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Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women

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Aim: To quantify the effects of hormone-replacement therapy (HRT) on components of the metabolic syndrome in postmenopausal women.

Methods: Comprehensive searches of electronic databases were performed from April 1966 to October 2004. We included randomized controlled trials that were of at least 8 weeks duration and evaluated the effect of HRT on metabolic, inflammatory or thrombotic components. Insulin resistance was calculated by homeostasis model assessment (HOMA-IR). Subgroup analysis evaluated the effects for transdermal and oral treatment and for diabetic and non-diabetic women.

Results: Pooled results of 107 trials showed that HRT reduced abdominal fat [−6.8% (CI, −11.8 to −1.9%)], HOMA-IR [−12.9% (CI, −17.1 to −8.6%)] and new-onset diabetes [relative risk 0.7 (CI, 0.6–0.9)] in women without diabetes. In women with diabetes, HRT reduced fasting glucose [−11.5% (CI, −18.0 to −5.1%)] and HOMA-IR [−35.8% (CI, −51.7 to −19.8%)]. HRT also reduced low-density lipoprotein/high-density lipoprotein cholesterol ratio [−15.7% (CI, −18.0 to −13.5%)], lipoprotein(a) [Lp(a)] [−25.0% [CI, −32.9 to −17.1%)], mean blood pressure [−1.7% (CI, −2.9 to −0.5%)], E-selectin [−17.3% (CI, −22.4 to −12.1%)], fibrinogen [−5.5% (CI, −7.8 to −3.2%)] and plasminogen activator inhibitor-1 [−25.1% (CI, −33.6 to −15.5%)]. Oral agents produced larger beneficial effects than transdermal agents, but increased C-reactive protein (CRP) [37.6% (CI, 17.4–61.3%)] and decreased protein S [−8.6% CI, −13.1 to −4.1%)], while transdermal agents had no effect.

Conclusions: HRT reduces abdominal obesity, insulin resistance, new-onset diabetes, lipids, blood pressure, adhesion molecules and procoagulant factors in women without diabetes and reduced insulin resistance and fasting glucose in women with diabetes. Oral agents adversely affected CRP and protein S, while transdermal agents had no effects.

Keywords: hormone-replacement therapy, meta-analysis, metabolic syndrome, women
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Introduction

Menopause is associated with increased cardiovascular risk, thought to be due to atherogenic risk factors [1]. The metabolic syndrome increases in prevalence after menopause and consists of insulin resistance, abdominal obesity, dyslipidaemia, elevated blood pressure and proinflammatory and prothrombotic states [2]. This syndrome, also known as insulin resistance syndrome, usually precedes the development of diabetes mellitus and carries a twofold increased risk for cardiovascular events [3]. For those women who develop diabetes, the risk for cardiovascular morbidity and mortality is increased by two- to sixfold after adjusting for associated risk factors [4]. Abdominal obesity appears to be a significant cardiac risk factor, independent of weight [3,5].

Atherosclerosis is characterized by infiltration of lipid-rich lesions, endothelial production of cell-adhesion molecules such as E-selectin and stimulation of fibrous tissue by procoagulant factors such as fibrinogen and plasminogen activator inhibitor-1 (PAI-1) [6]. Elevated blood pressure is an independent risk factor for coronary heart disease and contributes to atherogenesis by stimulating smooth muscle growth and contraction [6]. Once atherosclerosis has developed, acute thrombosis or disruption of a vulnerable plaque can occur, often associated with inflammatory factors such as C-reactive protein (CRP) [6].

The metabolic effects of hormone-replacement therapy (HRT) in postmenopausal women have been extensively studied in randomized controlled trials, and recent articles have qualitatively reviewed the results in an attempt to explain the complex effect HRT has on cardiovascular events [7,8]. The purpose of this meta-analysis is to pool data from randomized controlled trials to quantitatively summarize the effect of HRT on components of the metabolic syndrome in both diabetic and non-diabetic women. Subgroup analysis will evaluate the differential effects of transdermal and oral agents.

Methods

Search Strategy

The MEDLINE, EMBASE, CINAHL and Cochrane databases were searched comprehensively to identify randomized controlled trials published between April 1966 and October 2004, evaluating the effect of HRT on body fat, glucose, insulin resistance, new-onset diabetes, lipids, blood pressure and inflammatory or thrombotic components. Trials were not excluded on the basis of language. The search was augmented by scanning selected journals and references of identified articles.

Trial Selection

Studies were included if they: (i) were randomized controlled trials of postmenopausal women that compared HRT to placebo or no hormone therapy; (ii) were of at least 8 weeks duration; and (iii) provided extractable data on lean body mass, waist circumference, abdominal fat, fasting glucose, fasting insulin, new-onset diabetes, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, lipoprotein(a) [Lp(a)], blood pressure, CRP, E-selectin, fibrinogen, PAI-1, protein C or protein S. For trials of women with known diabetes at baseline, data on fasting glucose and insulin were extracted.

We chose these outcomes because they were the most common measurements of the metabolic syndrome and are thought to be significant cardiovascular or thrombotic risk factors. Outcomes that were less well studied, including intercellular adhesion molecule (ICAM-1), vascular cell-adhesion molecule (VCAM-1), factor VII, tissue plasminogen activator, antithrombin III and von Willebrand factor, were evaluated separately and are reported in the discussion.

Trial duration of at least 8 weeks was chosen to allow changes to occur in these parameters. For crossover trials with treatment durations of less than 12 weeks, a 4-week washout period was required for inclusion. For studies with multiple publications from the same group of participants, one publication containing the most information was chosen for inclusion.

Assessment of Validity

The methodological quality of each trial was assessed for the following quality domains: (i) randomization and allocation concealment; (ii) blinding of patients and people administering the treatment; and (iii) reporting of dropouts and use of intention-to-treat analysis. Trials were characterized for each domain separately using a 3-point scale, and quality assessment was used for a sensitivity analysis.

Data Extraction

Two investigators extracted data from the selected articles, without being blinded to the study results. In addition, we attempted to contact the investigators to obtain more information. For women without known diabetes

at baseline, the outcomes measured were the incidence of new-onset diabetes and the change in mean waist circumference, abdominal fat mass (measured by dual energy photon or X-ray absorptiometry), lean body mass (measured by absorptiometry or urinary creatinine excretion rate), fasting glucose, fasting insulin, LDL cholesterol, HDL cholesterol, triglycerides, Lp(a), systolic and diastolic blood pressure (or mean blood pressure), CRP, E-selectin, fibrinogen, PAI-1 (antigen or activity), protein C and protein S. For women with diabetes, the outcomes measured were change in mean fasting glucose and fasting insulin.

The data on new-onset diabetes were extracted according to the definitions provided. The Heart Estrogen/Progestin Replacement Study and Women's Health Initiative trials defined diabetes by self-report, a fasting glucose level $\geq$6.9 mmol/l ($\geq$126 mg/dl) or initiation of diabetes medication [9,10]. The Postmenopausal Estrogen/Progestin Intervention Trial provided unpublished data; baseline diabetes was defined by a glucose $\geq$7.6 mmol/l ($\geq$140 mg/dl) and incident diabetes by self-report or disease complication [11]. The Women's Health Osteoporosis Progestin Estrogen Trial provided unpublished data; diabetes was defined by a glucose >7.77 mmol/l or an abnormal glucose tolerance test [12].

Because significant asymmetry has been noted in the distribution of CRP and PAI-1, data were extracted on mean values with standard deviations or median values and per cent change, with associated p-values. A sensitivity analysis was performed to evaluate the effect of including trials with median values. For the other analyses, only mean values were extracted.

Data Synthesis

For each variable, we determined the net change in mean group values from baseline for both the control and treatment groups, recorded as the per cent change from baseline. The placebo response was subtracted from the treatment response to obtain the net treatment effect, reported as a percentage of the baseline placebo value. For the assessment of CRP and PAI-1, median and mean values were logarithmically transformed for the analysis and reported as a percentage of the baseline value.

For trials that provided data on both fasting glucose and fasting insulin, an index of insulin resistance was calculated by homeostasis model assessment (HOMA-IR) using the formula: insulin (mU/l) times glucose (mmol/l) divided by 22.5 [13]. We chose this method because it could be calculated easily in a large number of studies and has been shown to be closely correlated with the standard insulin sensitivity index [14].

For the evaluation of LDL and HDL cholesterol, the results are reported for each value separately and also as the LDL to HDL ratio. For the evaluation of blood pressure, the mean arterial pressure was studied, calculated as diastolic pressure plus one-third of pulse pressure, as it is a measure of both systolic and diastolic blood pressure and is a significant risk factor for cardiovascular events [15].

The net treatment effects for each analysis were pooled to obtain a weighted mean difference using the random-effects model for continuous outcomes, with statistical significance set at $p < 0.05$. The random-effects model was used because it accounts for the possibility of significant interstudy heterogeneity [16].

To assess the risk for new-onset diabetes, the ratio of new cases to total participants without known diabetes at baseline was expressed as a relative risk (RR) by dividing the treatment rate by the control rate. The results were pooled to obtain a summary RR using the random-effects model for dichotomous outcomes.

The analyses were performed using REVIEW MANGER 4.2 (Cochrane Library Software, Oxford, UK). To test for interstudy heterogeneity, the Chi-squared value was calculated for the assumption of homogeneity. To increase sensitivity in the assessment of potential heterogeneity, statistical significance was set at $p < 0.1$.

The results were evaluated separately for women with and without known diabetes at baseline, because HRT may have differential effects in these two groups. If diabetes was not listed as an inclusion criterion, the trial was considered to be in non-diabetics. In trials of women with known diabetes, fasting glucose and HOMA-IR were evaluated because both have been shown to be strong cardiovascular risk factors [17,18].

Subgroup analysis evaluated the differential effects of oral and transdermal agents. When possible, the data were further subdivided into oral conjugated and oral esterified oestrogens and also into low-dose and high-dose agents. The results of the subgroups were compared to each other using the test for interaction [19].

Results

Search Results

The electronic database search identified 1772 articles, of which 247 were potentially relevant trials of the effect of HRT on components of the metabolic syndrome in postmenopausal women. After scanning journals and references from selected articles, an additional 13 trials were identified. Of these 260 trials, 107 met inclusion

criteria (Appendix). Trials were excluded for the following reasons: eight were not randomized; four were in perimenopausal women; 22 did not provide a control group; 15 were of less than 8 weeks duration; six cross-over trials did not have adequate washout period; 53 reported data on patients already included in the analysis; and 45 did not provide extractable data on the variables studied. Twenty-six of the excluded trials provided information for patients already included in the analysis.

Trial Characteristics

The analysis included 107 trials, with a total of 33 315 participants followed for 49 973 patient-years. The mean trial duration was 1.5 years (range 0.15–5 years), with a mean study size of 311 participants. The mean age of participants (±s.d.) at baseline was 60.3 ± 5.9 years in the treatment group and 61.5 ± 5.7 years in the control group. The mean dropout rate was estimated to be 9.2% in the treatment group and 7.2% in the control group. Interventions included conjugated equine oestrogen, oral esterified oestrogens or transdermal oestrogen, alone or in combination with a progestin. Control groups received placebo, calcium supplementation or no treatment.

Quantitative Data Synthesis

A summary of the main results can be found in table 1.

Abdominal Obesity

For women without known diabetes, HRT increased lean body mass [3.3% (CI, 0.02–6.6%)] and reduced waist circumference [−0.8% (CI, −1.2 to −0.4%)] and abdominal fat [−6.8% (CI, −11.8 to −1.9%)], compared to placebo or no treatment (figure 1).

Insulin Resistance and Diabetes

For women without diabetes, calculated insulin resistance (HOMA-IR) was reduced by 12.9% (CI, 8.6–17.1%) for HRT compared to controls (figure 2). HRT reduced fasting glucose by 2.5% (CI, 1.5–3.5%) and fasting insulin by 9.3% (CI, 4.9–13.7%). In subgroup analysis, there was no significant difference in HOMA-IR for transdermal agents [−6.8% (CI, −17 to 3.5%)] or oral agents [−13.5% (−18.3 to −8.8%)], $p = 0.2$ for interaction. However, the results for transdermal agents did not reach statistical significance. There was no significant difference in results between conjugated and esterified oestrogens or between unopposed and combined treatment. The RR for developing diabetes mellitus was 0.7 (CI, 0.6–0.9), indicating a 30% reduction in new-onset diabetes for those receiving HRT.

For women with diabetes, HRT reduced HOMA-IR by 35.8% (CI, 19.8–51.7%) compared to placebo or no treatment. HRT reduced fasting glucose by 11.5% (CI, 5.1–18.0%) and fasting insulin by 20.2% (CI, 4.2–36.3%). A greater reduction in HOMA-IR was seen in women with diabetes compared to those without known diabetes, $p = 0.007$.

Lipids and Lipoproteins

Overall, HRT increased HDL cholesterol [5.1% (CI, 3.6–6.7%)] and reduced LDL cholesterol [−11.0% (CI, −12.3

Table 1 Results for hormone-replacement therapy (HRT) combined, and for transdermal and oral agents, in women without known diabetes

Outcome	HRT – all agents (%)	Transdermal agents (%)	Oral agents (%)	p for interaction
HOMA-IR	−12.9* (−4.9 to −13.7)	−6.8 (−17 to 3.5)	−13.5* (−18.3 to −8.8)	NS
LDL/HDL	−11.0* (−12.3 to −9.6)	−8.4* (−13.8 to −2.8)	−17.4* (−20.0 to −14.9)	0.004*
Triglycerides	2.1 (−0.6 to 4.8)	−6.5 (−14.7 to 1.8)	6.0* (4.3 to 7.6)	0.004*
Lp(a)	−25.0* (−32.9 to −17.1)	−22.8* (−44.4 to −1.2)	−25.1* (−33.2 to −17.1)	NS
Mean BP	−1.7* (−2.9 to −0.5)	−0.8 (−3.3 to 1.6)	−2.2* (−4.1 to −0.3)	NS
CRP	37.7* (17.4 to 61.3)	2.0 (−23.0 to 34.0)	47.0* (29.0 to 67.0)	0.02*
E-selectin	−17.3* (−22.4 to −12.1)	−6.0 (−19.8 to 7.9)	−18.6* (−23.9 to −13.3)	NS
Fibrinogen	−5.5* (−7.8 to −3.2)	−4.7* (−7.6 to −1.8)	−5.8* (−8.7 to −2.8)	NS
PAI-1 antigen	−25.1* (−33.6 to −15.5)	−3.0 (−23.0 to 35.0)	−27.0* (−38.0 to −22.0)	0.03*
Protein C	−0.8 (−4.2 to 2.6)	−1.2 (−7.4 to 5.1)	−1.7 (−7.0 to 3.7)	NS
Protein S	−4.8 (−10.7 to 1.2)	−2.2 (−9.9 to 5.6)	−8.6* (−13.1 to −4.1)	0.01*

The p-values comparing transdermal and oral agents are reported. NS, not significant; HOMA-IR, homeostasis model assessment; LDL/HDL, low-density lipoprotein/high-density lipoprotein; Lp(a), lipoprotein(a); BP, blood pressure; CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1.
*$p < 0.05$.

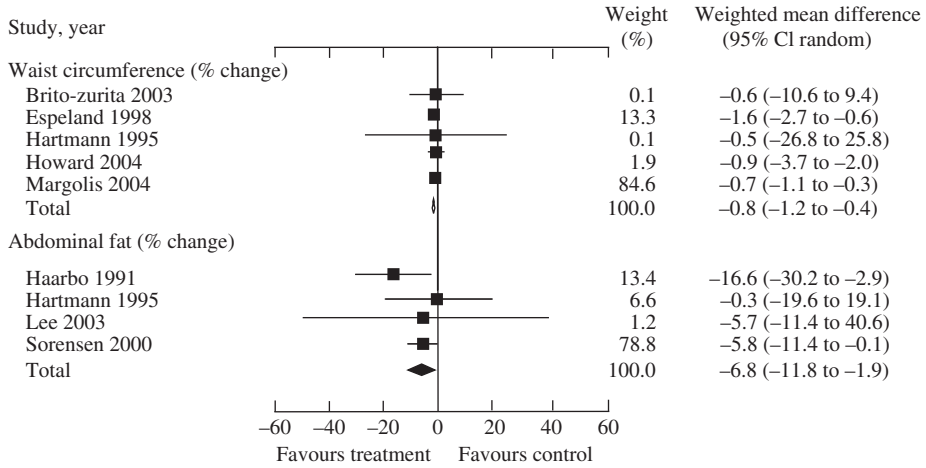


Fig. 1 Effect of hormone-replacement therapy on abdominal obesity in women without diabetes. Waist circumference and abdominal fat (% change) values are given.

to −9.6%)], LDL/HDL ratio [−15.7% (CI, −18.0 to −13.5%, figure 3a)] and Lp(a) [−25% (CI, −32.9 to −17.1%)] compared to placebo or no treatment. HRT had no effect on triglycerides [2.1% (CI, −0.6–4.8%, figure 3b)].

In subgroup analysis of LDL/HDL, oral agents produced greater reductions [−17.4% (CI, −20.0 to −14.9%)] than transdermal agents [−8.4% (CI, −13.8 to −2.8%)], $p = 0.004$ for interaction. Conjugated oestrogens produced greater reductions [−22.4% (CI, −25.6 to −19.1%)] than oral esterified oestrogens [−11.3% (CI, −13.2 to −9.4%)], $p < 0.0001$. Unopposed oestrogens and combined oestrogen–progestin treatment produced similar results, $p = 0.3$. Further subgroup analysis compared low-dose (0.3 mg) with high-dose (0.625 mg or 1.25 mg) conjugated oestrogens and found a significant dose-dependent effect on LDL/HDL ($p = 0.0001$). For the analysis of Lp(a), all subgroups produced equivalent reductions with no significant differences between them, $p > 0.3$.

In subgroup analysis of triglycerides, oral agents increased levels [6.0% (CI, 4.3–7.6%)], while transdermal agents had no effect [−6.5% (CI, −14.7–1.8%)], $p = 0.004$. Small increases were found with both conjugated oestrogens [6.3% (CI, 3.7–8.9%)] and oral esterified oestrogens [6.1% (CI, 4.0–8.1%)], $p = 0.9$.

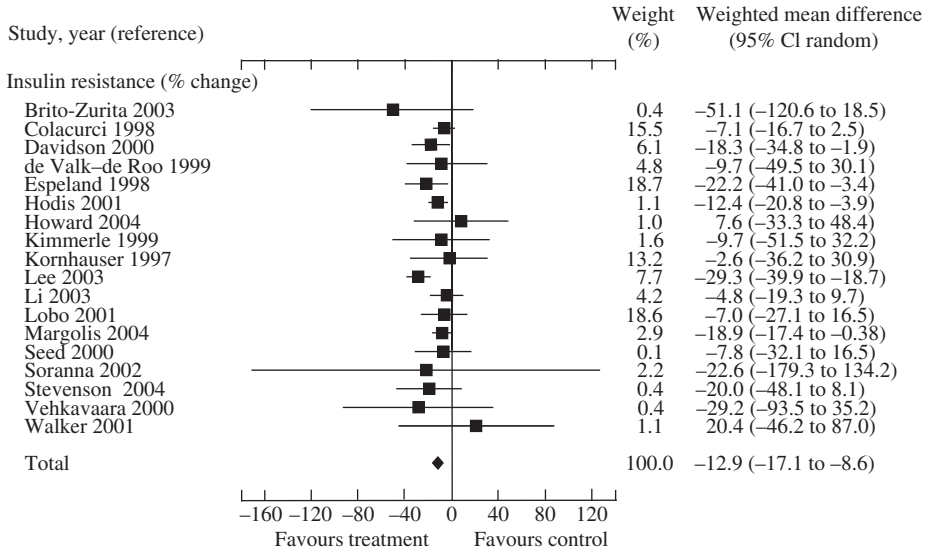


Fig. 2 Effect of hormone-replacement therapy on calculated insulin resistance in women without diabetes (% change).

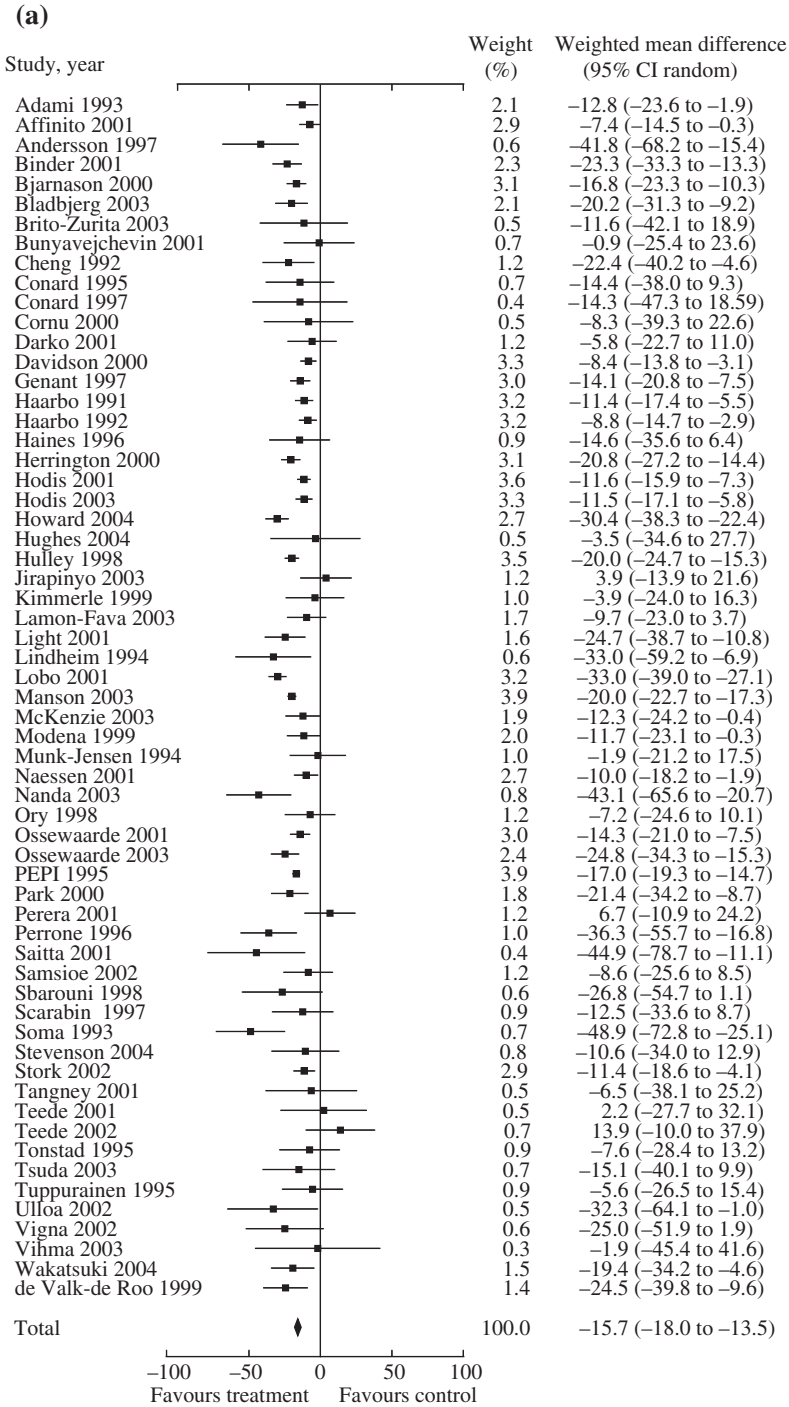


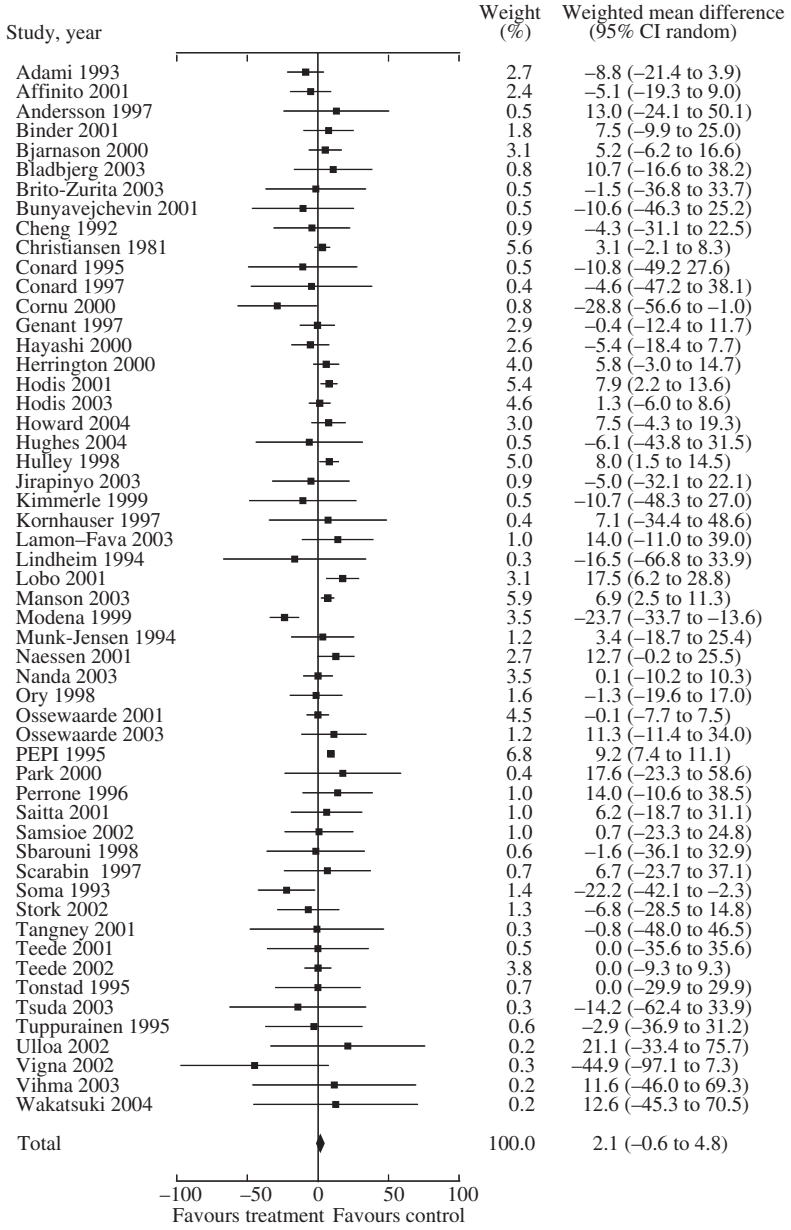
Fig. 3 Effect of hormone-replacement therapy on lipids in women without diabetes: (a) low-density lipoprotein/high-density lipoprotein cholesterol ratio (% change); (b) triglyceride (% change).

Unopposed oral oestrogen increased levels [6.1% (CI, 4.0–8.1%)], while combined oestrogen–progestin treatment had no effect [1.5% (CI, −2.0–5.0%)], $p = 0.03$.

Mean Blood Pressure

Overall, HRT produced a small reduction in mean blood pressure [−1.7% (CI, −2.9 to −0.5%)]. In subgroup analysis, only conjugated oestrogens reduced blood

(b)



pressure [−2.2% (CI, −4.1 to −0.3%)], while transdermal agents [−0.8% (CI, −3.3–1.6%)] and oral esterified oestrogens [−1.3% (CI, −3.1–0.5%)] did not have significant effects. However, there was no significant difference between subgroups, $p > 0.1$.

Inflammatory Components

Overall, HRT increased CRP [37.6% (CI, 17.4–61.3%)], but reduced E-selectin [−17.3% (CI, −22.4 to −12.1%, figure 4)]. Oral agents significantly increased CRP [47.0% (CI, 29.0–67.0%)], while transdermal agents had no effect [2.0% (CI, −23.0–34.0%)], $p = 0.02$. There was no significant difference between conjugated oestrogens [59.0% (CI, 36.0–84.0%)] and oral esterified oestrogens [36.0% (CI, 12.0–65.0%)], $p = 0.2$. Unopposed oestrogens produced greater increases [95.0% (CI, 63.0–135.0%)] than combined treatment [29.0% (CI, 10.0–51.0%)], $p = 0.0009$. Subgroup analysis of low-dose (0.3 mg) and high-dose (0.625 mg or 1.25 mg)

conjugated oestrogens found a significant dose-dependent effect on CRP ($p = 0.0006$). For the analysis of E-selectin, all subgroups produced reductions without significant differences between groups, $p > 0.1$.

Thrombotic Components

HRT reduced the procoagulant factors fibrinogen [−5.5% (CI, −7.8 to −3.2%)] and PAI-1 [−25.1% (CI, −33.6 to −15.5%, figure 5)], compared to placebo or no treatment. HRT, as a group, had no effect on the coagulation inhibitors protein C [−0.8% (CI, −4.2 to 2.6%)] or protein S [−4.8% (CI, −10.7 to 1.2%)].

In subgroup analysis of PAI-1, oral agents produced significant reductions [−27.0% (CI, −38.0 to −22.0%)], while transdermal agents had no effect [−3.0% (CI, −23.0 to 35.0%)], $p = 0.03$. There was no significant difference between conjugated oestrogens [−23.0% (CI, −35.0 to −8.0%)] and oral esterified oestrogens [−28.0% (CI, −37.0 to −19.0%)], $p = 0.5$. Unopposed oestrogens produced greater reductions [−37.0% (CI, −47.0 to −25.0%)] than combined treatment [−19.0% (CI, −25.0 to −12.0%)], $p = 0.01$. For the analysis of fibrinogen, similar reductions were seen with all subgroups.

In subgroup analysis of protein C, there were no differences between oral and transdermal agents, conjugated oestrogens and oral esterified oestrogens or unopposed oestrogen and combined treatment, $p > 0.7$. Oral agents significantly reduced protein S [−8.6% (CI, −13.1 to −4.1)], while transdermal agents had no effect [−2.2% (CI, −9.9 to 5.6%)], $p = 0.01$. There was no significant difference between the results of conjugated oestrogens [−10.2% (CI, −15.5 to −5.0%)] and oral esterified oestrogens [−5.7% (CI, −13.7 to 2.3)] or between unopposed and combined treatment.

Interstudy Variability

As expected from the subgroup analysis, there was evidence for significant interstudy heterogeneity in the analysis of LDL/HDL ratio ($p < 0.00001$), triglyceride ($p = 0.0001$), blood pressure ($p = 0.001$), CRP ($p < 0.00001$), protein S ($p = 0.05$) and PAI-1 ($p = 0.02$). No significant heterogeneity was noted in other analyses.

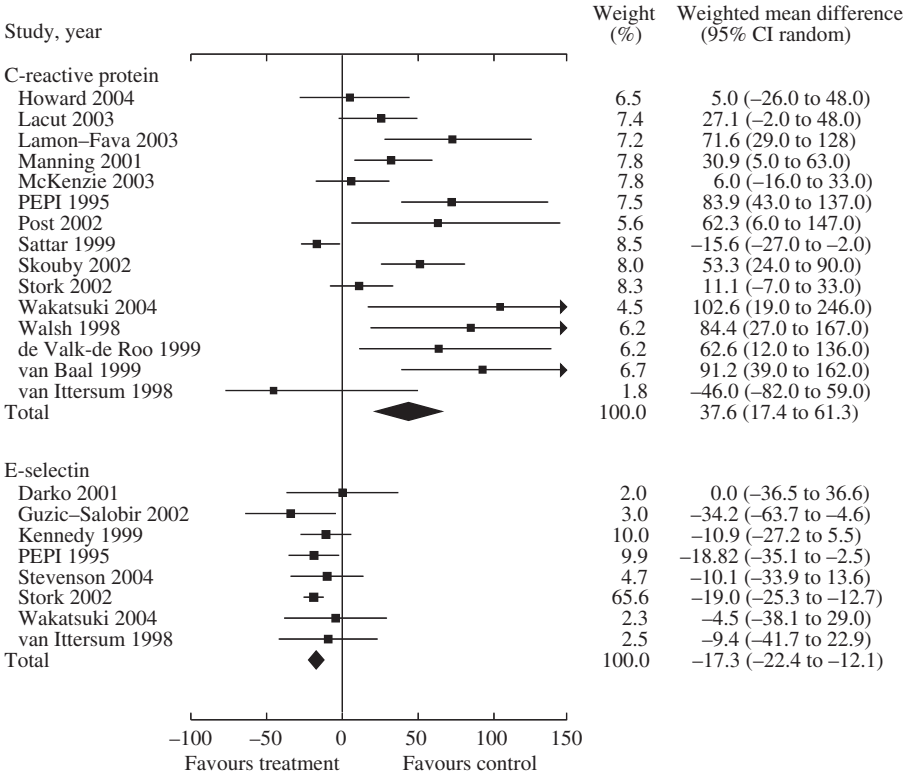


Fig. 4 Effect of hormone-replacement therapy on inflammatory components in women without diabetes. C-reactive protein and E-selectin (% change) values are given.

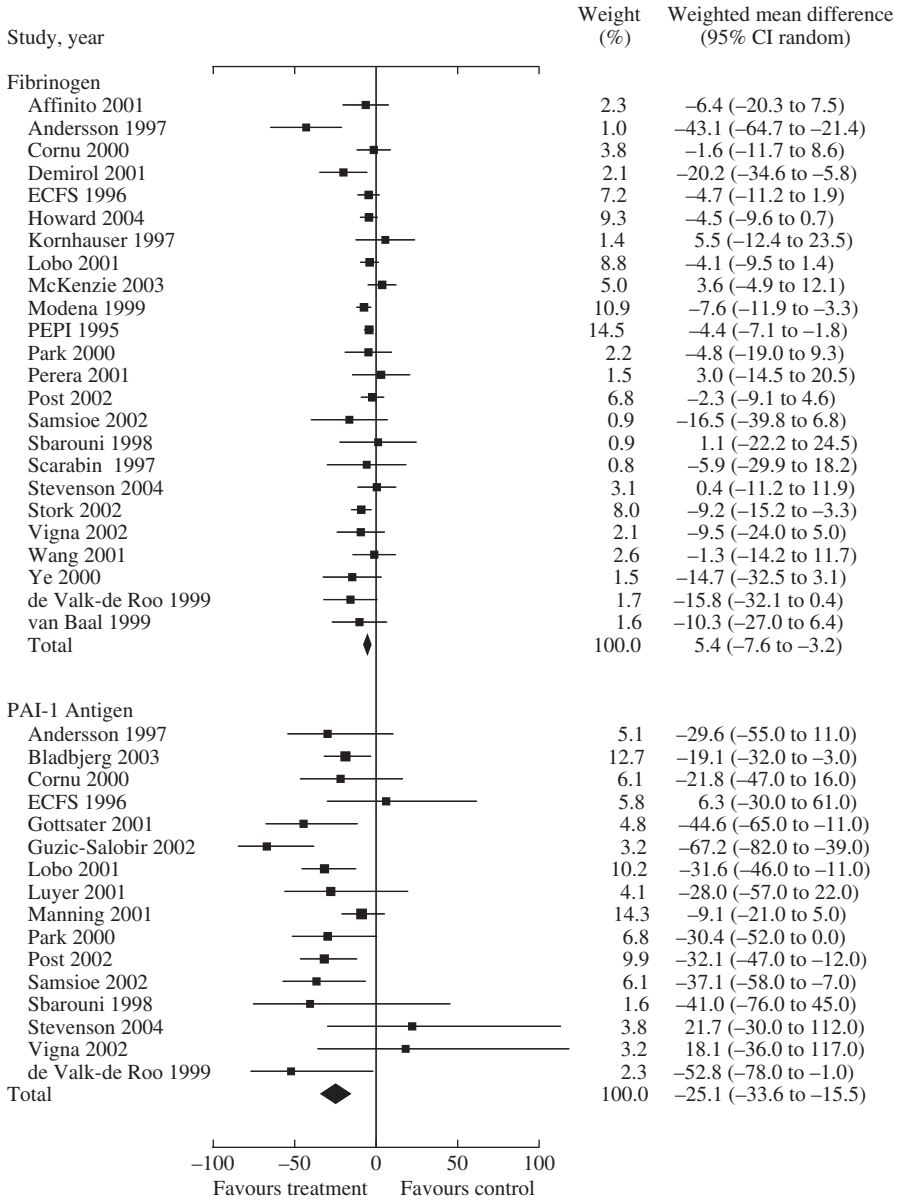


Fig. 5 Effect of hormone-replacement therapy on procoagulant factors in women without diabetes. Fibrinogen and plasminogen activator inhibitor-1 (PAI-1) (% change) are given.

Sensitivity Analysis

A sensitivity analysis was performed to evaluate the effect of including the 22 trials with the lowest score in at least one quality domain. When these trials were excluded, the results changed by less than 4 percentage points and did not change significance for any analysis, $p > 0.7$. In another sensitivity analysis, trials providing median values for CRP and PAI-1 were excluded; the results were still significant and changed by less than 4 percentage points, $p > 0.8$.

Discussion

This meta-analysis outlines a complex relationship between various types and doses of HRT and metabolic risk factors. In pooled data from 107 trials, with 33 315 participants followed for a mean duration of 1.5 years, HRT increased lean body mass and HDL cholesterol and reduced abdominal obesity, insulin resistance, new-onset diabetes, LDL cholesterol, Lp(a), mean blood pressure, E-selectin, fibrinogen and PAI-1, all of which should have beneficial effects on atherosclerotic risk.

Oral agents, in general, had greater beneficial effects on these variables than transdermal agents. However, oral agents increased triglycerides and CRP and decreased protein S, which could increase cardiovascular and thrombotic risk, while transdermal agents had no adverse effects. The addition of a progestin to oral oestrogen tended to decrease the magnitude of the beneficial and adverse effects. Conjugated estrogens tended to produce larger beneficial and adverse effects than oral esterified oestrogens.

Additional analysis found that HRT reduced the cell-adhesion molecules, ICAM-1 and VCAM-1 and the coagulation activator factor VII. These changes would also be associated with reduced risk for atherosclerosis. HRT did not affect the procoagulant factors tissue plasminogen activator, antithrombin III or von Willebrand factor.

The metabolic syndrome, which consists of abdominal obesity, insulin resistance, dyslipidaemia, hypertension and inflammatory or prothrombotic states, rapidly increases in prevalence after menopause [20]. Each of the metabolic abnormalities associated with the syndrome is interrelated and also appears to be independent risk factors for the development of atherosclerosis and subsequent cardiovascular events [3,5,15,17,21–27]. The reductions in components of the metabolic syndrome seen with HRT could reduce the development of atherosclerosis, if treatment is started early in the disease process.

These beneficial effects on components of the metabolic syndrome could help explain the reduction in total mortality [28] and cardiac events (Salpeter *et al.*, submitted for publication) seen in pooled trials of younger postmenopausal women. In both observational studies [29] and randomized trials (Salpeter *et al.*, submitted for publication), no initial increase in cardiac events is seen with short-term use in younger women, indicating that there may be a true primary preventive effect on cardiovascular disease if started before the development of atherosclerosis, without a significantly increased prothrombotic effect.

The rise in CRP with oral HRT may be responsible for the increase in thrombotic cardiac events and strokes seen with initiation of treatment in older women, both in clinical trials and in observational studies [30–33]. CRP is a significant risk factor for acute cardiovascular events and progression of unstable plaque, especially in those with underlying atherosclerosis, while having little association with the development of early atherosclerosis [34–38]. Continued treatment with HRT in older women is associated with decreased cardiac events, possibly related to the beneficial effects on atherosclerotic risk factors [30–32]. Of note, in this meta-analysis, the level of CRP after treatment with oral agents was 2.2 mg/l which is still considered to be within normal limits [38,39]. There is some evidence that concomitant use of exercise or statin therapy in women on HRT can blunt the increase in CRP [40–42]. Aspirin use appears to have the greatest cardioprotective benefits in those with elevated CRP levels [43].

Oral oestrogens increase triglyceride levels slightly, but the clinical significance of this is unclear. Elevated triglycerides are often associated with low levels of HDL cholesterol, obesity and diabetes mellitus, all of which are strong cardiac risk factors. Triglycerides are clearly associated with increased cardiovascular risk, but this association may be lost or diminished when fasting insulin and LDL particle size are accounted for [44,45]. It is possible that oral oestrogens stimulate hepatic production of non-atherogenic triglyceride particles.

The reduction in protein S levels with oral HRT may be responsible, in part, for the increased risk in venous thromboembolic events seen with initiation of treatment [30–32,46]. HRT had no effect on protein C levels; however, there is evidence that oral oestrogens may increase resistance to activated protein C [47,48]. Decreases in protein S activity and sensitivity to activated protein C are both considered risk factors for venous thrombosis [49,50].

This study has several limitations. There was a marked variation in study size, type and dose of medication used and method of administration. Evidence for significant heterogeneity was noted in some of the analyses. The purpose of this meta-analysis was to assess cardiovascular risk factors, not morbidity or mortality. It is not clear whether the metabolic factors studied are truly responsible for the clinical outcomes seen or are merely surrogate biomarkers. There is emerging evidence that HRT has differential effects on HDL and LDL particle size and distribution, which could influence clinical outcomes [51–54]. Some of the results seen in this meta-analysis show statistically significant changes, but it is unclear whether these modest changes are in fact clinically significant. The data for this meta-analysis came from only published trials, so there is a potential for publication bias. However, funnel plots of effect size vs. standard error for these analyses showed no evidence of bias. Despite these limitations, this meta-analysis attempts to clarify the effects of HRT on cardiovascular risk in postmenopausal women.

In summary, transdermal oestrogens, with or without a progestin, produce mild beneficial effects on abdominal obesity, insulin resistance, glucose control, lipids, lipoproteins, cell-adhesion molecules and procoagulant factors. Oral oestrogens, especially conjugated

oestrogens, produce stronger beneficial effects but have adverse effects on CRP, triglycerides and coagulation inhibitors. These effects are dose dependent and are diminished by the addition of a progestin. Some of the differences in effect between oral and transdermal agent may be related to the fact that transdermal agents do not undergo hepatic metabolism.

We are slowly beginning to understand the mechanism of action of HRT in postmenopausal women, with the hope of targeting treatment in individual women to maximize benefits while minimizing risks. For older women with underlying cardiovascular disease, the risks of oral HRT appear to outweigh the potential benefits. However, we may find that transdermal oestrogens can safely reduce cardiovascular risk factors in younger postmenopausal women who desire HRT.

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