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Hormone Replacement Therapy for Menopausal Symptoms and the Risk of Cardiometabolic Disease: Current Evidence and Future Directions

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ABSTRACT

Background: The transition through menopause is accompanied by a series of adverse metabolic changes which are associated with an increased risk of cardiometabolic disease, a major cause of mortality in women after midlife. Whilst the indication for menopausal hormone replacement therapy (HRT) is the control of menopausal symptoms, understanding and discussing the cardiometabolic impacts of HRT are necessary to facilitate informed decision-making at treatment initiation and continuation, and to select appropriate regimens.

Methodology: A narrative review.

Results: Existing evidence suggests that HRT is likely to impact the development of metabolic risk factors including visceral fat accumulation, adverse changes in lipid profile, blood pressure and glycaemic control. Findings from randomised controlled trials have refined our understanding of the impact of HRT on cardiometabolic outcomes including coronary heart disease and stroke. Furthermore, recent research has highlighted the impact of the menopause on the development and severity of metabolic dysfunction-associated steatotic liver disease (MASLD) that has been poorly studied in the context of HRT. The route of oestrogen administration, timing of initiation and type of progestogen are all likely to affect the impact of HRT on many of these outcomes. There has recently been extensive media interest in HRT in some countries resulting in increased prescription rates. Understanding the impact of HRT on cardiometabolic risk is therefore particularly important. In this narrative review, we discuss the existing evidence and clinical guidelines on the effect of HRT on cardiometabolic risk factors and the risk of coronary heart disease, stroke and MASLD, highlighting areas of uncertainty and priorities for further research.

1 | Introduction

The menopause is a turning point in life for the development of cardiometabolic disease [1, 2] and despite overall reductions in mortality rate from cardiovascular disease in recent decades, worsening trends in mortality are emerging for women at midlife [3, 4]. The assessment of the impact of hormone replacement therapy (HRT) treatment during the menopause on cardiovascular outcomes has a controversial history, particularly following the initial publications of the two parallel Women's Health Initiative (WHI) randomised controlled studies (RCTs) that studied the impact of either conjugated equine oestrogen

(CEE)-only or CEE combined with medroxyprogesterone acetate (MPA) compared to placebo, which led to a sharp decline in HRT uptake, at least partly due to reporting of breast cancer risks [5–8]. Despite further research of the cardiometabolic effects of HRT since the WHI RCTs, there remain significant areas of disagreement between guideline-forming bodies, particularly with respect to the timing of HRT on cardiovascular disease risk [9–12]. Furthermore, recent evidence has implicated the menopause, and potentially HRT, on the development of metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD) [13].

In recent years, potentially due to increased media interest and celebrity endorsement of HRT, prescription rates have risen dramatically in the United Kingdom [14, 15], though there remain disparities in HRT uptake representing health inequalities [16]. Understanding key messages from clinical guidelines on the cardiometabolic effects of HRT and highlighting deficiencies in existing evidence is therefore particularly important.

In this narrative review, the impact of HRT on components of the metabolic syndrome (obesity, lipid profile, hypertension and diabetes) is reviewed, as well as the effect of HRT (including timing and route of administration) on coronary heart disease (CHD), stroke and MASLD (summarised in Figure 1). The evidence included is from studies predominantly undertaken on people who were biologically female at birth and in this article the term 'women' is used accordingly. However, trans men and some non-binary individuals may also experience menopause and are inadequately represented in existing research and historical datasets. Whilst there has been a significant focus on the metabolic impact of oestrogen replacement, progestogens are likely to influence this effect, and are subclassified into synthetic and body-identical forms (Table 1), which differ widely in their potency and biological activities [17]. Although there are questions about the long-term safety of testosterone as a component of symptomatic menopause treatment [18], this review will focus on systemic oestrogen and progestogens. Finally, best practice points for management of cardiometabolic health after menopause will be provided and areas for future research highlighted.

2 | Impact of HRT on Cardiometabolic Risk Factors

2.1 | Weight

Menopause is associated with a redistribution of adipose. Whilst premenopausal women have a tendency to accumulate adipose in gluteofemoral, 'gynoid' depots', after the menopause, adipose redistributes to abdominal/visceral, 'android' depots [19, 20]. This has important implications as adipocytes in these two regions are functionally distinct [21] and whilst subcutaneous depot adipose accumulation is considered metabolically protective, visceral adiposity is associated with insulin resistance [22] and increased cardiometabolic risk [23]. Whilst some studies have demonstrated a reduction in visceral or abdominal fat with HRT [24–27], others have not [28, 29], and these inconsistent findings may be due to differences in study design.

Overall weight gain observed over the menopause transition (approximately 0.5 kg per year [y]) appears to be due to age rather than hormonal changes [30, 31]. Weight gain is a major concern for people considering HRT, and perceptions of weight gain following treatment initiation contribute to poor compliance [32]. However, published data would support a neutral effect of HRT on weight. A Cochrane systematic review concluded that there is no evidence of an adverse effect of combined or oestrogen-only HRT on body mass index (BMI) [33]. However, due to actions on the renin-angiotensin system, both oestrogen and progestogens can cause fluid retention [24, 34] manifesting as bloating or oedema, which may lead to the perception of increased lean/fat mass. If such problems arise, they can often be resolved or mitigated with a dose reduction, a change in the delivery route of oestrogen, or a change in progestogen [32, 35]. The mainstay for managing weight at midlife should be exercise and calorie restriction [11, 31] and whilst the effect of HRT on BMI appears to be neutral, HRT may have a beneficial effect of attenuating visceral fat.

2.2 | Lipid Profile

The menopause is associated with unfavourable changes in plasma lipid profile, characterised by higher concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein (apo)-B and lipoprotein(a) [36, 37]. Although HRT generally leads to largely favourable changes in lipid profile in postmenopausal women, the route of administration and the progestogen component modify this effect [38]. A meta-analysis reported that HRT significantly decreased levels of total cholesterol and LDL-C [38]. Oral HRT increases serum triglyceride (TG) levels [38] whereas transdermal HRT has a more neutral or even lowering effect on TG [38–41].

This meta-analysis, which pooled together data from different progestogens, indicated that combined regimens significantly increased total cholesterol, LDL-C and high-density lipoprotein cholesterol (HDL-C) when compared to oestrogen-only regimens, suggesting that progestogens blunt the beneficial effect of oestrogens on lipid profile [38]. The impact of specific progestogens on lipid profile are comprehensively reviewed elsewhere [42]. Some, but not all studies report that MPA worsens components of lipid profile [43, 44]. Dydrogesterone and micronised progesterone appear to have a more neutral effect on lipid profile [42, 45, 46]. One study suggests that drospirenone may have beneficial effects on total cholesterol, LDL-C and HDL-C levels [47].

2.3 | Blood Pressure

Preclinical studies suggest that oestrogen exerts a beneficial effect on endothelial function by promoting production of vasoactive mediators such as nitric oxide which regulate vascular tone [48]. However, the impact of oestrogen-based therapies on blood pressure appears to vary by route of administration. Oral oestrogen appears to increase the risk of hypertension. A secondary analysis of the WHI RCTs reported that the rate of incident hypertension was 18% higher during the intervention phase of the oral CEE-only and oral CEE + MPA arms

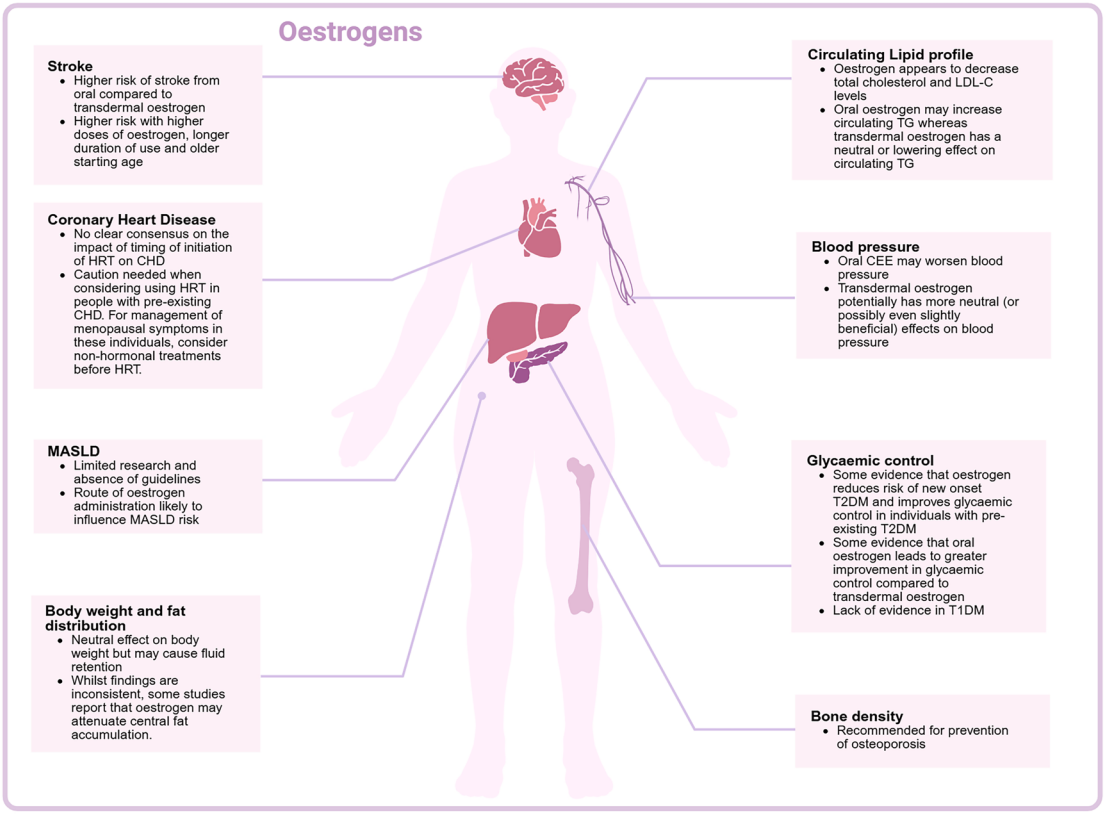

FIGURE 1 | Overview of the cardiometabolic effects of menopausal hormone replacement therapy. Upper panel: Effects of oestrogens. Lower panel: Effects of progestogens. Created in BioRender. Tomlinson, J. (2026) https://BioRender.com/0y9rki6. CEE, conjugated equine oestrogen; CHD, coronary heart disease; HRT, hormone replacement therapy; LDL-C, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; MPA, medroxyprogesterone acetate; NICE, National Institute for Health and Care Excellence; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TG, triglyceride.

TABLE 1 | Classification of oestrogens and progestogens used in menopausal hormone replacement therapy.

Oestrogens			
Route			**Form**
Oral			Conjugated equine oestrogens
			Oestradiol (E2)
Transdermal			Oestradiol (E2)
Progestogens			
	Synthetic		
Body-identical	**Pregnane-derivate**	**19-Norpregnane derivative**	**Structurally related to testosterone**
Micronised progesterone (PO/PV)	Medroxyprogesterone acetate (PO)	Nomegestrol acetate (PO)	Levonorgestrel (TD/IUS)
	Cyproterone acetate (PO)		Desogestrel (PO)
	Dydrogesterone (PO)		Drospirenone (PO)
			Norethisterone acetate (PO/TD)

compared to placebo, and this increased risk dissipated in the post-intervention phase of the study [49]. In the CEE + MPA study the absolute risk increase (ARI) of hypertension was 103 cases per 10 000 person-years (py) and in the CEE-only study the ARI was 75 cases per 10 000 py [49]. A recently published meta-analysis reported an increase in systolic BP with the use of oral CEE + progestogen (SMD = 0.60 mmHg, 95% CI = 0.19–1.01) [50]. The effect of oral oestrogen on BP seems to vary between formulations, with a lower risk of worsening BP from oral oestradiol (E2) compared to oral CEE. Use of CEE was associated with an 8% higher risk of hypertension compared to E2 (CEE versus E2 hazard ratio [HR] 1.08, 95% CI 1.04–1.14) in a prospective population-based study [51]. Furthermore, a study in normotensive or hypertensive postmenopausal women randomised to either 1 mg oral E2 or placebo reported no significant difference in BP after 2 years [52]. Adding to this evidence, a meta-analysis reported no significant effect of oral E2 + progestogen or oral E2 alone on BP [50].

Studies on transdermal oestrogen report more neutral, or even beneficial effects on BP [53–55]. An RCT showed that oral CEE + MPA increased angiotensin II levels and had a neutral effect on BP in normotensive women, whilst transdermal E2 + MPA decreased diastolic and mean BP [56]. Non-oral oestrogen used at the lowest dose and shortest duration of time appears to be associated with the lowest risk of hypertension [51]. A small study reported that HRT discontinuation may predispose some women to hypertension but this potential risk needs to be further studied [57].

A randomised, double-blinded, crossover study concluded that 6-weeks of micronised progesterone without oestrogen did not affect BP, systemic arterial compliance or flow mediated dilation [58]. In a randomised study, low dose oral E2 sequentially combined with 10 mg/day dydrogesterone led to a significant decrease in daytime diastolic and night-time systolic/mean arterial BP compared to the group receiving no therapy [59]. Given the likely neutral effect of oral E2 on BP [52], the beneficial effect on BP observed in this study may be from dydrogesterone [59]. Drospirenone, a spironolactone derivate progestogen, has also demonstrated beneficial effects on systolic BP [60]. In a randomised double-blinded trial, significant reductions were reported in 24-h systolic BP at 2 and 3 mg drospirenone combined with E2 but not with E2-alone or 1 mg drospirenone combined with E2 [60]. Further clinical studies are needed to validate differences between progestogens.

2.4 | Glycaemic Control

The fall in circulating oestrogen levels after menopause is believed to contribute to pancreatic beta cell dysfunction [61] and increased visceral fat [62], which increase the risk of type 2 diabetes mellitus (T2DM) [63]. Data from the WHI RCTs suggest that women assigned HRT had lower rates of treated diabetes than women assigned placebo during the intervention phase. In the CEE + MPA study, the HR was 0.86 (95% CI 0.76–0.98), corresponding to an absolute risk reduction (ARR) of 16 cases per 10 000 py [64]. In the CEE-only study, the HR was 0.81 (95% CI 0.70–0.94), corresponding to an ARR of 21 cases per 10 000 py [64]. A meta-analysis of 107 trials showed that HRT reduced the risk of new-onset T2DM (RR 0.7, CI 0.6–0.9) [65]. Furthermore, HRT significantly improved fasting glucose levels (−11.5%, CI −18.0 to −5.1%) and HOMA-IR (−35.8%, CI −51.7 to −19.8%) for those with pre-existing T2DM [65]. A more recent meta-analysis, including RCTs involving participants with either type 1 or type 2 diabetes, reported a change in HbA1c of −6.08 mmol/mol (95% CI −8.80 to −3.36) and in fasting glucose of −1.15 mmol/L (95% CI −1.78 to −0.51) in their pooled analysis [66]. However, in both of these meta-analyses, the magnitude of the improvement in these parameters may be unreliable as not all included studies controlled for changes in other glucose-lowering medication.

Compared to transdermal oestrogen, oral oestrogen appears to have greater beneficial effects on glycaemic control [65, 67]. A meta-analysis reported that oral oestrogen led to a significant

reduction in HbA1c by −6.63 mmol/mol (95% CI −9.74 to −3.52), whilst no significant difference was observed with transdermal E2 (−3.66 mmol/mol, 95% CI −8.16 to 0.85) [66].

Though yet to be rigorously tested, some progestogens are believed to have an adverse effect on glycaemic control and insulin resistance [67]. Mechanistic studies have shown that MPA and levonorgestrel attenuate the beneficial effects of oestrogen on insulin sensitivity [68], possibly due to their glucocorticoid and androgenic properties [67, 69]. Micronised progesterone and dydrogesterone appear to have more neutral effects on carbohydrate metabolism [67, 70–72].

Whilst recommendations from the North American Menopause Society (NAMS) and The International Menopause Society (IMS) highlight the beneficial effect of HRT on glycaemic control and reduction of new cases of T2DM [10, 11], the National Institute for Health and Care Excellence (NICE) adopts a more conservative stance [9]. Although oral oestrogen may be more beneficial for glycaemic control, its impact on other cardiovascular risk factors and risk of venous thromboembolism (particularly if BMI is raised) needs to be considered. There is a lack of evidence on the impact of HRT in people with type 1 diabetes [73].

3 | Coronary Heart Disease

3.1 | The Impact of Timing of Initiation of HRT

The timing hypothesis suggests that the benefits and risks of HRT for cardiovascular outcomes (particularly CHD) vary by time since menopause, and whilst there is some supportive evidence, it is not universally accepted and diverging opinions on its validity exist [9–11, 74–77]. Although early observational studies showed that oestrogen-only and combined HRT reduced CHD risk and mortality [78–81], the first publications of the WHI RCTs were at odds with these findings [5, 6], and the reduction in prescribing and uptake of HRT following these publications has been well documented [5–7]. A higher rate of CHD was reported in the CEE + MPA arm compared to placebo (HR 1.29, 95% CI 1.02–1.63, ARI 6 cases per 10 000 py), and notably the elevation in CHD risk was most apparent during the first year after initiating treatment (HR 1.81, 95% CI 1.09–3.01) [6, 82]. The CEE-only trial in women with a history of hysterectomy reported a HR for CHD of 0.91 (95% CI 0.75–1.12, ARR 5 cases per 10 000 py) compared to placebo after a mean follow-up of 6.8 years [5]. The timing hypothesis was able to explain the discrepancy between results from RCT and observational studies as women enrolled into the WHI RCTs were older (mean age 63 years, on average 12 years from menopause) [7, 83], and more likely to have established atherosclerosis initiation [7, 84–86]. Post hoc subgroup analyses of the WHI RCTs were subsequently released and outcomes stratified by timing in relation to menopause. HRs vary based on whether data from extended post-intervention follow-up was used and whether groups were stratified by decade of age or time since menopause [64, 87, 88]. Manson et al., in figure 6 of their manuscript [64], showed that during the cumulative follow-up period (including intervention and postintervention follow-up phases) of the CEE + MPA RCT, for women aged 50–59, 60–69 and 70–79 years, the CHD HR was 1.27 (95% CI 0.93–1.74), 0.97 (95% CI 0.79–1.18) and 1.17 (95% CI 0.95–1.44) respectively (*P* for trend 0.99) [64]. In the CEE-only study, the CHD HR for women aged 50–59, 60–69 and 70–79 years was 0.65 (95% CI 0.44–0.96), 1.00 (95% CI 0.82–1.23) and 1.01 (95% CI 0.80–1.28) respectively (*p* for trend 0.12) [64]. Although the test statistic for a trend did not pass the threshold for significance in the CEE-only study, the lower HR in the 50–59 years subgroup of the CEE-only RCT is notable. A statistically significant result was however found for the risk of total myocardial infarction (MI) stratified by decade of age in the cumulative follow-up period of the CEE-only RCT (50–59 years HR 0.60 (95% CI 0.39–0.91), 60–69 years HR 1.03 (95% CI 0.82–1.31), 70–79 years HR 1.25 (95% CI 0.95–1.65); *P* for trend 0.007) (figure 6 from Manson et al. [64]). When interpreting data from post hoc analyses of the WHI studies, it is important to appreciate that MI was a secondary outcome and that there are limitations of these subgroup analyses. *p* values and significance thresholds were not adjusted for multiple comparisons and should therefore be interpreted with caution. In another post hoc analysis of the WHI RCTs taking into consideration prior use of HRT before enrolment, little evidence supporting a favourable effect of HRT for women initiating HRT soon after the menopause was reported [88].

The Danish Osteoporosis Prevention Study (DOPS), a trial often cited to support the timing hypothesis, was an open label RCT in postmenopausal women (mean age 50, average 7 months from menopause) randomised to triphasic oral E2 and norethisterone acetate (2 mg oestradiol for the first 12 days, 2 mg oestradiol and 1 mg norethisterone acetate for the next 10 days, 1mg oestradiol for the next 6 days), 2 mg E2 for those who had undergone a hysterectomy, or no treatment [89]. After 10 y, women receiving HRT had a significantly reduced risk of a composite cardiovascular outcome (mortality, heart failure, or myocardial infarction) compared to the control group (16 in HRT group vs. 33 in control group, HR 0.48, 95% CI 0.26–0.87) [89]. However, this study is limited by the small number of events and unblinded nature of the intervention [89] and for these reasons, DOPS is sometimes excluded from evidence summaries [74]. A 2015 Cochrane systematic review, which included data from DOPS, conducted a subgroup analysis to assess the impact of time of HRT initiation relative to the menopause, concluded that those who started HRT within 10 years of the menopause or were aged less than 60 years had a lower risk of a composite CHD outcome (death from cardiovascular causes and non-fatal MI) (RR 0.52, 95% CI 0.29–0.96), whereas those who started HRT more than 10 years after the menopause or were aged more than 60 years had no significant change in the same composite CHD outcome (RR 1.07, 95% CI 0.96–1.20) [90]. Whilst some evidence demonstrates a cardioprotective effect of HRT in younger women soon after menopause, an awareness of the methodological limitations of these studies is needed before applying these findings to clinical practice.

The Early versus Late Intervention Trial with Estradiol (ELITE) trial and the Kronos Early Oestrogen Prevention Study (KEEPS) set out to test components of the timing hypothesis by measuring the impact of HRT on surrogate cardiovascular disease markers by recruiting postmenopausal women at predefined intervals following menopause. The ELITE trial compared 1 mg/day oral E2, plus progesterone vaginal gel administered sequentially in women who

were < 6 years since menopause and women who were > 10 years since menopause, on the rate of change in carotid-artery intima–media thickness (CIMT) [91]. After 5 years follow-up, HRT was associated with less progression of CIMT thickness compared to placebo in women < 6 years since the menopause, but no difference with placebo was found in women who were > 10 years since menopause [91]. However, the KEEPS study, which randomised recently postmenopausal women (within 3 months to 6 years of natural menopause) to placebo, oral CEE 0.45 mg/day, or transdermal E2 50 μg/day with 200 mg of oral progesterone for 12 days per month, did not find a benefit of oral or transdermal HRT on CIMT progression in their study population after 4 years [92, 93].

Guideline-forming bodies differ in their recommendations on the impact of timing of initiation of HRT on CHD risk. NAMS and the IMS highlight potential benefits of HRT in women with no pre-existing cardiovascular disease younger than 60 years or within 10 years of menopause onset [10, 11]. On the other hand, the US Preventive Services Task Force (USPSTF) [74, 94] and NICE refrain from supporting a timing effect of HRT on risk of CHD, underscoring limitations in existing evidence [9]. The evidence review by NICE highlights that observational studies which support the timing hypothesis may be limited by residual confounding which was not consistently corrected for (e.g., sociodemographic status, BMI, smoking and physical activity), many of which have an impact on cardiovascular disease and are known to differ between HRT users and non-users [9, 95].

3.2 | Oral Versus Transdermal Oestrogen and CHD Risk

There is some evidence that transdermal E2 leads to a lower risk of CHD compared to oral E2 [96, 97, 98]. In the WHI Observational Study, a lower but non-significant rate of major CHD events was observed in people using transdermal E2 compared to those using oral CEE after adjusting for age, sociodemographic factors, lifestyle factors and vascular risk factors (HR 0.63, 95% CI 0.37–1.06), although statistical power for comparison between route of administration of HRT in this study was limited [99]. A systematic review which assessed the risk of vascular events in women who use oral compared to transdermal oestrogen reported no significant difference in the risk of myocardial infarction [100]. However, the 4 studies which assessed the impact of route of administration on CHD in this meta-analysis were observational [101–104]. A recent Swedish study leveraged data in women aged 50–58 years using nationwide health registries and conducted an emulated target trial designed to limit selection bias [105]. The study reported that the use of oral continuous-combined HRT was associated with an adjusted HR for CHD of 1.21 (95% CI 1.00–1.46) whereas transdermal combined and transdermal unopposed oestrogen were associated with adjusted CHD HRs of 0.62 (95% CI 0.41 to 0.96) and 0.98 (95% CI 0.62–1.61) respectively [105]. Oral E2 undergoes first pass metabolism in the liver before entering the circulation, and leads to changes in the profile of coagulation factors and higher levels of C-reactive protein (CRP) compared with the transdermal route [98, 106]. There are shared aetiological factors between arterial and venous thrombosis [107], and it is plausible that some of the processes underlying the increased risk of venous thrombosis with oral E2 could also contribute to a higher risk of CHD.

3.3 | HRT In Women With Pre-Existing Cardiovascular Disease

Secondary prevention studies of HRT in individuals with pre-existing CHD have reported some evidence of harm. Similarly to the CEE + MPA WHI RCT, the Heart and Oestrogen/progestin Replacement Study (HERS), which recruited postmenopausal women with pre-existing CHD (mean age 66.7 years), reported a particularly high risk of CHD in women randomised to CEE + MPA in the first year of treatment [108]. The Women's Angiographic Vitamin and Oestrogen (WAVE) RCT reported that HRT had a potential for harm in women with angiographically confirmed CHD [109]. The British Menopause Society recommends using non-hormonal therapy for first-line management of menopausal symptoms in women with pre-existing cardiovascular disease, and if non-hormonal therapies are ineffective to consider non-oral oestrogen using a shared-decision making approach [110].

The mechanism behind the potential harmful effects of HRT in older women or women with pre-existing CHD might be due to the stimulatory effects of oestrogen on matrix metalloproteinases (MMPs), which may subsequently degrade the outer matrix of the atherosclerotic plaque (believed to be more abundant in older people), increasing plaque instability and risk of rupture [7, 111]. Younger women are likely to have a lower burden of atherosclerotic plaques for MMPs to act upon and are therefore protected from these adverse events, whilst retaining the beneficial effects of oestrogen on endothelial function and lipid profile [112]. Whilst this presumptive mechanism is largely based on findings from preclinical studies, it offers an explanation for the age-dependent effects of HRT put forward by the timing hypothesis.

3.4 | The Impact of Progestogens on Risk of CHD

Historically, MPA is one of the most widely studied progestogens in the context of CHD risk [113]. Early mechanistic studies on primates support an adverse effect of MPA on surrogate markers of cardiovascular function such as coronary artery hyperreactivity [114] and vasospasm [115] compared to progesterone. Major doubt was raised on the safety of MPA after a higher HR for CHD was observed in the CEE-MPA RCT (HR 1.29, 95% CI 1.02–1.63) compared to CEE-only RCT (HR 0.91, 95% CI 0.75–1.12) [5, 6, 116]. However, the Women's Oestrogen–Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), which randomised postmenopausal women to oral E2, oral E2 combined with sequentially administered MPA, or placebo, reported no significant difference in the mean change in % coronary artery stenosis between the three groups after 3.3 years mean follow-up [117]. Similarly, the Oestrogen Replacement and Atherosclerosis (ERA) study reported no significant difference in the minimal coronary artery diameters at follow-up between the CEE-only group (mean 1.87, standard error [SE] 0.02 mm), CEE + MPA group (mean 1.84, SE 0.02 mm) and placebo group (mean 1.87, SE 0.02 mm) after adjustment for baseline measurements [118].

Whilst micronised progesterone is perceived to have a more favourable effect on cardiovascular risk than synthetic

progestogens [17], a crossover study comparing CEE + MPA to CEE combined with micronised progesterone reported similar effects of both treatments on endothelium-dependent vasodilator responsiveness and markers of inflammation and haemostasis [119]. Other studies have highlighted potentially beneficial effects of specific progestogens on surrogate markers of vascular disease. CEE and nomogestrel decreased serum hs-CRP, a marker of inflammation implicated in atherosclerosis, by 25% ($p = 0.01$), whereas CEE-only and CEE + MPA both significantly increased serum hs-CRP levels [120]. Overall, there is a lack of high quality, adequately powered RCTs designed to assess the impact of different progestogens on CHD.

4 | Stroke

Whilst there is a lack of RCTs directly comparing different routes of administration of HRT on stroke risk, observational studies have typically shown that HRT regimes containing oral oestrogen lead to a higher risk of ischaemic stroke than those containing transdermal oestrogen [121, 122]. Indeed, the WHI RCTs reported a stroke HR of 1.37 (95% CI 1.07–1.76, ARI 9 cases per 10 000 py) for oral CEE + MPA and a HR of 1.35 (95% CI 1.07–1.70, ARI 11 cases per 10 000 py) for oral CEE-only in the intervention phase of the study [64]. A Cochrane meta-analysis showed that HRT regimes encompassing oral oestrogen conferred an absolute risk of stroke of 6 per 1000 women (mean length of follow-up 4.21 years). Furthermore, this meta-analysis reported that in those that started HRT < 10 years after menopause where the baseline risk of stroke is low, there was no significant increased risk of stroke [90]. On the other hand, those who started HRT > 10 years after the menopause had an increased risk of stroke (RR 1.21, 95% CI 1.06–1.38) [90]. Notably, the relationship between oestrogen and stroke risk appears to be dose-dependent. A nested case–control study compared the risk of stroke associated with different transdermal doses of oestrogen, and concluded that the risk of stroke was increased with high dose (> 50 μg) but not low dose (< 50 μg) transdermal oestrogen [122].

Evidence of differential impacts across different progestogens on stroke risk appears to be limited. Observational data suggests that adding a progesterone to transdermal oestrogen may not increase stroke risk [122]. A French cohort study assessing the impact of the type of progesterone on stroke risk found that norpregnanes were associated with an increased risk of ischaemic stroke (OR 2.25; 95% CI 1.05–4.81), whilst neither progesterone (OR 0.78; 95% CI 0.49–1.26) norpregnanes (OR 1.00; 95% CI 0.60–1.67) had a significant effect on stroke risk [123]. Current recommendations from NICE and NAMS highlight the greater risk of stroke when starting HRT > 60 years [9, 10]. NICE recommends that oral HRT and regimens containing higher oestrogen doses are associated with higher stroke risk [9].

Importantly, there appear to be ethnic disparities in the risk of stroke and possibly in the impact of HRT on stroke risk. The incident rate of stroke was higher in non-Hispanic African American women (306 per 100 000 py) compared to non-Hispanic white (279 per 100 000 py), and Hispanic white or African American women (147 per 100 000 py) in the WHI Observational Study [124]. Subgroup analysis of stroke by ethnicity in the CEE-only WHI RCT is limited by low event rates in certain groups. Stroke event counts by ethnicity were: white (CEE 106 vs. placebo 70), black (28 vs. 19), Hispanic (6 vs. 3), American Indian (1 vs. 1), Asian/Pacific Islander (0 vs. 2) in the CEE-only and placebo groups, respectively [125]. Although stroke HRs for black and Hispanic people were initially similar to white people, after adjustment for treatment adherence the HRs appeared more distinct (black 3.48, 95% CI 1.12–10.80; Hispanic 4.03, 95% CI 0.45–36.11; white 1.67, 95% CI 1.12–2.50) (126). Whilst this could suggest that the risks of HRT vary in people from different ethnic backgrounds, these data should be interpreted with considerable caution due to substantial uncertainty and sparse data. Although identifying ethnic differences in the benefits and risks of HRT has been established as a research priority [9, 126], existing evidence on the influence of ethnicity on health outcomes is limited and further research is needed.

5 | MASLD

MASLD affects 1-in-4 women worldwide [13, 127], and is the leading indication for liver transplantation in women [128]. MASLD is associated with increased mortality not only from liver-related causes, but also from cardiovascular disease [129], and mortality rates are rising faster in women than in men [130]. The prevalence of MASLD increases after the menopause [2] and a longer period of time since cessation of menstruation increases the risk of MASLD fibrosis [131] which is a reliable predictor of adverse health outcomes [132, 133]. Oestrogen-deficient murine models have recapitulated the multisystem metabolic dysfunction characteristic of MASLD, which oestrogen replacement has alleviated [134–137].

Existing clinical studies on the effect of HRT on MASLD development are scarce with significant methodological limitations and have produced conflicting results. A post hoc analysis of a randomised double-blinded, placebo-controlled study reported that oral 1 mg E2 and 0.5 mg norethisterone acetate led to an improvement in liver enzymes after 6 months (ALT −14 U/L, $p = 0.002$; AST −9.2 U/L, $p < 0.001$; ALP −60.8 U/L, $p < 0.001$; GGT, $p = 0.035$) [138]. A cross-sectional study in the USA which defined MASLD as ≥ 1 elevated liver enzyme level in the absence of any other explanation reported a lower prevalence of MASLD in HRT users (OR, 0.69; 95% CI, 0.48–0.99; $p < 0.05$) [139]. An observational study which defined MASLD by steatosis on ultrasound (in the absence of an alternative explanation) also reported a lower MASLD prevalence in users of HRT (26.4% in HRT users vs. 39.9% in non-users) [140]. Not all studies report a beneficial effect of HRT on MASLD. A retrospective cohort study which defined MASLD by steatosis on ultrasound reported a rise in prevalence of MASLD after 12 months of oral oestrogen replacement (25.3%–29.4%) [141]. However, transdermal oestrogen replacement led to a fall in MASLD prevalence after 12 months (24%–17.3%) [141]. A cross-sectional study which combined liver biopsy data from 3 separate clinical trials reported that HRT was associated with more severe hepatic lobular inflammation in postmenopausal women ($p < 0.05$). Further analysis suggested that progesterone, not oestrogen, was responsible for the increased histological severity of disease [142]. The observational or post hoc

nature of these studies, many of which use unreliable parameters to 'diagnose' or track progression of disease [143, 144], limits the validity of findings, and there is insufficient evidence to provide clinical recommendations on the effect of HRT on MASLD [10].

It is important to highlight that some guidelines cite liver disease as a caution [145] or even a contraindication [10] for systemic HRT. Individuals with cirrhosis are at risk of thrombosis [9, 146] and oestrogen may increase the risk of cholestasis [147], which promotes MASLD development [148]. However, these wide-ranging statements may not be applicable to postmenopausal women with early-stage MASLD, who, as evidenced by real-world data, are widely using HRT [149]. Such recommendations may lead to unnecessary hesitation in prescribing/using HRT for those who take a precautionary approach. Transdermal HRT avoids the supraphysiological hepatic exposure to oestrogen from the oral route, carries a lower risk of cholestasis [150] and venous thromboembolism (VTE) [9], and may be a more suitable agent for MASLD prevention/limitation. This might partially explain why lower prevalences of MASLD were observed in people using transdermal compared to oral HRT in an observational study [141].

Whilst we are far from understanding whether HRT is a potential therapeutic strategy in managing postmenopausal MASLD, understanding this relationship is important to support informed decision-making when considering HRT for menopausal symptoms. Well-designed randomised clinical studies with biopsy outcomes or gold-standard non-invasive techniques are required to elucidate the effect of HRT on MASLD. The cardiometabolic impacts and uncertainties of HRT are summarised in Figure 1.

6 | Key Clinical Points

- The transition to menopause is associated with an increase in central adiposity, atherogenic dyslipidaemia and an increased risk of type 2 diabetes mellitus.
- Whilst HRT is not licensed for primary or secondary prevention of cardiometabolic disease, discussing cardiometabolic effects of treatment when prescribing HRT for control of menopausal symptoms supports informed decision-making.
- A consultation regarding HRT is an opportunity to address cardiovascular risk factors, regardless of whether HRT is initiated or not. Lifestyle modification is the mainstay of maintenance of metabolic health after the menopause.
- The existence of a 'timing effect' of the initiation of HRT on the risk of coronary heart disease is not universally accepted.

7 | Future Research

- Further research on potential factors that affect the risks and benefits of HRT will help stratify and individualise risk, informing shared-decision making. Data from prospective clinical trials and real world data will offer a clearer understanding of these factors.
- Further studies are required to establish the effects of HRT on cardiometabolic outcomes in under-represented groups (e.g., ethnic minorities, trans men and non-binary people registered female at birth)
- Although some evidence suggests some progestogens (e.g., micronised progesterone and dydrogesterone) may have certain more favourable metabolic properties than others, more research is required to establish whether specific progestogens lead to more favourable cardiometabolic outcomes than others
- The impact of HRT on the development and progression of MASLD requires further exploration

8 | Conclusions and Future Directions

Although HRT is not licensed for primary or secondary prevention of cardiometabolic disease, understanding its cardiometabolic effects is crucial to promote informed decision making. Whilst better non-hormonal treatments for menopausal symptoms are on the horizon [151], HRT remains the most effective treatment for menopausal symptoms and it is crucial for prescribers to be aware of the latest guidelines and areas of uncertainty in the evidence base (Figure 1).

Despite significant advancements in past decades, the impact of HRT on cardiometabolic disease remains a topic of debate. Recent erosion of support for the timing hypothesis [9] further exacerbates an already complicated topic for healthcare practitioners and patients. Additionally, the impact of HRT on MASLD is very poorly studied and research associating progesterone with lobular inflammation raises significant safety concerns [142], and clarifying or refuting this risk is imperative.

Historically, the studies of HRT have included a majority of white women from higher socioeconomic classes [35], and the results of these studies are arguably not generalisable to other populations, and significant areas of uncertainty exist around health outcomes in under-represented groups. Resolving uncertainties on the cardiometabolic effects of HRT is critical for supporting the autonomy and health of postmenopausal women.

Author Contributions

J.D., S.H., S.D. and J.W.T. contributed to the conception and planning of the manuscript. J.D., S.D., A.S., S.H., R.V. and J.W.T. contributed to drafting and revisions.

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Conflicts of Interest

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The authors have nothing to report.

References

1. R. E. Nappi, P. Chedraui, I. Lambrinoudaki, and T. Simoncini, "Menopause: A Cardiometabolic Transition," *Lancet Diabetes and Endocrinology* 10, no. 6 (2022): 442–456.

2. S. Ballestri, F. Nascimbeni, E. Baldelli, A. Marrazzo, D. Romagnoli, and A. Lonardo, "NAFLD as a Sexual Dimorphic Disease: Role of Gender and Reproductive Status in the Development and Progression of Nonalcoholic Fatty Liver Disease and Inherent Cardiovascular Risk," *Advances in Therapy* 34, no. 6 (2017): 1291–1326.

3. L. J. Shaw, C. J. Pepine, J. Xie, et al., "Quality and Equitable Health Care Gaps for Women," *Journal of the American College of Cardiology* 70, no. 3 (2017): 373–388.

4. S. Allender, P. Scarborough, M. O'Flaherty, and S. Capewell, "Patterns of Coronary Heart Disease Mortality Over the 20th Century in England and Wales: Possible Plateaus in the Rate of Decline," *BMC Public Health* 8, no. 1 (2008): 148.

5. G. L. Anderson, M. Limacher, A. R. Assaf, et al., "Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy: The Women's Health Initiative Randomized Controlled Trial," *Journal of the American Medical Association* 291, no. 14 (2004): 1701–1712.

6. J. E. Rossouw, G. L. Anderson, R. L. Prentice, et al., "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial," *JAMA* 288, no. 3 (2002): 321–333.

7. R. A. Lobo, "Where Are We 10 Years After the Women's Health Initiative?," *Journal of Clinical Endocrinology and Metabolism* 98, no. 5 (2013): 1771–1780.

8. L. Yang and A. T. Toriola, "Menopausal Hormone Therapy Use Among Postmenopausal Women," *JAMA Health Forum* 5, no. 9 (2024): e243128-e.

9. Menopause: Identification and management 2024, https://www.nice.org.uk/guidance/ng23.

10. The North American Menopause Society, "The 2022 Hormone Therapy Position Statement of the North American Menopause Society," *Menopause* 29, no. 7 (2022): 767–794.

11. R. J. Baber, N. Panay, A. Fenton, and Group IMSW, "2016 IMS Recommendations on Women's Midlife Health and Menopause Hormone Therapy," *Climacteric* 19, no. 2 (2016): 109–150.

12. Force UPST, "Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: US Preventive Services Task Force Recommendation Statement," *JAMA* 328, no. 17 (2022): 1740–1746.

13. P. C. Eng, R. Forlano, T. Tan, P. Manousou, W. S. Dhillo, and C. Izzi-Engbeaya, "Non-Alcoholic Fatty Liver Disease in Women–Current Knowledge and Emerging Concepts," *JHEP Reports* 5, no. 10 (2023): 100835.

14. Authority NBS, "Hormone Replacement Therapy England April 2015 to June 2024," (2024), https://nhsbsa-opendata.s3.eu-west-2.amazonaws.com/hrt/hrt_June_2024_v001.html.

15. D. Alsugeir, L. Wei, M. Adesuyan, S. Cook, N. Panay, and R. Brauer, "Hormone Replacement Therapy Prescribing in Menopausal Women in the UK: A Descriptive Study," *BJGP Open* 6, no. 4 (2022): BJGPO.2022.0126.

16. J. A. Hirst, W. M. Mtika, C. Coupland, S. Dixon, J. Hippisley-Cox, and S. Hillman, "Inequalities in Hormone Replacement Therapy Prescribing in UK Primary Care: Population Based Cohort Study," *BMJ Medicine* 4, no. 1 (2025): e001349.

17. F. Z. Stanczyk, J. P. Hapgood, S. Winer, and D. R. Mishell, Jr., "Progestogens Used in Postmenopausal Hormone Therapy: Differences in Their Pharmacological Properties, Intracellular Actions, and Clinical Effects," *Endocrine Reviews* 34, no. 2 (2013): 171–208.

18. D. Zhao, E. Guallar, P. Ouyang, et al., "Endogenous Sex Hormones and Incident Cardiovascular Disease in Post-Menopausal Women," *Journal of the American College of Cardiology* 71, no. 22 (2018): 2555–2566.

19. A. Dehghan, S. K. Vasan, B. A. Fielding, and F. Karpe, "A Prospective Study of the Relationships Between Change in Body Composition and Cardiovascular Risk Factors Across the Menopause," *Menopause* 28, no. 4 (2021): 400–406.

20. A. P. Frank, R. de Souza Santos, B. F. Palmer, and D. J. Clegg, "Determinants of Body Fat Distribution in Humans May Provide Insight About Obesity-Related Health Risks," *Journal of Lipid Research* 60, no. 10 (2019): 1710–1719.

21. A. K. Ziegler and C. Scheele, "Human Adipose Depots' Diverse Functions and Dysregulations During Cardiometabolic Disease," *NPJ Metabolic Health and Disease* 2, no. 1 (2024): 34.

22. H. E. Lebovitz and M. A. Banerji, "Point: Visceral Adiposity Is Causally Related to Insulin Resistance," *Diabetes Care* 28, no. 9 (2005): 2322–2325.

23. S. Agrawal, M. D. Klarqvist, N. Diamant, et al., "BMI-Adjusted Adipose Tissue Volumes Exhibit Depot-Specific and Divergent Associations With Cardiometabolic Diseases," *Nature Communications* 14, no. 1 (2023): 266.

24. B. E. Reubinoff, J. Wurtman, N. Rojansky, et al., "Effects of Hormone Replacement Therapy on Weight, Body Composition, Fat Distribution, and Food Intake in Early Postmenopausal Women: A Prospective Study," *Fertility and Sterility* 64, no. 5 (1995): 963–968.

25. M. B. Sørensen, A. M. Rosenfalck, L. Højgaard, and B. Ottesen, "Obesity and Sarcopenia After Menopause Are Reversed by Sex Hormone Replacement Therapy," *Obesity Research* 9, no. 10 (2001): 622–626.

26. H. Y¨ ksel, A. R. Odabaşi, S. Demircan, et al., "Effects of Oral Continuous 17β-Estradiol Plus Norethisterone Acetate Replacement Therapy on Abdominal Subcutaneous Fat, Serum Leptin Levels and Body Composition," *Gynecological Endocrinology* 22, no. 7 (2006): 381–387.

27. G. E. Papadakis, D. Hans, E. Gonzalez Rodriguez, et al., "Menopausal Hormone Therapy Is Associated With Reduced Total and Visceral Adiposity: The OsteoLaus Cohort," *Journal of Clinical Endocrinology and Metabolism* 103, no. 5 (2018): 1948–1957.

28. C. K. Sites, G. D. L'Hommedieu, M. J. Toth, M. Brochu, B. C. Cooper, and P. A. Fairhurst, "The Effect of Hormone Replacement Therapy on Body Composition, Body Fat Distribution, and Insulin Sensitivity in Menopausal Women: A Randomized, Double-Blind, Placebo-Controlled Trial," *Journal of Clinical Endocrinology and Metabolism* 90, no. 5 (2005): 2701–2707.

29. A. S. Ryan, B. J. Nicklas, and D. M. Berman, "Hormone Replacement Therapy, Insulin Sensitivity, and Abdominal Obesity in Postmenopausal Women," *Diabetes Care* 25, no. 1 (2002): 127–133.

30. J. R. Guthrie, L. Dennerstein, and E. C. Dudley, "Weight Gain and the Menopause: A 5-Year Prospective Study," *Climacteric* 2, no. 3 (1999): 205–211.

31. S. R. Davis, C. Castelo-Branco, P. Chedraui, et al., "Understanding Weight Gain at Menopause," *Climacteric* 15, no. 5 (2012): 419–429.

32. I. van Seumeren, "Weight Gain and Hormone Replacement Therapy: Are Women's Fears Justified?," *Maturitas* 34 (2000): S3–S8.

33. E. J. Kongnyuy, R. J. Norman, I. H. Flight, M. C. Rees, and Cochrane Gynaecology and Fertility Group, "Oestrogen and Progestogen Hormone Replacement Therapy for Peri-Menopausal and Post-Menopausal Women: Weight and Body Fat Distribution," *Cochrane Database of Systematic Reviews* 2011, no. 4 (1996): CD001018.

34. N. S. Stachenfeld, "Hormonal Changes During Menopause and the Impact on Fluid Regulation," *Reproductive Sciences* 21, no. 5 (2014): 555–561.

35. A. Mukherjee and S. R. Davis, "Update on Menopause Hormone Therapy; Current Indications and Unanswered Questions," *Clinical Endocrinology* (2025).

36. I. Gregersen, E. Høibraaten, K. B. Holven, et al., "Effect of Hormone Replacement Therapy on Atherogenic Lipid Profile in Postmenopausal Women," *Thrombosis Research* 184 (2019): 1–7.

37. C. A. Derby, S. L. Crawford, R. C. Pasternak, M. Sowers, B. Sternfeld, and K. A. Matthews, "Lipid Changes During the Menopause Transition in Relation to Age and Weight: The Study of Women's Health Across the Nation," *American Journal of Epidemiology* 169, no. 11 (2009): 1352–1361.

38. G. Nie, X. Yang, Y. Wang, et al., "The Effects of Menopause Hormone Therapy on Lipid Profile in Postmenopausal Women: A Systematic Review and Meta-Analysis," *Frontiers in Pharmacology* 13 (2022): 850815.

39. A. Wakatsuki, Y. Okatani, N. Ikenoue, and T. Fukaya, "Different Effects of Oral Conjugated Equine Estrogen and Transdermal Estrogen Replacement Therapy on Size and Oxidative Susceptibility of Low-Density Lipoprotein Particles in Postmenopausal Women," *Circulation* 106, no. 14 (2002): 1771–1776.

40. S. Adami, M. Rossini, N. Zamberlan, F. Bertoldo, R. Dorizzi, and V. Lo Cascio, "Long-Term Effects of Transdermal and Oral Estrogens on Serum Lipids and Lipoproteins in Postmenopausal Women," *Maturitas* 17, no. 3 (1993): 191–196.

41. G. Casanova, A. M. dos Reis, and P. M. Spritzer, "Low-Dose Oral or Non-Oral Hormone Therapy: Effects on C-Reactive Protein and Atrial Natriuretic Peptide in Menopause," *Climacteric* 18, no. 1 (2015): 86–93.

42. Y. Jiang and W. Tian, "The Effects of Progesterones on Blood Lipids in Hormone Replacement Therapy," *Lipids in Health and Disease* 16, no. 1 (2017): 219.

43. C. J. Kim, Y. K. Min, W. S. Ryu, J. W. Kwak, and U. H. Ryoo, "Effect of Hormone Replacement Therapy on Lipoprotein(a) and Lipid Levels in Postmenopausal Women: Influence of Various Progestogens and Duration of Therapy," *Archives of Internal Medicine* 156, no. 15 (1996): 1693–1700.

44. A. J. Sai, J. C. Gallagher, and X. Fang, "Effect of Hormone Therapy and Calcitriol on Serum Lipid Profile in Postmenopausal Older Women: Association With Estrogen Receptor-Alpha Genotypes," *Menopause* 18, no. 10 (2011): 1101–1112.

45. J. J. Nieto, D. Cogswell, D. Jesinger, and P. Hardiman, "Lipid Effects of Hormone Replacement Therapy With Sequential Transdermal 17-Beta-Estradiol and Oral Dydrogesterone," *Obstetrics and Gynecology* 95, no. 1 (2000): 111–114.

46. V. T. Miller, J. LaRosa, V. Barnabei, et al., "Effects of Estrogen or Estrogen/ Progestin Regimens on Heart Disease Risk Factors in Postmenopausal Women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial," *Journal of the American Medical Association* 273, no. 3 (1995): 199–208.

47. D. F. Archer, I. H. Thorneycroft, M. Foegh, et al., "Long-Term Safety of Drospirenone-Estradiol for Hormone Therapy: A Randomized, Double-Blind, Multicenter Trial," *Menopause* 12, no. 6 (2005): 716–727.

48. G. SenthilKumar, B. Katunaric, H. Bordas-Murphy, J. Sarvaideo, and J. K. Freed, "Estrogen and the Vascular Endothelium: The Unanswered Questions," *Endocrinology* 164, no. 6 (2023): bqad079.

49. Y. Swica, M. P. Warren, J. E. Manson, et al., "Effects of Oral Conjugated Equine Estrogens With or Without Medroxyprogesterone Acetate on Incident Hypertension in the Women's Health Initiative Hormone Therapy Trials," *Menopause* 25, no. 7 (2018): 753–761.

50. L. F. Campos, G. de Andra Costa, M. D. Feitosa, et al., "Effect of Hormone Therapy on Blood Pressure and Hypertension in Postmenopausal Women: A Systematic Review and Meta-Analysis," *Menopause* 31, no. 6 (2023): 556–562.

51. C. Z. Kalenga, A. Metcalfe, M. Robert, K. A. Nerenberg, J. M. MacRae, and S. B. Ahmed, "Association Between the Route of Administration and Formulation of Estrogen Therapy and Hypertension Risk in Postmenopausal Women: A Prospective Population-Based Study," *Hypertension* 80, no. 7 (2023): 1463–1473.

52. A. Z. Steiner, H. N. Hodis, R. A. Lobo, D. Shoupe, M. Xiang, and W. J. Mack, "Postmenopausal Oral Estrogen Therapy and Blood Pressure in Normotensive and Hypertensive Subjects: The Estrogen in the Prevention of Atherosclerosis Trial," *Menopause* 12, no. 6 (2005): 728–733.

53. G. Mercuro, S. Zoncu, I. Pilia, A. Lao, G. B. Melis, and A. Cherchi, "Effects of Acute Administration of Transdermal Estrogen on Postmenopausal Women With Systemic Hypertension," *American Journal of Cardiology* 80, no. 5 (1997): 652–655.

54. B. K. Yoon, J. Sung, Y. M. Song, et al., "Effects of Menopausal Hormone Therapy on Ambulatory Blood Pressure and Arterial Stiffness in Postmenopausal Korean Women With Grade 1 Hypertension: A Randomized, Placebo-Controlled Trial," *Clinical Hypertension* 27, no. 1 (2021): 18.

55. C. Z. Kalenga, J. L. Hay, K. F. Boreskie, et al., "The Association Between Route of Post-Menopausal Estrogen Administration and Blood Pressure and Arterial Stiffness in Community-Dwelling Women," *Frontiers in Cardiovascular Medicine* 9 (2022): 913609.

56. J. Ichikawa, H. Sumino, S. Ichikawa, and M. Ozaki, "Different Effects of Transdermal and Oral Hormone Replacement Therapy on the Renin-Angiotensin System, Plasma Bradykinin Level, and Blood Pressure of Normotensive Postmenopausal Women," *American Journal of Hypertension* 19, no. 7 (2006): 744–749.

57. M. P. Warren, O. Richardson, S. Chaudhry, et al., "Quality of Life and Hypertension After Hormone Therapy Withdrawal in New York City," *Menopause* 20, no. 12 (2013): 1255–1263.

58. S. Y. Honisett, B. Pang, L. Stojanovska, K. Sudhir, and P. A. Komesaroff, "Progesterone Does Not Influence Vascular Function in Postmenopausal Women," *Journal of Hypertension* 21, no. 6 (2003): 1145–1149.

59. C. Kaya, S. Dinçer Cengiz, B. Cengiz, and G. Akgün, "The Long-Term Effects of Low-Dose 17beta-Estradiol and Dydrogesterone Hormone Replacement Therapy on 24-h Ambulatory Blood Pressure in Hypertensive Postmenopausal Women: A 1-Year Randomized, Prospective Study," *Climacteric* 9, no. 6 (2006): 437–445.

60. W. B. White, V. Hanes, V. Chauhan, and B. Pitt, "Effects of a New Hormone Therapy, Drospirenone and 17-β-Estradiol, in Postmenopausal Women With Hypertension," *Hypertension* 48, no. 2 (2006): 246–253.

61. J. P. Tiano and F. Mauvais-Jarvis, "Importance of Oestrogen Receptors to Preserve Functional β-Cell Mass in Diabetes," *Nature Reviews. Endocrinology* 8, no. 6 (2012): 342–351.

62. J. C. Lovejoy, C. M. Champagne, L. de Jonge, H. Xie, and S. R. Smith, "Increased Visceral Fat and Decreased Energy Expenditure During the Menopausal Transition," *International Journal of Obesity* 32, no. 6 (2008): 949–958.

63. J. S. Brand, Y. T. van der Schouw, N. C. Onland-Moret, et al., "Age at Menopause, Reproductive Life Span, and Type 2 Diabetes Risk: Results From the EPIC-InterAct Study," *Diabetes Care* 36, no. 4 (2013): 1012–1019.

64. J. E. Manson, R. T. Chlebowski, M. L. Stefanick, et al., "Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials," *JAMA* 310, no. 13 (2013): 1353–1368.

65. S. R. Salpeter, J. M. Walsh, T. M. Ormiston, E. Greyber, N. S. Buckley, and E. E. Salpeter, "Meta-Analysis: Effect of Hormone-Replacement Therapy on Components of the Metabolic Syndrome in Postmenopausal Women," *Diabetes, Obesity and Metabolism* 8, no. 5 (2006): 538–554.

66. E. M. Speksnijder, G. V. de ten Noever Brauw, A. Malekzadeh, P. H. Bisschop, D. J. Stenvers, and S. E. Siegelaar, "Effect of Postmenopausal Hormone Therapy on Glucose Regulation in Women With Type 1 or Type 2 Diabetes: A Systematic Review and Meta-Analysis," *Diabetes Care* 46, no. 10 (2023): 1866–1875.

67. F. Mauvais-Jarvis, J. E. Manson, J. C. Stevenson, and V. A. Fonseca, "Menopausal Hormone Therapy and Type 2 Diabetes Prevention: Evidence, Mechanisms, and Clinical Implications," *Endocrine Reviews* 38, no. 3 (2017): 173–188.

68. S. R. Lindheim, D. M. Duffy, T. Kojima, M. A. Vijod, F. Z. Stanczyk, and R. A. Lobo, "The Route of Administration Influences the Effect of Estrogen on Insulin Sensitivity in Postmenopausal Women," *Fertility and Sterility* 62, no. 6 (1994): 1176–1180.

69. V. Wynn and I. Godsland, "Effects of Oral Contraceptives on Carbohydrate Metabolism," *Journal of Reproductive Medicine* 31, no. 9 Suppl (1986): 892–897.

70. A. Coquoz, C. Gruetter, and P. Stute, "Impact of Micronized Progesterone on Body Weight, Body Mass Index, and Glucose Metabolism: A Systematic Review," *Climacteric* 22, no. 2 (2019): 148–161.

71. R. Kimmerle, L. Heinemann, T. Heise, et al., "Influence of Continuous Combined Estradiol-Norethisterone Acetate Preparations on Insulin Sensitivity in Postmenopausal Nondiabetic Women," *Menopause* 6, no. 1 (1999): 36–42.

72. D. Crook, I. F. Godsland, J. Hull, and J. C. Stevenson, "Hormone Replacement Therapy With Dydrogesterone and 17β-Oestradiol: Effects on Serum Lipoproteins and Glucose Tolerance During 24 Month Follow Up," *BJOG: An International Journal of Obstetrics and Gynaecology* 104, no. 3 (1997): 298–304.

73. L. Mackay, L. Kilbride, K. A. Adamson, and J. Chisholm, "Hormone Replacement Therapy for Women With Type 1 Diabetes Mellitus," *Cochrane Database of Systematic Reviews* 2013, no. 6 (2013): CD008613.

74. G. Gartlehner, S. V. Patel, S. Reddy, C. Rains, M. Schwimmer, and L. Kahwati, "Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force," *Journal of the American Medical Association* 328, no. 17 (2022): 1747–1765.

75. S. D. Choi, E. M. Steinberg, H. H. Lee, and F. Naftolin, "The Timing Hypothesis Remains a Valid Explanation of Differential Cardioprotective Effects of Menopausal Hormone Treatment," *Menopause* 18, no. 2 (2011): 230–236.

76. S. R. El Khoudary, B. Aggarwal, T. M. Beckie, et al., "Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association," *Circulation* 142, no. 25 (2020): e506–e532.

77. R. D. Langer, J. A. Simon, A. Pines, et al., "Menopausal Hormone Therapy for Primary Prevention: Why the USPSTF Is Wrong," *Climacteric* 20, no. 5 (2017): 402–413.

78. M. J. Stampfer and G. A. Colditz, "Estrogen Replacement Therapy and Coronary Heart Disease: A Quantitative Assessment of the Epidemiologic Evidence," *Preventive Medicine* 20, no. 1 (1991): 47–63.

79. E. Barrett-Connor and D. Grady, "Hormone Replacement Therapy, Heart Disease, and Other Considerations," *Annual Review of Public Health* 19 (1998): 55–72.

80. D. Grady, S. M. Rubin, D. B. Petitti, et al., "Hormone Therapy to Prevent Disease and Prolong Life in Postmenopausal Women," *Annals of Internal Medicine* 117, no. 12 (1992): 1016–1037.

81. F. Grodstein, J. E. Manson, G. A. Colditz, W. C. Willett, F. E. Speizer, and M. J. Stampfer, "A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease," *Annals of Internal Medicine* 133, no. 12 (2000): 933–941.

82. J. E. Manson, J. Hsia, K. C. Johnson, et al., "Estrogen Plus Progestin and the Risk of Coronary Heart Disease," *New England Journal of Medicine* 349, no. 6 (2003): 523–534.

83. J. E. Kim, J. H. Chang, M. J. Jeong, et al., "A Systematic Review and Meta-Analysis of Effects of Menopausal Hormone Therapy on Cardiovascular Diseases," *Scientific Reports* 10, no. 1 (2020): 20631.

84. A. H. Maas, Y. T. van der Schouw, D. E. Grobbee, and Y. van der Graaf, "Hormone Replacement Therapy and Heart Disease: The Remains of the Oestrogen Hypothesis," *Netherlands Heart Journal* 11, no. 11 (2003): 459–464.

85. A. H. Maas, Y. T. van der Schouw, D. E. Grobbee, and Y. van der Graaf, "Rise and Fall of Hormone Therapy in Postmenopausal Women With Cardiovascular Disease," *Menopause* 11, no. 2 (2004): 228–235.

86. S. S. Bassuk and J. E. Manson, "The Timing Hypothesis: Do Coronary Risks of Menopausal Hormone Therapy Vary by Age or Time Since Menopause Onset?," *Metabolism* 65, no. 5 (2016): 794–803.

87. J. E. Rossouw, R. L. Prentice, J. E. Manson, et al., "Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause," *JAMA* 297, no. 13 (2007): 1465–1477.

88. R. L. Prentice, J. E. Manson, R. D. Langer, et al., "Benefits and Risks of Postmenopausal Hormone Therapy When It Is Initiated Soon After Menopause," *American Journal of Epidemiology* 170, no. 1 (2009): 12–23.

89. L. L. Schierbeck, L. Rejnmark, C. L. Tofteng, et al., "Effect of Hormone Replacement Therapy on Cardiovascular Events in Recently Postmenopausal Women: Randomised Trial," *BMJ* 345 (2012): e6409.

90. H. M. Boardman, L. Hartley, A. Eisinga, et al., "Hormone Therapy for Preventing Cardiovascular Disease in Post-Menopausal Women," *Cochrane Database of Systematic Reviews* 2015, no. 3 (2015): CD002229.

91. H. N. Hodis, W. J. Mack, V. W. Henderson, et al., "Vascular Effects of Early Versus Late Postmenopausal Treatment With Estradiol," *New England Journal of Medicine* 374, no. 13 (2016): 1221–1231.

92. V. M. Miller, F. Naftolin, S. Asthana, et al., "The Kronos Early Estrogen Prevention Study (KEEPS): What Have We Learned?," *Menopause* 26, no. 9 (2019): 1071–1084.

93. S. M. Harman, D. M. Black, F. Naftolin, et al., "Arterial Imaging Outcomes and Cardiovascular Risk Factors in Recently Menopausal Women: A Randomized Trial," *Annals of Internal Medicine* 161, no. 4 (2014): 249–260.

94. C. M. Mangione, M. J. Barry, W. K. Nicholson, et al., "Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: US Preventive Services Task Force

Recommendation Statement," *Journal of the American Medical Association* 328, no. 17 (2022): 1740–1746.

95. L. L. Humphrey, B. K. Chan, and H. C. Sox, "Postmenopausal Hormone Replacement Therapy and the Primary Prevention of Cardiovascular Disease," *Annals of Internal Medicine* 137, no. 4 (2002): 273–284.

96. M. S. Goldstajn, M. Mikus, F. A. Ferrari, et al., "Effects of Transdermal Versus Oral Hormone Replacement Therapy in Postmenopause: A Systematic Review," *Archives of Gynecology and Obstetrics* 307, no. 6 (2023): 1727–1745.

97. A. Silvestri, O. Gebara, C. Vitale, et al., "Increased Levels of C-Reactive Protein After Oral Hormone Replacement Therapy May Not Be Related to an Increased Inflammatory Response," *Circulation* 107, no. 25 (2003): 3165–3169.

98. W. Vongpatanasin, M. Tuncel, Z. Wang, D. Arbique, B. Mehrad, and I. Jialal, "Differential Effects of Oral Versus Transdermal Estrogen Replacement Therapy on C-Reactive Protein in Postmenopausal Women," *Journal of the American College of Cardiology* 41, no. 8 (2003): 1358–1363.

99. C. L. Shufelt, C. N. Merz, R. L. Prentice, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," *Menopause* 21, no. 3 (2014): 260–266.

100. K. Mohammed, A. M. Abu Dabrh, K. Benkhadra, et al., "Oral vs Transdermal Estrogen Therapy and Vascular Events: A Systematic Review and Meta-Analysis," *Journal of Clinical Endocrinology and Metabolism* 100, no. 11 (2015): 4012–4020.

101. J. Hippisley-Cox, M. Pringle, N. Crown, and C. Coupland, "A Case-Control Study on the Effect of Hormone Replacement Therapy on Ischaemic Heart Disease," *British Journal of General Practice* 53, no. 488 (2003): 191–196.

102. C. E. Chilvers, R. C. Knibb, S. J. Armstrong, K. L. Woods, and R. F. Logan, "Post Menopausal Hormone Replacement Therapy and Risk of Acute Myocardial Infarction–A Case Control Study of Women in the East Midlands, UK," *European Heart Journal* 24, no. 24 (2003): 2197–2205.

103. E. Lokkegaard, A. H. Andreasen, R. K. Jacobsen, L. H. Nielsen, C. Agger, and O. Lidegaard, "Hormone Therapy and Risk of Myocardial Infarction: A National Register Study," *European Heart Journal* 29, no. 21 (2008): 2660–2668.

104. C. S. de Vries, S. E. Bromley, and R. D. Farmer, "Myocardial Infarction Risk and Hormone Replacement: Differences Between Products," *Maturitas* 53, no. 3 (2006): 343–350.

105. T. Johansson, T. Karlsson, D. Bliuc, et al., "Contemporary Menopausal Hormone Therapy and Risk of Cardiovascular Disease: Swedish Nationwide Register Based Emulated Target Trial," *BMJ* 387 (2024): e078784.

106. F. Z. Stanczyk, I. Sriprasert, S. Chulapongwanich, J. L. Yang, and F. Fruzzetti, "Chapter 3. Impact of Estrogens on Hemostasis," *Frontiers in Endocrinology* 16 (2025): 1617731.

107. A. Delluc, K. Lacut, and M. A. Rodger, "Arterial and Venous Thrombosis: What's the Link? A Narrative Review," *Thrombosis Research* 191 (2020): 97–102.

108. S. Hulley, D. Grady, T. Bush, et al., "Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group," *Journal of the American Medical Association* 280, no. 7 (1998): 605–613.

109. D. D. Waters, E. L. Alderman, J. Hsia, et al., "Effects of Hormone Replacement Therapy and Antioxidant Vitamin Supplements on Coronary Atherosclerosis in Postmenopausal Women: A Randomized Controlled Trial," *Journal of the American Medical Association* 288, no. 19 (2002): 2432–2440.

110. Management of Menopause for Women With Cardiovascular Disease, "British Menopause Society Tool for Clinicians," (2024).

111. P. Hu, G. A. Greendale, S. L. Palla, et al., "The Effects of Hormone Therapy on the Markers of Inflammation and Endothelial Function and Plasma Matrix Metalloproteinase-9 Level in Postmenopausal Women: The Postmenopausal Estrogen Progestin Intervention (PEPI) Trial," *Atherosclerosis* 185, no. 2 (2006): 347–352.

112. G. M. Rubanyi, A. Johns, and K. Kauser, "Effect of Estrogen on Endothelial Function and Angiogenesis," *Vascular Pharmacology* 38, no. 2 (2002): 89–98.

113. C. Campagnoli, F. Clavel-Chapelon, R. Kaaks, C. Peris, and F. Berrino, "Progestins and Progesterone in Hormone Replacement Therapy and the Risk of Breast Cancer," *Journal of Steroid Biochemistry and Molecular Biology* 96, no. 2 (2005): 95–108.

114. R. G. Mishra, R. K. Hermsmeyer, K. Miyagawa, et al., "Medroxyprogesterone Acetate and Dihydrotestosterone Induce Coronary Hyperreactivity in Intact Male Rhesus Monkeys," *Journal of Clinical Endocrinology and Metabolism* 90, no. 6 (2005): 3706–3714.

115. R. D. Minshall, F. Z. Stanczyk, K. Miyagawa, et al., "Ovarian Steroid Protection Against Coronary Artery Hyperreactivity in Rhesus Monkeys1," *Journal of Clinical Endocrinology & Metabolism* 83, no. 2 (1998): 649–659.

116. C. L. Shufelt and J. E. Manson, "Menopausal Hormone Therapy and Cardiovascular Disease: The Role of Formulation, Dose, and Route of Delivery," *Journal of Clinical Endocrinology and Metabolism* 106, no. 5 (2021): 1245–1254.

117. H. N. Hodis, W. J. Mack, S. P. Azen, et al., "Hormone Therapy and the Progression of Coronary-Artery Atherosclerosis in Postmenopausal Women," *New England Journal of Medicine* 349, no. 6 (2003): 535–545.

118. D. M. Herrington, D. M. Reboussin, K. B. Brosnihan, et al., "Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis," *New England Journal of Medicine* 343, no. 8 (2000): 522–529.

119. K. K. Koh, D. K. Jin, S. H. Yang, et al., "Vascular Effects of Synthetic or Natural Progestagen Combined With Conjugated Equine Estrogen in Healthy Postmenopausal Women," *Circulation* 103, no. 15 (2001): 1961–1966.

120. M. Gol, P. Akan, E. Dogan, C. Karas, U. Saygili, and C. Posaci, "Effects of Estrogen, Raloxifene, and Hormone Replacement Therapy on Serum C-Reactive Protein and Homocysteine Levels," *Maturitas* 53, no. 3 (2006): 252–259.

121. E. Løkkegaard, L. H. Nielsen, and N. Keiding, "Risk of Stroke With Various Types of Menopausal Hormone Therapies," *Stroke* 48, no. 8 (2017): 2266–2269.

122. C. Renoux, S. Dell'aniello, E. Garbe, and S. Suissa, "Transdermal and Oral Hormone Replacement Therapy and the Risk of Stroke: A Nested Case-Control Study," *BMJ* 340 (2010): c2519.

123. M. Canonico, L. Carcaillon, G. Plu-Bureau, et al., "Postmenopausal Hormone Therapy and Risk of Stroke: Impact of the Route of Estrogen Administration and Type of Progestogen," *Stroke* 47, no. 7 (2016): 1734–1741.

124. L. Calancie, X. I. Leng, E. A. Whitsel, et al., "Racial Disparities in Stroke Incidence in the Women's Health Initiative: Exploring Biological, Behavioral, Psychosocial, and Social Risk Factors," *SSM - Population Health* 25 (2024): 101570.

125. S. L. Hendrix, S. Wassertheil-Smoller, K. C. Johnson, et al., "Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative," *Circulation* 113, no. 20 (2006): 2425–2434.

126. James Lind Alliance Priority Setting Partnerships (Menopause), https://www.jla.nihr.ac.uk/priority-setting-partnerships/menopause#tab-67281.

127. K. Riazi, H. Azhari, J. H. Charette, et al., "The Prevalence and Incidence of NAFLD Worldwide: A Systematic Review and Meta-Analysis," *Lancet Gastroenterology & Hepatology* 7, no. 9 (2022): 851–861.

128. M. Noureddin, A. Vipani, C. Bresee, et al., "NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications for Liver Transplant and Ethnic and Gender Variances," *American Journal of Gastroenterology* 113, no. 11 (2018): 1649–1659.

129. A. Mantovani, E. Scorletti, A. Mosca, A. Alisi, C. D. Byrne, and G. Targher, "Complications, Morbidity and Mortality of Nonalcoholic Fatty Liver Disease," *Metabolism* 111 (2020): 154170.

130. J. M. Paik, L. Henry, L. De Avila, E. Younossi, A. Racila, and Z. M. Younossi, "Mortality Related to Nonalcoholic Fatty Liver Disease Is Increasing in the United States," *Hepatology Communications* 3, no. 11 (2019): 1459–1471.

131. J. S. Klair, J. D. Yang, M. F. Abdelmalek, et al., "A Longer Duration of Estrogen Deficiency Increases Fibrosis Risk Among Postmenopausal Women With Nonalcoholic Fatty Liver Disease," *Hepatology* 64, no. 1 (2016): 85–91.

132. A. Unalp-Arida and C. E. Ruhl, "Liver Fibrosis Scores Predict Liver Disease Mortality in the United States Population," *Hepatology* 66, no. 1 (2017): 84–95.

133. J. B. Henson, T. G. Simon, A. Kaplan, S. Osganian, R. Masia, and K. E. Corey, "Advanced Fibrosis Is Associated With Incident Cardiovascular Disease in Patients With Non-Alcoholic Fatty Liver Disease," *Alimentary Pharmacology & Therapeutics* 51, no. 7 (2020): 728–736.

134. Z. Y. Chen, M. J. Panga, X. Zhang, et al., "Estrogen Alleviates Liver Fibrosis and Restores Metabolic Homeostasis in Ovariectomy-Induced Liver Injury and Carbon Tetrachloride (CCl4) Exposure," *European Journal of Pharmacology* 978 (2024): 176774.

135. L. Li, Y. Yao, Y. Wang, et al., "G Protein-Coupled Estrogen Receptor 1 Ameliorates Nonalcoholic Steatohepatitis Through Targeting AMPK-Dependent Signaling," *Journal of Biological Chemistry* 300, no. 3 (2024): 105661.

136. L. Zhu, W. C. Brown, Q. Cai, et al., "Estrogen Treatment After Ovariectomy Protects Against Fatty Liver and May Improve Pathway-Selective Insulin Resistance," *Diabetes* 62, no. 2 (2013): 424–434.

137. J. Dong, K. Dennis, R. Venkatakrishnan, L. Hodson, and J. W. Tomlinson, "The Impact of Estrogen Deficiency on Liver Metabolism: Implications for Hormone Replacement Therapy," *Endocrine Reviews* 46, no. 6 (2025): 790–809.

138. J. McKenzie, B. M. Fisher, A. J. Jaap, A. Stanley, K. Paterson, and N. Sattar, "Effects of HRT on Liver Enzyme Levels in Women With Type 2 Diabetes: A Randomized Placebo-Controlled Trial," *Clinical Endocrinology* 65, no. 1 (2006): 40–44.

139. J. M. Clark, F. L. Brancati, and A. M. Diehl, "Nonalcoholic Fatty Liver Disease," *Gastroenterology* 122, no. 6 (2002): 1649–1657.

140. G. S. A. Florentino, H. P. Cotrim, C. P. Vilar, A. V. A. Florentino, G. M. A. Guimarães, and V. S. T. Barreto, "Nonalcoholic Fatty Liver Disease in Menopausal Women," *Arquivos de Gastroenterologia* 50, no. 3 (2013): 180–185.

141. S. E. Kim, J. S. Min, S. Lee, D. Y. Lee, and D. Choi, "Different Effects of Menopausal Hormone Therapy on Non-Alcoholic Fatty Liver Disease Based on the Route of Estrogen Administration," *Scientific Reports* 13, no. 1 (2023): 15461.

142. J. D. Yang, M. F. Abdelmalek, C. D. Guy, et al., "Patient Sex, Reproductive Status, and Synthetic Hormone Use Associate With Histologic Severity of Nonalcoholic Steatohepatitis," *Clinical Gastroenterology and Hepatology* 15, no. 1 (2017): 127–131.e2.

143. C. X. Huang, X. D. Zhou, C. Q. Pan, and M. H. Zheng, "Screening for Metabolic Dysfunction-Associated Fatty Liver Disease: Time to Discard the Emperor's Clothes of Normal Liver Enzymes?," *World Journal of Gastroenterology* 30, no. 22 (2024): 2839–2842.

144. J.-F. Chen, Z.-Q. Wu, H.-S. Liu, et al., "Cumulative Effects of Excess High-Normal Alanine Aminotransferase Levels in Relation to New-Onset Metabolic Dysfunction-Associated Fatty Liver Disease in China," *World Journal of Gastroenterology* 30, no. 10 (2024): 1346–1357.

145. C. A. Stuenkel, S. R. Davis, A. Gompel, et al., "Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline," *Journal of Clinical Endocrinology & Metabolism* 100, no. 11 (2015): 3975–4011.

146. P. Jepsen, E. B. Tapper, T. Deleuran, et al., "Risk and Outcome of Venous and Arterial Thrombosis in Patients With Cirrhosis: A Danish Nation-wide Cohort Study," *Hepatology* 74, no. 5 (2021): 2725–2734.

147. D. J. Cirillo, R. B. Wallace, R. J. Rodabough, et al., "Effect of Estrogen Therapy on Gallbladder Disease," *Journal of the American Medical Association* 293, no. 3 (2005): 330–339.

148. J. P. Arab, S. J. Karpen, P. A. Dawson, M. Arrese, and M. Trauner, "Bile Acids and Nonalcoholic Fatty Liver Disease: Molecular Insights and Therapeutic Perspectives," *Hepatology* 65, no. 1 (2017): 350–362.

149. A. A. Florio, B. I. Graubard, B. Yang, et al., "Oophorectomy and Risk of Non-Alcoholic Fatty Liver Disease and Primary Liver Cancer in the Clinical Practice Research Datalink," *European Journal of Epidemiology* 34, no. 9 (2019): 871–878.

150. B. Liu, V. Beral, A. Balkwill, et al., "Gallbladder Disease and Use of Transdermal Versus Oral Hormone Replacement Therapy in Postmenopausal Women: Prospective Cohort Study," *BMJ* 337 (2008): a386.

151. A. Lee, "Fezolinetant: First Approval," *Drugs* 83, no. 12 (2023): 1137–1141.