

SUPPLEMENTAL MATERIAL

Supplemental Tables

Table S1. Full search terms in databases Ovid MEDLINE, Embase Classic + Embase, Scopus and Cochrane

| Database(s): Ovid MEDLINE(R) ALL 1946 to February 28 2023 | |
|---|---|
| # | Searches |
| 1 | exp menopause/ or perimenopause/ or postmenopause/ or exp Climacteric/ or Hot Flashes/ |
| 2 | (menopaus* or postmenopaus* or post-menopaus* or perimenopaus* or peri-menopaus* or hot-flash* or hot flash* or hot flush* or hot-flush* or climacter*).ti,ab,kf. |
| 3 | 1 or 2 |
| 4 | exp Diabetes Mellitus/ |
| 5 | exp diabetes mellitus/ or exp diabetes mellitus, type 1/ or exp diabetes mellitus, type 2/ |
| 6 | (diabet* 1 or diabet* mellitus 1 or diabet* type 1 or diabet* type I or type one diabet* or type I diabet* or insulin-dependent diabet* or insulin dependent diabet* or diabet* Mellitus Type 1 or diabet* type I or type 1 diabet* or type I diabet* or IDDM or T1DM or T1D or "type 2 diabet*" or "diabet* mellitus" or "diabet* type 2" or "type II diabet*" or "type two diabet*" or "noninsulin dependent diabet*" or "noninsulin-dependent diabet*" or "non-insulin dependent diabet*" or adult onset diabet*" or "matur* onset diabet*" or "adult-onset diabet*" or NIDDM or "dm type 2" or "type 2 dm").ti,ab,kf. |
| 7 | ((diabet* or dm) adj2 (type adj2 (one or "1" or I or two or "2" or II))).ti,ab,kf. |
| 8 | or/4-7 |
| 9 | exp hormone replacement therapy/ or exp estrogen replacement therapy/ |
| 10 | ((menopaus* or postmenopaus* or perimenopaus* or climacter* or cyclic or hormon* or progest* or ?estrogen* or combine* or estradiol) adj3 (replacement therap* or substitut* therap* or treatment* or therap*)).ti,ab,kf. |
| 11 | or/9-10 |
| 12 | 3 and 8 and 11 |
| 13 | ((exp animals/ or exp veterinary medicine/ or animal*.jw.) not humans/) or (experimental model or animal* or monkey* or horse* or racehorse* or sheep or ?ovine or lamb* or goat* or pig* or swine* or porcine* or pup* or dog* or canine* or bitch* or beagle* or feline* or rodent* or rabbit* or rat* or mice* or mouse or murine).ti,ab. |
| 14 | 12 not 13 |
| Database(s): Embase Classic+Embase 1947 to February 28 2023 | |

| | |
|--|---|
| # | Searches |
| 1 | exp menopause/ or exp menopause related disorder/ or exp "menopause and climacterium"/ or exp climacterium/ or exp postmenopause/ |
| 2 | (menopaus* or postmenopaus* or post-menopaus* or perimenopaus* or peri-menopaus* or hot-flash* or hot flash* or hot flush* or hot-flush* or climacter*).ti,ab,kw. |
| 3 | 1 or 2 |
| 4 | exp diabetes mellitus/ or exp non insulin dependent diabetes mellitus/ or exp insulin dependent diabetes mellitus/ |
| 5 | (diabet* 1 or diabet* mellitus 1 or diabet* type 1 or diabet* type I or type one diabet* or type I diabet* or insulin-dependent diabet* or insulin dependent diabet* or diabet* Mellitus Type 1 or diabet* type I or type 1 diabet* or type I diabet* or IDDM or T1DM or T1D or "type 2 diabet*" or "diabet* mellitus" or "diabet* type 2" or "type II diabet*" or "type two diabet*" or "noninsulin dependent diabet*" or "noninsulin-dependent diabet*" or "non-insulin dependent diabet*" or adult onset diabet*" or "matur* onset diabet*" or "adult-onset diabet*" or NIDDM or "dm type 2" or "type 2 dm").ti,ab,kw. |
| 6 | ((diabet* or dm) adj2 (type adj2 (one or "1" or I or two or "2" or II))).ti,ab,kw. |
| 7 | or/4-6 |
| 8 | 3 and 7 |
| 9 | exp hormone substitution/ or exp estrogen therapy/ |
| 10 | ((menopaus* or postmenopaus* or perimenopaus* or climacter* or cyclic or hormon* or progest* or ?estrogen* or combine* or estradiol) adj3 (replacement therap* or substitut* therap* or treatment* or therap*).ti,ab,kw. |
| 11 | or/9-10 |
| 12 | 3 and 7 and 11 |
| 13 | ((exp animals/ or exp veterinary medicine/ or animal*.jw.) not humans/) or (experimental model or animal* or monkey* or horse* or racehorse* or sheep or ?ovine or lamb* or goat* or pig* or swine* or porcine* or pup* or dog* or canine* or bitch* or beagle* or feline* or rodent* or rabbit* or rat* or mice* or mouse or murine).ti,ab. |
| 14 | 12 not 13 |
| Database(s): Scopus | |
| TITLE-ABS-KEY-AUTH (menopaus* OR postmenopaus* OR "post-menopaus*" OR perimenopaus* OR peri-menopaus* OR "hot-flash*" OR "hot flash*" OR "hot flush*" OR "hot-flush*" OR climacter*) AND TITLE-ABS-KEY-AUTH ("type 2 diabet*" OR "diabet* mellitus" OR "diabet* type 2" OR "type II diabet*" OR "type two diabet*" OR "noninsulin dependent diabet*" OR "noninsulin-dependent diabet*" OR "non-insulin dependent diabet*" OR adult onset diabet*" OR "matur* onset diabet*" OR "adult-onset diabet*" OR niddm OR "dm type 2" OR "type 2 dm" OR "juvenile diabet*" OR "diabet* 1" OR "diabet* mellitus 1" OR "diabet* type 1" OR "diabet* type I" OR "type one diabet*" OR "type I diabet*" OR "insulin-dependent diabet*" OR "insulin dependent diabet*" OR "diabet* Mellitus Type 1" OR "diabet* type I" OR "type 1 diabet*" OR "type I diabet*" OR iddm OR t1dm OR t1d) AND TITLE-ABS-KEY- | |

AUTH ((menopaus* OR postmenopaus* OR perimenopaus* OR climacter* OR cyclic OR hormon* OR progest* OR estrogen* OR combine* OR estradiol) W/3 ("replacement therap*" OR "substitut* therap*" OR treatment* OR therap*)) AND NOT TITLE-ABS-KEY-AUTH ("experimental model" OR animal* OR monkey* OR horse* OR racehorse* OR sheep OR ?ovine OR lamb* OR goat* OR pig* OR swine* OR porcine* OR pup* OR dog* OR AND canine* OR bitch* OR beagle* OR feline* OR rodent* OR rabbit* OR rat* OR mice* OR mouse OR murine) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "cp"))

Database(s): Clinicaltrials.gov

Condition Diabetes

Intervention Hormone therapy

ID Database(s): Cochrane Library (Central)

| | |
|-----|---|
| #1 | MeSH descriptor: [Diabetes Mellitus] explode all trees |
| #2 | diabet* |
| #3 | (1-#2) |
| #4 | MeSH descriptor: [Hormone Replacement Therapy] explode all trees |
| #5 | ((menopaus* or postmenopaus* or perimenopaus* or climacter* or cyclic or hormon* or progest* or ?estrogen* or combine* or estradiol) near/3 (replacement therap* or substitut* therap* or treatment* or therap*)) |
| #6 | (2-#5) |
| #7 | #3 AND #6 |
| #8 | MeSH descriptor: [Menopause] explode all trees |
| #9 | (menopaus* or postmenopaus* or post-menopaus* or perimenopaus* or "peri-menopaus*" or hot-flash* or hot flash* or hot flush* or hot-flush* or climacter*) |
| #10 | (3) |
| #11 | #7 and #10 |

Table S2. Data items in data extraction table

| Data item | Pre-defined definitions |
|---|--|
| Study setting | Setting in a hospital/clinic/multi-center/other |
| Location and time period of the trial | List the city and country where the trial was performed. List time period of the trial (in years). |
| Study design | E.g. parallel-group/crossover/other |
| Inclusion criteria | List all inclusion criteria of the study |
| Exclusion criteria | List all exclusion criteria of the study |
| Postmenopausal status definition | Stated definition of postmenopausal status in study |
| Included types of diabetes | Stated types of diabetes (e.g. type 1 / type 2) and stated definition of this type of diabetes |
| Type of analysis | E.g. intention-to-treat or per-protocol analysis |
| HT regimen | Type of HT, name of active component(s), dosage per day, and dosage per 4-week cycle |
| Control regimen | Type of control regimen (e.g. placebo, observation, standard treatment) and dosages per day |
| Treatment route | E.g. oral/transdermal/other |
| Treatment duration | Treatment duration in weeks |
| Wash-out period duration | If applicable, wash-out period duration in days |
| Other primary outcomes of the study | List all other primary outcomes of the study |
| Stated aim of the study | List the stated aim of the study |
| Number of patients (intervention group & control group) | Number of patients in intervention group and control group. If applicable, list number of patients in first arm of crossover trial and second arm of crossover trial |
| Age of participants | List mean age of participants \pm SD |
| Comorbidities of participants | List all known comorbidities: n (%) in each group |
| Medication use participants (other than glucose lowering drugs) | List all known co-medications: n (%) in each group |
| Menopause duration | Mean duration of menopause of included participants \pm SD |
| Diabetes duration | Mean duration of diabetes of included participants \pm SD |
| Funding details | Stated information on study funding |
| Baseline HbA1c (%) | Mean baseline HbA1c (%) \pm SD of HT and control group |
| Post-intervention HbA1c (%) | Mean post-intervention HbA1c (%) \pm SD of HT and control group |
| Mean difference HbA1c (%) | Mean difference HbA1c (%) \pm SD between HT and control group |
| Baseline fasting glucose (mmol/l) | Mean baseline fasting glucose (mmol/l) \pm SD of HT and control group |
| Post-intervention fasting glucose (mmol/l) | Mean post-intervention fasting glucose (mmol/l) \pm SD of HT and control group |
| Mean difference fasting glucose (mmol/l) | Mean difference fasting glucose (mmol/l) \pm SD between HT and control group |
| Baseline postprandial glucose (mmol/l) | Mean baseline postprandial glucose (mmol/l) \pm SD of HT and control group |

| | |
|---|---|
| Post-intervention postprandial glucose (mmol/l) | Mean post-intervention postprandial glucose (mmol/l) \pm SD of HT and control group |
| Mean difference postprandial glucose (mmol/l) | Mean difference postprandial glucose (mmol/l) \pm SD between HT and control group |
| Baseline use of glucose lowering drugs | For each type of medication: n (%) |
| Post-intervention use of glucose lowering drugs | For each type of medication: n (%) |

Abbreviations: HT, hormone therapy; SD, standard deviation

Table S3. Additional characteristics of included studies

| Author (year) | No. of patients (HT/control) | Study design | Age of participants* | Menopause duration (yrs)* | Inclusion criteria | Exclusion criteria |
|--|------------------------------|--------------|---|---|--|--|
| <i>Mosnier-Pudar et al. (1991) (4)</i> | 14/11 | P-RCT | HT: 54.4 ±3.4 Control: 56.6 ±4.0 | HT: 4.2 ±2.4 Control: 5.5 ±2.8 | - Postmenopausal women - Diabetes, controlled with a diet or oral therapy - Age 46-64 years | - HT in the month prior to inclusion |
| <i>Andersson et al. (1997) (5)</i> | 25/24 | C-RCT | 59.0 ±5.0 | 10.0 ±5.0 | - Postmenopausal women - Diabetes, controlled with a diet or oral therapy - Age 45-65 years - HbA1c ≥7.0% | - Insulin therapy - Regular smoking (>19 cigarettes/day) - Alcohol abuse - Use of steroid hormones <12 weeks before start of study |
| <i>Brussaard et al. (1997) (6)</i> | 20/20 | P-RCT | HT: 60.4 ±5.9 Placebo: 60.7 ±5.2 | Not stated | - Postmenopausal women - Diabetes controlled with diet and/or oral agents for more than 1 year or detectable plasma C-peptide concentrations after glucagon stimulation | - Manifest CHD, liver or renal disease - Endocrine disease other than diabetes, controlled with a diet or oral therapy - Plasma triglyceride levels >10 mmol/L - use of metformin, diuretics, lipid lowering drugs, corticosteroids, anticonvulsant therapy or postmenopausal HT within the previous 3 months |
| <i>Samaras et al. (1999) (7)</i> | 14/12 | C-RCT | 57.5 ±5.6 | 4.4 ±3.3 | Postmenopausal women - Type 2 diabetes | - Menopause duration >10 years - HT in the preceding 2 years - Weight loss > 3 kg in the preceding 6 months - Any severe concomitant illness |

| | | | | | | |
|--|--|-------|---|------------|---|---|
| <i>Manwaring et al. (2000)</i> (8) | 20/20 | C-RCT | 58.8 ±1.3 | Not stated | <ul style="list-style-type: none"> - Postmenopausal women - Type 2 diabetes, duration of ≥2 years - Treated by diet or oral glucose lowering drugs. | - Contraindication to estrogen therapy |
| <i>Aguilar-Salinas et al. (2001)</i> (9) | 24/30 | P-RCT | HbA1c< 8%: 56 ±2.9 HbA1c>8%: 54 ±5.8 | Not stated | <ul style="list-style-type: none"> - No menses for at least 1 year - Type 2 diabetes - Age 50-65 - No HT during the previous 6 months - BMI 28-35 kg/m2 | <ul style="list-style-type: none"> - Insulin treatment - HT in previous 3 months - Fasting plasma glucose >19.4 mmol/l on two different days |
| <i>Darko et al. (2001)</i> (3) | 11 oral 9 transdermal 13 controls | P-RCT | Not stated | Not stated | <ul style="list-style-type: none"> - Women with cessation of menses >1 year - Type 2 diabetes diagnosed after the age of 40 | <ul style="list-style-type: none"> - Use of insulin or lipid-lowering drugs - HT in the last 3 months - Significant medical comorbidities |
| <i>Friday et al. (2001)</i> (10) | 25/25 | C-RCT | 59 ±5 | Not stated | <ul style="list-style-type: none"> - Postmenopausal women - Type 2 diabetes - Fasting glucose 3.9-11.1 mmol/L, - HbA1c 7-11% | <ul style="list-style-type: none"> - Untreated hypothyroidism - Use of thiazide diuretics, corticosteroids, beta-adrenergic blockers or anabolic steroids |
| <i>Koh et al. (2001)</i> (11) | 20/20 | C-RCT | 59 ±7 | Not stated | <ul style="list-style-type: none"> - Postmenopausal women - History of type 2 diabetes - No history of CHD | - HT during the previous 2 months |
| <i>Perera et al. (2001)</i> (12) | 22/21 | P-RCT | HT: 61.2 ±3.7 Placebo: 62.8 ±4.9 | Not stated | <ul style="list-style-type: none"> - Postmenopausal women - Type 2 diabetes | Not stated |
| <i>Kanaya et al., (2003)</i> (13) | 381/353 | P-RCT | 66 ±6.3 | Not stated | <ul style="list-style-type: none"> - Postmenopausal women ≤79 years old, uterus present - Evidence of CHD based on baseline ECG or previous hospital discharge summary - Fasting glucose > 6.9 mmol/L, or reporting of diabetes diagnosis or diabetic complication, | <ul style="list-style-type: none"> - Myocardial infarction, coronary artery bypass surgery, or mechanical revascularization in previous 6 months - HT use within 3 months of the screening visit - Uncontrolled diabetes |

| | | | | | | |
|---------------------------------------|--------------------------------|--------------------|---|---|--|--|
| | | | | | or initiation of glucose lowering drugs | - Compliance with placebo medication during run-in phase <80% |
| <i>Manning et al. (2003)</i> (14) | 20/27 | First arm of C-RCT | 64 (60-69) | Not stated | - Postmenopausal women (absence of menstrual periods for >2 years) - Type 2 diabetes - No contra-indication for HT | - HbA1c >10% - Concomitant significant medical disorder |
| <i>McKenzie et al. (2003)</i> (15) | 19/23 | P-RCT | HT: 60.7 ±5.5 Placebo: 61.3 ±4.8 | Not stated | - Menopause either natural or surgically induced >1 year - Type 2 diabetes | - Poor glycemic control - Established cardiovascular, cerebrovascular, or peripheral vascular disease |
| <i>Honisett et al. (2004)</i> (16) | 19/19 | C-RCT | 58 ±3 | Not stated | - Postmenopausal women - Type 2 diabetes - Age 49-69 - Taking rosiglitazone therapy 4mg/day for 3 months | - Insulin therapy - Established cardiovascular disease, abnormalities of thyroid or hepatic function |
| <i>Scott et al. (2004)</i> (17) | T1DM: 27/29; T2DM: 47/47 | P-RCT | 61 ±6 | Not stated | Postmenopausal women - Type 1 diabetes and non-insulin treated women with type 2 diabetes | - Hysterectomy |
| <i>Thunell et al. (2006)</i> (18) | 31/23 | C-RCT | 62 ±5.3 | 12 ±6.7 | - Postmenopausal women - Type 2 diabetes - Treated with diet, oral agents and/or an evening dose of insulin - HbA1c >6.0% | - Use of HT in the 3 months prior to inclusion |
| <i>Kernohan et al. (2007)</i> (19) | 30/14 | P-RCT | 62.2 ±5.8 | HT: 13.0 ±1.4 Control: 14.0 ±4.7 | - Postmenopausal - Type 2 diabetes according to national guidelines - Stable oral therapy and/or diet - Age <70 years | - Poor glycemic control - Taking antihypertensive medication |

| | | | | | | |
|--------------------------------------|-------|-------|---|------------|--|--|
| <i>Iniguez et al. (2013)</i> (20) | 15/15 | P-RCT | 59.6 ±3.8 | Not stated | <ul style="list-style-type: none"> - Last menstrual period ≥ 1 years ago - Age 50-65 - Type 2 diabetes - Cholesterol ≥ 200 mg/dl | - HT use in 6 months before inclusion |
| <i>Bitoska et al. (2016)</i> (21) | 20/20 | P-RCT | HT: 49 ±14.94 Control: 48.5 ±13.86 | Not stated | <ul style="list-style-type: none"> - Postmenopausal women in natural menopause - Type 2 diabetes | <ul style="list-style-type: none"> - Hysterectomy - History of recent surgery - Chronic alcohol abuse |

*Data are expressed as mean ±SD or median (IQR).

Abbreviations: HT, hormone therapy; C-RCT, crossover RCT; P-RCT, parallel-group RCT; ET, estrogen (mono)therapy; CHD, coronary heart disease.

Table S4. Risk of bias of individual parallel-group trials

| <u>Study ID</u> | <u>D1</u> | <u>D2</u> | <u>D3</u> | <u>D4</u> | <u>D5</u> | <u>Overall</u> | |
|-----------------------------|-----------|-----------|-----------|-----------|-----------|----------------|--|
| Brussaard et al. 1997 | | | | | | | Low risk |
| Mosnier-Pudar et al. 1999 | | | | | | | Some concerns |
| Aguilar-Salinas et al. 2001 | | | | | | | High risk |
| Darko et al. 2001 | | | | | | | |
| Perera et al. 2001 | | | | | | | D1 Randomization process |
| Kanaya et al. 2003 | | | | | | | D2 Deviations from the intended interventions |
| Manning et al. 2003 | | | | | | | D3 Missing outcome data |
| McKenzie et al. 2003 | | | | | | | D4 Measurement of the outcome |
| Scott et al. 2004 | | | | | | | D5 Selection of the reported result |
| Kernohan et al. 2006 | | | | | | | |
| Iniguez et al. 2013 | | | | | | | |
| Botiska et al. 2016 | | | | | | | |

Table S5. Risk of bias of individual crossover trials

| <u>Study ID</u> | <u>D1</u> | <u>DS</u> | <u>D2</u> | <u>D3</u> | <u>D4</u> | <u>D5</u> | <u>Overall</u> | |
|-----------------------|-----------|-----------|-----------|-----------|-----------|-----------|----------------|---|
| Andersson et al. 1997 | ! | + | ! | + | + | ! | ! | + Low risk |
| Samaras et al. 1999 | - | - | ! | ! | + | ! | - | ! Some concerns |
| Manwaring et al. 2000 | ! | - | + | - | + | ! | - | - High risk |
| Friday et al. 2001 | ! | + | + | + | + | ! | ! | |
| Honisset et al. 2004 | ! | ! | ! | + | + | ! | ! | D1 Randomization process |
| Koh et al. 2001 | ! | - | + | + | + | ! | - | DS Bias arising from period and carryover effects |
| Thunell et al. 2006 | ! | ! | - | - | + | ! | - | D2 Deviations from the intended interventions |
| | | | | | | | | D3 Missing outcome data |
| | | | | | | | | D4 Measurement of the outcome |
| | | | | | | | | D5 Selection of the reported result |

Table S6. Univariate meta-regression analyses: Association between mean difference in HbA1c and mean age of participants, mean diabetes duration, mean baseline HbA1c, mean baseline fasting glucose, mean BMI, treatment duration and diabetes medication use

| Covariates | Number of studies in which the covariate was reported | Slope [95% CI] | p-value |
|---|--|-------------------------|---------|
| Mean age of participants | 14/15 studies (93%), all studies except Darko et al., 2001 (3) | 0.010 [-0.083, 0.103] | 0.816 |
| Mean diabetes duration | 8/15 studies (53%) (4-7, 9, 12, 14, 18) | 0.045 [-0.157, 0.242] | 0.618 |
| Mean baseline HbA1c | All studies | -0.106 [-0.397, 0.186] | 0.448 |
| Mean baseline fasting glucose | 10/15 studies (67%) (3, 5, 9, 12, 14-16, 18, 19, 21) | -0.204 [-0.402, -0.005] | 0.046* |
| Mean BMI | All studies | -0.004 [-0.196, 0.189] | 0.969 |
| Treatment duration | All studies | 0.0001 [-0.004, 0.04] | 0.995 |
| Permitted diabetes medication use in studies: - Oral agents (reference) - Oral agents and insulin | 11/15 studies (73%) (3, 5-7, 10, 12, 15, 16, 18, 19, 21) | 0.170 [-0.502, 0.841] | 0.582 |

*p value <0.05

Table S7. Univariate meta-regression analyses: Association between mean difference in fasting glucose and mean age of participants, mean diabetes duration, mean baseline HbA1c, mean baseline fasting glucose, mean BMI, treatment duration and diabetes medication use

| Covariates | Number of studies in which the covariate was reported | Slope [95% CI] | p-value |
|---|--|-------------------------|---------|
| Mean age of participants | 13/14 studies (93%), all studies except Darko et al., 2001 (3) | 0.038 [-0.154, 0.231] | 0.669 |
| Mean diabetes duration | 4/14 studies (29%) (5, 12, 14, 18) | -0.195 [-0.2003, 1.613] | 0.688 |
| Mean baseline HbA1c | 12/14 studies (86%) (3, 5, 10, 12-16, 18-21) | -0.502 [-1.190, 0.186] | 0.135 |
| Mean baseline fasting glucose | 12/14 studies (86%) (3, 5, 8, 12-16, 18-21) | -0.600 [-0.846, -0.355] | <0.001* |
| Mean BMI | All studies | 0.051 [-0.543, 0.645] | 0.854 |
| Treatment duration | All studies | 0.000 [-0.001, 0.002] | 0.513 |
| Permitted diabetes medication use in studies: - Oral agents (reference) - Oral agents and insulin | 10/14 studies (71%) (3, 5, 8, 10, 12, 15, 16, 18, 19, 21) | 0.361 [-1.410, 2.132] | 0.651 |

*p value <0.05

Table S8. Summary of findings

| Population: Postmenopausal females with type 1 or type 2 diabetes Intervention: Hormone therapy Comparison: Placebo, observation or standard treatment | | | | |
|---|--|----------------------------------|---------------------------------|---|
| Outcomes | Mean difference [95% CI] | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
| HbA1c (%) | -0.56 [-0.80, -0.31] (-6.08 mmol/mol [-8.80, -3,36]) | 488 (15 studies) | ⊕⊕○○ Low | - |
| Fasting glucose (mmol/l) | -1.15 [-1.78, -0.51] | 1259 (15 studies) | ⊕⊕⊕○ Moderate | - |
| Postprandial glucose | Not estimable | 48 (2 studies) | ⊕○○○ Very low | - |
| Use of glucose lowering drugs | Not estimable | See comment | See comment | No studies reported on differences in use of glucose lowering drugs |

Supplemental Figures

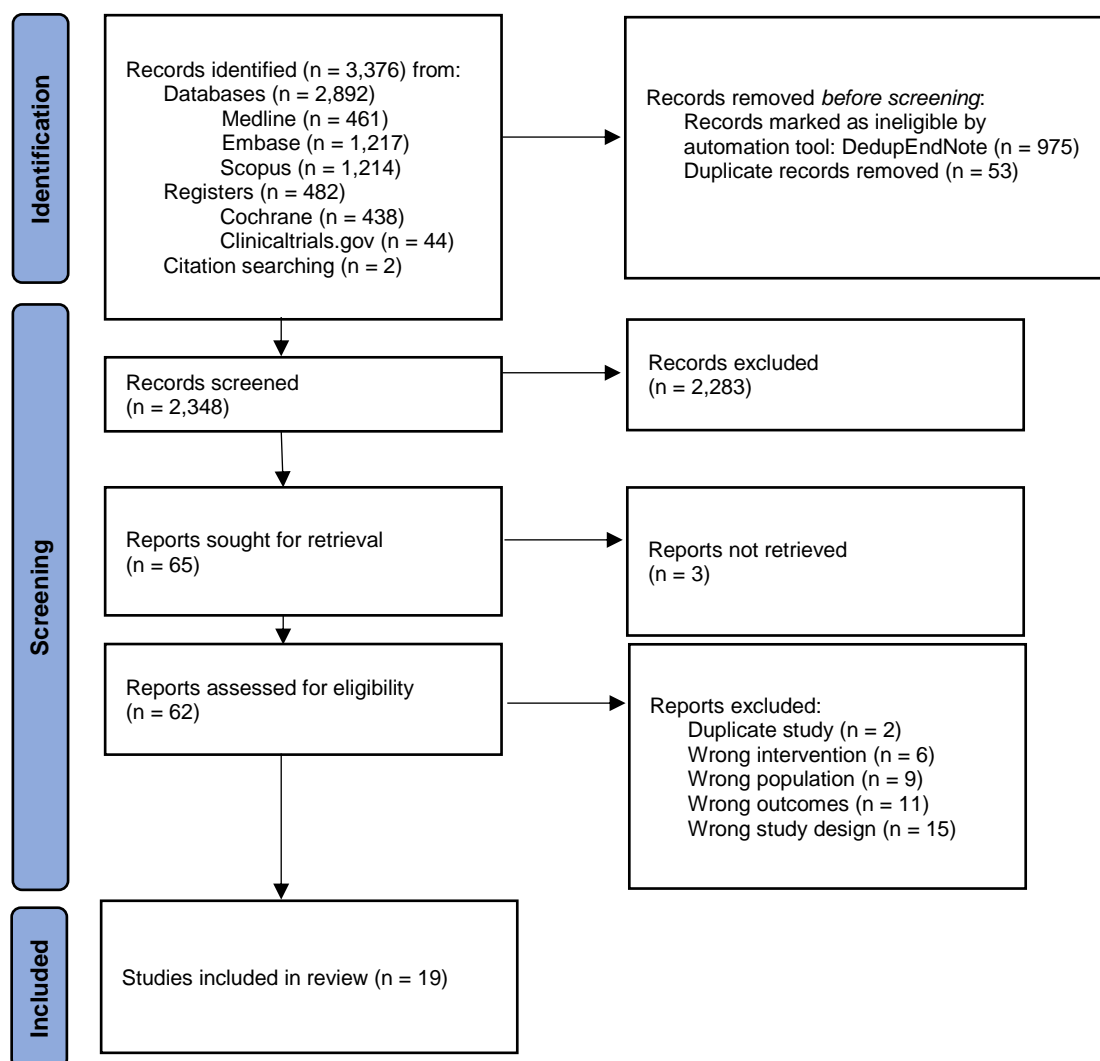
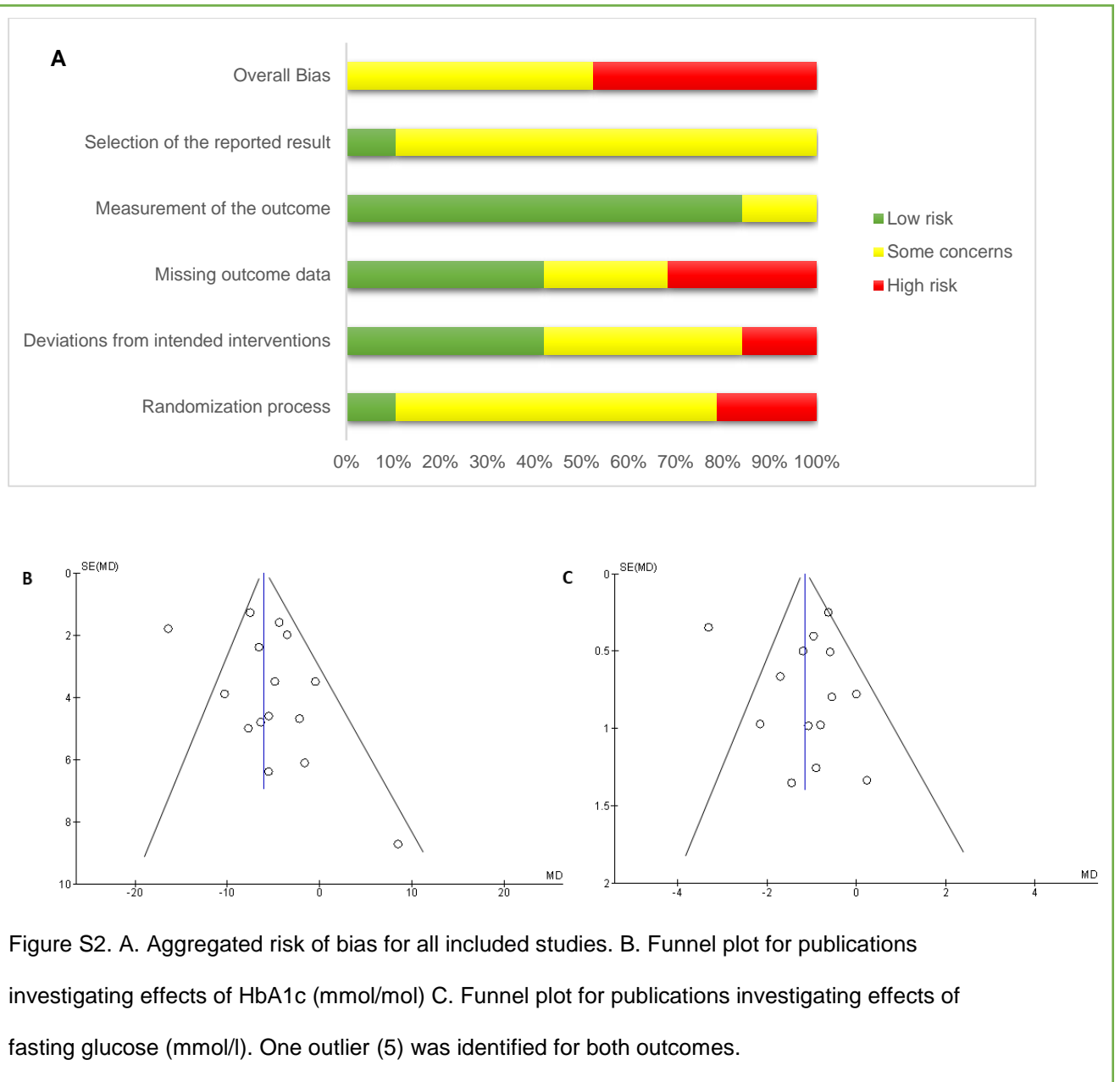


Figure S1. PRISMA flowchart.



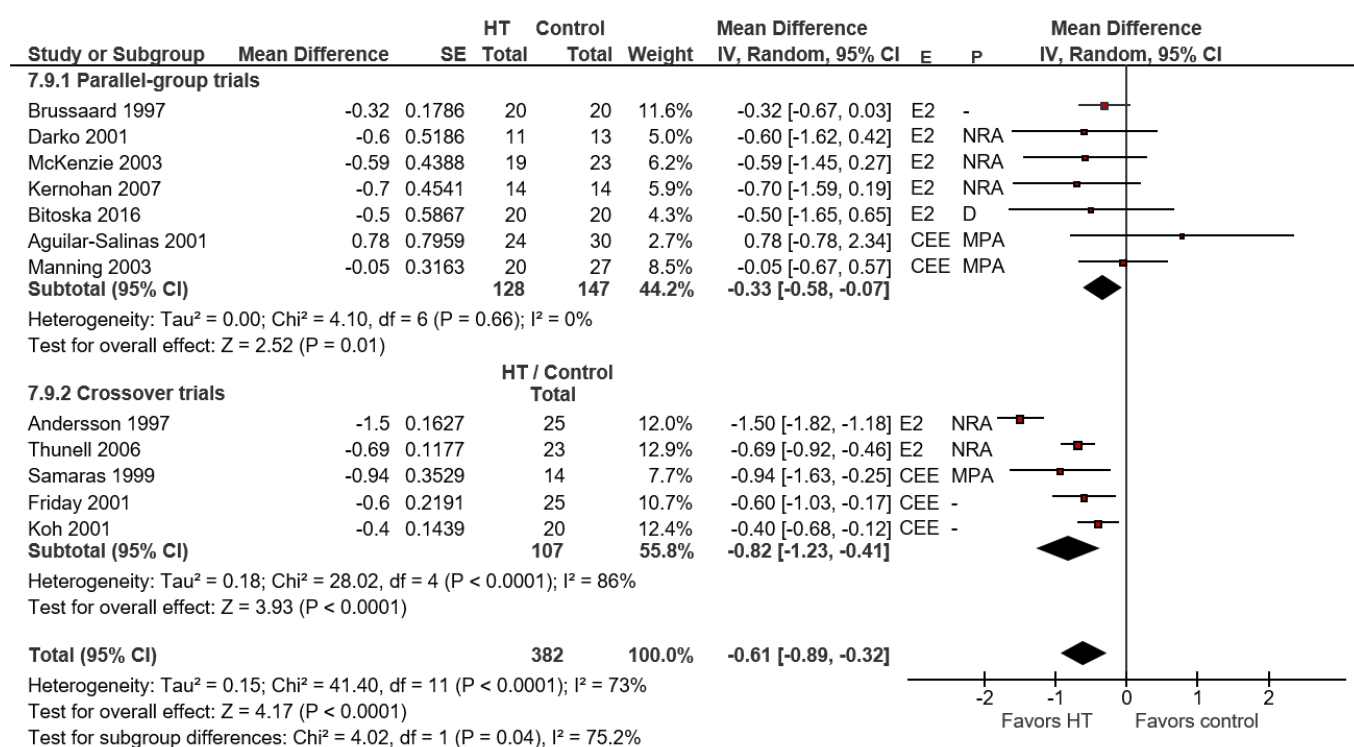


Figure S3. Oral HT reduced HbA1c in postmenopausal women with type 2 diabetes. Meta-analysis of mean HbA1c (%) difference in type 2 diabetes patients, comparing oral HT with controls, and stratified by the type of randomized-controlled trial (parallel-group or crossover trial) and type of estrogen therapy. IV, inverse variance; HT, hormone therapy; E, estrogen preparation; P, progestogen preparation; E2, 17-beta-estradiol; CEE, conjugated equine estrogens; P4, progesterone; NRA, norethisterone; D, drospirenone; MPA, medroxyprogesterone acetate.

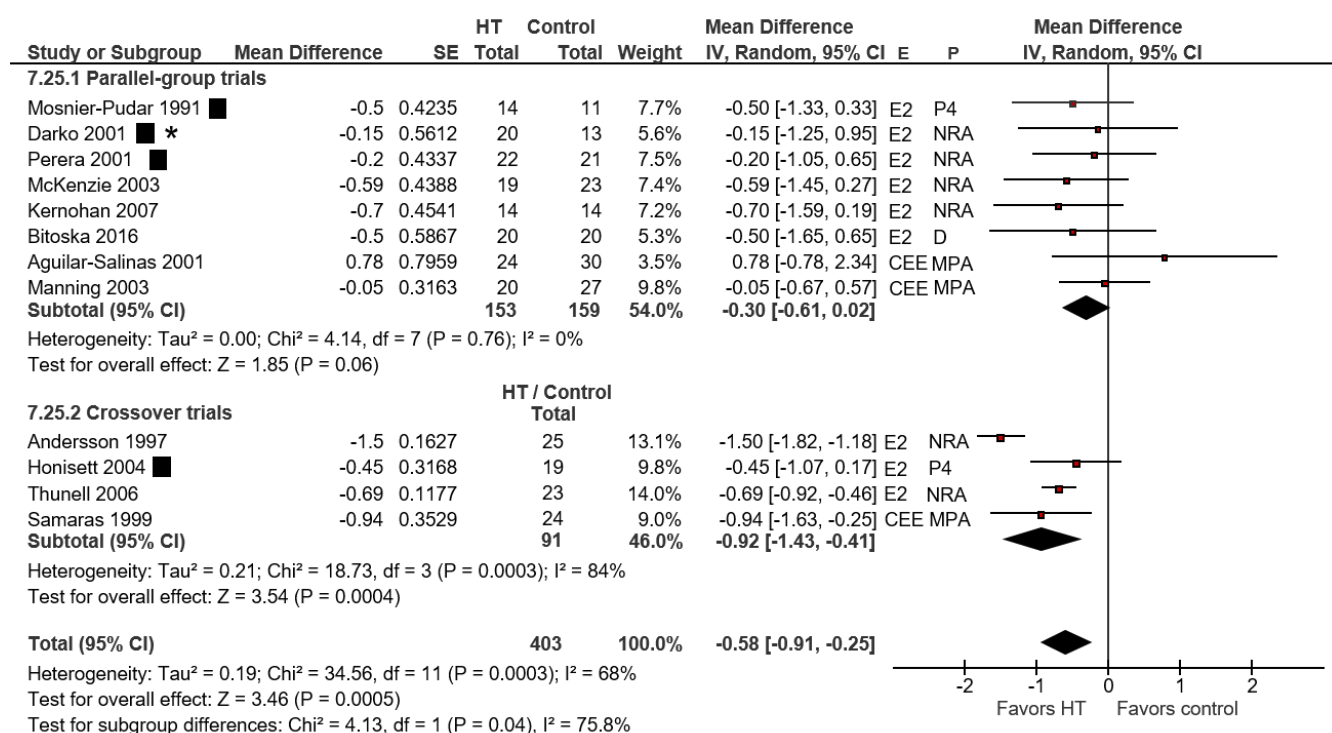


Figure S4. Combined HT reduced HbA1c in postmenopausal women with type 2 diabetes. Meta-analysis of mean HbA1c (%) difference in type 2 diabetes patients, comparing combined HT (estrogen + progestogen) with controls, and stratified by the type of randomized-controlled trial (parallel-group or crossover trial) and type of estrogen therapy. Studies using transdermal HT are shown with a black square. *Use of both transdermal HT and oral HT (3). IV, inverse variance; HT, hormone therapy; E, estrogen preparation; P, progestogen preparation; E2, 17-beta-estradiol; CEE, conjugated equine estrogen; P4, progesterone; NRA, norethisterone; D, drospirenone; MPA, medroxyprogesterone acetate.

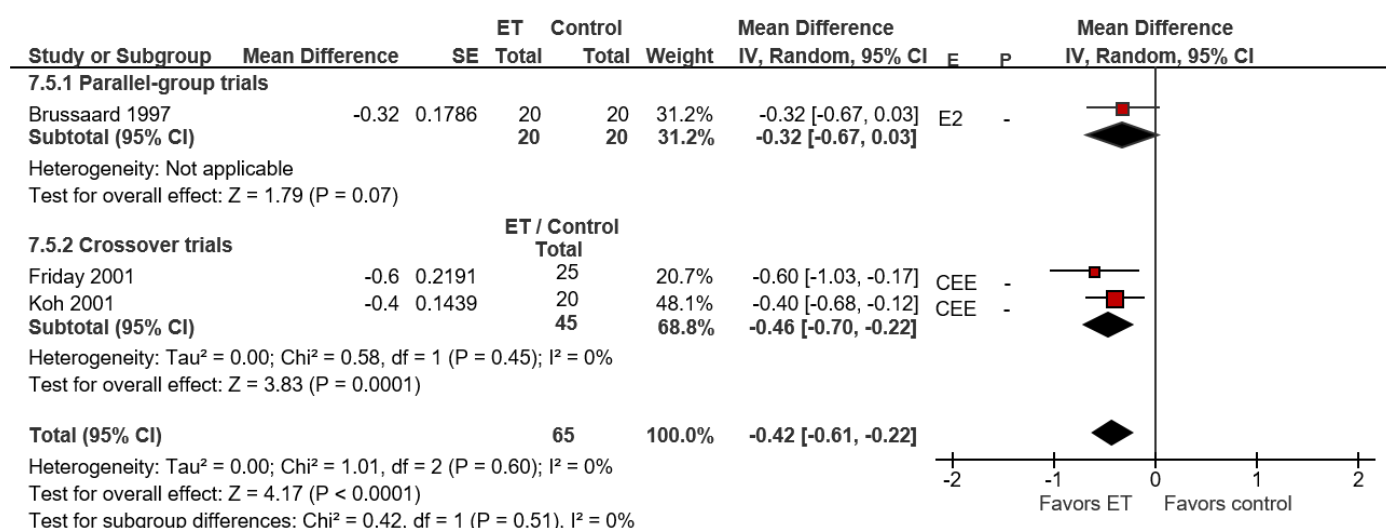


Figure S5. ET reduced HbA1c in postmenopausal women with type 2 diabetes.

Meta-analysis of HbA1c (%) in type 2 diabetes patients treated with estrogen monotherapy compared with the controls, and stratified by type of randomized-controlled trial (parallel-group or crossover trial) and type of estrogen therapy. IV, inverse variance; ET, estrogen therapy; E, estrogen preparation; P, progestogen preparation; E2, 17-beta-estradiol; CEE, conjugated equine estrogen.

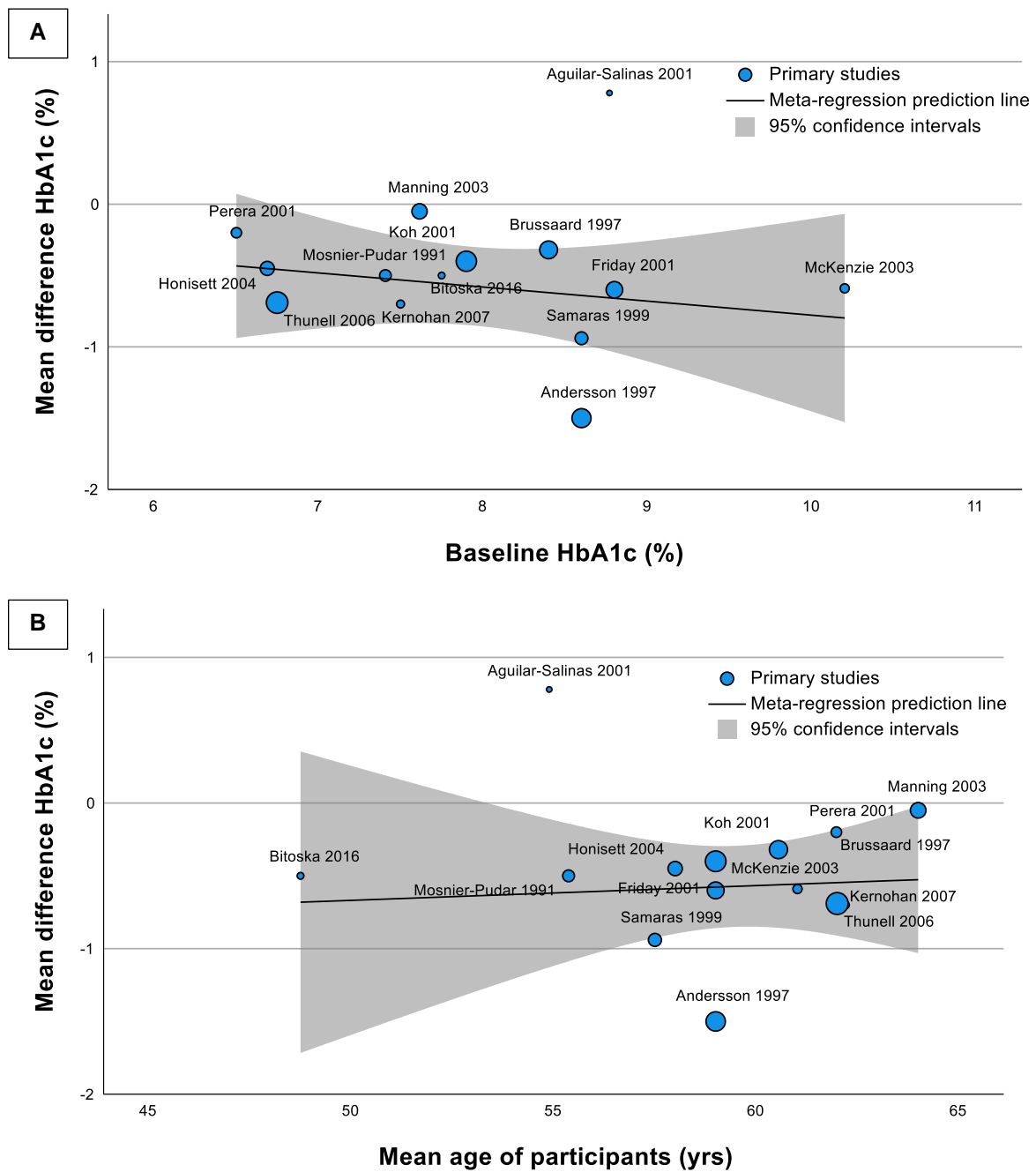


Figure S6. **No association between mean difference in HbA1c and mean age of participants or mean baseline HbA1c values of participants.** A. Bubble plot showing the meta-regression prediction line between HbA1c mean difference and baseline HbA1c (slope = -0.095 [95% CI -0.405, 0.214], $p = 0.513$). B. Bubble plot showing the meta-regression prediction line between HbA1c mean difference and mean age of participants (slope = 0.006 [95% CI -0.90, 0.101], $p = 0.896$).

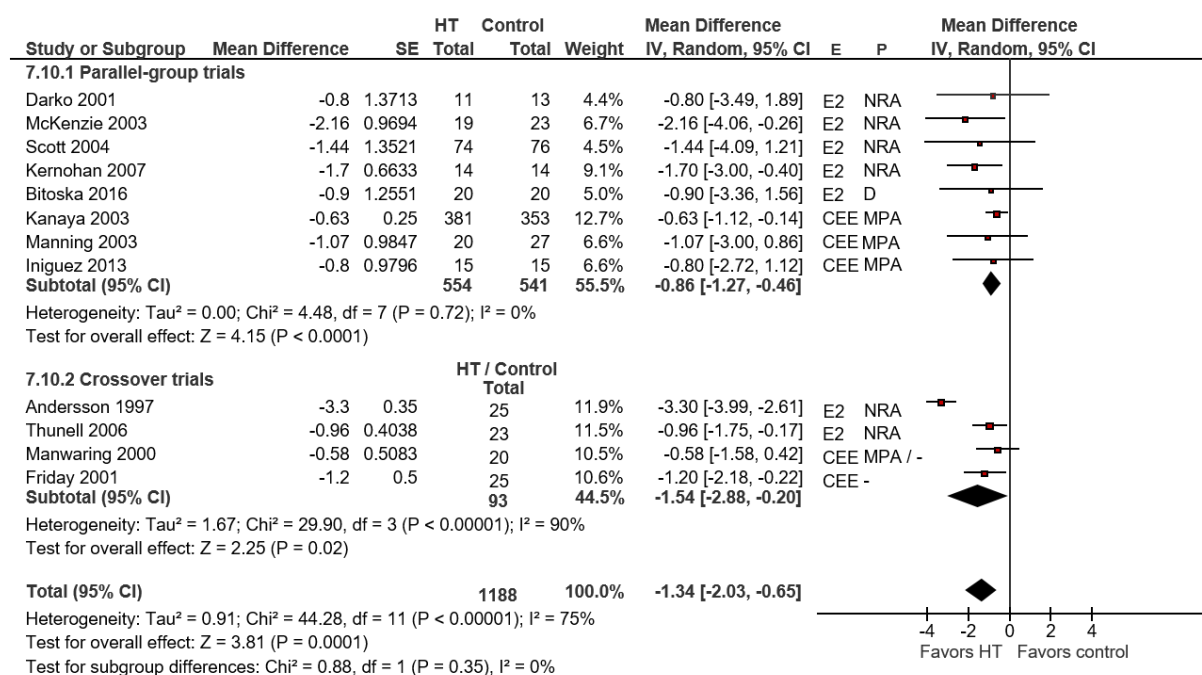


Figure S7. Oral HT reduced fasting glucose in postmenopausal women with type 1 and type 2 diabetes. Meta-analysis comparing mean fasting glucose (mmol/L) difference in type 1 and 2 diabetes patients between the oral HT group and control group. Only one study by Scott et al. (17) included type 1 diabetes patients. IV, inverse variance; HT, hormone therapy; E, estrogen preparation; P, progestogen preparation; E2, 17-beta-estradiol; CEE, conjugated equine estrogen; P4, progesterone; NRA, norethisterone; D, drospirenone; MPA, medroxyprogesterone acetate.

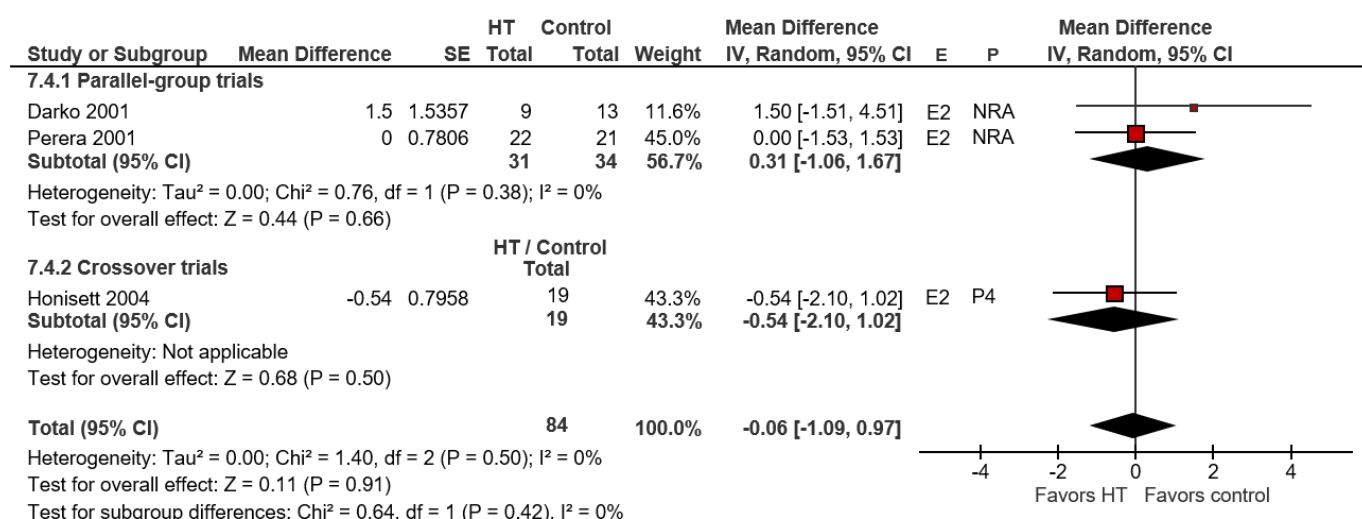


Figure S8. No difference in fasting glucose following transdermal HT in postmenopausal women with type 2 diabetes. Meta-analysis comparing mean fasting glucose (mmol/L) difference in 2 diabetes patients between the transdermal HT group and control group. IV, inverse variance; HT, hormone therapy; E, estrogen preparation; P, progestogen preparation; E2, 17-beta-estradiol; P4, progesterone; NRA, norethisterone.

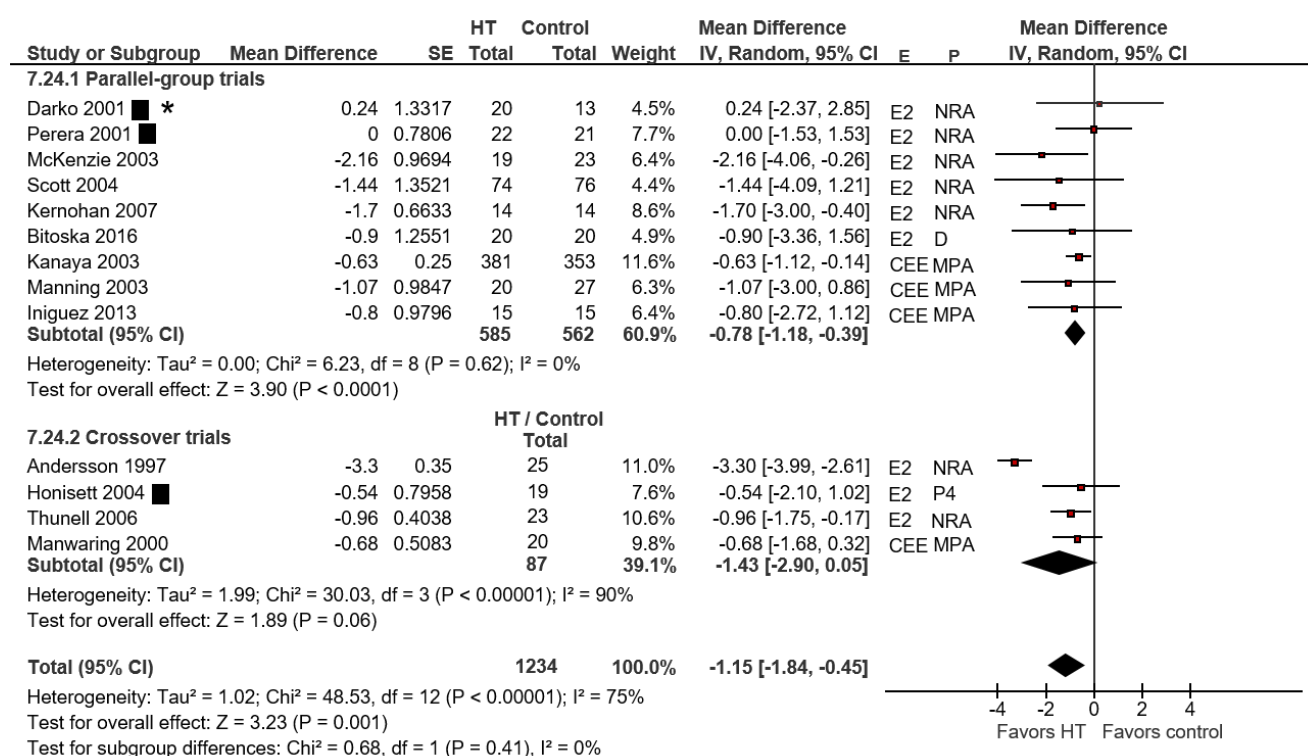


Figure S9. Combined HT reduced fasting glucose in postmenopausal women with type 1 and type 2 diabetes. Meta-analysis comparing mean fasting glucose (mmol/L) difference in type 1 and 2 diabetes patients between the combined HT group (estrogen + progestogen) and control group. Only one study by Scott et al. (17) included type 1 diabetes patients. Studies using transdermal HT are shown with a black square. IV, inverse variance; HT, hormone therapy; E, estrogen preparation; P, progestogen preparation; E2, 17-beta-estradiol; CEE, conjugated equine estrogen; P4, progesterone; NRA, norethisterone; D, drospirenone; MPA, medroxyprogesterone acetate.

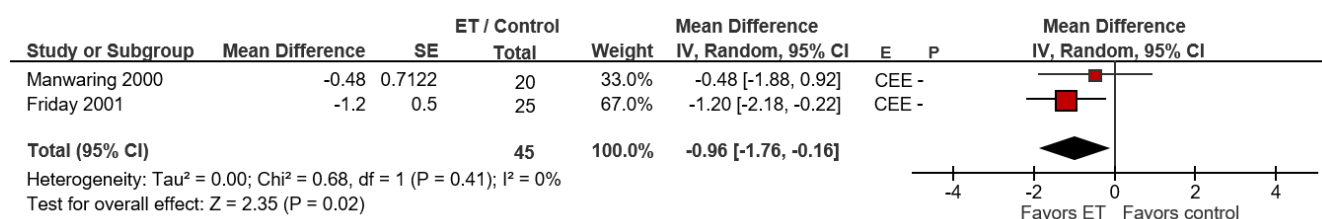


Figure S10. ET reduced fasting glucose in postmenopausal women with type 2 diabetes. Meta-analysis of crossover trials comparing mean fasting glucose (mmol/L) difference in type 2 diabetes patients between the estrogen monotherapy group and control group. IV, inverse variance; ET, estrogen therapy; E, estrogen preparation; P, progestogen preparation; E2, 17-beta-estradiol; NRA, norethisterone.

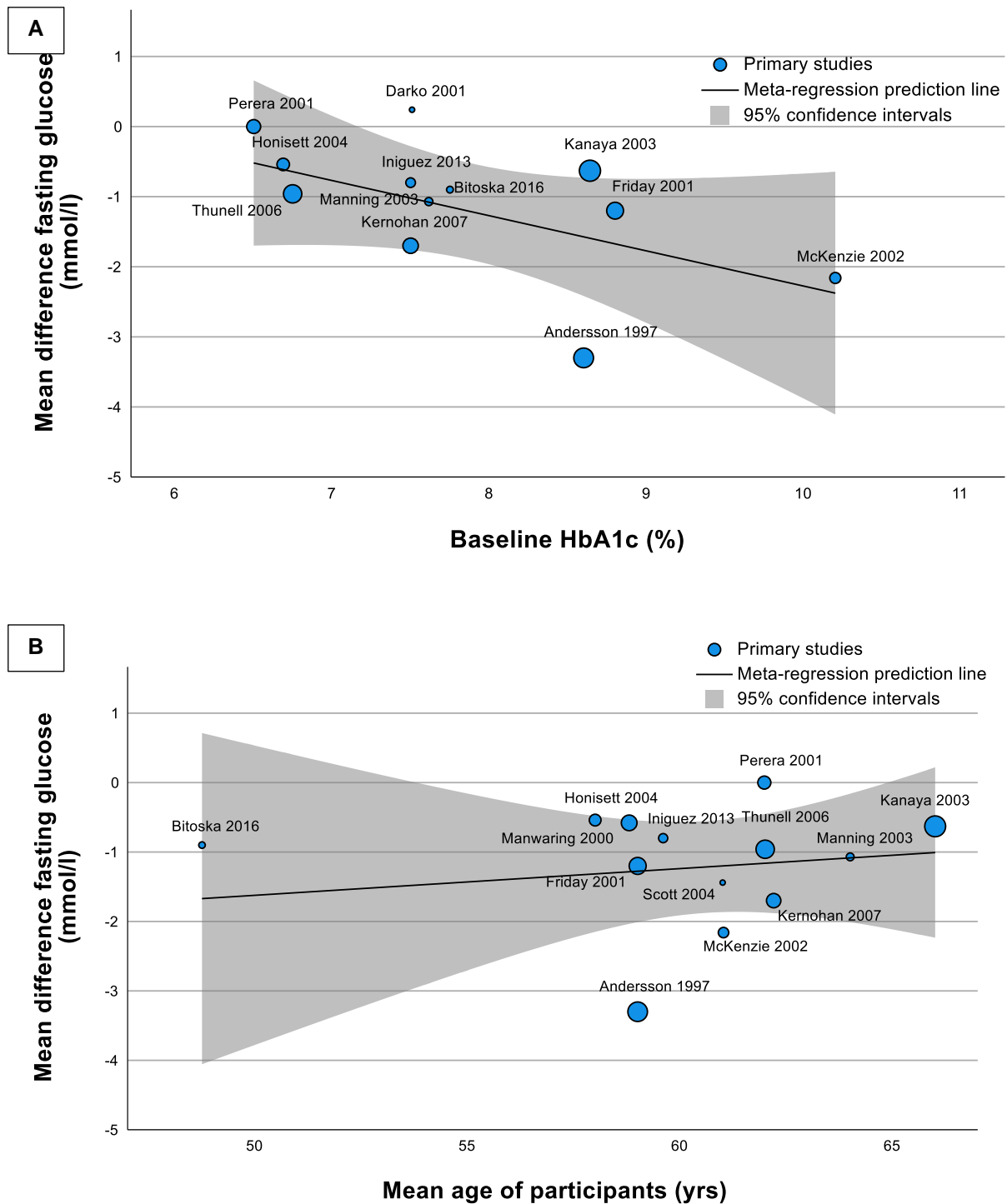


Figure S11. **No significant association between effect size in fasting glucose levels and the covariates mean age of participants or mean baseline HbA1c values of participants.** A. Bubble plot showing the meta-regression prediction line between fasting glucose mean difference and baseline HbA1c values (-0.493 [95% CI $-1.20, 0.213$], $p = 0.146$). B. Bubble plot showing the meta-regression prediction

line between fasting glucose mean difference and mean age of participants (slope = 0.062 [95% CI -0.138, 261], $p = 0.497$).

REFERENCES

1. Jenner WJ, Kanji R, Mirsadraee S, Gue YX, Price S, Prasad S, et al. Thrombotic complications in 2928 patients with COVID-19 treated in intensive care: a systematic review. *J Thromb Thrombolysis*. 2021;51(3):595-607.
2. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost*. 2000;83(3):416-20.
3. Darko DA, Dornhorst A, Kennedy G, Mandeno RC, Seed M. Glycaemic control and plasma lipoproteins in menopausal women with Type 2 diabetes treated with oral and transdermal combined hormone replacement therapy. *Diabetes Res Clin Pract*. 2001;54(3):157-64.
4. Mosnier-Pudar H, Faguer B, Guyenne TT, Tchobroutsky G. [Effects of deprivation and replacement by percutaneous 17 beta estradiol and oral progesterone on blood pressure and metabolic parameters in menopause patients with non-insulin-dependent diabetes]. *Arch Mal Coeur Vaiss*. 1991;84(8):1111-5.
5. Andersson B, Mattsson LA, Hahn L, Mårin P, Lapidus L, Holm G, et al. Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*. 1997;82(2):638-43.
6. Brussaard HE, Gevers Leuven JA, Frolich M, Kluft C, Krans HM. Short-term oestrogen replacement therapy improves insulin resistance, lipids and fibrinolysis in postmenopausal women with NIDDM. *Diabetologia*. 1997;40(7):843-9.
7. Samaras K, Hayward CS, Sullivan D, Kelly RP, Campbell LV. Effects of postmenopausal hormone replacement therapy on central abdominal fat, glycemic control, lipid metabolism, and vascular factors in type 2 diabetes: a prospective study. *Diabetes Care*. 1999;22(9):1401-7.
8. Manwaring P, Morfis L, Diamond T, Howes LG. The effects of hormone replacement therapy on plasma lipids in type II diabetes. *Maturitas*. 2000;34(3):239-47.
9. Aguilar-Salinas CA, Arita Melzer O, Sauque Reyna L, Lopez A, Velasco Perez ML, Guillen LE, et al. Effects of estrogen/medrogestone therapy on the apoprotein B-containing lipoproteins in postmenopausal women with type 2 diabetes mellitus under satisfactory and non-satisfactory glycemic control. *Isr Med Assoc J*. 2001;3(2):137-43.
10. Friday KE, Dong C, Fontenot RU. Conjugated equine estrogen improves glycemic control and blood lipoproteins in postmenopausal women with type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86(1):48-52.
11. Koh KK, Kang MH, Jin DK, Lee SK, Ahn JY, Hwang HY, et al. Vascular effects of estrogen in type II diabetic postmenopausal women. *J Am Coll Cardiol*. 2001;38(5):1409-15.
12. Perera M, Sattar N, Petrie JR, Hillier C, Small M, Connell JM, et al. The effects of transdermal estradiol in combination with oral norethisterone on lipoproteins, coagulation, and endothelial markers in postmenopausal women with type 2 diabetes: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2001;86(3):1140-3.
13. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2003;138(1):1-9.
14. Manning PJ, Sutherland WH, Allum AR, de Jong SA, Jones SD. HRT does not improve urinary albumin excretion in postmenopausal diabetic women. *Diabetes Res Clin Pract*. 2003;60(1):33-9.
15. McKenzie J, Jaap AJ, Gallacher S, Kelly A, Crawford L, Greer IA, et al. Metabolic, inflammatory and haemostatic effects of a low-dose continuous combined HRT in women with type 2 diabetes: potentially safer with respect to vascular risk? *Clin Endocrinol (Oxf)*. 2003;59(6):682-9.
16. Honisett SY, Stojanovska L, Sudhir K, Kingwell BA, Dawood T, Komesaroff PA. Hormone therapy impairs endothelial function in postmenopausal women with type 2 diabetes mellitus treated with rosiglitazone. *J Clin Endocrinol Metab*. 2004;89(9):4615-9.

17. Scott AR, Dhindsa P, Forsyth J, Mansell P, Kliofem Study Collaborative G. Effect of hormone replacement therapy on cardiovascular risk factors in postmenopausal women with diabetes. *Diabetes Obes Metab.* 2004;6(1):16-22.
18. Thunell L, Andersson B, Glassell M, Mattsson LA. The effect of continuous combined HRT on glucose homeostasis and plasma lipids. A placebo-controlled study in postmenopausal women with type 2 diabetes. *Maturitas.* 2006;53(4):430-8.
19. Kernohan AF, Sattar N, Hilditch T, Cleland SJ, Small M, Lumsden MA, et al. Effects of low-dose continuous combined hormone replacement therapy on glucose homeostasis and markers of cardiovascular risk in women with type 2 diabetes. *Clin Endocrinol (Oxf).* 2007;66(1):27-34.
20. Iñiguez H. RM, Vásquez C., Trujillo-Hernández B. Eficacia sobre el perfil lipídico de la terapia de reemplazo hormonal más pravastatina en mujeres posmenopáusicas diabéticas. *Archivos de Medicina.* 2013;9:3-4.
21. Bitoska I, Krstevska B, Milenkovic T, Subeska-Stratrova S, Petrovski G, Mishevskaja SJ, et al. Effects of Hormone Replacement Therapy on Insulin Resistance in Postmenopausal Diabetic Women. *Open Access Maced J Med Sci.* 2016;4(1):83-8.