

Menopause research: randomized clinical trials

Randomized clinical trials (RCTs), started over 30 years ago, have looked at different interventions for menopausal and postmenopausal health. Trials may be undertaken over several years with post-intervention follow-up.

The Women's Health Initiative

Designed in the early 1990s, the US Women's Health Initiative (WHI) randomized trials considered hormone therapy, calcium and vitamin D supplements and dietary modification versus placebo in healthy postmenopausal women aged 50–79.

Hormone therapy trial

Intervention: Estrogen was in the form of conjugated equine estrogen 0.625 mg (CEE) ($n = 10,739$) and the progestogen in the form of medroxyprogesterone acetate 2.5 mg (MPA) ($n = 16,608$), taken once daily.

Original key findings: Compared with placebo, combined therapy reduced fractures and increased invasive breast cancer risk. Estrogen alone reduced fractures and invasive breast cancer incidence and death.

18-year follow-up: Hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular or cancer mortality during a cumulative follow-up of 18 years.

Calcium and Vitamin D Trial

Intervention: Calcium carbonate with 1000 mg elemental calcium combined with vitamin D3 400 IU per day, taken in two divided doses daily, or placebo, taken as one pill twice a day ($n = 36,282$).

Findings: After 7 years, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, did not reduce the incidence of colorectal cancer and increased the risk of kidney stones.

Dietary Modification Trial

Intervention: Low-fat dietary pattern compared with a usual dietary pattern ($n = 48,835$).

Findings: After 8 years, no significant benefit on any outcome (risk of breast or colorectal cancers or coronary heart disease) was found.

A randomized clinical trial (RCT) is a study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention. The experimental group has the intervention being tested, while the comparison or control group has an alternative intervention, a dummy intervention (placebo) or no intervention at all.

Kronos Early Estrogen Prevention Study (KEEPS)

- Designed to study the effect of hormone therapy on subclinical atherosclerosis and on cognitive function in healthy women aged 42–58 up to 3 years after menopause.

Intervention: Oral CEE (0.450 mg daily) or transdermal estradiol 50 µg patches twice a week or placebo ($n = 727$); or oral micronized progesterone 200 mg daily for 12 days each month in estrogen users.

Findings: At 4 years, women in both estrogen arms had fewer menopausal symptoms, improved sleep quality, better sexual functioning and higher bone mineral density than women in the placebo group. There was no difference in the rate of increase in carotid intima media thickness in the three study arms but estrogen users tended to have a slower progression of coronary artery calcification. No effect was found of hormone use on cognitive performance.

Danish Osteoporosis Prevention Study (DOPS)

- Designed to study the effect of hormone therapy on osteoporotic fractures and on composite end-points, including death and admission to hospital for myocardial infarction or heart failure in peri- or postmenopausal women with their last period within the past 2 years.

Intervention: Sequential MHT with oral estradiol with or without norethisterone acetate (for women with a uterus) or no treatment ($n = 1006$)

Findings: After 11 years of treatment, women in the hormone therapy arm had 52% lower risk of death, myocardial infarction or heart failure (RR 0.48, CI 0.26–0.87), an effect that persisted until the 16th year of follow-up.

The Early versus Late Intervention Trial with Estradiol (ELITE)

- Designed specifically to test the timing hypothesis of the effects of hormone use in healthy postmenopausal women without cardiovascular disease.

Intervention: Oral 17β-estradiol (1 mg per day, plus progesterone [45 mg] vaginal gel administered sequentially [i.e., once daily for 10 days of each 30-day cycle] for women with a uterus) or placebo (plus sequential placebo vaginal gel for women with a uterus) ($n = 643$).

Findings: At 5 years, estradiol therapy was associated with less progression of subclinical atherosclerosis than placebo when therapy was initiated within 6 years after menopause, but not when it was initiated after 10 or more years. Also, estradiol initiated within 6 years of menopause did not affect verbal memory, executive functions, or global cognition differently than therapy begun 10 or more years after menopause.

Further information

EMAS CareOnline 2020 <https://emas-online.org/emas-careonline>

NICE Glossary <https://www.nice.org.uk/glossary>

The Women's Health Initiative <https://www.whi.org>