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Systematic Review and Meta-Analysis

Effect of Menopausal Hormonal Therapy on Cardiovascular Disease Risk Reduction in Women with Menopausal Condition: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Women with menopausal conditions are more likely to cardiovascular illness compared to women without menopausal problems. Menopausal Hormone Therapy (MHT) has been proposed to lowers the risk of cardiovascular disease events. However, current proof of the utility of this therapy is still needed.

Material and Methods: A systematic search was conducted in PubMed, Cochrane Library, and Science Direct were searched for RCTs, as well as cohort or case-control research that evaluated the impact of monitoring on the incidence of cardiovascular diseases in patients undergoing hormone replacement therapy. Data were analyzed using a fixed/random effect model based on using heterogeneity to evaluate odds ratios (ORs) and 95% CIs, and calculated through the Inverse Variance method.

Results: Four RCTs involving 8,198 patients on MHT and compared with 8,249 control patients met the inclusion criteria. The pooled analysis showed no significant reduction in the risk of cardiovascular disease events among women treated with MHT compared with placebo (OR = 0.98; 95% CI 0.88–1.09; p = 0.72). There was no statistical evidence of heterogeneity across studies (I^2 = 0%, p = 0.50). All studies were assessed as a low overall risk of bias.

Conclusion: Six of seven studies found no difference in disease-free or overall survival between MIS and open RH. One study reported worse outcomes with RRH among patients with FIGO IIB disease and multi-agent NACT (HR 2.5–3.0; p<0.05), suggesting risk in higher-stage, heavily pretreated cases. Overall, robotic-assisted RH appears to be a safe and effective alternative to open surgery for appropriately selected FIGO IB_2–IIA_2 cervical cancer patients after NACT.

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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality among women worldwide [1]. The incidence of cardiovascular disease shows a strong sex-related pattern. Premenopausal women pose a lower risk of hypertension, atherosclerosis, myocardial dysfunction, heart failure, and myocardial ischemia compared to age-matched men. These protective effects gradually decrease after menopause, leading to an increased risk of cardiovascular events in postmenopausal women [2]. The Framingham study indicates that the incidence of CVD in postmenopausal women is two- to six-fold higher compared to the premenopausal women [3]. This increased risk is primarily due to changes in endogenous sex hormones, drastic changes in the distribution of body fat and lipoproteins, and vascular remodeling. Esterogen poses cardioprotective effects; therefore, menopausal hormone therapy (MHT) has been proposed and is believed to help lower the risk of cardiovascular disease.

Several trials have investigated the association between MHT and cardiovascular outcomes. According to certain research, MHT may reduce CVD risk when initiated near the onset of menopause [4]. Nonetheless, some research, such as the Women's Health Initiative

(WHI), reported an increased risk of thromboembolic and coronary events among the MHT group [5]. The inconsistent findings have caused clinical controversy regarding the cardiovascular safety and benefits of MHT. Recent evidence proposed that the cardiovascular effects of MHT may depend on several factors, including the timing of initiation, the route of administration, and the type of hormone formulation [6]. The "timing hypothesis" proposes that the cardiovascular effects of MHT may differ depending on the timing of the therapy initiation after menopause.

However, earlier meta-analyses were based on older trials using high-dose or outdated formulations and included patients with past menopause onset. MHT regimens, including lower-dose formulations, bioidentical preparations, and transdermal therapy, may differ from those used in earlier studies. Therefore, this review aims to systematically evaluate and analyse the relationship between MHT use and cardiovascular outcomes [1,4,7].

MATERIAL AND METHODS

Literature Search

A comprehensive literature search was performed in PubMed, Cochrane Library, and Science Direct to search for randomized controlled trials (RCTs), Cohort or case-control studies evaluating the impact of MHT on the incidence of CVD. To ensure comprehensive retrieval, Medical Subject Headings (MeSH) were applied. The main search terms were ("Menopausal Hormonal Therapy" OR "Hormone Replacement Therapy" OR "Estrogen Replacement Therapy") AND ("Menopause" OR "Postmenopause") AND ("Cardiovascular Diseases" OR "Coronary Disease" OR "Ischemic Heart Disease" OR "Atherosclerosis" OR "Heart Attack"). The articles included were from 2015 to 2025 to ensure the evidence reflects the most recent clinical data regarding MHT and cardiovascular outcomes. The literature search process will then be presented as a PRISMA flowchart [8], as shown in Fig.1.

Inclusion Criteria

Eligible studies included observational research articles (Cohort or Case-Control) and RCTs that examined postmenopausal women with or without a history of hysterectomy without age restriction, receiving MHT compared to those receiving placebo or no treatment, and reported cardiovascular outcomes.

Exclusion Criteria

Studies were excluded if they were non-human or preclinical, secondary analyses, or non-original studies such as reviews, editorials, or commentaries. Publications not available in full text or not written in English were excluded.

Expected Outcomes

The primary outcome is to assess the variation in the prevalence of heart disease among individuals who received hormone replacement therapy with control patients.

Assessment of Bias and Article Quality

Evaluation of quality and bias risk in the articles found was carried out using Risk of Bias 2 (RoB 2) [9], an assessment checklist often used to assess the quality of RCT studies. The assessment components will include sample selection methods, detection, exposure, and data reporting (Table 3).

Data Analysis

Data analysis was performed using the Inverse-Variance method. Odds ratios (OR) were used to calculate dichotomous data with a 95% confidence interval (CI). Heterogeneity was assessed by clinical judgment, $\chi 2$ test (p-value> 0.10 was considered statistically significant), and I^2 statistics. Heterogeneity was categorized as low ($I^2 < 25\%$), moderate ($I^2 = 25\%$–50%), or high ($I^2 = 75\%$). If there was significant heterogeneity ($I^2 > 50\%$), a random-effects model was applied instead of the fixed-effect model that the calculation model assumed. Statistical analysis was conducted using the Review Manager (RevMan) version 5.3.5 [10].

Protocol and Registration

This review protocol has been submitted for registration in PROSPERO and is currently under review.

RESULTS

From the search process, 6,557 studies were found, and 6,423 were removed due to duplicates and needing the appropriate publication year. After screening, most of them were excluded because they were meta-analyses, did not have control groups, did not have the appropriate year, and/or did not have the appropriate topic.

A total of 4 studies from 2015 to 2025 were included in this study, consisting of 4 RCTs. There were 8198 patients with Menopausal Hormonal Therapy (MHT) and 8249 control patients using a placebo. The population. Table 1 and Table 2 displays the attributes of each research.

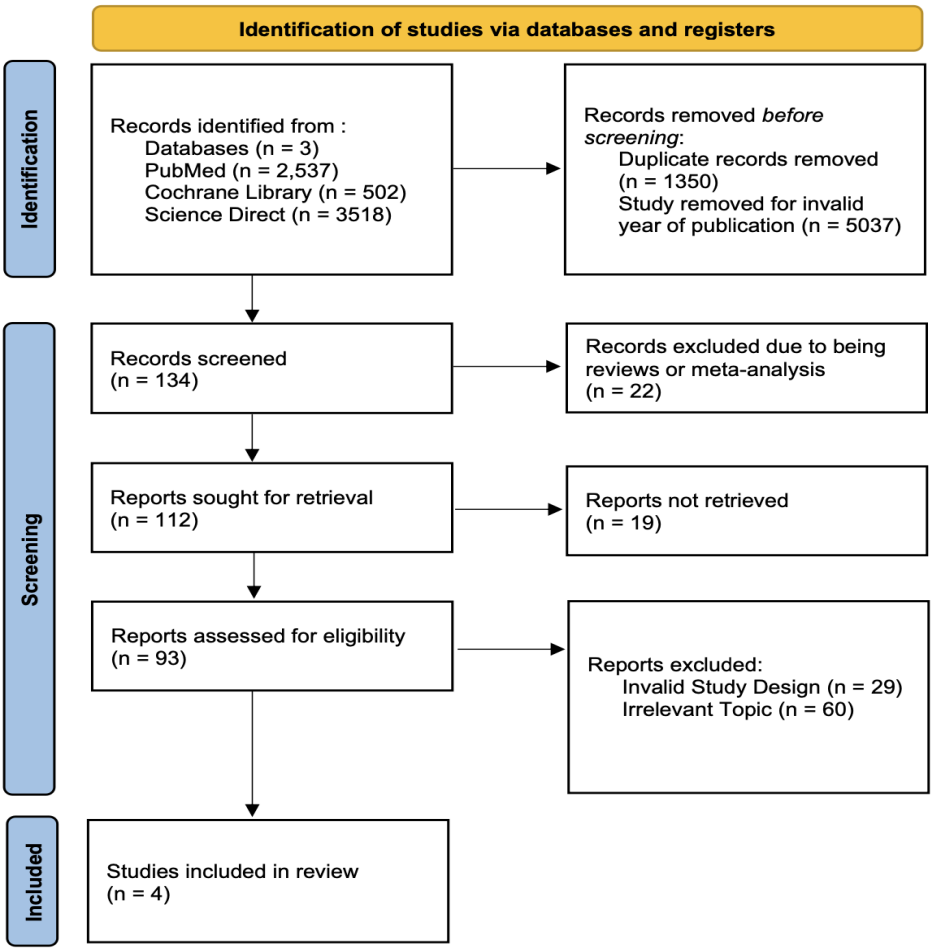


Fig.1. PRISMA Flowchart of the Study

Risk of Bias

All RCTs' potential for bias might be seen in Table 3, with all studies showing a low overall risk of bias assessment.

Cardiovascular Disease Events

There were four studies [11–14] that reported the incidence of cardiovascular disease in the sample. A total of 8,198 patients received MHT and 8,249 received a placebo. The pooled analysis showed no significant difference in the incidence of cardiovascular disease between the MHT and placebo groups (OR = 0.98, 95% CI [0.88–1.09], $p = 0.72$). There was no evidence of heterogeneity across the studies ($\chi^2 = 2.37$, $p = 0.50$, $I^2 = 0\%$). Overall, these findings suggest that MHT does not significantly affect the risk of cardiovascular disease compared with placebo (Fig.2).

DISCUSSION

The association between menopause and cardiovascular disease is questioned because, compared to men, women are more prone to acquire cardiovascular disease, which is influenced by traditional risk factors for cardiovascular disease, such as middle age [13]. Several observations support the idea that menopause is linked to cardiovascular disease, including the fact that following menopause, women's triglyceride, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) levels were higher while their HDL-C levels were lower [14]. Moreover, estrogen decrease after menopause contributes to endothelial dysfunction, increased vascular inflammation, and insulin resistance, which are mechanisms underlying atherosclerosis. These physiological changes strengthen the hypothesis that hormonal transition plays an important role in cardiovascular risk development during menopause [15].

Table 1. Extraction Results of Journal Analysis

Author (Year)	Country	Center	Study Design	Study Subject Characteristics	Results
Huang *et al.,* 2018 [11]	America	Multi-center	Randomized Clinical Trial	Postmenopausal women younger than 80 years with Without a history of hysterectomy and having at least one of the following: MI, coronary artery bypass graft surgery, percutaneous angioplasty, or more than 50% angiographic narrowing of a coronary artery	– The proportion of women with clinically significant hot flushes at baseline did not differ significantly between the EPT and placebo groups (15% vs 17%; P = 0.16) – When compared to a placebo, EPT raised the incidence of Women who had baseline flushes experienced nine times as many CHD incidents in the first year (hazard ratio = 9.01; 95% CI, 1.15-70.35).
Manson *et al.,* 2019 [12]	America	Multi-center	Randomized Clinical Trial	Postmenopausal women ages 50 to 79, with prior hysterectomy	– When analyzed independently, CEE did not correlate with a statistically significant rise or fall in the global index, all-cause mortality, breast cancer, or CHD in any of the groups. – Likewise, in women with and without BSO, CEE did not substantially correlate with these four outcomes over the course of an 18-year cumulative follow-up.
Prentice *et al.,* 2020 [13]	America	Multi-center	Randomized Clinical Trial	Postmenopausal women younger than 80 years with no prior hysterectomy and a history of at least one of the following: MI, coronary artery bypass graft surgery, percutaneous angioplasty, or more than 50% angiographic narrowing of a coronary artery	– The hazard ratio does not differ significantly between CEE + MPA and placebo for the global index, its multivariate extension, or any of its 8 components. – For the global index, its multivariate extension, or any of its eight components, there is no discernible difference in the hazard ratio between CEE + MPA and placebo.
Poornima *et al.,* 2017 [14]	America	Multi-center	Randomized Clinical Trial	Postmenopausal women aged 50–59 years at randomization, prior hysterectomy, randomized to conjugated equine estrogen (CEE) 0.625 mg/day or placebo; mean follow-up age 64.4 years, n=1020 participants in WHI-CACS substudy (517 CEE, 503 placebo).	– During intervention: Both CEE alone and CEE + MPA significantly increased incident hypertension by ~18% vs placebo. HR ≈ 1.18 in both trials. Absolute excess risk: 75–103 additional hypertension diagnoses per 10,000 person-years. – Postintervention: No significant difference (CEE HR 1.06; CEE+MPA HR 1.02). Risk declined after discontinuation. – Oral CEE 0.625 mg/day, with or without MPA 2.5 mg/day, increases risk of incident hypertension during use, but effect disappears after therapy stops.

Table 2. Type of Intervention in Each Journal Analysis

Author (Year)	Outcome Measured	Intervention		Control		Periodic Follow-up
		Sample	Type of Intervention	Sample	Type of Control	
Huang *et al.,* 2018 [11]	Hot Flushes and Risk of CHD	1,387	EPT (2.5 mg of medroxyprogesterone acetate and 0.625 mg of conjugated equine estrogens)	1,382	Placebo	More than 4 years
Manson *et al.,* 2019 [12]	Risk of CHD	5,310	EPT (CEE [Premarin], 0.625 mg/day)	5,429	Placebo	7.2 years (intervention) with 18 years of follow-up
Prentice *et al*., 2020 [13]	Risk factors include colorectal cancer, endometrial cancer, pulmonary embolism, stroke, CHD, hip fractures, and all-cause mortality.	2,837	EPT (2.5 mg of medroxyprogesterone acetate and 0.625 mg of conjugated equine estrogens)	2,683	Placebo	18 years of follow-up after 7.2 years of intervention
Poornima *et al*., 2017 [14]	Coronary heart disease (CHD), cardiovascular disease (CVD), and total mortality by CAC category	517	Oral Conjugated Equine Estrogen (CEE) 0.625 mg/day	503	Placebo	8 years

significant cardioprotective effects against ischemia-reperfusion injury. This protection involves several pathways, such as ERα and ERβ signaling, enhancement of endothelial function, increased nitric oxide synthase activity and protein S-nitrosylation, activation of PI3K/Akt pathways, and modulation of inflammatory responses. Estrogen also supports cardiomyocyte and stem-cell survival and contributes to tissue repair post-infarction [16].

Estrogen supports mitochondrial integrity by activating mitochondrial estrogen receptors that help to maintain mitochondrial membrane stability, prevent the opening of the mitochondrial permeability, and preserve ATP production under cellular stress [17,18]. In the vascular wall, estrogen inhibits the proliferation and migration of vascular smooth muscle cells, decreasing the progression of the atherosclerotic plaque and enhancing the stability of the plaque through the anti-inflammatory and extracellular matrix-modulating pathways [19,20]. Another key mechanism is the regulation of calcium homeostasis. Esterogen maintains the SERCA2a activity and reduces intracellular calcium overload, which otherwise exacerbates reperfusion injury [21].

Moreover, estrogen modulates the Renin Angiotensin Aldosterone System (RAAS) by downregulating angiotensin II and ACE activity, contributing to lower vascular tension and improved vasodilatory responsiveness prior to menopause [22,23]. As estrogen levels decline after menopause, this pathway becomes less active, explaining the rise in hypertension and arterial stiffness in postmenopausal women. These mechanisms demonstrate how estrogen gives cardioprotective effects and helps maintain low cardiovascular vulnerability during the premenopausal period [24].

When MHT treatment is started early in the menopausal period, before extensive atherosclerotic disease develops, it has positive effects. Research from the WHI supports this condition, demonstrating that the risk of cardiovascular disease was neutral for women who received MHT prior to ten years of menopause and elevated for the group of menopausal women after twenty years [25]. The ELITE study supports that estradiol medication was linked to the development of atherosclerosis six years after menopause [26]. This aligns with the timing hypothesis, which suggests that cardiovascular response to MHT depends on the timing of initiation to the menopause onset. Early administration may be associated with vascular protection by maintaining endothelial function and delaying plaque formation. Thus, delayed initiation in older women with pre-existing atherosclerosis may increase cardiovascular events [12,14].

Several studies following the ELITE and WHI studies showed that the cardiovascular effect of MHT depends on vascular biological conditions at the initial therapy. Larger analysis showed that women who initiated therapy before age 60 or within a decade of menopause experienced lower all-cause mortality and did not exhibit increased cardiovascular events, in contrast to women who began therapy after age 70, who showed higher stroke and thromboembolic risk [27]. Previous systematic review confirmed that estrogen provides distinct effects depending on baseline endothelial integrity. In early postmenopause, endothelial nitric oxide bioavailability and anti-inflammatory signaling are preserved, whereas in advanced atherosclerosis, estrogen may destabilize vascular plaques [28].

MHT administration is still not advised for the main or secondary cardiovascular disease prevention, despite several studies demonstrating the advantages of MHT use in menopausal women. For people at elevated risk of heart disease, even MHT is not advised [26]. However, recent studies on the benefits of MHT administration still need to be completed. According to the recent 2020 American Heart Association (AHA) and 2022 North American Menopause Society (NAMS) guidelines, MHT should not be prescribed only for the prevention of CVD. However, both guidelines emphasize that initiating MHT within 10 years of menopause may present a more favorable benefit, particularly for vasomotor symptom management [25, 27]. These underline that cardiovascular outcomes are influenced by timing, dosage, route of administration, as well as whether estrogen is used alone or combined with progesterone.

Recent guidelines emphasize the need for individualized risk assessment, as the effect of MHT varies widely between individuals. A study by Lobo *et al.* showed that the response to MHT in cardiometabolic risk is influenced by factors such as obesity, history of hypertension, family history of heart disease, and systemic inflammatory status. Furthermore, the 2020 AHA Scientific Statement also highlighted that MHT remains safe for the treatment of severe vasomotor symptoms when administered within a 10-year window after menopause, with close evaluation of thrombotic risk [28,29].

The route of administration has an important influence on the metabolic and vascular actions of menopausal hormone therapy. Oral estrogen is subject to first-pass metabolism in the liver, which enhances the synthesis of clotting factors, triglycerides, and inflammatory markers such as C-reactive protein. This mechanism is believed to contribute to a higher thrombotic and inflammatory potential compared with other routes. In contrast, transdermal estrogen bypasses

hepatic metabolism and provides steadier circulating estradiol levels. Because it has minimal effects on hepatic protein synthesis and coagulation pathways, it is often considered the safer option for women with cardiometabolic risk factors, including obesity, hypertension, or insulin resistance [12,27].

Recent studies have strengthened that the transdermal estrogen has a safer thrombotic profile. A large meta-analysis of over 80,000 women showed that oral estrogen is associated with a two-fold higher risk of venous thromboembolism (VTE) compared to transdermal estrogen, primarily due to activation of the coagulation pathway through first-pass hepatic metabolism [30]. Furthermore, oral estrogen has been shown to increase CRP, triglycerides, and clotting factor VII levels, while transdermal formulations showed minimal or no significant changes [31]. These findings support current guideline preferences for transdermal delivery, particularly in women with obesity, hypertension, or metabolic syndrome.

The dose and formulation of therapy are also clinically relevant. Higher doses of estrogen increase the likelihood of venous thromboembolism and stroke, whereas physiological or lower replacement doses usually provide effective symptom control with less vascular risk [31]. The type of progestogen combined with estrogen further modifies cardiovascular outcomes. Micronized progesterone and dydrogesterone appear to have a more favorable effect on lipid metabolism and endothelial function, while synthetic progestins such as medroxyprogesterone acetate may reduce or negate estrogen's vascular benefits [11].

The timing of MHT initiation remains a central factor. Starting therapy within ten years of menopause onset has been associated with improved endothelial function and reduced arterial stiffness, likely through nitric oxide–mediated vasodilation. By contrast, delayed initiation after prolonged estrogen deficiency may aggravate vascular inflammation and plaque instability [13]. Overall, the cardiovascular profile of MHT depends on a combination of timing, route, dosage, and hormone formulation. Understanding these interrelated factors is essential for tailoring therapy to individual risk profiles and ensuring its safe use in postmenopausal women.

This meta-analysis attempts to answer whether the administration of MHT in patients who have experienced menopause has better outcomes, especially in recent studies. In searching articles for this meta-analysis, only 4 RCT studies were found that compared MHT administration with placebo. Possible factors are the limited sample size and implementation in terms of cost and time, which takes work. The disadvantage of using experimental research is its difficulty in ethical feasibility. This study does not take observational data because it is prone to relatively higher bias, cannot assess therapeutic efficacy, and cannot show unexpected outcomes of treatment [32]. Thus, using RCT research is the best option for this study [33].

RCTs in MHT are generally limited in duration (3–7 years), while cardiovascular effects require long-term observation because atherosclerosis progression is slow. Furthermore, many RCTs exclude women with high-risk factors, so their results may not fully reflect the actual clinical population. A methodological study by Hernán confirmed that MHT RCTs are often not "pragmatic" and do not capture real-world variations such as differences in adherence, formulation changes, or the use of modern low-dose MHT. Therefore, RCTs do provide high internal validity but cannot replace long-term observational data, especially regarding rare events such as VTE and stroke [34,35].

This study found that the administration of MHT to menopausal women did not significantly lower the chance of developing cardiovascular disease. However, the percentage of cardiovascular disease events in women who received MHT was lower than placebo. The forest plot picture in this study also shows that MHT administration is better than placebo administration. Although the difference was not statistically significant, the direction of effect suggests a potential cardioprotective tendency, consistent with the WHI estrogen-alone extension trial and post-hoc analyses of younger postmenopausal women [12,13]. These findings reinforce that while MHT should not be viewed as a cardiovascular prevention strategy, early initiation in appropriately selected women may yield neutral or slightly favorable cardiovascular outcomes.

The results of this meta-analysis are consistent with several post-hoc analyses of the WHI study showing that in women aged 50–59 years, estrogen therapy alone reduced the incidence of CAC progression and reduced long-term total mortality at up to 20 years of follow-up. The ELITE-Extension study demonstrated that transdermal estradiol therapy in women who initiated therapy less than 6 years after menopause slowed BMI progression without increasing thrombotic risk. These findings support the hypothesis that the protective effect of MHT does exist, but is only evident in groups that fit within the therapeutic window [27,28].

Based on meta-analyses and recent data analyses, although MHT does not consistently reduce cardiovascular events in all populations, there are compelling protective signals in certain subgroups. For example, a meta-analysis of 33 RCTs involving over 44,000 women who initiated the study showed that the risk of overall cardiovascular (CVD) events was not significantly different between MHT users and controls (RR = 0.97), but hormone therapy improved functional vascular flow as measured by flow-mediated dilation (FMD) while also increasing the risk of stroke and venous thromboembolism [36]. In women with pre-

existing cardiovascular disease, another meta-analysis found that MHT did not increase the incidence of non-fatal myocardial infarction, cardiovascular death, or stroke, but estradiol appeared to provide vascular improvement through increased FMD. More broadly, analyses in women with prediabetes or type 2 diabetes also reported that MHT use was associated with a reduced risk of stroke, coronary heart disease (CHD), and atherosclerotic cardiovascular disease (ASCVD), suggesting that the protective effect may be more pronounced in populations with certain metabolic profiles. Bozkurt et al showed that MHT did not increase the risk of incident heart failure, but associated with a reduction in overall mortality in patients who already had heart failure [37–39].

This meta-analysis has several limitations. Only four RCTs were included, leading to limited power and possible publication bias. The heterogeneity of intervention types (estrogen-only vs. combined therapy), differences in delivery routes (oral vs. transdermal), and variation in follow-up durations could have influenced the pooled effect estimates. The disadvantage of using experimental research is its difficulty in ethical feasibility. This study does not take observational data because it is prone to relatively higher bias, cannot assess therapeutic efficacy, and cannot show unexpected outcomes of treatment. Thus, using RCT research is the best option for this study [40]. Despite these constraints, RCT-based synthesis provides a higher internal validity compared to observational data and strengthens the evidence regarding MHT and cardiovascular risk. Future studies should aim to explore the effect of MHT stratified by time since menopause, route of administration, and baseline cardiovascular risk. Large-scale individual participant data meta-analyses would also be valuable in clarifying which subgroups might derive the greatest benefit.

CONCLUSION

There is no discernible difference in women who get hormone replacement therapy's risk of cardiovascular disease events treatment and those who do not following menopause. Hormone replacement treatment is not advised for the prevention of cardiovascular disease.

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CONFLICT OF INTEREST

There is no conflict of interest for each involved author.

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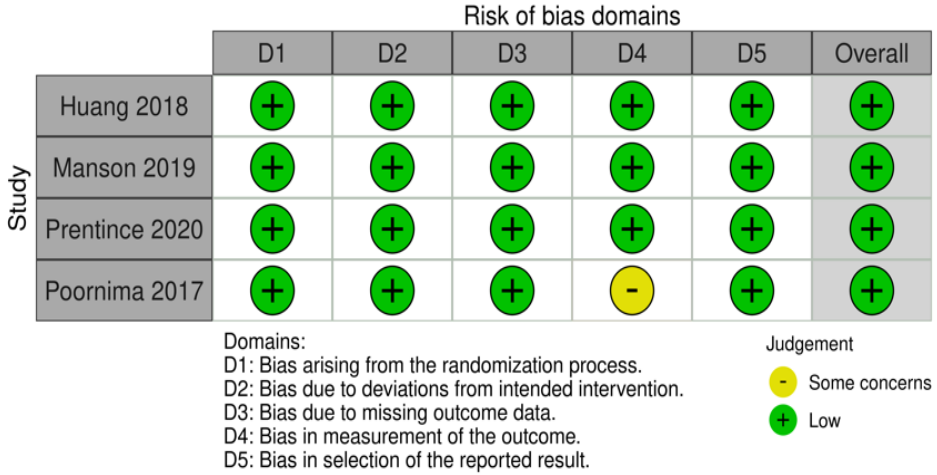
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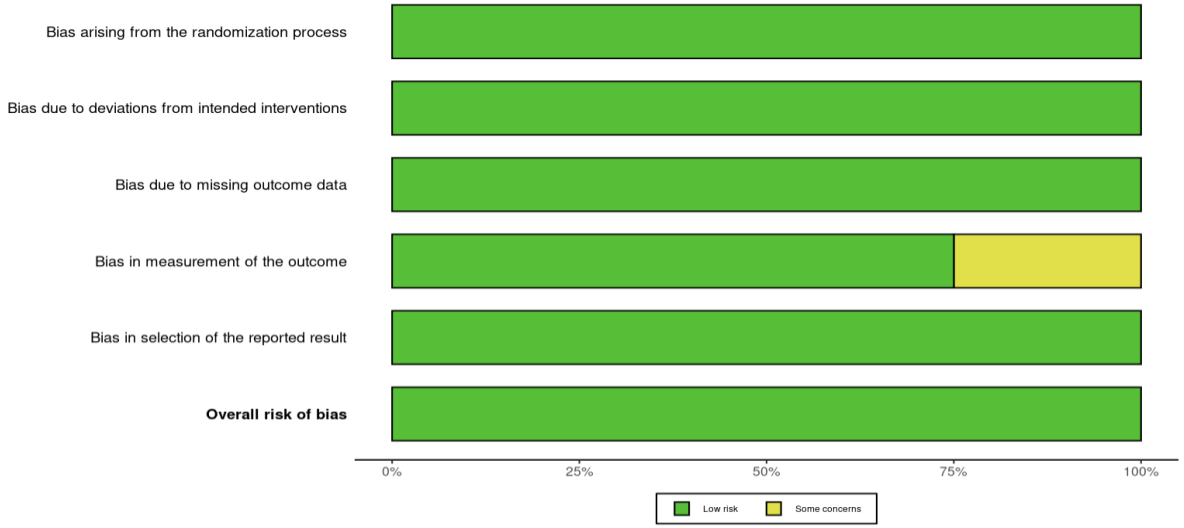
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Table 3. Bias assessment based on RoB Study 2





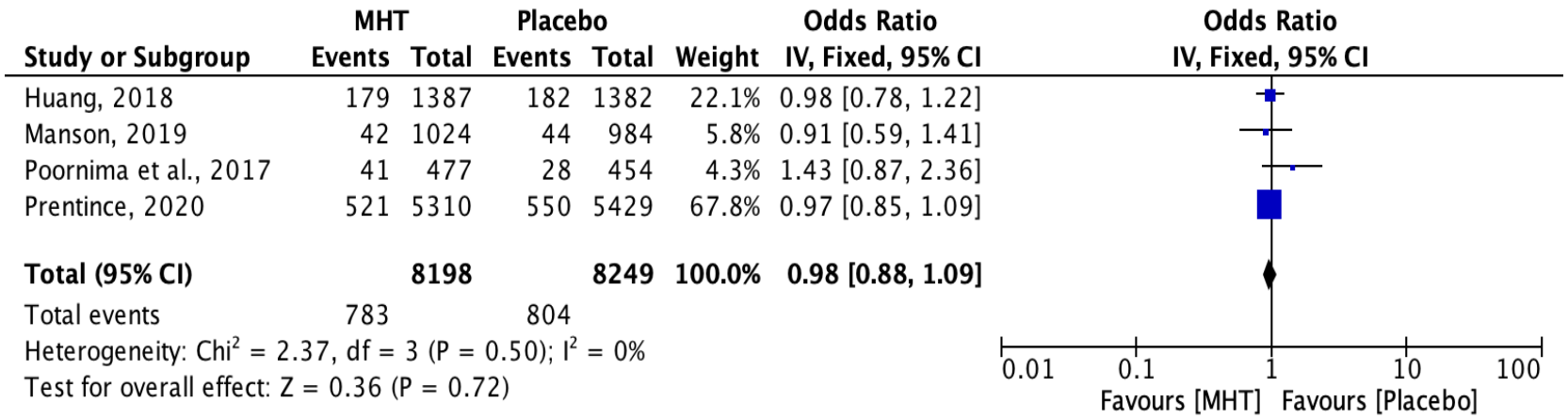


Fig.2. Forest Plot of the Use of MHT versus Placebo on Cardiovascular Disease Event