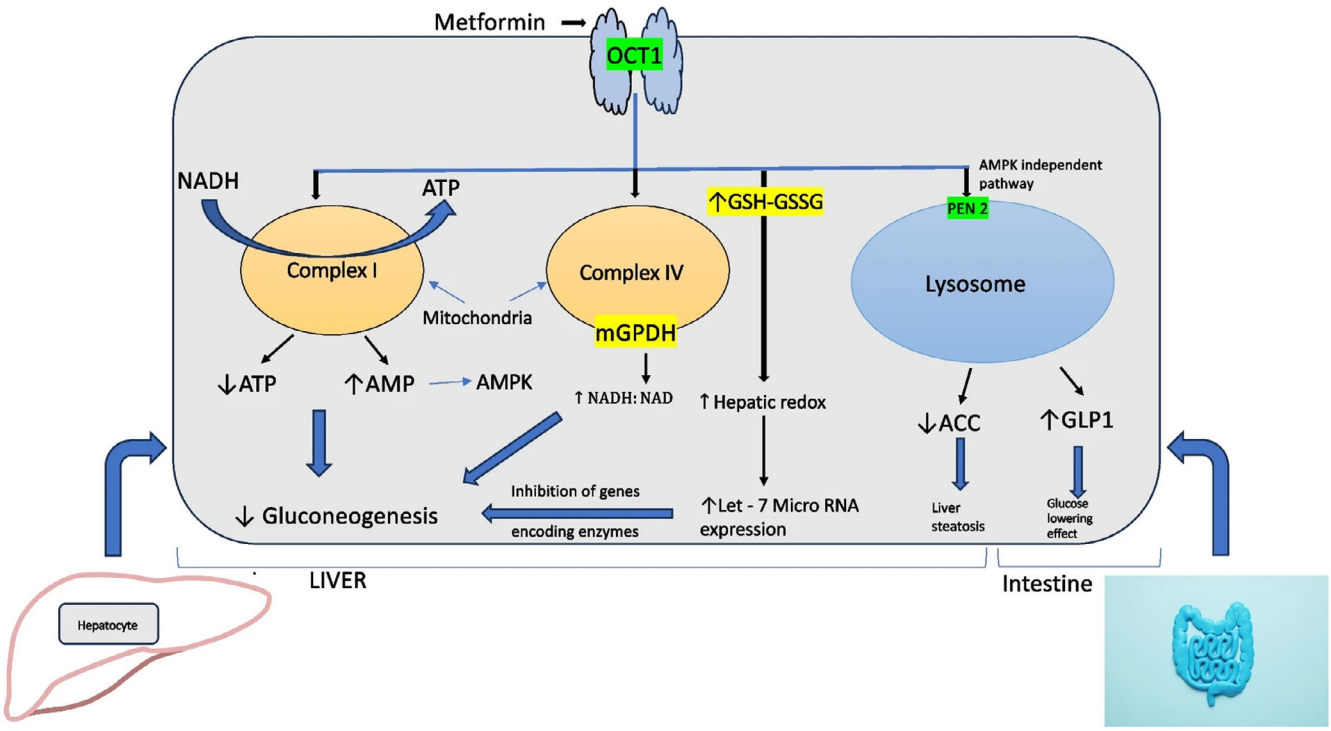


FIGURE 2 Metformin's Mechanism of Action (copyright from Chaudhary S, Kulkarni A. Metformin: Past, Present and Future. Current Diabetes Reports. 2024;24 (6):119–130).

thereby decreasing the activity of protein kinase A (PKA). PKA inhibits the glycolytic enzyme pyruvate kinase; thus, its suppression promotes glycolysis over gluconeogenesis, leading to reduced glucose levels.[23] These cellular pathways may also be influenced by hormonal status. Oestrogen, for example, has been shown to interact with AMPK signalling. Oestradiol treatment induces a rapid, dose-dependent activation of AMPK in murine skeletal muscle, suggesting that oestrogen withdrawal during menopause may contribute to interindividual variation in metformin's therapeutic benefits.[24]

Beyond hepatic and cardiovascular effects, metformin is also proposed to decrease adiposity and increase (glucagon-like peptide) GLP-1 plasma levels and leptin sensitivity, which improve satiety and reduce weight gain.[25] While the liver is traditionally considered the primary site of metformin's glucose-lowering action, growing evidence suggests that the gastrointestinal tract also plays a crucial role in its action.[26] Very recent evidence demonstrates that Complex I inhibition[27] and AMPK activation[27,28] in intestinal cells are crucial in metformin's mechanism of action, perhaps even more than direct hepatic effects.

Metformin also contributes to weight stability through mechanisms in the intestine, including enhancing splanchnic glucose-lactate-glucose turnover[29] as well as the induction of the appetite-suppressing metabolic N-lactoyl-phenylalanine produced by the intestine.[30] Furthermore, host-gut microbiota interactions are also suggested to contribute to metformin's glucose-lowering effects, possibly through the production of short-chain fatty acids (FAs) that interact with the host and increase short-chain FA levels in faeces.[31] Treatment with metformin has also been linked to an increased abundance of beneficial bacteria such as *Akkermansia muciniphila* and *Lactobacillus* species. These changes are associated with improved intestinal barrier function and reduced inflammation, which may help explain its therapeutic potential in conditions like ulcerative colitis.[32]

Over the decades, metformin has earned its prominent role in clinical practice due to its numerous benefits for patients with T2D, including improving insulin sensitivity, weight reduction, better lipid profiles and enhanced endothelial function.[33] Additionally, metformin has been shown to reduce the risk of diabetic complications such as stroke, cardiovascular events and mortality in patients with T2D and obesity.[34,35] With its long-standing history in clinical use, metformin is well-supported by extensive data validating its safety and efficacy in combination with other antidiabetic agents, such as sulfonylureas, DPP-4 inhibitors and SGLT2 inhibitors. These combinations allow more comprehensive and effective blood glucose control without significantly increasing the risk of hypoglycaemia or other serious adverse events.[36] However, despite its widespread and safe profile, metformin is not without risks. The most common adverse side effects are gastrointestinal symptoms, including nausea and vomiting, which occur in 20–30% of cases and often improve or subside over time.[37,38] The most serious adverse effect is lactic acidosis,[33] which occurs primarily in patients with diabetes who have severe or advanced kidney dysfunction, as these conditions impair the drug excretion.[39]

3 | EMERGING APPLICATION OF METFORMIN IN PREDIABETES

3.1 | Advantages

Metformin is currently the only antidiabetic medication recommended for prediabetes by ADA[40] and has been approved for prediabetes in at least 66 countries.[41] Several large-scale prospective studies have demonstrated its potential to prevent the progression to T2D and reduce the risk of diabetic complications. The Diabetes Prevention Program (DPP) was one of the first studies to highlight metformin's beneficial effects on coronary atherosclerosis in a pre-diabetic population. In this study, subclinical atherosclerosis, as indicated by coronary artery calcium (CAC), was significantly lower among men in the metformin group compared to those receiving a placebo. The age-adjusted mean CAC severity was 39.5 Agatston units (AU) (95% CI: 26.7, 58.4) in the metformin group versus 66.9 AU (95% CI: 45.3, 98.8) in the placebo group ($p = 0.04$). Additionally, the presence of CAC was lower in the metformin group (75%) compared to the placebo group (84%) ($p = 0.02$).[42] Such findings were further supported by the CODYCE (Coronary Endothelial Dysfunction) Multicentre Prospective Study, which showed that metformin therapy significantly reduced the risk of cardiovascular events in prediabetic patients by improving coronary endothelial function. Patients treated with metformin exhibited lower levels of inflammatory markers, including white blood cells (WBCs), granulocytes and TNFα. It was postulated that metformin reduces inflammatory tone and the leptin-to-adiponectin ratio in peri-coronary fat, which are two potential mechanisms leading to a lower incidence of major cardiac adverse events (17.4% versus 24.4%, $p < 0.05$) at the 24th month follow-up.[43]

Metformin's glucose-lowering effects also contribute to better glycaemic control in prediabetic individuals, which has been supported by a body of evidence and affirmed by the ADA guidelines.[44] A recent Chinese open-label randomized controlled trial (RCT) showed that metformin combined with standard lifestyle intervention further reduced the risk of developing diabetes than lifestyle intervention alone by around 17% (HR 0.83 [95% CI 0.70–0.99]; $p = 0.043$) over a 2-year follow-up.[45] A similar study among general practitioners in Australia found that patients on metformin, particularly those with higher baseline HbA1c levels (6.2% vs. 5.9%), achieved lower mean HbA1c and fasting blood glucose after 18–24 months of follow-up.[46] Furthermore, a study by Safiah et al. demonstrated a significant reduction in mean fasting blood glucose (101.7 versus 84.1 mg/dL, $p = 0.017$) and HbA1c (5.6% versus 5.4%, $p = 0.001$) in female patients after 12 months of metformin therapy.[47]

Multiple meta-analyses further reinforce metformin's utility in preventing T2D in the population with prediabetes. For example, Patel et al. reported based on 17 studies that the pooled risk ratio (RR) for developing T2D indicated a 35% lower risk (RR: 0.65; 95% CI: 0.53, 0.80) of progressing to T2D among prediabetic individuals receiving metformin compared to controls.[48] Another meta-analysis of 12 RCTs showed that adding metformin to lifestyle intervention

significantly reduced HbA1c levels and the risk of T2D development by 15% (RR: 0.85; 95% CI: 0.75–0.97).[49]

3.2 | Disadvantages

Despite its benefits, metformin's efficacy in prediabetes is not without caveats. The DPP and similar diabetes prevention trials primarily studied individuals at high risk for T2D progression, and they suggested substantial heterogeneity in treatment outcomes, where metformin was notably more effective in participants who were under 60 years old, with a body mass index (BMI) ≥35 kg/,[2] demonstrating greater degrees of fasting hyperglycaemia, and with a history of GDM if the subject is a female with a live birth.[50] Davidson et al. further questioned the necessity of metformin in prediabetes.[51] He argued that not all individuals with prediabetes progress to T2D, as some remain stable or even return to normal glucose regulation. Furthermore, individuals with prediabetes are generally not at significant risk of microvascular complications associated with diabetes. Davidson et al. posited that metformin offers 'no immediate advantage' other than further lowering already sub-diabetic glycemia levels. He also highlighted the risk of long-term side effects, such as Vit B12 deficiency, if metformin is used for the long term (especially ≥4 years)[52] and at higher doses (≥ 1500 mg/day).[53,54] Last but not least, lifestyle modifications alone may be a viable, or even superior, alternative to metformin in managing prediabetes. The Look AHEAD study (Action for Health in Diabetes) demonstrated that intensive lifestyle interventions, such as weight loss, led to modest remission rates of T2D[55] and significant improvements in cardiovascular profiles.[56] Similarly, the DPP revealed that the cumulative incidence of diabetes was the lowest in the lifestyle intervention arm compared to the metformin treatment arm,[57] regardless of the protective effects of hormones (e.g. oestrogen) against T2D.

While metformin remains a commonly used therapy for T2D, emerging alternatives such as tirzepatide—a novel dual glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA) – are gaining attention for their potential advantages.[58] Compared with metformin, even with its well-established efficacy, tirzepatide has demonstrated superior glycaemic control and significant weight reduction in clinical trials.[59] However, its considerably higher cost—estimated at $59 000 per quality-adjusted life year (QALY) gained[60] – currently limits its widespread adoption. Although tirzepatide is associated with a higher incidence of gastrointestinal side effects compared to metformin,[59] it may offer a more comprehensive therapeutic profile for patients, such as those diagnosed with severe kidney dysfunction.[61] As such, the potential application of tirzepatide in prediabetic women during the perimenopausal stage remains a promising area for future therapeutic exploration.

3.3 | The Rebuttal

Despite these contending views, metformin remains the cornerstone of pharmacological management in prediabetes for a couple of reasons. To start with, Herman et al.[50] proposed that metformin should be used in high-risk individuals meeting DPP eligibility criteria, as it offers proven benefits in preventing T2D and associated complications. He further noted that there was often a 3–8 years delay between the onset and diagnosis of T2D, during which many patients already develop microvascular complications. Therefore, early intervention with metformin—an effective, safe and cost-efficient drug—can help mitigate diabetes progression before complications manifest.[52] Secondly, while lifestyle modifications may be superior to metformin monotherapy, it heavily depends on the patients' compliance and the intensity of the lifestyle moderation. Indeed, as shown in the Look AHEAD study, most participants regained their body weight 1 year after receiving lifestyle intervention.[62] Realistically, while lifestyle modifications remain the first line in all treatment, they may be inadequate in the management of high-risk individuals with prediabetes, particularly in those who are not fit for intense physical activity or have dietary restrictions. In fact, the Look AHEAD trial also showed that intensive weight-loss lifestyle modifications subsequently proved limited in reducing the rate of cardiovascular events in overweight or obese adults with T2D.[63] Only those participants with significant weight loss of 5–10% showed reduced cardiovascular risks. Therefore, a pharmacological option in prediabetes management remains relevant and necessary in clinical practice in high-risk prediabetic populations.

The efficacy, safety and cost-effectiveness of metformin therapy have been established among very high-risk individuals. The likelihood of achieving beneficial effects is greatest when metformin is prescribed to those who meet the DPP eligibility criteria.[50] Given the variability in treatment response, metformin therapy should be prioritized for individuals at highest risk—such as younger, more obese, more hyperglycaemic individuals, including women with a history of GDM.[50]

4 | TOPIC 2: SEX-SPECIFIC DIFFERENCES IN THE EFFECTS OF METFORMIN

The prevalence of impaired glucose tolerance (IGT) among women is projected to remain high at 10.5% by 2045, affecting both premenopausal and perimenopausal women similarly to men in the same age group.[7] However, IGT prevalence in women during the postmenopausal stage is expected to exceed that of men aged 70 to 74 years,[7] potentially due to the loss of protective hormonal effects, such as oestrogen, against type 2 diabetes.[64] This phenomenon may be explained by the menopausal transition and postmenopausal changes, including alterations in sex steroid hormones, body composition, fat distribution and metabolic and lipid profiles, all of which heighten diabetes risk.[4] Understanding these trends underscores the need for targeted interventions addressing gender-specific risks across the lifespan.

Evidence has shown that sex plays a pivotal role in modulating responses to metformin treatment. The Metformin and AcaRbose in Chinese as the initial Hypoglycaemic treatment (MARCH) study, with 121 metformin-treated females (ages 45–56.50 years) versus 193 metformin-treated males (ages 42–55 years), found that women on metformin had lower fasting and 2-h postprandial glucose levels compared to

men after 24 and 48 weeks of treatment.[65] Other studies have similarly reported sex dimorphism in metformin-related signalling pathways, including changes in AMPK and positive regulation of autophagy machinery following short-term metformin administration, resulting in sex-specific responses to metformin-induced analgesia in neuropathic pain.[66]

Emerging evidence has proposed several plausible mechanistic speculations to explain metformin-related sex differences. Firstly, although the precise mechanisms of metformin's cellular action remain poorly understood, it is known to elicit various molecular responses, some of which are influenced by sex hormones. For instance, oestradiol activates the PI3K-Akt pathway via Erβ, which leads to reduced inhibition of FOXO1 and FOXO2, suppression of p21 (cyclin-dependent kinase inhibitor) and the subsequent inhibition of proinflammatory and proapoptotic effects. These pathways may play a role in sex-specific responses to metformin.[67]

Secondly, differing gut microbiota might contribute to differing metformin responses. With the emergence of advanced sequencing technologies, it has become apparent that metformin mitigates the imbalance in gut microbiota associated with T2D and its subsequent impact on host metabolism by altering the composition and operation of the intestinal microbiome.[67] Women are known to have distinct gut microbiota profiles at baseline due to the influence of sex hormones.[68] For instance, progesterone has been shown to promote the growth of oral Bacteroides species,[69] which is relevant as various studies have demonstrated a positive relationship between Bacteroides abundance and metformin's therapeutic effects.[67] This sex difference could also explain why women experience higher rates of gastrointestinal side effects, such as diarrhoea, despite taking lower doses of metformin compared to men.[70] Studies have linked metformin-induced changes in gut microbiota to gastrointestinal symptoms, including diarrhoea,[71] which may explain why women are more likely to discontinue metformin after starting treatment.[72,73]

Thirdly, beyond gastrointestinal side effects such as diarrhoea, nausea, abdominal discomfort and flatulence, studies have shown that women more often experience other adverse drug reactions (ADRs) from metformin, such as headache and fatigue.[70] For example, 39.6% of females reported the occurrence of an ADR compared to 30.9% of males.[74] These adverse effects are likely to result in women switching to another oral hypoglycaemic agent (OHGA) or decreasing the metformin dose while adding another OHGA,[75] where abdominal discomfort most often leads to the withdrawal of metformin.[74]

Lastly, differences in body weight may contribute to sex-based disparities in metformin response. The use of a fixed dosing regimen for all adults may result in higher drug exposure in women, who generally have lower body weight compared to men[76] despite some studies suggesting no significant sex differences.[77,78] Further research is warranted to investigate the observed higher incidence of side effects and treatment discontinuation among women. Such studies should explore potential associations with body fat distribution, including visceral adiposity, as well as muscle and bone health and various degrees of insulin resistance.

Therefore, metformin's interactions with hormone levels are believed to influence both its treatment effects and long-term side effects. Given the significant hormonal changes in a life course—menarche, pregnancy and menopause—it is essential to assess the varied effectiveness of metformin during each stage. In particular, the perimenopausal stage brings stark hormonal fluctuations that may substantially influence metformin's effectiveness in treating prediabetes. Recognizing and accounting for these hormonal changes is critical to optimizing metformin therapy for women throughout their lifespan.

5 | TOPIC 3. EFFECTS OF METFORMIN ON WOMEN AT DIFFERENT PERIMENOPAUSAL STAGES

Menopause is retrospectively defined as 12 consecutive months of amenorrhoea, marking the loss of ovarian follicular activity.[79] Perimenopause, also known as the menopausal transition, refers to the period spanning from shortly before menopause to the final menstrual period, characterized by hormonal fluctuations, irregular menstrual cycles and various symptoms as the body transitions towards menopause. In the general female population, perimenopause typically spans the 40-50th age range and could extend slightly beyond, up to the early 50s. However, the exact timing can vary between individuals.[80] Consequently, the terms premenopausal and postmenopausal refer to the stages before and after perimenopause, respectively—though their definitions may vary across individuals, studies and populations.

5.1 | Metformin effectiveness for T2D prevention across perimenopausal stages

Metformin demonstrates varying levels of efficacy among women at different stages of menopause. It was found to be more effective in the pre-menopausal group (mean age 45.7 years) with an unadjusted cumulative incidence of diabetes in 6.6 cases per 100 person-years and in the postmenopausal group (mean age 55.1 years) with 8.9 cases per 100 person years.[81] Interestingly, when the postmenopausal group was further divided into women with natural menopause (mean age 56.4 years) and those who underwent bilateral oophorectomy (mean age 53.0 years), metformin was more effective in the former than the latter, with an incidence rate of diabetes in 5.0 cases per 100 person-years versus 10.3 cases per 100 person-years, respectively.[81] To the best of our knowledge, no other publicized study compared the effectiveness of metformin across different menopausal stages; there are only studies on metformin effectiveness that acknowledge the presence of different menopausal stages in their study subjects.[82]

Several mechanisms have been speculated to underlie these observations (Figure 3). Firstly, metformin has reported effects on weight reduction and inflammatory markers, particularly in postmenopausal women. It decreases adiposity and increases glucagon-like

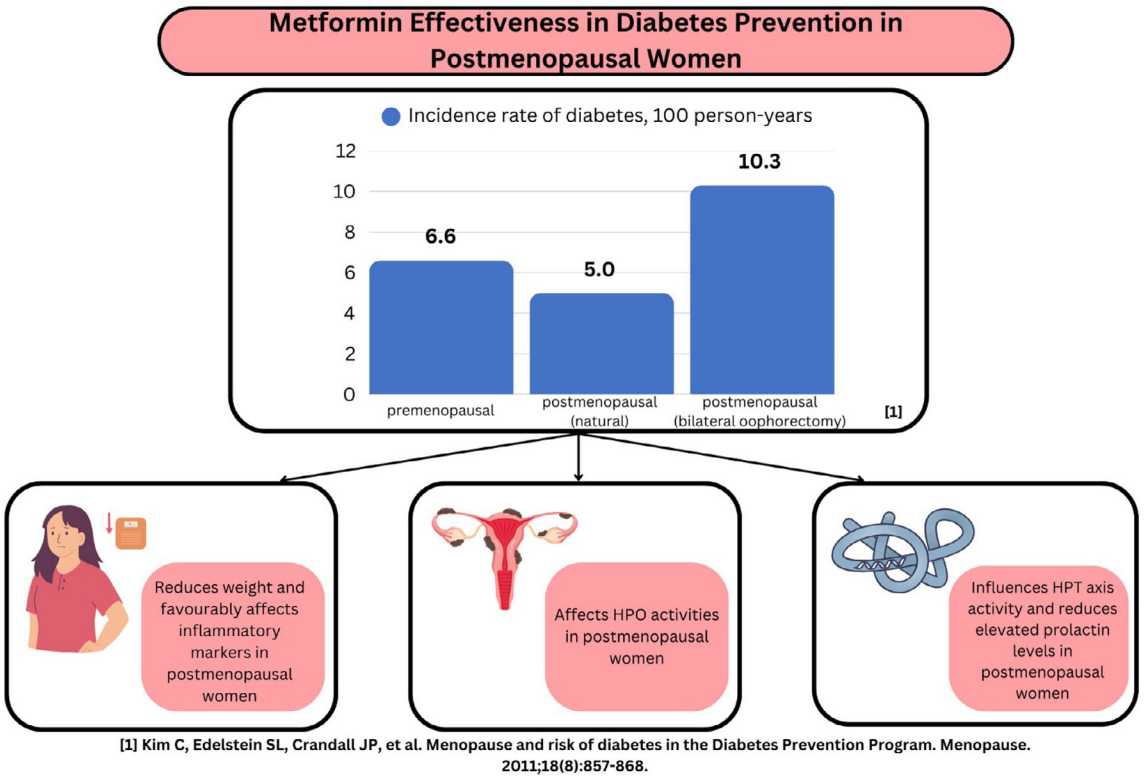


FIGURE 3 Metformin's Effectiveness in Diabetes Prevention in Postmenopausal Women. This figure illustrates the variability in metformin's effectiveness in diabetes prevention among postmenopausal women via weight reduction and influence on inflammatory markers, HPO activities and HPT axis activity.

peptide 1 (GLP-1) and leptin sensitivity, contributing to improved satiety and reduced weight. In centrally obese type 2 diabetic patients, metformin use resulted in a reduction of at least 16% in visceral fat, likely due to upregulation of fat oxidation-related enzymes in the liver, brown adipose tissue and skeletal muscle.[83]

Secondly, metformin affects hypothalamic–pituitary–ovarian (HPO) axis activity in postmenopausal women, depending on dosage, baseline gonadotropin levels, insulin resistance and improvements in insulin sensitivity.[84,85] A study by Krysiak et al. demonstrated that in postmenopausal women with type 2 diabetes, high-dose metformin (3 g/day) significantly reduced serum follicle-stimulating hormone (FSH) levels by 30% and tended to reduce serum levels of luteinizing hormone (LH) by 25%.[84] The effect correlated with baseline gonadotropin levels, suggesting that metformin's impacts may differ between the early and late postmenopausal phases.[84] Similarly, metformin reduces LH levels and the LH/FSH ratio in women with polycystic ovarian syndrome (PCOS), improving glucose regulation by addressing insulin resistance and hyperinsulinemia. This modulation can improve the hormonal environment and metabolic outcomes. By reducing LH and improving insulin sensitivity, metformin may enhance glucose-lowering effects in hyperinsulinemic conditions, as seen in women with PCOS. The interplay between gonadotropins and metformin's action is evident in hormonal normalization and metabolic improvements.[86] In contrast, moderate-dose metformin (1.7 g/day) showed no effect on gonadotropins in postmenopausal prediabetic women.[84] Neither high-dose nor moderate-dose metformin affected serum levels of thyrotropin, prolactin and oestradiol, as well as the estimated glomerular filtration rate.[84]

Thirdly, metformin influences hypothalamic–pituitary–thyroid (HPT) axis activity[85] and reduces elevated prolactin levels in postmenopausal women, with both effects being modulated by oestradiol levels, reported by Krysiak et al. in two separate studies.[85,87] Metformin's lowering effect on thyrotropin levels and thyroid secretory capacity, as well as its ability to reduce prolactin levels, is more pronounced in women undergoing oestradiol replacement therapy compared to oestradiol-naïve women.[87] These impacts correlate with baseline thyrotrope and prolactin function and improvements in insulin sensitivity, highlighting the critical role of oestradiol in modulating metformin's effects on the HPT axis and prolactin levels.[85,87]

5.2 | Metformin's role in polycystic ovary syndrome (PCOS), breast tissue inflammation and cancer and endometrial disorders

Obesity and insulin resistance have been reported as key contributors to PCOS, anovulation and luteal phase deficiency in premenopausal women.[88] Metformin effectively alleviated these conditions (Figure 4) by lowering PCOS-related hyperandrogenism via reducing serum testosterone levels by approximately 20–25% in women with PCOS,[3]

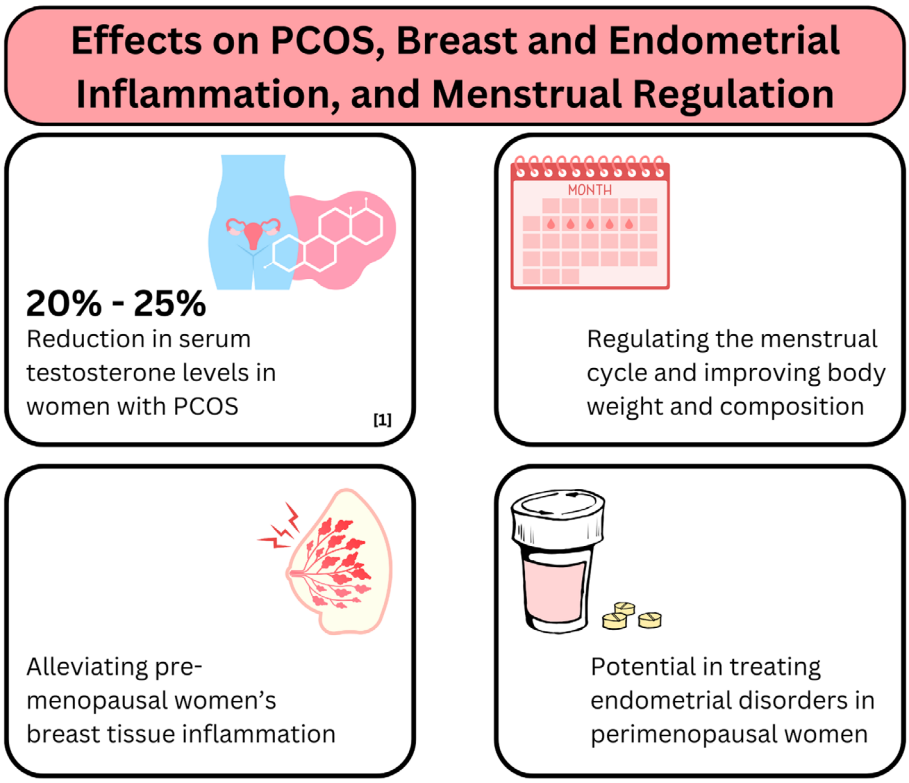


FIGURE 4 Metformin's Role in Polycystic Ovary Syndrome (PCOS), Breast Tissue Inflammation and Cancer and Endometrial Disorders. This figure presents various benefits of metformin on PCOS, menstrual regulation, breast tissue inflammation, breast cancer and endometrial disorders.

primarily through its insulin-lowering effect[89] or more recently proposed as countering insulin resistance.[90] Similarly, metformin has shown effectiveness in premenopausal women with a history of PCOS and/or hyperinsulinemia due to insulin resistance, improving fertility outcomes associated with this disorder.[91] In addition to addressing hormonal imbalance, metformin regulates the menstrual cycle and improves body weight and composition (Figure 4). A meta-analysis including 38 RCTs involving 3495 women with PCOS demonstrated these benefits mentioned above, albeit with significant heterogeneity even after adjusting for potential confounders. This suggests that genetic factors or other implicit factors might affect metformin's efficacy.[92] Since the meta-analysis focused on younger women with a mean age of 27.3 years, future research is required to see if these findings could be applied to perimenopausal women.

It was also reported that metformin exerts favourable effects on breast tissue inflammation (Figure 4). A study by Giles et al. on premenopausal women with metabolic syndrome found that metformin significantly reduced CD68 density (a marker of macrophages) in breast adipose tissue compared to placebo (34 vs. 37, $p = 0.01$), highlighting its anti-inflammatory potential.[5] Supporting this, an animal study on ovariectomized female Wistar rats demonstrated that metformin modestly improved a key marker suggestive of improved metabolic health– hepatic lipid accumulation (21% decrease in metformin-treated rats compared to untreated controls), reduced adipose tissue inflammation (indicated by halving the number of CD68+ adipose tissue macrophages and crown-like structures (CLS) in rats rapidly gaining weight following ovariectomy) and decreased mammary tumour size while inhibiting new tumour formation (tumour burden 86% lower than untreated counterparts) – suggesting its potential as a breast cancer treatment for perimenopausal women.[93]

Moreover, metformin may serve as a promising alternative to progesterone in treating endometrial disorders (Figure 4). Elgarhy et al. conducted a research study by comparing the antiproliferative effectiveness of metformin and medroxyprogesterone acetate among perimenopausal women with disordered proliferative endometrium and simple endometrial hyperplasia (mean ages 49.02 and 49.87 years, respectively). The team demonstrated comparable efficacy, such as metformin effectively resolving benign endometrial proliferative lesions.[6] Such findings highlight metformin's potential therapeutic role in perimenopausal endometrial health.

6 | TOPIC 4. FUTURE PERSPECTIVE OF METFORMIN USE IN PERIMENOPAUSAL WOMEN

Guidelines on prediabetes management in perimenopausal women remain underdeveloped due to several limitations in existing studies. Firstly, most evidence is derived from populations with diabetes rather than those with prediabetes and even less specifically from female populations. However, as prediabetes should not be considered merely a risk factor but a serious pathological condition with significant complications,[94] drawing conclusions from such studies for prediabetes management guidelines is limited.

Secondly, research has not extensively covered all phases of menopause. The lack of targeted research on the perimenopausal

population is particularly significant, given the fluctuating hormone levels during this phase, which can alter the response to metformin. Most evidence either focuses on older females or encompasses a broad population, without specifically addressing perimenopausal women. Notably, there are no substantial pilot studies on the effects of metformin in the perimenopausal population. Thirdly, evidence of sex differences in metformin's efficacy and side effect profile further highlights the importance of considering these hormonal variations. It is reasonable to anticipate that metformin's pharmacokinetics and therapeutic effects may differ in women undergoing the hormonal transitions associated with menopause. In this context, alterations in drug elimination—primarily due to changes in renal function and hormonal fluctuations aforementioned—are likely more significant than any changes in absorption or reabsorption processes. However, sparse evidence has investigated the direct interaction between hormonal therapy—or the hormonal fluctuations associated with menopause—and the biomarkers involved in metformin's mechanism of action, such as leptin, GLP-1 and the host-gut microbiota. Despite some studies[83,95] suggesting potential associations, the pathophysiology underlying the varied response to metformin in the perimenopausal population remains poorly understood.

Finally, the use of metformin in women with gynaecological conditions such as polycystic ovary syndrome (PCOS) has been extensively studied in premenopausal populations. It is now recommended in major clinical guidelines for the management of PCOS[96] and has been approved for this indication in more than 13 countries.[97] Although the interplay between menopausal status and PCOS remains poorly understood, it is well recognized that the metabolic consequences of PCOS often persist beyond the reproductive years. In some cases, PCOS may evolve through and beyond menopause, with hyperandrogenism—a key driver of long-term metabolic risk—underpinning the association between PCOS in menopausal women and metabolic syndrome (MetS).[98] As a result, the use of metformin in perimenopausal women may be further complicated by the presence of other hormone-dependent gynaecological conditions, such as PCOS.

Beyond its established role in glycaemic control, metformin has shown potential benefits in cognitive function, sexual health and mood regulation, though evidence remains mixed. In cognitive domains, metformin may exert neuroprotective effects through AMPK activation and reduced inflammation, with some studies suggesting reduced dementia risk, while others raise concerns over long-term use and vitamin B12 deficiency.[99] Regarding sexual function, metformin appears particularly beneficial in women with PCOS, improving hormonal balance and metabolic profiles.[91] Similarly, metformin may alleviate depressive symptoms, especially in populations with metabolic or hormonal dysregulation, possibly through improvements in insulin sensitivity and reductions in systemic inflammation.[100] Importantly, racial and ethnic differences influence metformin's effectiveness, largely due to genetic polymorphisms in drug transporters such as organic cation transporter 1 (OCT1), as well as variable glycaemic responses. While East and South Asians often exhibit heightened sensitivity to metformin, African American and Hispanic populations have also shown favourable outcomes.[101] These observations highlight the need for more inclusive research and personalised approaches in metformin therapy, especially in women at the perimenopausal stage.

7 | CONCLUSION

With the rising prevalence of prediabetes, there is a pressing need to pay heed to the unique hormonal profiles of the perimenopausal population—a population often under-represented in clinical research and underserved in practice. However, the long-term efficacy and safety of metformin in this group remain uncertain, as current evidence is limited and does not sufficiently account for individual variability across different stages of menopause. As such, this review does not seek to guide clinical use but rather to underscore the need for further investigation. Advancing this field will require well-designed, large-scale RCTs and targeted studies focusing on clearly defined perimenopausal and menopausal stages to rigorously test the hypotheses discussed herein.

ACKNOWLEDGEMENTS

This Review was commissioned by the Editor was part of a Themed Issue on Women's Health made possible by funding from Merck. Sponsor identity was not disclosed to authors prior to publication. All figures cited from original articles were granted use by the corresponding authors. We sincerely thank them for the citation of their original work.

CONFLICT OF INTEREST STATEMENT

All authors have nothing to disclose.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16442.

DATA AVAILABILITY STATEMENT

Since all data were extracted from online database via review process, data availability statement is not applicable to this review.

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How to cite this article: Lim BSY, Chen M, Li H-Y, Li L-J. Metformin use in prediabetes: A review of evidence and a focus on metabolic features among peri-menopausal women. *Diabetes Obes Metab*. 2025;27(Suppl. 3):3-15. doi:10.1111/dom.16442