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REVIEW

Cardiovascular risk of hormone replacement therapy in menopausal women with diabetes: a systematic review and meta-analysis of clinical trials and observational studies

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ABSTRACT

Introduction: Studies have shown the relative cardiovascular safety of hormone replacement therapy (HRT) for women in the general population. Evidence on women with diabetes remains scarce. We aimed to investigate the risk of cardiovascular disease (CVD) in menopausal women with diabetes who use HRT compared to non-users.

Methods: Search across Medline, Embase, Web of Sciences, and Cochrane databases up to November 2023 was conducted. We combined keywords of menopause, diabetes, HRT, and various CVD outcomes. Non-English studies, observational studies other than cohort and case–control, reviews, and conference abstracts were excluded. Bias was checked using validated risk-of-bias tools. Random-effects model was used to calculate pooled relative risks (RR) for similar outcomes.

Results: Out of 7625 identified articles, 19 (6 clinical trials and 13 observational studies) were included, primarily from Europe and the U.S.A. Most studies had moderate risk of bias. Meta-analysis of myocardial infarction (MI) risk from nine observational studies ($n =$ ~34,626) showed a pooled RR of 0.83 (95% CI 0.62–1.12). Limited data precluded meta-analysis for the clinical trials and other outcomes from observational studies.

Conclusions: Observational studies do not suggest an increased risk of MI in menopausal women with diabetes prescribed HRT. Further research with a more robust method is warranted to validate this finding.

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KEYWORDS
Cardiovascular risk; diabetes; hormone replacement therapy; menopause; systematic review

1. Introduction

Cardiovascular disease (CVD) claims approximately 17.9 million lives annually, representing nearly one-third of all global deaths [1]. Women account for 53% of all the estimated 620 million patients worldwide living with CVD [2]. Coronary heart disease (CHD) and stroke are the leading causes of death for women [2]. Compared to men, women accounted for 58% of stroke-related deaths in the United Kingdom (UK) in 2022 [3]. The rising global prevalence of diabetes mellitus is one of the underlying drivers of the high prevalence of CVD, and this is particularly true for women. In women, a diagnosis of diabetes may increase the risk of myocardial infarction (MI) by 150% [4] and the risk of stroke by 228% [5]. Compared to men, the risk of CVD in women with diabetes is more pronounced; women with diabetes are estimated to have a 44% greater risk of incident CHD compared to men with diabetes [6] and a 27% higher risk of stroke [7]. This increased risk of CVD seen in women with diabetes is partly driven by age; women develop CVD later than men, partly due to the protective role of female sex hormones, which is lost during menopause [8,9]. Estrogen deficiency during the menopausal transition is thought to be associated with alterations of the peripheral vasculature [10], possibly leading to the onset of CVD.

Hormone replacement therapy (HRT) has been a cornerstone treatment for the relief of menopausal symptoms, such as hot flashes and vaginal dryness [9]. HRT replaces the female hormones, such as estrogen, that are at a lower level as women experience menopause. As such, the initial perception of HRT was that it conferred cardioprotective effects against the risk of CVD [11]. However, a series of clinical studies, known as the Women's Health Initiative (WHI), revealed an unexpected increase in HRT-linked CVD risks, such as eight excess strokes per 10,000 person-years in women using oral HRT [12]. In the wake of the WHI's findings, many subsequent studies have sought to provide further evidence on how HRT affects postmenopausal women's risk of CVD.

The use of HRT was affected by WHI trials since its first publication in 2002. However, with the development of transdermal and local formulations, use of HRT has increased again in recent years [13]. The increased prescribing rates may also be explained by evidence from the WHI subgroup analyses regarding the benefit of HRT in women aged 50–59 years [13,14]. This was echoed by a recent systematic review of randomized controlled

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Article highlights

- Evidence on the cardiovascular safety of HRT in women with diabetes remains scarce.
- Our narrative review of RCTs shows that HRT does not affect the risk of CHD or PAD but increases the risk of AF and stroke in menopausal women with diabetes.
- The results of our meta-analyses of observational studies suggest there is no evidence to support that HRT use is associated with an increased risk of MI in women with diabetes.

trials (RCTs) and observational studies which suggests the use of low-dose HRT in the first year after menopause onset is associated with a low risk of harm [15].

All established evidence on the safety of HRT treatment is based on research in the general population. An RCT conducted in 2006 [16] explored the impact of HRT on blood glucose and total cholesterol levels among postmenopausal women with type 2 diabetes. The study revealed a reduction in fasting glucose and total cholesterol levels compared to the placebo group [16]. Nevertheless, it is important to note that these outcomes offer only partial insight, as changes in cholesterol and glucose levels merely serve as markers for CVD risk. The National Institute for Health and Care Excellence (NICE) guidelines state that CVD risk factors, one of them being diabetes, are not a contraindication to HRT as long as these risk factors are optimally managed [17].

Considering diabetes is a significant risk factor for CVD, it is crucial to understand how HRT use can affect the risk of CVD in women with diabetes. To our knowledge, there has been no systematic review and meta-analysis on the cardiovascular safety of HRT in women with diabetes. Therefore, we conducted a review to summarize the risk of CVD in this population by comparing women with diabetes who use HRT with non-users.

2. Methods

2.1. Eligibility criteria

Our study adhered to the PRISMA guidelines to ensure comprehensive and transparent reporting [18]. To structure the eligibility criteria for inclusion of literature, a pre-defined PICOS (Population, Intervention, Comparator, Outcome, Study Design) framework was used. The target population focused on menopausal women with type 1 or type 2 diabetes. The intervention group was users of any form of HRT and the comparison group was non-users of HRT. Our main outcomes consisted of coronary heart disease (CHD, including fatal or non-fatal MI), stroke, venous thromboembolism (VTE, including pulmonary embolism (PE)/deep vein thrombosis (DVT)), arrhythmia/atrial fibrillation (AF), heart failure (HF), peripheral arterial diseases (PAD), and other CVD-related death. Additional outcomes included cardiac procedures or other CVD-related hospitalizations.

We included RCTs and observational studies with cohort or case–control study designs. We did not restrict the publication year of the studies other than the limitations of the databases coverage. Reports written in a language other than English, reviews, and conference abstracts with no adequate information were excluded.

2.2. Search strategy

We used Medline OVID, Embase OVID (1947–2023), Web of Science, and Cochrane Trial, with the latest search performed on 8 November 2023. We used a combination of MeSH terms and free-text keywords related to *menopause, diabetes, hormone replacement therapy*, and *cardiovascular outcomes*. A detailed keyword search strategy is outlined in Supplementary File 1. Additionally, we conducted reference searching by extracting reference lists from existing systematic reviews in the general population, particularly focusing on identifying subgroup analyses in women with diabetes.

2.3. Study selection and data extraction

HWR and another reviewer, AK, examined titles and/or abstracts of reports obtained through the search strategy, along with those from additional sources. HWR and AK independently assessed the full texts of potential eligible reports. We contacted 11 authors whose full-text reports were not available to optimize reports retrieval. Six authors replied with the requested full papers. Any discrepancies regarding eligibility were resolved through consensus or adjudicated by other reviewers (LW, RB).

A pre-designed form was used to extract data from the included studies. Extracted information encompassed study authors and contacts; study setting; study design; data source and study population; participant demographics and baseline characteristics; details of the interventions and control conditions along with dose, form, duration if available; definition of menopause and diabetes; study methodology including sample size, recruitment and study completion rates, outcomes and their definitions, times of outcomes measurement if available; information for assessment of the risk of bias; and the results of the studies. We further contacted two authors to confirm and request data for meta-analysis purposes. One author replied, but the requested data was not available. HWR summarized the information from each included study and AK reviewed the information for completeness and accuracy. Any disagreement was resolved through discussion.

2.4. Risk of bias

The risk of bias of each individual study was assessed using risk-of-bias tool (RoB 2) for randomized trials and risk of bias in non-randomized studies – of Interventions (ROBINS-I) for observational studies. HWR and WNI assessed the risk of bias independently. We displayed risk of bias using the Risk-of-bias VISualization (robvis) tool [19].

2.5. Data synthesis

Data were summarized in tables, covering mainly the subject characteristics, methods, type of interventions, type of outcomes, and results from each study. We provided a summary of CVD risk by displaying odds ratios (OR), hazard ratios (HR), and rate ratio along with the 95% confidence intervals (CI). In every outcome, statistical significance was considered if the CI did not cross one. Studies that reported similar outcomes were identified and summarized using a meta-analysis. Meta-analyses were conducted

for outcomes investigated by at least three studies. We used random-effect models to summarize the effects of HRT. The random-effect model assumes that observed estimates can vary across studies due to real differences in treatment effects among studies. This model is able to capture the uncertainty caused by heterogeneity in studies [20]. We performed meta-analyses by summarizing the pooled relative risks (RRs) for similar outcomes.

Our study focused on current HRT usage, defined as estrogen with or without progestin. For studies with overlapping data, we considered the year of the study and the potential bias from each study for selection. To evaluate heterogeneity, we utilized the I^2 statistic, with an I^2 value exceeding 50% indicating significant heterogeneity. To assess robustness and reduce potential bias of missing results, we conducted sensitivity analyses based on study design, analysis and type of HRT (estrogen-only and estrogen plus progestin). Subgroup analyses were initially planned based on diabetes type (type 1 and type 2), menopausal stage (perimenopause, menopause, post-menopause), and age. However, these analyses could not be conducted due to the lack of availability of detailed information, as the authors did not provide sufficient data or perform subgroup analyses on these variables. Assessment of potential publication bias was planned by using funnel plots. Meta-analyses were conducted using Review Manager v.5.4.1 [21], including the creation of forest plots.

3. Results

3.1. Study selection

We identified a total of 7,625 articles from four databases and additional sources. After excluding duplicates, we screened 5808 reports by title and abstracts. We reviewed 90 full texts from the primary search and 156 from the additional searches to determine eligibility, resulting in the inclusion of 19 articles. Figure 1 depicts the PRISMA flow diagram of the study selection process.

3.2. Study characteristics

The included studies were published between 1998 and 2016, comprising 13 observational studies and 6 RCT reports. Among the observational studies, there were six main analyses, consisting of three case–control, two cohort, and one case–cohort studies. There were no RCTs or observational studies which were published after 2016. Most studies utilized data from Europe and the U.S.A.; one study was from Taiwan. The majority of the studies featured sample sizes smaller than a thousand. Information regarding mean follow-up and/or exposure to HRT was lacking in most studies. The age ranges were similar across studies (min–max, aged 30–80). Unfortunately, we were unable to extract the exact age of women with diabetes from the studies with subgroup analyses. Table 1 shows the study characteristics.

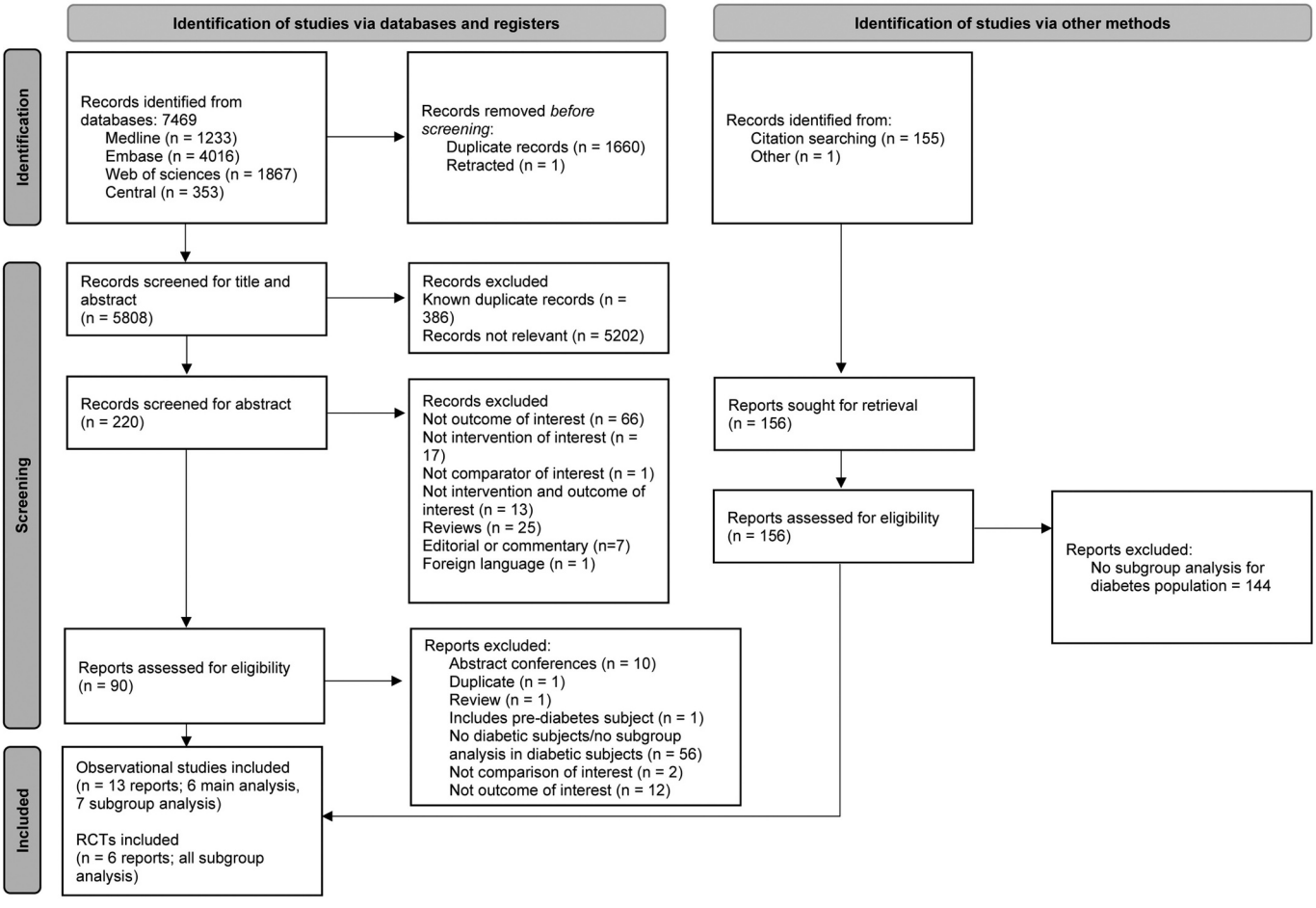


Figure 1. Study flow.

Table 1. Study Characteristics

Authors, year	Setting/ country	Study design	Data source	Mean follow-up	No. Participants	Age (mean/ range in years)	Interventions	Comparator	Outcomes
Randomized Controlled Trials (all provided subgroup analyses)									
Manson et al., 2003 [25]	USA	RCT, double-blind	WHI Trial	5.2 years (overall population)	374 estrogen + progestin 360 placebo	63.3 ± 7.1 (overall population)	conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day)	placebo	CHD
Hsia et al., 2004 [26]	USA	RCT, double-blind	WHI Trial	5.6 years (overall population)	374 estrogen + progestin 360 placebo	63.3 ± 7.1 (overall population)	conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day)	placebo	PAD
Hsia et al., 2006a [23]	USA	RCT, double-blind	WHI Trial	7.1 years (overall population)	7.7% estrogen alone and 4.4% placebo from overall population (5310 CEE vs 5429 placebo)	63.6 (overall population)	conjugated equine estrogens (0.625 mg per day)	placebo	CHD
Hsia et al., 2006b [22]	USA	RCT, double-blind	WHI Trial	7.1 years (overall population)	410 conjugated equine estrogens 411 placebo	63.6 ± 7.3 (overall population)	conjugated equine estrogens (0.625 mg per day)	placebo	PAD
Hendrix et al., 2006 [24]	USA	RCT, double-blind	WHI Trial	7.1 years (overall population)	410 conjugated equine estrogens 411 placebo	63.6 (overall population)	conjugated equine estrogens (0.625 mg per day)	placebo	Stroke
Perez et al., 2012 [27]	USA	RCT, double-blind	WHI Trial	5.6 years for E+P and 7.1 years for E-alone (overall population)	E+P trial: 361 E+P 347 placebo E-alone trial: 387 E-alone 379 placebo Combined trials: 748 active HRT 726 placebo	~63 in all groups	estrogen alone (0.625 mg per day), estrogen (0.625 mg per day) plus progestin (2.5 mg per day)	placebo	AF

Observational Studies

Authors, year	Setting/ country	Study design	Data source	Years of data collection	No. Participants	Age (mean/ range in years)	Interventions	Comparator	Outcomes
Kaplan et al., 1998 [38]	Washington State, USA	Case-control	Group Health Cooperative of Puget Sound, July1986 - December 1994	8	212 cases 122 controls	cases: 68.1 controls: 69.5	estrogen with/without progesterone (current, past)	never use	MI
Lawrenson et al., 1999 [41]	UK	Case-control	UK primary care database (MediPlus Database), January 1993 - September 1996	3	102 cases 204 controls	50-64	HRT, not specified	never use	CHD
Petitti et al., 2000 (subgroup) [30]	USA	Case-control	Any of 10 Kaiser Permanente Northern California hospitals, November 1991 - November 1994	3	30 cases 13 controls	65-74 dominated (overall population)	estrogen with/without progestin (current)	non-current use	MI
Lorenzo et al., 2000 (subgroup) [37]	UK	Case-control	General Practice Research Database, January 1991 - December 1995	4	1013 cases 5000 controls Diabetes 86 cases 170 controls	50-74 (overall population)	oral estrogen, transdermal estradiol, and/or progestogen (current)	never use	MI
Gami et al., 2003 [34]	Minnesota, USA	Case-control	Mayo Clinic Coronary Care Unit Database, January 1998 - December 2000	2	99 cases 306 controls	cases: 74 ± 13 controls: 73 ± 10	estrogen with/without progesterone, estrogen + progesterone (current)	never use	MI

(*Continued*)

Table 1. (Continued).

Observational Studies									
Ferrara et al., 2003 [42]	Northern California, USA	Cohort	The Northern California Kaiser Permanente Diabetes Registry, 1995–1998	3	Without recent MI: 2526 unopposed estrogen 2088 estrogen + progestin 19806 none	64.9	unopposed etrogen, estrogen + progestin (current)	non-current use	MI
Newton et al., 2003 [32]	Washington State, USA	Case-cohort	Group Health Cooperative, January 1986 - December 1992	6	103 estrogen 83 estrogen + progestin 351 never used	68.9	current unopposed estrogen, current estrogens with progestins, past estrogen with/without progestin	never use	CV events: MI, coronary revascularization, or fatal CVD
Lokkegaard et al., 2003 (subgroup) [35]	Denmark	Cohort prospective	Questionnaires in 1993 (observation until end of 1998)	5	178 women with diabetes	≥45 (overall population)	estrogen with/without progesterone (ever, previous, current)	never use	IHD, MI
Grodstein et al., 2006 (subgroup) [36]	USA	Cohort	Questionnaires from Nurses Health Study, 1976 - 2000	24	36 estrogen 14 estrogen + progestin	30-55 (overall population)	estrogen alone, estrogen + progestin (current)	never use	CHD
Lokkegaard et al., 2008 (subgroup) [39]	Denmark	Cohort	The Danish Sex Hormone Register Study (DaHoRS), January 1995 - December 2001	6	1417 current users 1094 previous users 9919 never users	51-69 (overall population)	estrogen with/without progestogen, tibolone (current, previous)	never use	MI
Rockman et al., 2012 (subgroup) [31]	Cleveland, OH, USA	Cohort	Life Line Screening database, 2003 - 2008	5	78,966 women with diabetes ~37,253 HRT ~41,895 non-HRT	64.3 (overall population)	ever use HRT, not specified	never use	PAD
Chen et al., 2015 [33]	Taiwan	Cohort	National Health Insurance system of Taiwan, 2003-2009	6	428 conjugated equine estrogens 1284 controls	median: 59	conjugated equine estrogens (0.625 mg per day)	never use estrogen in the study period	Stroke
Canonico et al., 2016 (subgroup) [40]	France	Nested case-control	French National Health Insurance database (Jan 2009 - Dec 2011)	2	377 cases 497 controls	cases: 56.7 ± 2.8controls: 56.6 ± 2.7 (overall population)	oral/transdermal estrogen; not clear if with/without progesterone (current)	non-current use	Stroke

RCT, Randomized Controlled Trial; WHI, Women's Health Initiative; E+P, estrogen plus progesterone; E-alone, estrogen-alone; HRT, hormone replacement therapy; CHD, coronary heart disease; PAD, peripheral arterial disease; AF, atrial fibrillation; MI, myocardial infarction; IHD, ischemic heart disease; N/A, not available.

3.2.1. Randomized controlled trials

All six RCTs were derived from the WHI Trials, providing subgroup analyses of women with diabetes for specific outcomes. The WHI trial comprised around 400 women with diabetes in each group. The mean age for the total population of women in the RCTs was approximately 63 years old; however, there was no information on the age of women with diabetes. The longest mean follow-up from RCTs was 7.1 years [22–24] and the shortest was 5.2 years [25]. Outcomes reported in the trials were CHD [23,25], PAD [22,26], AF [27], and stroke [24].

Information on baseline characteristics was retrieved from additional publications [28,29]. History of diabetes was based on physician's diagnosis that required oral medication or insulin. However, none of the six RCTs disclosed information on the type of diabetes (type 1 or 2) or the use of specific antidiabetic medications.

3.2.2. Observational studies

The study with the smallest sample size ($n = 43$) was conducted by Petiti et al. [30] and the study with the biggest sample size ($n = 78{,}966$) was by Rockman et al. [31]. The longest mean follow-up from observational studies was 6.8 years [32], and the shortest follow-up was 6.5 months [33]. The age ranges were generally similar across studies; however, Gami et al. [34] included an older population (mean age ~73 years old) and Newton et al. [32] included women aged 45 to 80. Diabetes definitions or verifications were based on various methods across studies, consisting of self-report questionnaires [30,31,35,36], diagnostic codes [33,37], diabetes diagnosis in medical records [34,38], antidiabetic medications [34,39–41], or laboratory measurement criteria [32]. The type of diabetes in the studies was not specified in any of the 13 studies. Outcomes reported in the observational studies were MI [30,34,35,37–39,42], CHD (composite outcomes of MI and other cardiovascular events) [36,41], stroke [33,40], and PAD [31]. We regarded CHD and cardiovascular events from Lawrenson and Newton [32,41] as myocardial infarction.

3.3. Results of individual studies

3.3.1. Randomized controlled trials

Sub-group analyses from the WHI trials in women with diabetes showed that HRT neither increases nor decreases the risk of CHD [23,25] or PAD [22,26]. RCTs reported an increased risk for atrial fibrillation (HR 1.73 [95% CI 1.08–2.78]) and ischemic stroke (HR 2.34 [95% CI 1.14–4.81]) in estrogen-alone users with diabetes [27]. Results of RCTs are presented in Table 2.

3.3.2. Observational studies

The results of the 13 observational studies are shown in Table 3. Newton et al. [32] demonstrated significant MI risk reduction associated with HRT use (estrogen: HR 0.48 [95% CI 0.30–0.78] and estrogen plus progestin: HR 0.43 [95% CI 0.22–0.85]) as well as Grodstein et al. [36] (estrogen: HR 0.67 [95% CI 0.46–0.99] and estrogen plus progestin: HR 0.54 [95% CI 0.30–0.96]), while Lokkegaard et al. [35] showed an increased risk of MI (OR 9.15 [95% CI 2.02–41.44]). Ferrara et al. [42] suggested a significant risk reduction of MI for the use of estrogen plus progestin (HR 0.77 [95% CI 0.61–0.97]), but not estrogen-alone (HR 0.88 [95% CI 0.73–1.05]). For the outcome of stroke, Chen et al. [33] showed significant risk reduction (HR 0.34 [95% CI 0.12–0.97]), whereas Canonico et al. [40] did not. Results by Rockman et al. [31] showed evidence of a reduced risk of PAD associated with HRT use (OR 0.77 [95% CI 0.73–0.81]).

3.3.3. Effect of estrogen dosage

Amongst the studies that constitute this systematic review, only the study by Ferrara et al. [42] conducted a subgroup analysis on the association between dose of estrogen-only and the risk of developing an acute MI within 3 years. The study stratified dosages of estrogen HRT between low-dose, medium-dose and high-dose. Results showed some evidence that lower and medium estrogen doses compared to none were associated with a greater reduction in acute MI risk with HR 0.49 [95% CI 0.2828–0.85] and HR 0.81 [95% CI 0.69–0.96], respectively. There was no evidence that higher estrogen doses were linked to a change in risk of acute MI (HR 1.07 [95% CI 0.77–1.48]).

3.3.4. Duration of HRT usage

Two studies [38,42] were able to stratify by time since HRT initiation. While Ferrara et al. [42] assessed the usage of HRT for both less than and more than 1 year since initiation, Kaplan et al. [38] looked at cumulative estrogen duration of use ranging between various time intervals. Ferrara et al. [42] found that exposure to HRT for at least or less than 1 year was not associated with a lower risk of acute MI (≥1 year, HR 0.81 [95% CI 0.66–1.00]; <1 year, HR 1.03 [95% CI 0.74–1.44]). Kaplan et al. [38] showed how cumulative duration of estrogen use was associated with MI risk, with use exceeding 6 years conferring an 82% reduction in MI risk (RR 0.18, [95% CI 0.04–0.83]). However, the linear trend per year did not show benefit nor harm (RR 0.78 [95% CI 0.56–1.08]).

3.4. Meta-analysis for MI outcome

We conducted a meta-analysis focusing on studies with myocardial infarction as the outcome, as there were insufficient studies available for meta-analyses on other outcomes. The analysis focused on current usage that includes estrogen with or without progestin. Our analysis included nine studies with a total sample size of approximately ~34,626 individuals, yielding a pooled RR of 0.83 (95% CI 0.62–1.12) with an I^2 statistic of 56%. The forest plot can be seen in Figure 2. Sensitivity analyses were performed based on study design, analysis, and type of HRT. Meta-analysis of cohort studies only ($n = 4$) showed no evidence of an increase in the risk of MI associated with HRT use (RR 0.94 [95% CI 0.62–1.42]). A meta-analysis of case–control studies only ($n = 5$) showed no evidence of a change in MI risk either (RR 0.70 [95% CI 0.45–1.1]). Subanalyses by type of study showed strong evidence of an association between HRT use and a decreased risk of MI in hypothesis testing studies ($n = 4$) only (RR 0.72 [95% CI 0.58–0.88]). A meta-analysis in which the results of post-hoc analyses were summarized showed no change in the risk of MI (RR 1.22 [95% CI 0.70–2.14]). Figure 3 presents the forest plots for sensitivity analyses by study design

Table 2. CVD results of individual RCTs

Author, year	Menopause definition	Diabetes definition	Outcome/case definition	Interventions	Comparator	Unadjusted effect estimate (95% CI)	Adjustedeffect estimates(95% CI)	Adjusted for
Manson et al., 2003 [25]	Postmenopausal women with intact uterus.	History of diabetes was based on physician's diagnosis that required oral medication or insulin [29].	CHD: hospitalized MI, definite silent MI, and coronary death adapted from standardized criteria [51]	conjugated equine estrogens (0.625 mg per day) plus medroxy progesterone acetate (2.5 mg per day)	placebo	N/A	Medication-treated: HR 1.31 (0.73–2.34) All cases: HR 1.45 (0.84–2.51)	age and the presence of CHD at base line
Hsia et al., 2004 [26]	Postmenopausal women with intact uterus.	History of diabetes was based on physician's diagnosis that required oral medication or insulin [29].	PAD: overnight hospitalization with either symptoms or intervention, and was categorized as carotid artery disease, abdominal aortic aneurysm, or lower extremity arterial disease	conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day)	placebo	0.94 (95% CI in graph, not significant)		N/A
Hsia et al., 2006a [23]	Postmenopausal women with prior hysterectomy.	History of diabetes was based on physician's diagnosis that required oral medication or insulin [29].	CHD: hospitalized MI, definite silent MI, and coronary death adapted from standardized criteria [51]	conjugated equine estrogens (0.625 mg per day)	placebo	N/A	Medication-treated: HR 1.02 (0.67-1.55) All cases: HR 1.13 (0.76-1.69)	age and the presence of CHD at base line
Hsia et al., 2006b [22]	Postmenopausal women with prior hysterectomy.	History of diabetes was based on physician's diagnosis that required oral medication or insulin [29].	PAD: overnight hospitalization with either symptoms or intervention, and was categorized as carotid artery disease, abdominal aortic aneurysm, or lower extremity arterial disease	conjugated equine estrogens (0.625 mg per day)	placebo	N/A	HR 0.69 (0.34-1.43)	age, prevalent peripheral arterial disease at baseline, and randomization status in the Dietary Modification trial
Hendrix et al., 2006 [24]	Postmenopausal women with prior hysterectomy.	History of diabetes was based on physician's diagnosis that required oral medication or insulin [29].	Stroke: rapid onset of a neurological deficit >24 hours attributable to an obstruction or rupture of the arterial system that was not known to be secondary to other causes	conjugated equine estrogens (0.625 mg per day)	placebo	N/A	Ischemic stroke:HR 2.34 (1.14–4.81)*	age, previous stroke, and dietary modification randomization assignment
Perez et al., 2012 [27]	Postmenopausal women with prior hysterectomy (E-alone trial) and without (E+P trial).	History of diabetes was based on physician's diagnosis that required oral medication or insulin [29].	AF: women with AF on follow-up ECG orany single ICD-9 code of 427.31 from review of Medicare claims orhospital records were classified as having new onset AF	estrogen alone, estrogen + progestin	placebo	N/A	E+P trial:HR 1.15 (not significant) E-alone trial:HR 1.73 (1.08-2.78)* Combined trial:HR 1.49 (1.02-2.13)*	age, race, hypertension, smoking, diabetes mellitus, body mass index, and CHD

CHD, coronary heart disease; MI, myocardial infarction; PAD, peripheral arterial disease; AF, atrial fibrillation; HR, hazard ratio; E+P, estrogen plus progesterone; E-alone, estrogen-alone; ICD, International Classification of Diseases; N/A, not available; CI, confidence interval. Asterisk (*) indicates statistical significance.

Table 3. CVD results of individual observational studies

Author, year	Menopause definition	Diabetes definition	HRT definition	Outcome/case definition	Interventions	Comparator	Unadjustedeffect estimate(95% CI)	Adjustedeffect estimates (95% CI)[a]	Adjusted for
Kaplan et al., 1998 [38]	Postmenopausal women; women aged >55 was presumed postmenopausal if there was no indication of menopause in the medical records.	Diabetes was based on medical record that showed treated diabetes.	current user: if women's most recent estrogen provided enough pills to last through the reference date	MI was based on standardized criteria [52]	estrogen with/without progesterone	never use	N/A	OR 0.51 (0.22-1.15)	age, study year, weight, current angina, duration of treated diabetes
Lawrenson et al., 1999 [41]	Postmenopausal women, definition not specified.	Diabetes if prescribed for insulin/OAD or evidence of diabetes monitoring.	HRT in last 12 months	CHD included MI, angina, or IHD; no further definition.	HRT, not specified	never use	OR 0.67 (0.36-1.27)	OR 0.58 (0.28-1.23)	Type of diabetes, smoking status, serum cholesterol, obesity, previous hysterectomy
Petitti et al., 2000 (subgroup) [30]	Postmenopausal if had bilateral oophorectomy or reported ceased menstrual period.	Diabetes was based on participants who answered "yes" to questions about medication use.	current user: use in month before the index date (self-reported)	MI based on American Heart Association Council on Epidemiology diagnosis criteria [53]	estrogen with/without progestin	non-current use	N/A	OR 2.00 (0.2-27.6)	age, education, and race/ethnicity (White/Asian vs all others).
Lorenzo et al., 2000 (subgroup) [37]	Postmenopausal women, definition not specified.	Diabetes presents if there was recorded code at any time before the index date.	current user: women who used HRT at any time in the 6-month period before the index date	MI was based on international standardized criteria [53]	oral estrogen, transdermal estradiol, and/or progestogen	never use	OR 1.4 (0.6-3.3), not clear whether unadjusted or not		N/A
Gami et al., 2003 [34]	Postmenopausal if stated in the medical record, history of bilateral oophorectomy, or age >50 years.	Diabetes was based on medical record or taking diabetic medications upon admission.	current user: women with medications that were reported upon admission (self-reported)	MI defined by international standardized criteria [53]	estrogen with/without progesterone, estrogen + progesterone	never use	N/A	Estrogen without prior CHD: OR 0.5 (0.2-1.5) E+P: OR 1.8 (0.5–6.2)	age and admission
Ferrara et al., 2003 [42]	Women aged ≥50 from Diabetes Registry.	N/A	current user: if subject's cumulative medication supply lasted through a given date or had ended less than 3 months earlier	MI based on ICD-9th Revision as code 410.x.	unopposed etrogen, estrogen + progestin	no current HRT	N/A	Unopposed estrogen: HR 0.88 (0.73–1.05) E+P:HR 0.77 (0.61–0.97)*	age, ethnicity, education, obesity, diabetes duration, hypoglycemic therapy, glycosylated hemoglobin, hypertension, lipid-loweringmedications, smoking, alcohol, and exercise

(*Continued*)

Table 3. (Continued).

Author, year	Menopause definition	Diabetes definition	HRT definition	Outcome/case definition	Interventions	Comparator	Unadjustedeffect estimate(95% CI)	Adjustedeffect estimates (95% CI)[a]	Adjusted for
Newton et al., 2003 [32]	Perimenopause: amenorrhea for 6-12 months, menopause symptoms before 56 years old in hysterectomized women without bilateral oophorectomy, or age <55 years with symptom or taking estrogen. Postmenopause: amenorrhea for >12 months, a physician statement, bilateral oophorectomy, or age >55 years.	Type 2 Diabetes: two fasting glucose measurement ≥ 140 mg/dl, two nonfasting ≥200 or one of each; Hba1c>7.5%; prescribed for insulin/OAD; hospitalized because of diabetes without ketoacidosis.	current user: N/A past user: if the prescription was not refilled within 180 days after the runout date	CV events included nonfatal MI, coronary revascularization (coronary artery bypass, angioplasty/ stent, thrombolysis), or fatal CV diseases. Diagnosis based on ICD-9 and Current Procedural Terminology (CPT) codes.	unopposed estrogen, estrogens + progestins	never use	N/A	Unopposed estrogen: HR 0.48 (0.30–0.78)* E+P: HR 0.43 (0.22–0.85)*	age, CDS (modeled as a time-dependent variable), duration of diabetes, insulin use, history of myocardial infarction, angina, congestive heart failure, stroke, peripheral vascular disease, lower extremity amputation, lower extremity ulcer, revascularization (coronary artery bypass, coronary angioplasty, carotid endarterectomy, or lower extremity vascular bypass), and current smoker at start of follow-up.
Lokkegaard et al., 2003 (subgroup) [35]	Menopause was self-reported through questionnaire.	Diabetes was self-reported through questionnaire.	definition not specified (self-reported)	MI was based on ICD-10 codes 410 and I21I23.	estrogen with/without progesterone (estradiol-17beta + norethisterone acetate)	never use	N/A	MI:OR 9.15 (2.02-41.44)* IHD:OR 4.15 (1.38-12.45)*	smoking, hypertension
Grodstein et al., 2006 (subgroup) [36]	Postmenopausal from the time of natural menopause or hysterectomy with bilateral oophorectomy.	N/A	current user: use within the last month (self-reported)	Nonfatal MI based on WHO criteria (WHO, 1971); most deaths were reported by participants's families.	estrogen alone, estrogen + progestin	never use	N/A	Estrogen alone: HR 0.67 (0.46–0.99)* E+P:HR 0.54 (0.30–0.96)*	age, BMI, hypercholesterolemia, hypertension, parental history of heart disease 60 years, diabetes,cigarette smoking, husband's education, alcohol intake, physical activity, vitamin E supplementation, multivitamin supplements, aspirin use.
Lokkegaard et al., 2008 (subgroup) [39]	Women aged ≥51.	Diabetes was defined if treated with antidiabetic medications.	N/A	MI was based on ICD-10 code DI21–22.	estrogen with/without progestogen, tibolone	never use	N/A	RR 1.01 (0.73-1.4)	education, habitation, and calendar year

(*Continued*)

Table 3. (Continued).

Author, year	Menopause definition	Diabetes definition	HRT definition	Outcome/case definition	Interventions	Comparator	Unadjustedeffect estimate(95% CI)	Adjustedeffect estimates (95% CI)[a]	Adjusted for
Rockman et al., 2012 (subgroup) [31]	Postmenopause was self-reported through questionnaire.	Diabetes was self-reported through questionnaire.	ever use (self-reported)	PAD exam included carotid artery duplex ultrasound scan, abdominal ultrasound to screen abdominal aortic aneurysm, and calculation of the ABI (ABI <0.9 considered PAD)	ever use HRT, not specified	never use	N/A	OR 0.77 (0.73-0.81)*	age of >70 years, race, positive smoking history, and a history of hypertension, hypercholesterolemia
Chen et al., 2015 [33]	Women aged ≥55.	Diabetes was based on ICD-9-CM codes 250.X.	use at least 60 days within 3 months during 2003-2009	Ischemic stroke was based on ICD-9-CM codes 433–438.	conjugated equine estrogen (0.625 mg per day)	never use estrogen in the study period	N/A	HR 0.34 (0.12–0.97)*	age, comorbidities, socioeconomic status, urbanization, and other medications associated with ischemic stroke
Canonico et al., 2016 (subgroup) [40]	Women aged 51 to 62 years.	Antidiabetic medications used as a proxy of diabetes.	current user: if a woman had at least one reimbursement of HT at any time during the 3 last months before index date	Ischemic stroke was based on ICD-10 codes I60 to I64.	oral/transdermal estrogen; not clear if with/wo progesterone	non-current use	N/A	oral: OR 2.69 (0.11-65.2) transdermal: OR 0.38 (0.10-3.26)	age, zip code, and index date.

[a]For current-use unless definition for current-use was not provided

CHD, coronary heart disease; MI, myocardial infarction; PAD, peripheral arterial disease; AF, atrial fibrillation; IHD, ischemic heart disease; OR, odds ratio; HR, hazard ratio; RR, rate ratio; E+P, estrogen plus progesterone; E-alone, estrogen-alone; ICD, International Classification of Diseases; HRT, hormone replacement therapy; OAD, oral antidiabetic; N/A, not available; CI, confidence interval. Asterisk (*) indicates statistical significance.

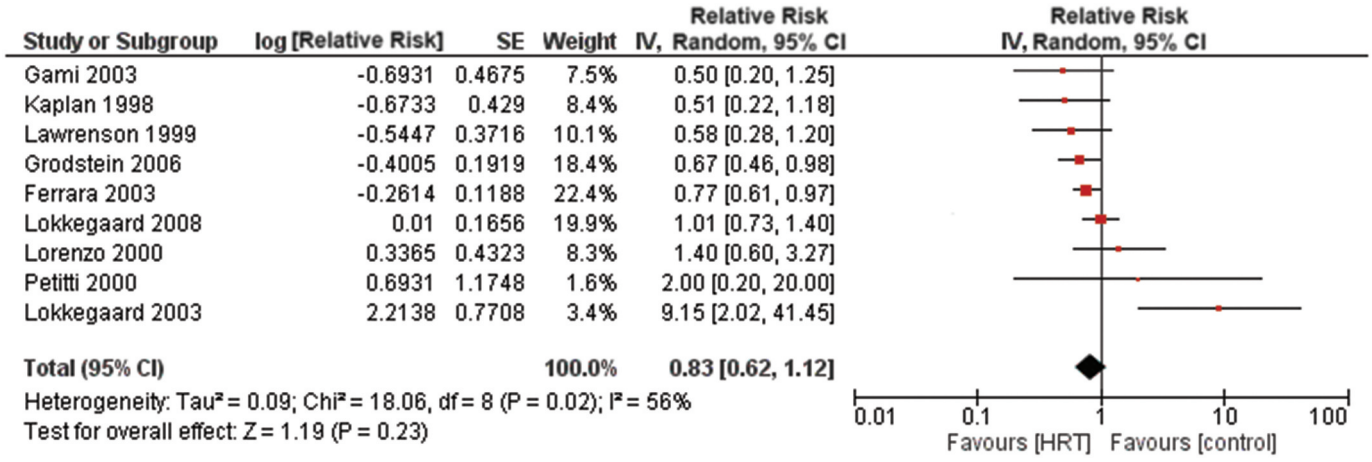


Figure 2. Meta-analysis of HRT use in MI outcome among the observational studies.

and type of analysis. We identified four studies [32,34,36,42] that separated their analyses according to the use of progestin for MI outcome. Results showed statistically significant protective effect for both estrogen-only (RR 0.67 [95% CI 0.49–0.92]) and estrogen plus progestin (RR 0.67 [95% CI 0.46–0.98)] (see Figures 4 and 5).

3.5. Risk of bias

Risk of bias is presented in Figures 6 and 7. Assessing bias in studies with subgroup analyses was challenging due to limited information, especially to assess confounding and selection bias since baseline characteristics for subgroup populations were not available. The information related to the randomization process for WHI trials, including random sequence generation, allocation concealment, and baseline differences, was not adequately reported for subgroup populations. Thus, hindering the assessment of bias arising from randomization. However, the overall bias across all reports is considered low. For observational studies with main analyses, the majority exhibited a moderate risk of bias.

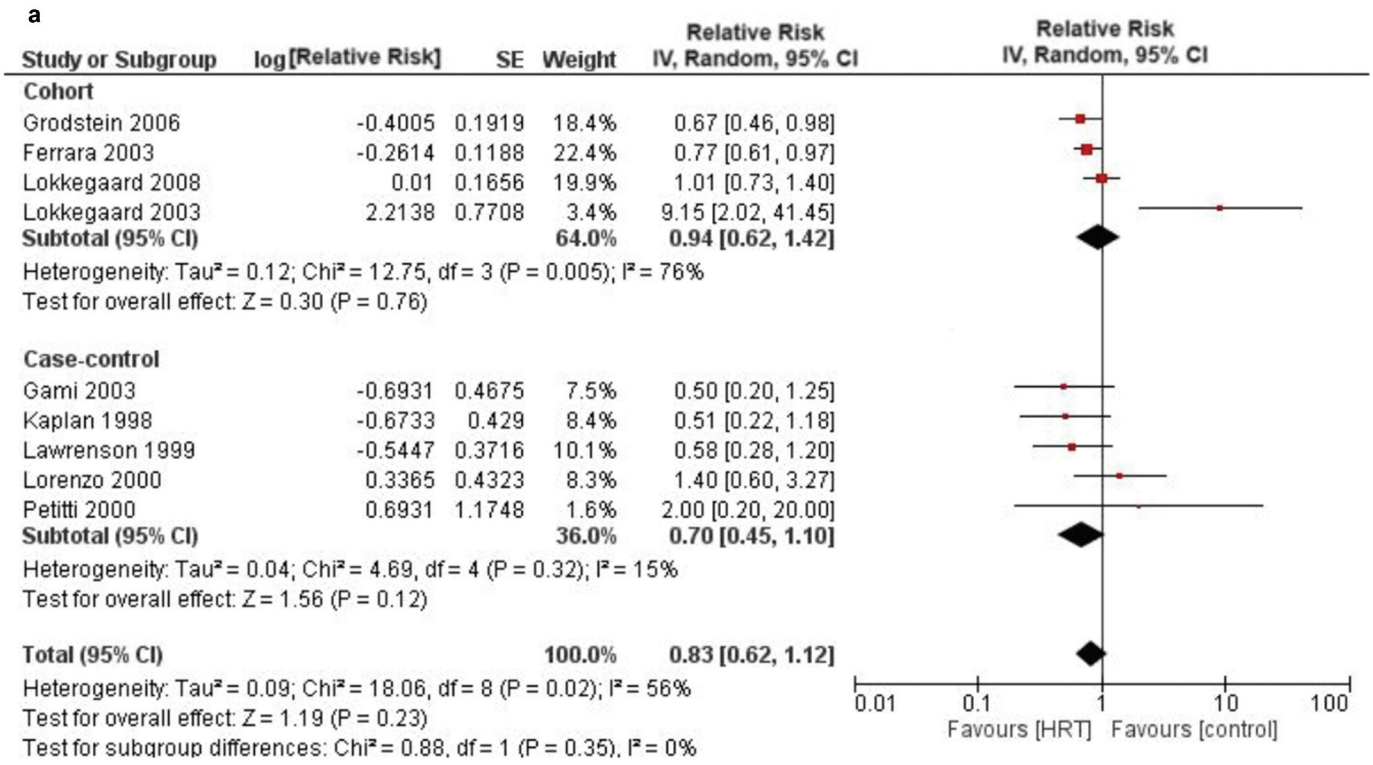
4. Discussion

4.1. Summary and interpretation

This study summarizes all available literature on the potential association of HRT use and changes in CVD risk in a population of women with diabetes. Our main finding is that there is no evidence that HRT use changes the risk of various CVD outcomes in women with diabetes. The results of our primary meta-analysis show there is no evidence that HRT changes the risk of MI. However, caution is warranted in interpreting the findings due to the moderate heterogeneity and inconsistent results in sensitivity analyses. The observed heterogeneity may stem from methodological differences across studies, such as variations in study design, small sample sizes, and other potential sources of bias. Excluding post hoc subgroup analyses from the meta-analysis resulted in a statistically significant protective effect of HRT on MI. Given the limitations inherent in subgroup analyses – namely, the potential reduction in study power due to smaller sample sizes and the lack of balanced baseline characteristics – there remains a possibility that HRT exerts a protective effect against MI in women with diabetes. Moreover, separate analyses for estrogen-only and estrogen plus progestin demonstrated decreased risk of MI. Given the differences in clinical characteristics between women who use monotherapy estrogen and estrogen plus progestin, these findings may hold significant clinical relevance. However, research with bigger sample sizes and more robust methods are needed to confirm these findings.

Though there are no systematic literature reviews that have wholly evaluated HRT usage in women with type 1 or type 2 diabetes and their risk of cardiovascular outcomes, the results of this review can be compared against the findings of narrative reviews [43,44]. The studies acknowledge that women with diabetes are predisposed to an already increased risk of cardiovascular diseases, though there is some evidence to suggest that HRT can confer a cardioprotective effect to offset this risk. HRT appears to improve important CVD risk factors, such as blood pressure, low-density lipoprotein (LDL) cholesterol, triglycerides, lipoprotein (a), adhesion, and coagulation molecules [44]. Transdermal HRT was associated with beneficially lower triglyceride levels, as well as showing no correlation in increasing mean blood pressure levels in postmenopausal hypertensive women with diabetes [43]. Those results, however, are only markers for cardiovascular outcomes. Our study provided direct evidence on CVD outcome rather than the CVD risk factors. Dunne et al. [43] also support our findings in terms of MI. A systematic review for MI in the general population demonstrated a summary estimate of 0.79 [95% CI 0.75–0.84] [45], meanwhile our study in women with diabetes showed a point estimate of an RR of 0.83 [95% CI 0.62–1.12]. This comparison is somewhat in line with Dunne's review [43] that stated the protective effect of HRT against ischemic heart disease in women with diabetes may not be as significant as that in the general population.

The results of our narrative systematic literature review show that some of the results between the studies included in this review are conflicting. For studies that specifically focussed on



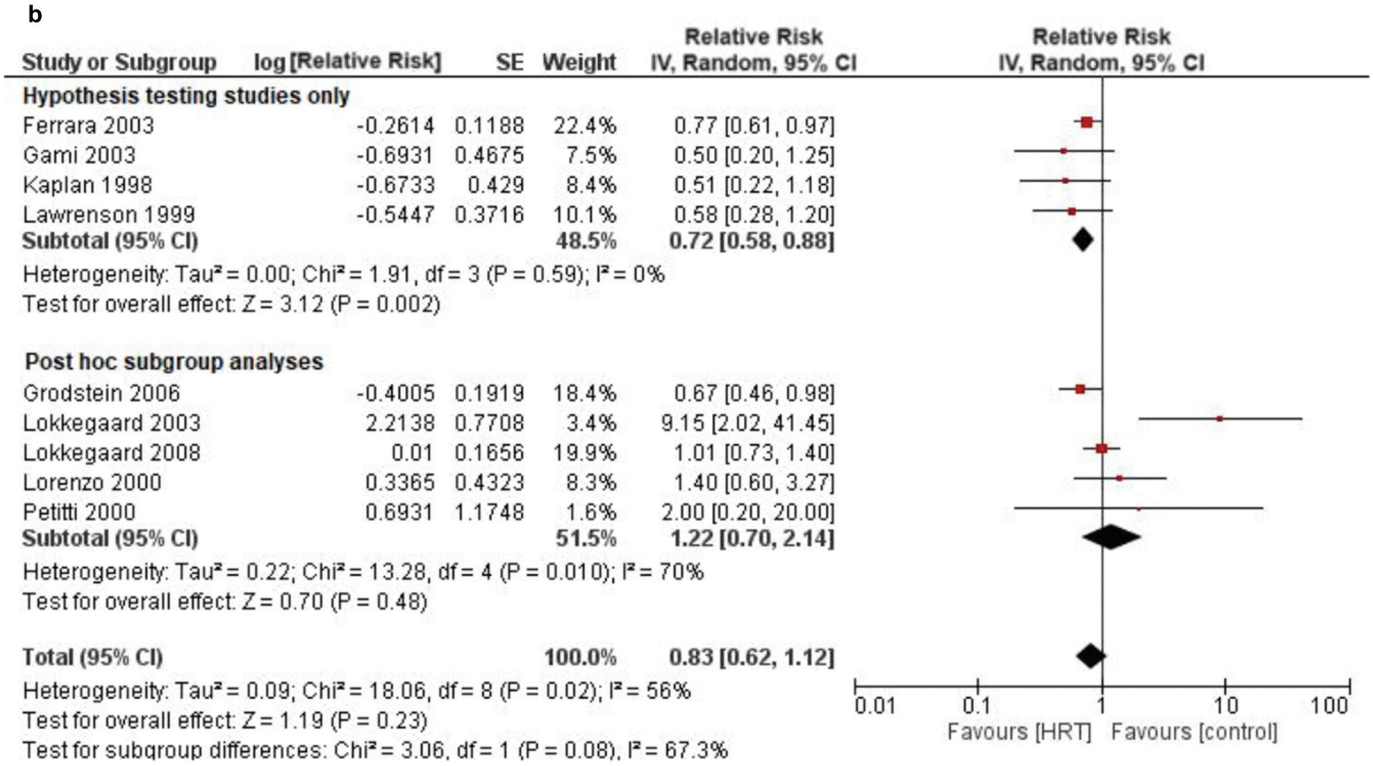


Figure 3. Sensitivity analyses based on (a) study design and (b) analysis among the observational studies.

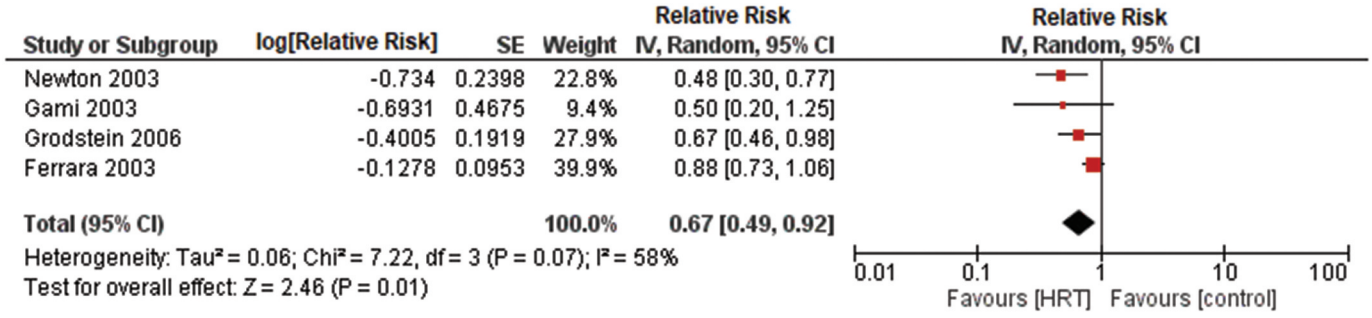


Figure 4. Meta-analysis of estrogen-only in MI outcome among observational studies.

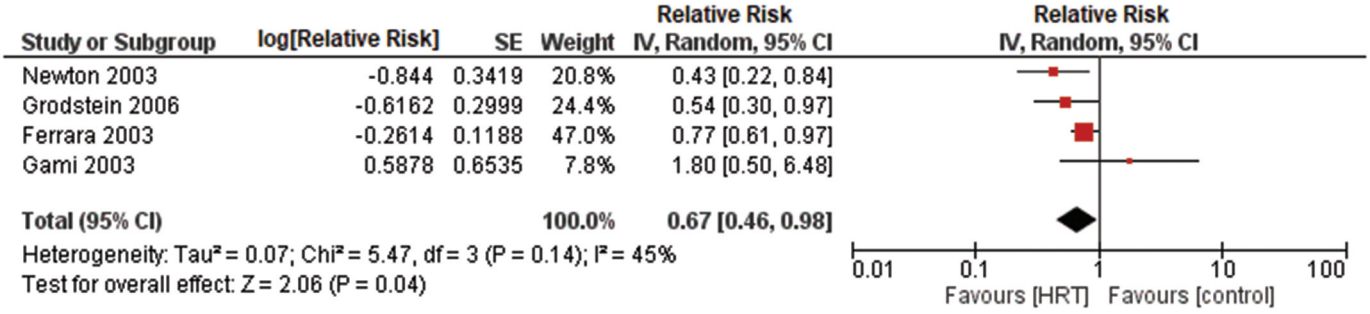


Figure 5. Meta-analysis of estrogen plus progestin in MI outcome among observational studies.

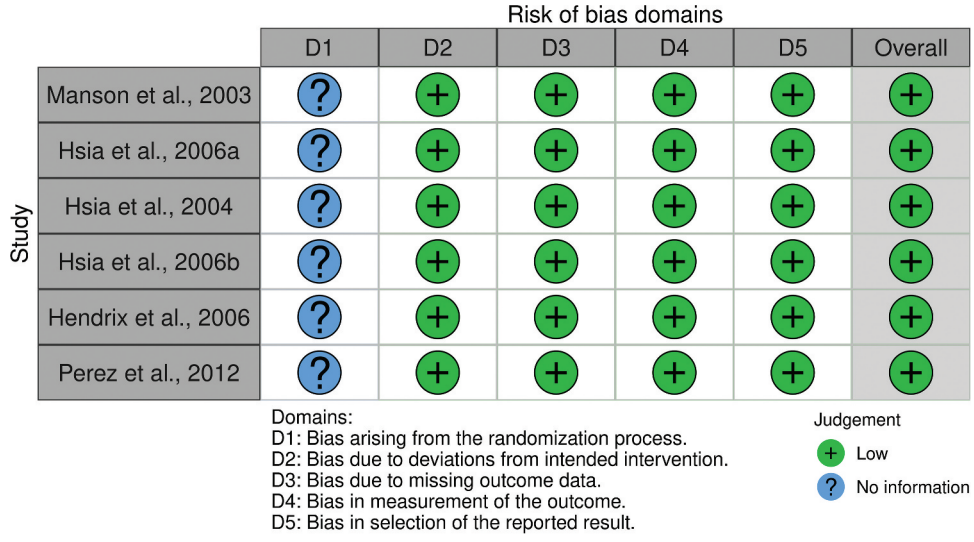


Figure 6. Risk of Bias of Randomized Clinical Trials.

stroke as an outcome, one RCT showed an increased risk of stroke in conjugated equine estrogen (CEE) users [24], while observational studies showed a protective role of CEE [33] or no increased risk [40]. The discrepancy in findings may be attributed to differences in the age of the study populations, with Chen et al. [33] and Canonico et al. [40] involving slightly younger (mean/median: <60 years old) individuals compared to the RCTs. A systematic review in the general population highlighted that individuals under 60 years old who took HRT within 10 years of menopause did not exhibit an increased risk of stroke [15], which may also apply to women with diabetes. However, since the studies did not consider the time since menopause, we can only speculate that age may have contributed to the conflicting results. The results of the RCTs and observational studies are somewhat expected to differ as confounding bias may have affected the results of observational studies. For example, Canonico et al. [40] classified women with

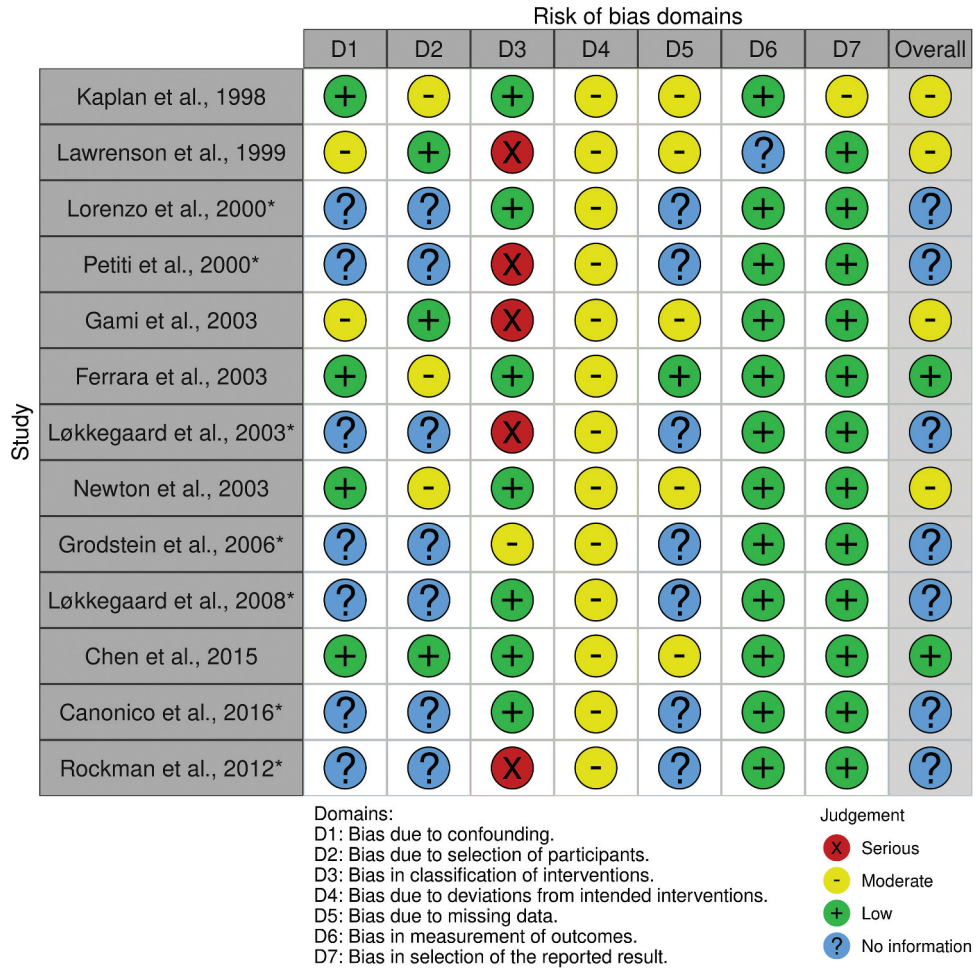


Figure 7. Risk of bias of observational studies (asterisk (*) refers to sub-group analysis).

diabetes using antidiabetic medications as a proxy for diabetes rather than diagnosis confirmation, which could introduce bias because some people with diabetes can be treated with lifestyle modification instead of medications for diabetes. However, we believe that the risk of bias in Chen et al. [33] was low due to the utilization of propensity score matching which limits confounding from known and measured variables.

One RCT and one observational study in this systematic literature review focussed specifically on the risk of PAD in users of HRT. The RCT [26] and observational study [31] reported different results, with Rockman et al. [31] suggesting a protective effect of HRT while the RCT indicated no change in risk [26]. Rockman et al. [31] measured postmenopausal status and diabetes through self-reported questionnaires, which may raise potential misclassification compared to data collections from medical records or pharmacy systems. Rockman et al. [31] also defined intervention as an ever-user (by asking participants a question 'Have you ever been on hormone replacement therapy?'), which further affects the precision of their results and most likely led to an overestimation of HRT use.

This review included the results of an RCT in which findings suggested an increased risk of AF in CEE-alone users, but not in women using estrogen plus progestin [27]. This finding is consistent with the broader population in the same study, where incident AF reached statistical significance in the CEE-alone trial (HR, 1.17 [95% CI 1.00–1.36], $p = 0.045$). Unfortunately, observational studies specifically assessing AF as an outcome in women with diabetes were not found. Since AF is strongly associated with VTE [46], it is important to investigate the AF risk in a real-world population.

Most studies examining MI outcome found no evidence of a change in risk of MI associated with HRT use, including the WHI trials. Three observational studies [32,36,42] reported significant findings, with Ferrara et al. [42] being the largest among all studies, and, therefore, enhance the ability to detect true effects due to high statistical power. However, Newton et al. [32] and Grodstein et al. [36] did not specifically define CHD or cardiovascular events as MI, which may bias the result. Grodstein et al. [36] only included younger women, aged 30–55 years old, which may limit the generalizability of their findings to postmenopausal populations.

Dosage and duration of HRT are important in determine a causal association of HRT and CVD [15]. The only study that assessed the effect of various dosage on CVD risk in women with diabetes is Ferrara et al. [42]. They showed that lower doses (<0.625 mg of oral estrogens or <0.02 mg of estradiol) and medium doses (0.625 mg of oral estrogen and 0.05 mg of estradiol) may have cardioprotective effects against the risk of an acute MI, while higher doses do not pose an increased risk of acute MI. Duration of HRT use was assessed by two studies

[38,42]. Overall, while the two studies did not result in statistical significance in most durations assessed, one can infer that there may be a pattern in which longer cumulative usage of estrogen can return a cardioprotective effect against the risk of an MI. However, the small sample size included in the studies warrants further research with bigger sample sizes to confirm these results.

We assessed bias by using standardized tools from Cochrane. The WHI trials were considered low risk of bias. However, results from the WHI trial discussed in this review were derived from subgroup analyses; we emphasize caution in interpreting subgroup results due to the potential for imbalanced characteristics, unless randomization is stratified [22,23,25,47]. Case–control studies were deemed to have a serious risk of bias in the classification of intervention due to potential recall bias; most case–control studies conducted questionnaires or interviews with subjects, and the authors did not confirm the self-reported information to the medical or pharmacy system. Moderate bias regarding deviation from intended intervention was attributed mainly to the unavailability of adherence information. Observational studies with subgroup analyses report lacked sufficient baseline characteristics and specific methodologies, thus precluding an overall analysis of risk of bias based on the ROBINS-I.

4.2. Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis on the association between HRT and CVD in menopausal women with diabetes. In our search strategy, our keywords primarily focused on studies involving menopausal women with diabetes. Nevertheless, we also attempted to identify post hoc subgroup analyses in women with diabetes within the general population through citation searches. Despite these efforts, it is possible that relevant subgroup analyses were missed, as our review relied on identifying subgroup analyses from recent systematic reviews only. Results from post hoc subgroup analyses could also be biased because the original investigators did not aim to balance the baseline characteristics in women with diabetes. As mentioned above, when we removed post hoc analyses from the meta-analysis, we found a statistically significant decreased pooled relative risk of MI in women exposed to HRT. Additionally, most observational studies in this review featured a small sample size, potentially reducing the statistical power of the analyses. Our review also lacked detailed results on CVD risk stratified by age, time since menopause, HRT dosage and duration due to data insufficiency. Furthermore, we planned to identify publication bias, but the number of studies was less than 10, thus identification was not feasible. Other important gap is that the review was unable to account for studies specifically investigating the impact of HRT on women with type 1 diabetes. This lack of clarity means it is harder to make meaningful interpretations of how HRT usage risk differs between women with type 1 and type 2 diabetes.

4.3. Implications

Although acceptance of HRT has regained in recent years, some physicians may remain hesitant to prescribe HRT to women with diabetes where evidence is still limited. Examining the potential elevation of cardiovascular risk among HRT users within women with diabetes is imperative, considering the recognized status of diabetes as a significant cardiovascular risk factor [48]. However, HRT has been shown to improve glycemic control [49,50], which may contribute to its beneficial impact on cardiovascular safety in postmenopausal women with diabetes.

The study's findings offer some reassurance to women with diabetes using HRT for postmenopausal symptom relief that the risk of experiencing MI later in life is low. Ultimately, however, the evidence arising from this review is not sufficiently robust to draw conclusions with regard to the cardiovascular safety of HRT. Thus, further original research is required to provide further evidence to guide the prescribing of HRT for menopausal women who live with diabetes.

Abbreviations

AF	atrial fibrillation
CEE	conjugated equine estrogen
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DVT	deep vein thrombosis
E-alone	estrogen-alone
E+P	estrogen plus progesterone
HF	heart failure
HR	hazard ratio
HRT	hormone replacement therapy
ICD	International Classification of Diseases
LDL	low-density lipoprotein
MI	myocardial infarct
N/A	not available
OAD	oral antidiabetic
OR	odds ratio
PAD	peripheral arterial disease
PE	pulmonary embolism
PICOS	Population, Intervention, Comparator, Outcome, Study Design
RCT	randomized controlled trial
RoB 2	risk of bias 2
ROBINS-I	Risk of Bias in Non-randomized Studies – of Interventions
RR	relative risk
VTE	venous thromboembolism
WHI	women's health initiative

Registration and protocol

The study protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42023479335). Protocol can be accessed in https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023479335.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with

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Availability of data and other materials

Data sharing not applicable – no new data generated.

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