Medicines Adverse Reactions Committee

Meeting date	12/03/2026	Agenda item	3.2.3
Title	Menopausal hormone therapy (MHT): Risks of breast cancer, cardiovascular disease, and cognitive impairment		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

MHT type	**Active ingredient(s)**	**Formulation(s)**
Estrogen alone	estradiol	oral tablet, transdermal patch, transdermal gel,
	conjugated estrogens	oral tablet
	estriol	oral tablet, vaginal cream, vaginal pessary
Progestogen alone	medroxyprogesterone	oral tablet
	progesterone	oral capsule
Estrogen + progestogen	estradiol + norethisterone	oral tablet
Other	tibolone	oral tablet

Pharmac funding	Some medicines are funded
Previous MARC meetings	Reviewed by the MARC in the early 2000s
International action	Reviewed by the US FDA, EMA, Health Canada
Classification	Prescription medicine
Usage data	About 85,000 New Zealanders used estradiol in some form in the 2023/24 financial year

Advice sought	**The Committee is asked to advise:**
	• On the recent evidence on the risks of breast cancer, cardiovascular disease, and cognitive impairment with the use of MHT. The Committee may wish to comment on the following:
	  ○ If the risks differ for estrogen alone or estrogen-progestogen regimens, for different formulations or routes of administration, the age that MHT is initiated or time since menopause, the duration of MHT use.
	  ○ The persistence of these risks.

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1 PURPOSE

Menopausal hormone therapy (MHT), previously known as hormone replacement therapy (HRT), are medicines used to reduce menopausal symptoms. MHT is used either in regimens containing estrogen alone or estrogen in combination with a progestogen. There are different formulations available such as oral tablets, transdermal patches and gels, and vaginal preparations.

Long-term, large-scale studies on MHT were published under the Women's Health Initiative (WHI) over 20 years ago. The WHI estrogen-progestogen study was prematurely stopped in 2002 because investigators reported an increased risk of breast cancer with combined estrogen-progestogen treatment vs. placebo. There was also an increased risk of cardiovascular disease compared with placebo. Although the WHI study for estrogen alone did not find an increased risk of breast cancer, there was an increased risk of cardiovascular disease compared with placebo. Two other WHI studies that evaluated MHT for dementia prevention in women aged 65 to 79 years reported an increased risk of probable dementia compared to placebo for both estrogen alone and combined estrogen-progestogen.

Additional studies have been published on the risks of breast cancer, cardiovascular disease (CVD) and cognitive impairment with the use of MHT since the WHI studies. These have triggered reviews and regulatory actions by the European Medicines Agency (EMA) and Health Canada for breast cancer. Most recently the United States Food and Drug Administration (US FDA) has also conducted a review and requested removal of boxed warnings on CVD, breast cancer and probable dementia.

This paper discusses the recent studies published on the risks of breast cancer, cardiovascular disease, and cognitive impairment with MHT that were included in the US FDA's review.

2 MENOPAUSAL HORMONE THERAPY (MHT)

2.1 Indications and choice

MHT with an estrogen alleviates the symptoms of estrogen deficiency and can be prescribed for women experiencing symptoms that affect their quality of life. The benefits of short-term MHT generally outweigh the risks in most women, especially those aged <60 years or within 10 years of menopause [1].

Estrogen is given with a progestogen in women with a uterus to prevent endometrial hyperplasia. Tibolone has estrogenic and progestogenic activity with weak androgenic activity and can be used if estrogen is not tolerated [1].

The choice of MHT depends on the overall balance of indication, risk and convenience. The woman's age or time since final menstrual period, whether she has an intact uterus and any potential contraindications should be considered [1].

Many of the MHT products also include an indication for the prevention of osteoporosis in postmenopausal women.

Premarin (conjugated estrogens), Provera (medroxyprogesterone), and Utrogestan 200 mg capsule (progesterone) have other non-MHT indications for use:

- Premarin: hypoestrogenic states.
- Provera: diagnosis of primary and secondary amenorrhoea, treatment of dysfunctional (anovulatory) uterine bleeding, and treatment of endometriosis.
- Utrogestan 200 mg: via vaginal route for prevention of preterm birth, and luteal phase support.

2.2 Products

There are a number of estrogen-containing MHT products approved for use in New Zealand. These are available as oral tablets, transdermal patches and gels, or vaginal preparations. Those that have a registration status of consent given or provisional consent are shown in Table 1, along with progestogen-only formulations that have an indication for use in MHT.

Table 1: HRT/MHT products with registration status of consent given or provisional consent

PRODUCT NAME	FORMULATION(s)	STRENGTH(s)
Estrogen alone		
estradiol		
Estradiol (Viatris)	transdermal patch	25 mcg/24h, 50 mcg/24h, 75 mcg/24h, 100 mcg/24h
Estradiol Sandoz[1]	transdermal patch	37.5 mcg/24h, 50 mcg/24h, 75 mcg/24h, 100 mcg/24h
Estradot	transdermal patch	25 mcg/24h, 37.5 mcg/24h, 50 mcg/24h, 75 mcg/24h, 100 mcg/24h
Lyllana[1]	transdermal patch	0.025 mg/24h, 0.05 mg/24h, 0.075 mg/24h, 0.1 mg/24h
Estrogel	transdermal gel	0.06% w/w
Sandrena	transdermal gel	0.1%
Estrofem (estradiol hemihydrate)	tablet	1 mg, 2 mg
Progynova (estradiol valerate)	tablet	1 mg, 2 mg
conjugated estrogens		
Premarin	tablet	0.3 mg, 0.625 mg
estriol		
Ovestin	vaginal cream pessary tablet	0.1% 0.5 mg 2 mg
Progestogen alone		
medroxyprogesterone		
Provera	tablet	2.5 mg, 5 mg, 10 mg
progesterone		
Progesterone ADVZ	capsule	100 mg
Utrogestan	capsule	100 mg, 200 mg[2]
Estrogen + progestogen		
estradiol + norethisterone		
Kliogest	tablet	2 mg + 1 mg
Kliovance	tablet	1 mg + 0.5 mg
Trisequens	tablet	pack containing Kliovance, Estrofem 1 mg, Estrofem 2 mg
Other		
tibolone		
Livial	tablet	2.5 mg

Source: Medsafe Product/Application search (extracted 29 January 2026)
Pharmac-funded medicines are highlighted in green
[1] Provisional consent
[2] Utrogestan 200 mg capsule also approved for use via vaginal route for MHT

2.3 Usage

According to Pharmac, about 85,000 New Zealanders used estradiol in some form in the 2023/24 financial year. Demand for estradiol patches has tripled growing from 1.3 million patches dispensed in 2020/21 to over 4.7 million patches in 2023/24 and this is expected to continue increasing.

The number of people who have received an initial dispensing of a Pharmac-funded MHT by individual product is shown in Table 2 and by formulation in Table 3.

Table 2: Number of people with an initial dispensing of Pharmac-funded MHT, by individual product

Product	2020	2021	2022	2023	2024
estradiol					
25 mcg/day patch	7956	12,087	18,880	33,431	50,719
50 mcg/day patch	11,099	15,088	24,158	49,770	63,461
75 mcg/day patch	3202	3393	6636	12,503	29,561
100 mcg/day patch	9192	7229	10,343	18,086	42,872
0.06% gel[1]	not funded				5298
1 mg tablet	1524	1374	1342	1409	1440
2 mg tablet	792	752	751	795	820
estradiol valerate					
1 mg tablet	7113	7199	8022	8943	11,392
2 mg tablet	7156	7770	8433	9114	11,009
conjugated estrogens[3]					
0.3 mg tablet	1085	928	834	734	594
0.625 mg tablet	1115	954	840	727	622
estriol					
2 mg tablet	736	687	688	713	763
0.5 mg pessaries	7871	8320	8677	9288	10,656
1 mg/g cream	75,789	82,792	89,899	102,160	117,353
medroxyprogesterone[3]					
2.5 mg tablet	4519	5387	6520	6139	5119
5 mg tablet	7070	8017	9558	8681	7726
10 mg tablet	13,186	14,249	14,535	15,934	17,311
progesterone					
100 mg capsule[2]	411	486	8326	48,928	75,255
estradiol + norethisterone					
2 mg + 1 mg tablet	1725	1724	1808	1807	1551
1 mg + 0.5 mg tablet	4583	4610	4757	4688	3862
Trisequens	877	846	842	846	686
Grand total	**167,001**	**183,892**	**225,849**	**334,696**	**458,070**

Source: Pharmaceutical Data web tool (extracted 29 January 2026)

[1] Funded since 1 November 2024

[2] Funded before 1 December 2022 for pre-term labour only

[3] Includes use in non-MHT indications

Table 3: Number of people with an initial dispensing of Pharmac-funded MHT, by formulation

Formulation	2020	2021	2022	2023	2024
Oral (estrogen only)[3]	19,521	19,664	20,910	22,435	26,640
Oral (progestogen only)[2, 3]	25,186	28,139	38,939	79,682	105,411
Oral (estrogen + progestogen)	7185	7180	7407	7341	6099
Transdermal patch	31,449	37,797	60,017	113,790	186,613
Transdermal gel[1]	not funded				5298
Vaginal	83,660	91,112	98,576	111,448	128,009

Source: Pharmaceutical Data web tool (extracted 29 January 2026)
[1] Funded since 1 November 2024
[2] Utrogestan funded before 1 December 2022 for pre-term labour only
[3] Includes use in non-MHT indications

Comments:

As noted by Pharmac, the use of MHT products is increasing over time and has more than doubled in 2024 compared to 2020.

For estrogen-containing products, transdermal patches and topical vaginal products are more commonly used compared to oral formulations.

2.4 Risks associated with MHT

The risks of cardiovascular disease, breast cancer, and dementia were identified from the WHI studies published in the early 2000s. The Women's Health Initiative (WHI) focused on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161,809 postmenopausal women in the age range of 50 to 79 years into a set of clinical trials and one observational study at 40 clinical centres in the United States. The WHIMS studies were smaller sub-studies, focusing specifically on cognitive health and probable dementia.

The WHI studies and other studies looking at multiple outcomes are detailed in this section.

2.4.1 WHI 2002 study (combined estrogen-progestogen) [2]

This particular WHI 2002 study was a randomised controlled primary prevention trial (planned duration 8.5 years) in which 16,608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited. Participants received either a combined estrogen-progestogen (conjugated equine estrogen 0.625 mg/day + medroxyprogesterone acetate 2.5 mg/day), or placebo.

The primary outcome was coronary heart disease (CHD; non-fatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarising the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

On 31 May 2002 after a mean 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial earlier than planned because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic indicated the benefit-risk balance was negative. The estimated hazard ratios (HR) were as follows:

- CHD: 1.29 (95% CI 1.02-1.63), 286 cases
- Breast cancer: 1.26 (95% CI 1.00-1.59), 290 cases
- Stroke: 1.41 (95% CI 1.07-1.85), 212 cases
- PE: 2.13 (95% CI 1.39-3.25), 101 cases

- Colorectal cancer: 0.63 (95% CI 0.43-0.92), 112 cases
- Endometrial cancer: 0.83 (95% CI 0.47-1.47), 47 cases
- Hip fracture: 0.66 (95% CI 0.45-0.98), 106 cases
- Death due to other causes: 0.92, (95% CI 0.74-1.14), 331 cases.

Corresponding HRs for composite outcomes were:

- Cardiovascular disease (arterial and venous): 1.22 (95% CI 1.09-1.36)
- Cancer: 1.03 (95% CI 0.90-1.17)
- Combined fractures: 0.76 (95% CI 0.69-0.85)
- Mortality: 0.98 (95% CI 0.82-1.18)
- Global index: 1.15 (95% CI 1.03-1.28).

Absolute excess risks per 10,000 person-years attributable to estrogen-progestogen were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10,000 person-years.

2.4.2 WHI 2004 study (estrogen alone) [3]

This WHI 2004 study was a parallel trial to the combined estrogen-progestogen one above. Despite the early termination of the WHI 2002 study, this estrogen-only study was continued with careful scrutiny. Enrolled were 10,739 postmenopausal women aged 50-79 years with prior hysterectomy. Women were randomly assigned to receive either conjugated equine estrogen 0.625 mg/day, or placebo.

In February 2004 after a median 7.2 years of intervention duration, the National Institutes of Health decided to terminate the intervention phase of this study prior to the scheduled close-out interval of Oct 2004 to Mar 2005. The estimated HRs were as follows:

- CHD: 0.91 (95% CI 0.75-1.12), 376 cases
- Breast cancer: 0.77 (95% CI 0.59-1.01), 218 cases
- Stroke: 1.39 (95% CI 1.10-1.77), 276 cases
- PE: 1.34 (95% CI 0.87-2.06), 85 cases
- Colorectal cancer: 1.08 (95% CI 0.75-1.55), 119 cases
- Hip fracture: 0.61 (95% CI 0.41-0.91), 102 cases.

Corresponding HRs for composite outcome were:

- Cardiovascular disease: 1.12 (95% CI 1.01-1.24)
- Cancer: 0.93 (95% CI 0.81-1.07)
- Fractures: 0.70 (95% CI 0.63-0.79)
- Mortality: 1.04 (95% CI 0.88-1.22)
- Global index: 1.01 (95% CI 0.91-1.12).

For the outcomes significantly affected by estrogen alone, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10,000 person-years. The estimated excess risk for all monitored events in the global index was a non-significant 2 events per 10,000 person-years.

Comments:

The increased risks of breast cancer and cardiovascular disease with MHT have been known for many years. Around the time that the WHI studies were published, the MARC reviewed these safety concerns on the following occasions:

- 106th meeting, 14 Jun 2001: The safety of hormone replacement therapy
- 109th meeting, 27 Mar 2002: Safety issues with hormone replacement therapy
- 111th meeting, 11 Sep 2002: HRT and cancer/stroke/heart disease
- 114th meeting, 26 Jun 2003: Hormone replacement therapy, breast cancer and mammography.

2.4.3 WHIMS 2003 study (combined estrogen-progestogen) [4]

The Women's Health Initiative Memory Study (WHIMS) is a randomised, double-blind, placebo-controlled clinical trial which began enrolling participants from the WHI estrogen-progestogen trial in May 1996. Of the 4894 eligible participants of the WHI study, 4532 (92.6%) postmenopausal women free of probable dementia aged 65 years or older were enrolled in this WHIMS 2003 study. Incidence of probable dementia (primary outcome) and mild cognitive impairment (secondary outcome) were identified through a structured clinical assessment.

The mean (SD) time between the date of randomisation into WHI and the last Modified Mini-Mental State Examination (3MSE) for all participants was 4.05 (1.19) years. Overall, 61 women were diagnosed with probable dementia, 40 (66%) in the estrogen-progestogen group compared with 21 (34%) in the placebo group. The HR for probable dementia was 2.05 (95% CI 1.21-3.48; 45 vs. 22 cases per 10,000 person-years). This increased risk would result in an additional 23 cases of dementia per 10,000 women per year. Alzheimer's disease was the most common classification of dementia in both study groups. Treatment effects on mild cognitive impairment did not differ between groups (HR 1.07, 95% CI 0.74-1.55; 63 vs. 59 cases per 10,000 person-years).

Comments:

This study found an increased risk of probable dementia for women in the estrogen-progestogen group vs. placebo but there was no difference between the groups for mild cognitive impairment.

2.4.4 WHIMS 2004 study (estrogen alone) [5]

This WHIMS 2004 study evaluated the effect of estrogen alone on incidence of probable dementia among community-dwelling women aged 65 to 79 years with prior hysterectomy. The study also compared the effect of estrogen alone with the effect of estrogen-progestogen (as reported in the WHIMS 2003 study). Of 3200 eligible women free of probable dementia enrolled in the WHI 2004 study, 2947 (92.1%) were enrolled in WHIMS.

The main outcome measure was global cognitive function measured annually with the 3MSE. Scores can range from 0 to 100. During a mean follow-up of 5.4 years, mean (SE) 3MSE scores were 0.26 (0.13) units lower among women assigned to estrogen alone compared with placebo. For pooled hormone therapy (estrogen group combined with estrogen-progestogen group), the mean (SE) decrease was 0.21 (0.08). Removing women with dementia, mild cognitive impairment or stroke from the analyses lessened these differences. For women assigned to estrogen alone compared with placebo, the relative risk of having a 10-unit decrease in 3MSE scores (>3 SDs) was estimated to be 1.47 (95% CI 1.04-2.07).

Comments:

The 3MSE score for women in the estrogen alone group was 0.26 units lower than the placebo group. This difference is highly unlikely to be clinically relevant. The significance of having a 10-unit decrease in the 3MSE score was not well described. It is also unclear if there were specific types of dementia investigated in the study and how this relates to 3MSE scores.

2.4.5 Overview of the 2 WHI studies, 2013 [6]

Manson et al noted there are questions on the risks and benefits of MHT for chronic disease prevention. They conducted a comprehensive, integrated overview of findings from the 2 WHI trials with extended post-intervention follow-up. Both estrogen alone and estrogen-progestogen MHT were included.

During the estrogen-progestogen intervention phase, the numbers of CHD cases were 196 for estrogen-progestogen vs. 159 for placebo (HR 1.18, 95% CI 0.95-1.45) and 206 vs 155, respectively, for invasive breast cancer (HR 1.24, 95% CI 1.01-1.53). Other risks included increased stroke, pulmonary embolism, dementia (in women aged ≥65 years), gallbladder disease, and urinary incontinence. Benefits included decreased hip fractures, diabetes, and vasomotor symptoms. Most risks and benefits dissipated post-intervention, although some elevation in breast cancer risk persisted during cumulative follow-up (434 cases for estrogen-progestogen vs. 323 for placebo; HR 1.28, 95% CI 1.11-1.48).

For estrogen alone, risks and benefits were more balanced with 204 CHD cases for estrogen alone vs. 222 cases for placebo (HR 0.94, 95% CI 0.78-1.14) and 104 vs. 135, respectively for invasive breast cancer (HR 0.79, 95% CI 0.61-1.02). Cumulatively, there were 168 vs. 216 cases of breast cancer diagnosed (HR 0.79, 95% CI 0.65-0.97). Results for other outcomes were similar to estrogen-progestogen.

Neither regime affected all-cause mortality. For estrogen alone, younger women aged 50-59 years had more favourable results for all-cause mortality, myocardial infarction and the global index. Absolute risks of adverse events measured by the global index per 10,000 women annually taking estrogen-progestogen ranged from 12 excess cases for ages 50-59 years to 38 for ages 70-79 years; for women taking estrogen alone, from 19 fewer cases for ages 50-59 years to 51 excess cases for ages 70-79 years. Quality of life outcomes had mixed results in both trials.

The authors conclude MHT has a complex pattern of risks and benefits. Findings from the intervention and extended post-intervention follow-up of the 2 WHI trials do not support use of this treatment for chronic disease prevention, although it is appropriate for symptom management in some women.

Comments:
This was a re-analysis of the WHI studies with a follow-up period. Unsurprisingly, the findings are similar to the WHI studies.

2.4.6 Other earlier studies

Grady et al (1992) [7] critically reviewed the risks and benefits of MHT for asymptomatic postmenopausal women who are considering long-term hormone therapy to prevent disease or to prolong life. They looked at literature published in English since 1970 on the effect of estrogen MHT and estrogen-progestogen MHT on endometrial cancer, breast cancer, CHD, osteoporosis and stroke. Meta-analytic statistical methods were used to pool estimates. They found evidence that estrogen MHT decreases risk for CHD and hip fracture, but long-term treatment increases risk for endometrial cancer and may be associated with a small increase in risk for breast cancer. The increase in endometrial cancer risk can probably be avoided by adding a progestogen to the estrogen regimen for women who have a uterus. They conclude MHT should probably be recommended for women who have had a hysterectomy and for those with CHD or at high risk for CHD. For other women, the best course of action is unclear.

Salpeter et al (2004) [8] conducted a meta-analysis to assess mortality associated with MHT in younger and older postmenopausal women. A search of databases to identify RCTs of MHT from 1966 to Sep 2002 was performed and augmented by scanning some journals and references of articles. The MHT used in these studies ranged from oral tablets to transdermal products, with a mix of estrogen-only and estrogen-progestogen MHT. Pooled data from 30 trials with 26,708 participants showed the OR for total mortality associated with MHT was 0.98 (95% CI 0.87-1.12). MHT reduced mortality in the younger age group (OR 0.61, 95% CI 0.39-0.95) but not in the older age group (OR 1.03, 95% CI 0.90-1.18). For all ages combined, treatment did not significantly affect the risk for cardiovascular or cancer mortality, but reduced mortality from other

causes (OR 0.67, 95% CI 0.51-0.88). The authors conclude MHT reduced total mortality in trials with mean age <60 years. No change in mortality was seen in trials with mean age >60 years.

2.5 Regulator reviews

2.5.1 US FDA (cardiovascular disease, breast cancer, dementia)

The US FDA's review completed in November 2025 included information from the scientific literature, an expert panel, and a public comment period. As a result, the FDA initiated removal of boxed warnings and references to risks of cardiovascular disease, breast cancer, and probable dementia. This was announced in a news release and in a safety communication.

A boxed warning was added to the data sheets of estrogen-containing HRT/MHT following findings from the WHI studies. In the subsequent years, the FDA received questions about whether these boxed warnings are warranted particularly for estrogen-only vaginal formulations. Usage data suggests MHT may be underutilised among women likely to benefit from treatment.

The primary aim of the WHI trials was to evaluate the impact of hormone therapy on cardiovascular disease and other chronic medical conditions in post-menopausal women across all ages with the average participant aged 63 years. However, the average age of women experiencing menopause in the US is 51 years. To help address this, FDA considered multiple additional analyses and long-term follow-up of the WHI participants since the initial results.

The FDA stated they were requesting the following changes to prescribing information of MHT products:

- For all products (systemic and local vaginal): remove from the boxed-warning language related to cardiovascular diseases, breast cancer and probable dementia; remove language related to endometrial cancer except in systemic estrogen-alone products; remove recommendation to use the lowest effective dose for the shortest amount of time.
- For systemic products: add consideration of starting hormone therapy for moderate to severe vasomotor symptoms in women <60 years old or <10 years since menopause; add WHI data in women 50-59 years old; retain boxed warning on endometrial cancer in systemic estrogen-alone products; retain information on cardiovascular diseases, and breast cancer warnings as reported in the WHI studies and Lancet 2019 meta-analysis.
- For local vaginal estrogen products: condense safety information and prioritise information most relevant to the local vaginal formulation.

Comments:

The US FDA's safety communication included a link to their references. These references are summarised under each risk: those pre-dating the WHI studies in the 'Association with MHT' sections and those published after the WHI studies in the 'Recent literature' sections. There is one additional study described in section 5.4.4.

Boxed warnings are used in some countries to highlight special warning statements in data sheets. In New Zealand, while sponsors can choose to include boxed warnings in their data sheets (eg, clozapine) this is not actively encouraged because their effectiveness in influencing prescribing decisions is thought to be limited. None of the MHT NZ data sheets include boxed warnings.

2.5.2 EMA PRAC (breast cancer)

The PRAC reviewed new information on the known risk of breast cancer with HRT in May 2020. This was based on a meta-analysis published in the *Lancet* in 2019 (see section 3.4.1 of this report). The PRAC recommended the following changes to the SmPCs:

- For combined estrogen-progestogen and estrogen-only MHT: updates to reflect that the known higher risk of breast cancer in women using MHT becomes clear after approximately 3 years of use. After stopping MHT, the extra risk will decrease with time, and the time needed to return to baseline depends on the duration of prior MHT use. The new information indicates that the risk may persist for 10 years or more in women who have used MHT for more than 5 years.
- For tibolone-containing MHT, the updated product information will reflect that no data for persistence of risk after stopping treatment are available, but a similar pattern cannot be ruled out.
- For low dose vaginally applied estrogen, the product information will be updated to reflect that the evidence has not shown an increase in breast cancer risk in women who had no breast cancer in the past. It is not known if it can be safely used in women who had breast cancer in the past.

2.5.3 Health Canada (breast cancer)

[redacted]

3 BREAST CANCER

Breast cancer is the uncontrolled growth of abnormal breast cells due to abnormal gene changes or mutations. Abnormal gene changes or mutations are acquired over time with aging. 85-90% of breast cancers are caused by this process, and 5-10% are due to an inherited gene mutation [9].

3.1 Risk factors

The two biggest risks for breast cancer are [9]:

- Gender: Over 99% of cases occur in women
- Age: 3 of 4 diagnoses occur in women aged >50 years. The average age at time of diagnosis is 58 years.

Other risk factors include [10]:

- Genetic mutations (eg, BRCA1 and BRCA2)
- Reproductive history
- Breast density
- Personal history of breast cancer or certain noncancerous breast diseases
- Family history of breast or ovarian cancer
- Previous treatment using radiation therapy.

Comments:

According to Healthify, the average age of menopause is 51 years. This age (>50 years) therefore coincides with when women are likely to start MHT and is also the age that most women are diagnosed with breast cancer.

3.2 Epidemiology in New Zealand [9]

Breast cancer is the most common cancer in women and the third most common cancer overall. More than 3700 New Zealanders are diagnosed with breast cancer every year, of which 26 are men. This equates to 10 women diagnosed with breast cancer each day, of which 1 will be Māori. About 1 in 10 women will be diagnosed with breast cancer at some point in their lives.

More than 650 people die from breast cancer each year and it is the leading cause of death for women <65 years old. Māori women are 33% more likely, and Pacific women are 52% more likely to die from breast cancer than other women.

3.3 Association with MHT

In addition to the two WHI studies summarised in section 2.3 of this report, there were two other well-known studies investigating the association of breast cancer with MHT which are summarised below.

3.3.1 Million women study 2003 [11]

This study was set up to investigate the effects of specific types of MHT on incident and fatal breast cancer. A total of 1,084,110 UK women aged 50-64 years were recruited into the Million Women Study (MWS) between 1996 and 2001, provided information about their use of MHT and other personal details, and were followed up for cancer incidence and death.

Half the women had used MHT with 9364 incident invasive breast cancers and 637 breast cancer deaths registered after an average of 2.6 and 4.1 years of follow-up, respectively. Current users of MHT at recruitment were more likely than never users to develop breast cancer (adjusted relative risk 1.66, 95% CI 1.58-1.75) and die from it (1.22, 95% CI 1.00-1.48). Past users were not at an increased risk of incident or fatal disease (1.01, 95% CI 0.94-1.09 and 1.05, 95% CI 0.82-1.34, respectively). The relative risk was significantly increased for

current users of preparations containing estrogen only (1.30, 95% CI 1.21-1.40), estrogen-progestogen (2.00, 95% CI 1.88-2.12), and tibolone (1.45, 95% CI 1.25-1.68) but the magnitude of the associated risk was substantially greater for estrogen-progestogen than for other types of MHT.

Ten years' use of MHT is estimated to result in five additional breast cancers per 1000 users for estrogen-only preparations and 19 additional cancers per 1000 users of estrogen-progestogen.

Comments:

As with the WHI 2002 study, the MWS found an increased risk of breast cancer for current users of combined estrogen-progestogen.

For current users of estrogen-only, the findings differed with the MWS reporting an increased risk of breast cancer in current users vs. the WHI 2004 study finding a lower risk compared to placebo.

3.3.2 Lancet 1997 meta-analysis (Collaborative Group on Hormone Factors in Breast Cancer) [12]

The Collaborative Group on Hormone Factors in Breast Cancer brought together and re-analysed about 90% of the worldwide epidemiological evidence on the risk of breast cancer with use of MHT.

Individual data on 52,705 women with breast cancer (cases) and 108,411 women without breast cancer (controls) from 51 studies in 21 countries were collected, checked, and analysed centrally.

Among current users of MHT or those who ceased use 1-4 years previously, the relative risk of breast cancer diagnosed increased by a factor of 1.023 (95% CI 1.011-1.036) for each year of use. This increase is comparable with the effect on breast cancer of delaying menopause since the RR of breast cancer increased by a factor of 1.028 (95% CI 1.021-1.034) for each year older at menopause among never-users of MHT. For all studies combined there was a significant increase in the relative risk of breast cancer associated with ever-use of MHT compared with never-use (RR 1.14, SE 0.03, 2p=0.00001). For current or recent users with a duration of MHT use for ≥5 years, the relative risk of having breast cancer diagnosed was 1.35 (95% CI 1.21-1.49).

In North America and Europe, the cumulative incidence of breast cancer between the ages of 50 and 70 in never-users of HRT was about 45 per 1000 women. The cumulative excess numbers of breast cancers diagnosed between the ages of 50 and 70 years per 1000 women who began use of MHT at age 50 and used it for 5, 10, and 15 years were estimated to be 2 (95% CI 1-3), 6 (95% CI 3-9) and 12 (95% CI 5-20), respectively. Whether MHT affects mortality from breast cancer is not known.

After ≥5 years of MHT cessation, there was no significant excess of breast cancer overall or in relation to duration of use. Of the many factors examined that might affect the association, only weight and BMI had a material effect.

Comments:

Data from this meta-analysis is included in some NZ data sheets. It provides analysis from epidemiological studies in contrast from the WHI studies which were randomised trials.

3.4 Recent literature

3.4.1 Lancet 2019 meta-analysis (Collaborative Group on Hormonal Factors in Breast Cancer) [13]

Title: Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence (click here for full text)

The Collaborative Group on Hormonal Factors in Breast Cancer was set up in 1992 and the collaboration has sought to bring together published and unpublished individual participant data from eligible epidemiological studies with information on the type and timing of MHT use. Studies were identified by searching many formal and informal sources regularly from 1 Jan 1992 to 1 Jan 2018.

Analyses assumed that never users would not start and past users would not restart MHT (and, for past users the time since last use was increased by 1 year annually until the index date). Conversely, women who last (before the index date) reported they were using MHT might have stopped before the index date. They were included as current users only if the index date was less than 5 years after the last report. Current users were included up to 5 years after last-reported MHT use.

Anonymised information on individual participants was obtained from 58 studies, including 143,887 postmenopausal women with invasive breast cancer (cases) and 424,972 without breast cancer (controls). The 24 prospective studies contributed 108,647 of the cases (75%). In these 108,647 postmenopausal women, the mean age of developing breast cancer was 65 years (SD 7) and 55,575 (51%) women had used MHT.

Among women who developed breast cancer in the prospective studies, mean age at menopause was 50 years (SD 6) and mean duration of MHT use was 10 years (SD 6) in current users, and 7 years (SD 6) in past users.

RRs were consistently greater for estrogen-progestogen than estrogen-only preparations, were greater in current than in past users, and in both current and past users the risk increased steadily with duration of use (Figure 1). For each MHT type, there was a significant excess risk even during years 1-4 of current use (estrogen-progestogen RR 1.60, 95% CI 1.52-1.69; estrogen-only RR 1.17, 95% CI 1.10-1.26). During years 5-14 current use the RRs were 2.08, 95% CI 2.02-2.15 for estrogen-progestogen and 1.33, 95% CI 1.28-1.37 for estrogen-only. In past users, excess duration-dependent risks persistent for more than a decade after stopping HRT/MHT use.

Few women had started MHT at ages 30-39 years but among those who were still current users 15 years later, there were significant risks with estrogen-progestogen and estrogen-only preparations. Substantial numbers of women started MHT in each of the age groups 40-44, 45-49, 50-54 and 55-59 years and for each group the RRs were similar (Figure 2). Few women had started MHT at ages 60-69 years and their excess risks during years 5-14 of current use were significant for estrogen-progestogen (RR 1.75, 95% CI 1.48-2.06) but not for estrogen-only MHT (RR 1.08, 95% CI 0.90-1.31) based only on 135 exposed cases.

Sensitivity analyses left the main findings largely unchanged.

Figure 3 shows breast cancer RRs during years 5-14 of current use according to the main constituents, doses, and formulation of the last-used MHT. For estrogen-only preparations, there was no heterogeneity of risk between equine estrogen and estradiol or between oral administration and transdermal. By contrast, there appeared to be little risk for topical vaginal estrogens (RR 1.09, 95% CI 0.97-1.23).

Figure 1: Type and timing of MHT use in current users and past users

Source: Figure 2 of Lancet 2019 meta-analysis

Figure 2: Age at first use: relative risks during years 5-14 of current MHT use

Source: Figure 3 of Lancet 2019 meta-analysis

Figure 3: Main types of MHT: relative risks during years 5-14 of current use

Source: Figure 4 of Lancet 2019 meta-analysis

During years 5-14 of use of an estrogen-progestogen combination, the RR was greater for estrogen plus daily progestogen than for estrogen plus intermittent progestogen (usually involving 10-14 days of progestogen per month); RR 2.30 (95% CI 2.21-2.40) and RR 1.93 (95% CI 1.84-2.01), respectively. The RR was significantly increased during years 5-14 of progestogen-only MHT (1.39, 95% CI 1.11-1.75) and of tibolone (1.57, 95% CI 1.43-1.72).

For a given preparation, the RRs during years 5-14 of current use were much greater for estrogen-receptor-positive tumours than for estrogen-receptor-negative tumours, were similar for women starting MHT at ages 40-44, 45-49, 50-54, and 55-59 years, and were attenuated by starting after age 60 years or by adiposity (with little risk from estrogen-only MHT in women who were obese).

After ceasing MHT, some excess risk persisted for more than 10 years; its magnitude depended on the duration of previous use, with little excess following <1 year of MHT use.

If these associations are largely causal, then for women of average weight in developed countries, 5 years of MHT starting at age 50 years would increase breast cancer incidence at ages 50-69 years by 1 in every 50 users of estrogen plus daily progestogen preparations; 1 in every 70 users of estrogen plus intermittent progestogen preparations; and 1 in every 200 users of estrogen-only preparations. The corresponding excesses from 10 years of MHT would be about twice as great.

Comment:

This meta-analysis led to regulatory actions being taken by the EMA and Health Canada, as described in section 2.5 of this report. The actions were to update the MHT EU and Canadian data sheets with information on the persistence of the risk.

The study found that women taking combined MHT for 1 to 4 years had a RR of 1.60 (95% CI 1.52-1.69) and for estrogen alone the RR was 1.17 (95% CI 1.10-1.26). During 5-14 years of use, the RRs were 2.08 and 1.33, respectively. The results from this study differ from the WHI 2004 study which found that estrogen-only MHT had a lower risk of breast cancer when compared to placebo.

It is unclear if this study was an actual meta-analysis or if it was a re-analysis of data from other studies. The method for identifying relevant studies for inclusion was not clearly described in the main article. The supplementary appendix contains more information stating 'potentially eligible epidemiological studies of MHT have continued to be sought regularly by personal contacts, by correspondence with collaborators both at meetings and electronically, by searches of review articles, by searches of references in journal articles, and after 1997 by frequent searches of MEDLINE and PubMed. Search terms varied…'

From the supplementary appendix, the 58 studies included in the authors' analysis were published a number of years ago. For all 58 studies (24 prospective studies, 34 retrospective studies) the median (IQR) was 2002 (1997, 2008), 2005 (2000, 2009) and 1995 (1992, 1998), respectively. This is important because the prescribing of MHT has changed (eg, more use of estrogen patches rather than oral CEE) particularly following publication of the WHI study in 2002.

It is difficult to know how past users and current users were defined. It is also unknown how women who switch between treatments were grouped, though the authors state few women switched between estrogen-only and estrogen-progestogen preparations.

3.4.2 Long-term follow-up of WHI trials (Chlebowski et al, 2020) [14]

Title: Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomised clinical trials (click here for full text)

The authors sought to assess the association of prior randomised use of estrogen-progestogen or prior randomised use of estrogen alone with breast cancer incidence and mortality in the WHI clinical trials.

This was a long-term follow-up of the two WHI studies that included 27,347 postmenopausal women aged 50-79 years with no prior breast cancer and negative baseline screening mammogram. Women were enrolled from 1993 to 1998 with follow-up to 31 December 2017.

Women with a uterus were randomised to receive 0.625 mg/day of conjugated equine estrogen (CEE) plus 2.5 mg/day of medroxyprogesterone (n=8506) or placebo (n=8102). Women with prior hysterectomy were randomised to receive 0.625 mg/day CEE alone (n=5310) or placebo (n=5429).

Use of estrogen-alone compared with placebo was associated with statistically significantly lower breast cancer incidence through cumulative follow-up (238 cases vs. 296; HR 0.78 95% CI 0.65-0.93) (Figure 4). Estrogen-alone use was associated with statistically significantly fewer deaths from breast cancer compared with placebo (30 deaths vs. 46; HR 0.60, 95% CI 0.37-0.97) (Figure 5). The association between estrogen-alone use and lower breast cancer incidence became statistically significant in year 5 and remained so subsequently (Figure 6).

Use of estrogen-progestogen was associated with statistically significantly higher breast cancer incidence through cumulative follow-up (584 cases vs. 447; HR 1.28, 95% CI 1.13-1.45) (Figure 4). Use of estrogen-progestogen was not statistically significantly associated with death from breast cancer (213 deaths vs. 172; HR 1.19, 95% CI 0.97-1.47) (Figure 5). The association with higher breast cancer in the estrogen-progestogen group became statistically significant in year 6 and remained significant subsequently (Figure 6).

Figure 4: Kaplan-Meier estimates for the association MHT with invasive breast cancer during cumulative follow-up

Source: Figure 1 of Chlebowski et al

Figure 5: Association of hormone therapy with breast cancer mortality during cumulative follow-up

Source: Portions of Figure 4 of Chlebowski et al

Figure 6: Plot of stratified score (log-rank) statistics updated annually based on cumulative data

Source: Figure 5 of Chlebowski et al

Comment:

This study used data from the two WHI studies mentioned in section 2.3 of this paper. The updated data in this study includes 424 more breast cancer cases (1565 in this study vs. 1141 in the WHI studies) and 36 more deaths from breast cancer (200 in this study vs. 164 in the WHI studies). Despite the additional cases, the findings are the same as the WHI studies (compared to placebo, estrogen-alone has a lower risk of breast cancer, but estrogen-progestogen has a higher risk of breast cancer) which is unsurprising.

The study goes one step further than the WHI studies by identifying these findings persisted for more than a decade after discontinuing use. It is also somewhat reassuring that there was no significant difference in breast cancer mortality between use of MHT vs. placebo.

3.5 Summary of findings

A summary of the findings from various published studies discussed in this paper on the risk of breast cancer with MHT is shown in Table 4.

Table 4: Summary of findings from studies on the risk of breast cancer with MHT

Study	Estrogen-progestogen	Estrogen alone	Overall
WHI, 2002 [2]	HR 1.26 (95% CI 1.00-1.59) vs. placebo	-	-
WHI, 2004 [3]	-	HR 0.77 (95% CI 0.59-1.01) vs. placebo	-
Overview of WHI studies, 2013 [6]	HR 1.24 (95% CI 1.01-1.53) vs. placebo	HR 0.79 (95% CI 0.61-1.02) vs. placebo	-
Million women study, 2003 [11]	RR 2.00 (95% CI 1.88-2.12) current users vs. never users	RR 1.30 (95% CI 1.21-1.40) current users vs. never users	RR 1.66 (95% CI 1.58-1.75) current users vs. never users
Lancet meta-analysis, 1997 [12]	-	-	RR 1.35 (95% CI 1.21-1.49) for women who had used HRT for 5 years or longer
Lancet meta-analysis, 2019 [13]	RR 1.60 (95% CI 1.52-1.69) during years 1-4 of current use RR 2.08 (95% CI 2.02-2.15) during years 5-14 current use	RR 1.17 (95% CI 1.10-1.26) during years 1-4 of current use RR 1.33 (95% CI 1.28-1.37) during years 5-14 current use	-
Long-term follow-up of WHI trials, 2020 [14]	HR 1.28 (95% CI 1.13-1.45) vs. placebo	HR 0.78 (95% CI 0.65-0.93) vs. placebo	-

Notes: CI: confidence interval, HR: hazard ratio, RR: relative risk, WHI: Women's Health Initiative

3.6 Discussion

The risk of breast cancer with the use of MHT was triggered by the WHI studies in the early 2000s. The WHI study for combined estrogen-progestogen found an increased risk of breast cancer vs. placebo (HR 1.26, 95% CI 1.00-1.59), but the estrogen alone study found a lower risk of breast cancer vs. placebo (HR 0.77, 95% CI 0.59-1.01). The increased risk of breast cancer with combined estrogen-progestogen was also seen in the Million Women Study (MWS) which found an increased risk for current users (RR 2.00, 95% CI 1.88-2.12), and their finding for estrogen alone was also increased for current users (RR 1.30, 95% CI 1.21-1.40).

The Lancet 2019 meta-analysis resulted in changes to the prescribing information as requested by the PRAC [redacted] and was also included in the FDA's wider review and removal of boxed warnings. This

meta-analysis found that women taking combined estrogen-progestogen for 1 to 4 years had a RR of 1.60 (95% CI 1.52-1.69) and for estrogen alone the RR was 1.17 (95% CI 1.10-1.26). During 5-14 years of current use, the RRs were even higher at 2.08 (95% CI 2.02-2.15) and 1.33 (95% CI 1.28-1.37), respectively. In past users, excess duration-dependent risks persisted for more than a decade after stopping MHT use. For topical vaginal estrogens, there appeared to be little risk (RR 1.09, 95% CI 0.97-1.23). Although this meta-analysis provides some additional insights, such as stratifying the risks according to the duration of use, and the persistence of these risks, the studies included in the analyses were not necessarily recent or new. Any changes in prescribing patterns of MHT over the last 20 years are unlikely to be accounted for.

Another study by Chlebowski et al looked at long-term follow-up of the two WHI studies. Although there were more breast cancer cases and deaths from breast cancer compared to the original WHI studies, the findings were the same as the WHI studies which is unsurprising. As with the Lancet 2019 meta-analysis, the findings persisted for more than a decade after discontinuing use.

There is some agreement in the data for combined estrogen-progestogen MHT having an increased risk of breast cancer. However, data for estrogen alone are less clear with some showing an increased risk and others a lower risk of breast cancer. There is some evidence to suggest the risk of breast cancer with vaginal formulations is less than systemic formulations. Both the Lancet 2019 meta-analysis and Chlebowski et al study found that the risk persisted for more than 10 years.

4 CARDIOVASCULAR DISEASE (CVD)

The risk of heart disease rises steeply for women post-menopause [15]. Estrogen has a protective effect on the heart helping to control cholesterol levels, reducing the risk of fat building up in the arteries, and keeping blood vessels healthy [16]. Once the ovaries stop producing estrogen, fat can build up in the arteries increasing risks of developing coronary heart disease (CHD), myocardial infarction or stroke [16].

The benefit of estrogen remains for about 10-15 years after menopause, then the risk for women increases to the same heart disease risks as men [15].

4.1 Risk factors

Risk factors for CVD in women that cannot be changed include [16]:

- Increasing age: CVD is most common in people aged 50 and over. The risk for women increases significantly once they reach menopause.
- Gender: While men are slightly more at risk of CVD than women, it is still a leading cause of death and disability in women.
- Family history.

Modifiable risk factors in women include [16]:

- High blood pressure
- History of pre-eclampsia
- Diabetes
- Stress
- High cholesterol
- Inactivity
- Overweight and obesity
- Poor nutrition
- Smoking
- Alcohol.

Women without known risk factors should have a heart check from 55 years of age. Women with known risks should get a check at 45, while Māori, Pasifika and South Asian women are advised to go for a check from age 40. Those with severe mental illness may need to be checked as early as 25 years old [15].

4.2 Epidemiology in New Zealand

More than 55 women die of CVD each week making it the single biggest cause of death for women in New Zealand. There are more than 65,000 women living with CVD in New Zealand. More than 3000 New Zealand women die from a heart attack each year [16].

4.3 Association with MHT

A number of studies that pre-date the WHI studies have investigated the risk of CVD with MHT.

Wilson et al (1985) [17] investigated the effect of estrogen on morbidity from CVD in 1234 postmenopausal women aged 50 to 83 years participating in the Framingham Heart Study's 12th biennial examination (index examination). Medicine history recorded at biennial examinations 8 through 12 was used to classify the degree of estrogen exposure before 8 years of observation for cardiovascular morbidity and mortality. Despite a favourable cardiovascular risk profile and control for the major known risk factors for heart disease, women using postmenopausal estrogen at one or more examinations had >50% elevated risk of cardiovascular morbidity and more than a two-fold risk for cerebrovascular disease after the index examination. Increased rates for myocardial infarction were observed particularly among estrogen users who smoked cigarettes. Conversely, among non-smokers estrogen use was associated only with an increased incidence of stroke. No

benefits from estrogen use were observed in the study group. Mortality from all causes and from CVD did not differ for estrogen users and non-users.

Stampfer et al (1985) [18] surveyed 121,934 female nurses aged 30 to 55 years and mailed them questionnaires beginning in 1976 to clarify the possible role of postmenopausal estrogen use in coronary heart disease (CHD). Information on hormone use and other potential risk factors was updated and the incidence of CHD was ascertained through additional questionnaires in 1978 and 1980 with a 92.7% follow-up. During 105,786 person-years of observation among 32,317 postmenopausal women who were initially free of CHD, 90 women had either non-fatal myocardial infarctions (65 cases) or fatal CHD (25 cases). Compared with the risk in women who had never used postmenopausal hormones, the age-adjusted relative risk (RR) of coronary disease in those who had ever used them was 0.5 (95% CI 0.3-0.8) and the risk in current users was 0.3 (95% CI 0.2-0.6). The RRs were similar for fatal and non-fatal disease and were unaltered after adjustment for cigarette smoking, hypertension, diabetes, high cholesterol levels, a parental history of myocardial infarction, past use of oral contraceptives, and obesity.

Stampfer & Colditz (1991) [19] noted the considerable epidemiological evidence that has accumulated on the effect of postmenopausal estrogens on CHD risk. Five hospital-based case-control studies yielded inconsistent but generally null results. However, these are difficult to interpret due to problems in selecting appropriate controls. Six population-based case-control studies found decreased RRs among estrogen users, though only one was statistically significant. Three cross-sectional studies of women with or without stenosis on coronary angiography each showed markedly less atherosclerosis among estrogen users. Of 16 prospective studies, 15 found decreased RRs which were statistically significant in most instances. The Framingham study alone observed an elevated risk which was not statistically significant when angina was omitted. A re-analysis of the data showed a non-significant protective effect among younger women and a non-significant increase in risk among older women. Overall, the bulk of the evidence strongly supported a protective effect of estrogens that is unlikely to be explained by confounding factors. A quantitative overview of all studies taken together yielded a RR of 0.56 (95% CI 0.50-0.61) and taking only the internally controlled prospective and angiographic studies, the RR was 0.50 (95% CI 0.43-0.56).

Barrett-Connor & Bush (1991) [20] reviewed the evidence that estrogen is protective against the development of CVD in women. To their knowledge, no studies in women had looked at endogenous estrogen levels as predictors of CVD. Studies of surrogate measures of endogenous estrogen such as parity, age at menarche, and age at menopause have provided inconsistent results. Current use of oral contraceptives increases risk in older women who smoke cigarettes but most studies of past use show no increased risk. Most, but not all, studies of MHT in postmenopausal women show around a 50% reduction in risk of a coronary event in women using unopposed oral estrogen. These important observations need to be confirmed in a double-blind RCT since protection is biologically plausible and the magnitude of the benefit would be quite large if selection factors can be excluded.

Hulley et al (1998) [21] conducted a randomised, blinded, placebo-controlled secondary prevention trial to determine if estrogen-progestogen treatment alters the risk of CHD events in postmenopausal women with established coronary disease. A total of 2763 women with coronary disease aged <80 years and postmenopausal with an intact uterus were included. They were randomised to either a combined estrogen-progestogen (conjugated equine estrogen 0.625 mg/day + medroxyprogesterone 2.5 mg/day; n=1380), or placebo (n=1383) and followed-up for an average of 4.1 years. The primary outcome was non-fatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularisation, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischaemic attack, and peripheral arterial disease. All-cause mortality was also considered. Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the treatment group and 176 women in the placebo group had MI or CHD (relative hazard (RH) 0.99, 95% CI 0.80-1.22). Within the overall null effect, there was a statistically significant time trend with more CHD events in the treatment group than in placebo in year 1 and fewer in years 4 and 5. More women in the treatment group than in the placebo group experienced VTE (34 vs. 12; RH 2.89, 95% CI 1.50-5.58) and gall

bladder disease. There were no significant differences in several other endpoints for which power was limited, including fracture, cancer and total mortality.

4.4 Recent literature

4.4.1 Cochrane review of RCTs (Boardman et al, 2015) [22]

Title: Hormone therapy for preventing cardiovascular disease in post-menopausal women (click here for full text)

This Cochrane review updated a previous review published in 2013. Databases and registers were searched on 25 Feb 2014. Selection criteria were RCTs of women comparing orally administered MHT with placebo or a no treatment control with a minimum 6-months follow-up.

An additional 6 trials were identified in this update and therefore the review included 19 trials with a total of 40,410 post-menopausal women. Study quality was good overall and generally at low risk of bias with findings dominated by the 3 largest trials.

There was high quality evidence that MHT in both primary and secondary prevention conferred no protective effects for all-cause mortality, cardiovascular death, non-fatal myocardial infarction, angina, or revascularisation (Tables 5 and 6). However, there was an increased risk of stroke in those in the MHT arm for combined primary and secondary prevention (RR 1.24, 95% CI 1.10-1.41). VTE was increased (RR 1.92, 95% CI 1.36-2.69) as were pulmonary emboli (RR 1.81, 95% CI 1.32-2.48) on hormone therapy relative to placebo. The absolute risk increase for stroke was 6 per 1000 women, VTE 8 per 1000 women, and pulmonary embolism 4 per 1000 women.

Table 5: MHT compared to placebo for primary prevention of CVD in post-menopausal women

Source: Summary of findings 1 of Boardman et al 2015 [22]

Table 6: MHT compared to placebo for secondary prevention of CVD in post-menopausal women

Source: Summary of findings 2 of Boardman et al 2015 [22]

Subgroup analyses

Those who started MHT <10 years after menopause had lower mortality (RR 0.70, 95% CI 0.52-0.95, moderate quality evidence) and CHD (composite of death from cardiovascular causes and non-fatal MI) (RR 0.52, 95% CI 0.29-0.96, moderate quality evidence) though they were still at increased risk of VTE (RR 1.74, 95% CI 1.11-2.73, high quality evidence) compared to placebo or no treatment (Table 7).

Table 7: MHT commenced <10 years after menopause for preventing CVD

[redacted]

Source: Summary of findings 3 of Boardman et al 2015 [22]

In those who started treatment >10 years after menopause there was high quality evidence that it had little effect on death or CHD between groups but there was an increased risk of stroke (RR 1.21, 95% CI 1.06-1.38, high quality evidence) and VTE (RR 1.96, 95% CI 1.37-2.80, high quality evidence) (Table 8).

The authors conclude their findings provide strong evidence that treatment with MHT in post-menopausal women overall, for either primary or secondary prevention of CVD events has little if any benefit and causes an increase in the risk of stroke and VTE.

Table 8: MHT commenced >10 years after menopause of preventing CVD

Source: Summary of findings 4 of Boardman et al 2015 [22]

Comments:

This Cochrane review was an update on the 2013 review and included 6 additional RCTs on oral MHT vs. placebo. The review found that MHT for both primary and secondary prevention of CVD had no protective effects for all-cause mortality, cardiovascular death, non-fatal myocardial infarction, angina, or revascularisation. However, there were increased risks of stroke and VTE.

The findings generally support that women starting MHT early in menopause (<10 years after menopause) are likely to have more benefit compared to women who start MHT later in menopause (>10 years after menopause).

4.4.2 Systematic review and meta-analysis (Kim et al, 2020) [23]

Title: A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases (click here for full text)

The authors conducted a systematic review and meta-analysis of RCTs and observational studies to assess the association between MHT and CVD. PubMed and Embase were searched for articles published from 2000 to 2019 using review methods based on the previous 2015 Cochrane review shown above.

A total of 26 RCTs and 47 observational studies were identified. Of the 26 RCTs, 18 (69.2%) were published before 2006, the year in which the WHI findings were being actively re-evaluated. Of the 47 observational studies, 61.7% were published after 2006. The study populations in the RCTs were older (median age 63.6 vs. 60.6 years, respectively) and had more underlying diseases than those in observational studies. Median follow-up duration of RCTs was shorter than observational studies (3.4 vs. 6.8 years).

Findings are summarised in Table 9. Increased risks of VTE were consistently identified in both study types: RCT summary estimate (SE) 1.70, (95% CI 1.33-2.16); observational studies 1.32 (95% CI 1.13-1.54). There was an increased risk of stroke in RCTs (SE 1.14, 95% CI 1.04-1.25) and a decreased risk of MI in observational studies (SE 0.79, 95% CI 0.75-0.84).

Table 9: Summary of findings in RCTs and observational studies

Source: Table 2 of Kim et al 2020 [23]

Notes: MHT: menopausal hormonal therapy, CVD: cardiovascular disease, CHD: coronary heart disease, CI: confidence interval, MI: myocardial infarction, PE: pulmonary embolism, VTE: venous thromboembolism. *Summary estimates (95% CI) were measured by fixed-effect models if I^2 was <30% and P for heterogeneity was >0.05; otherwise, the summary estimates (95% CI) were measured by random-effect models

Differential clinical effects depending on timing of initiation, underlying disease, regimen type, and route of administration were identified through subgroup analyses.

The authors conclude their findings support the idea that risks and benefits of MHT are likely to depend on the characteristics of the women who are treated. MHT is still not recommended for prevention of chronic diseases. However, it may have beneficial effects with respect to CVD and mortality in postmenopausal women with severe menopausal symptoms, after sufficient consideration of underlying diseases and timing of treatment initiation. Use of non-oral rather than oral types of MHT for menopausal symptoms may be suggested for women at high risk of VTE and stroke. Further studies to investigate the influence of ethnicity or specific MHT types are needed.

Comments:

This systematic review and meta-analysis included RCTs and observational studies, with findings presented by these study groupings.

RCTs had a shorter follow-up duration compared to observational studies which is not unexpected. Women in RCTs were older (median age 63.6 vs. 60.6 years), initiated MHT later after menopause and had more underlying medical conditions.

Both RCTs and observational studies found increased risks of VTE. Findings for all-cause death and cardiovascular death in RCTs trended towards the null, with possibly more of a beneficial effect seen in observational studies.

4.4.3 Time and timing of MHT (Hodis & Mack, 2022) [24]

Title: Menopausal hormone replacement therapy and reduction of all-cause mortality and cardiovascular disease: It's about time and timing (click here for full text).

The authors looked at the time and timing of MHT and reduction of all-cause mortality and CVD. Totality of evidence indicates MHT effects are determined by timing of initiation according to age and/or time-since-menopause, underlying health of target tissue and duration of therapy. Initiated in women <60 years of age during menopause, MHT significantly reduces all-cause mortality and CVD whereas other primary CVD prevention therapies such as lipid-lowering fail to do so.

The timing hypothesis

According to the hypothesis, estrogen exerts early beneficial effects of MHT on healthy endothelium, but adverse effects on established plaques. Randomised controlled atherosclerosis imaging trials and animal studies strongly support the healthy endothelium hypothesis showing that MHT is more effective in maintaining vascular health rather than treating established vascular disease manifested as atherosclerosis lesions.

Timing of initiation of MHT

Following the WHI studies, findings on CHD outcomes with MHT in RCTs contrasted those in observational studies. This was likely due to different populations of women in these two study designs. Observational studies show a 30-50% reduction in CHD in MHT users vs. non-users. RCTs have shown a null effect of MHT on CHD in analyses of women in all ages, typically 45-90 years old when randomised to MHT vs. placebo.

Meta-analyses and the Cochrane review show reductions in all-cause mortality and CHD in women initiating MHT <60 years old and/or <10 years since menopause.

Summary

Magnitude and type of MHT-associated risks, including breast cancer, stroke and VTE are rare (<10 events/10,000 women), not unique to MHT and comparable with other medicines. MHT is a sex-specific and time dependent primary CVD prevention therapy that concomitantly reduces all-cause mortality as well as other aging-related diseases with an excellent risk profile. Keeping in mind that prevention strategies must be personalised, HCPs and patients can use cumulated MHT data in making clinical decisions concerning chronic disease prevention including CVD and mortality reduction.

4.4.4 Secondary analysis of WHI trials (Rossouw et al, 2025) [25]

Title: Menopausal hormone therapy and cardiovascular diseases in women with vasomotor symptoms: A secondary analysis of the Women's Health Initiative randomised clinical trials (Annex 1)

The authors conducted a secondary analysis of the 2 WHI RCTs of MHT in postmenopausal women aged 50 to 79 years. Data were collected from Nov 1993 to Sep 2012 and data were analysed from Dec 2024 to May 2025. Participants were exposed to estrogen alone (conjugated equine estrogens, CEE, 0.625 mg/day), or estrogen-progestogen (CEE 0.625 mg/day + medroxyprogesterone 2.5 mg/day), vs. placebo.

The primary outcome was atherosclerotic CVD (ASCVD) modified from the American Heart Association definition to include any of non-fatal myocardial infarction, hospitalisation for angina, coronary revascularisation, ischemic stroke, peripheral arterial disease, carotid artery disease, and CVD death.

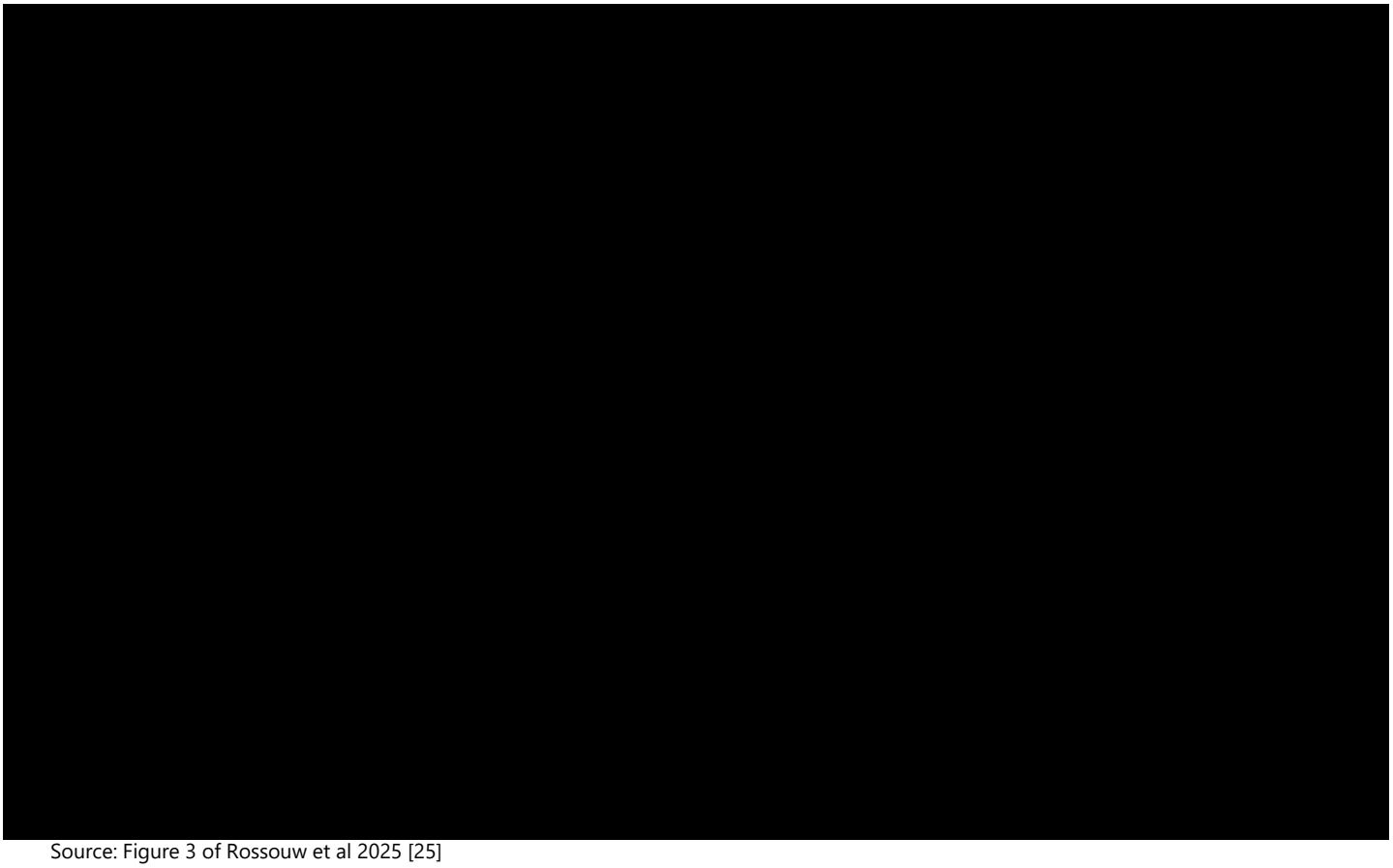
Of 27,347 postmenopausal women, there were 10,739 (39.3%) with a hysterectomy and 16,608 (60.7%) with an intact uterus. Median (SD) age was 63.4 (7.2) years. Median (IQR) follow-up was 7.2 (6.4-8.1) years and 5.6 (4.8-6.5) years for those in the estrogen alone trial and the estrogen-progestogen trial, respectively.

In the estrogen alone trial, moderate or severe vasomotor symptoms (VMS) were present at baseline in 905 (27.6%), 705 (14.7%), and 220 (8.7%) women aged 50-59 years, 60 to 69 years, and 70 to 79 years, respectively. In the estrogen-progestogen trial, moderate or severe VMS was present in 1225 (22.4%), 649 (8.7%), and 172

(4.8%), respectively. Among women with moderate or severe VMS at enrolment, 3382 (96.7%) recalled having symptoms near menopause onset. Estrogen alone reduced VMS by 41% across all age groups (overall RR 0.59, 95% CI 0.53-0.66). However, in the estrogen-progestogen trial, VMS reduction was attenuated with age (age 50-59 years RR 0.41, 95% CI 0.35-0.48; age 60-69 years RR 0.72, 95% CI 0.61-0.85; age 70-79 years RR 1.20, 95% CI 0.91-1.59).

Estrogen alone and estrogen-progestogen compared with placebo did not increase ASCVD risk overall and the risk was not modified by age or time since menopause or in women with VMS overall (Figure 7).

Figure 7: Overall effect of MHT on atherosclerotic cardiovascular disease and select subgroups



Source: Figure 3 of Rossouw et al 2025 [25]

Both estrogen alone and estrogen-progestogen appeared to have neutral effects on ASCVD in women with moderate or severe VMS aged 50 to 59 years (estrogen alone HR 0.85, 95% CI 0.53-1.35; estrogen-progestogen HR 0.84, 95% CI 0.44-1.57). While the estimated risk was higher for estrogen alone in women with VMS aged 60-69 years, there was no clear signal of harm (estrogen alone HR 1.31, 95% CI 0.90-1.90); estrogen-progestogen HR 0.84, 95% CI 0.51-1.39). However, women with VMS 70 years and older had increased risks of ASCVD (estrogen alone HR 1.95, 95% CI 1.06-3.59, 217 excess events per 10,000 person-years; estrogen-progestogen HR 3.22, 95% CI 1.36-7.63, 382 excess events per 10,000 person-years).

The authors conclude the findings support guideline recommendations for treatment of VMS with MHT in women aged 50 to 59 years, caution if initiating MHT in women aged 60 to 69 years, and avoidance of MHT in women aged 70 years and older.

Comments:

This secondary analysis of WHI trials looked at the risks of ASCVD by age group. In women aged 50 to 59 years and 60 to 69 years, there were no differences in women using MHT (estrogen alone or estrogen-progestogen) compared to placebo. However, in women aged 70 years and older, there was an increased risk of ASCVD in MHT users (estrogen alone or estrogen-progestogen) compared to placebo.

4.5 Summary of findings

A summary of the findings from various published studies discussed in this paper on the risk of CVD with MHT is shown in Table 10.

Table 10: Summary of findings from studies on the risk of CVD with MHT

Study	Estrogen-progestogen (vs. placebo)	Estrogen alone (vs. placebo)
WHI, 2002 [2]	CVD HR 1.22 (95% CI 1.09-1.36) CHD HR 1.29 (95% CI 1.02-1.63) Stroke HR 1.41 (95% CI 1.07-1.85	-
WHI, 2004 [3]	-	CVD HR 1.12 (95% CI 1.01-1.24) CHD HR 0.91 (95% CI 0.75-1.12) Stroke HR 1.39 (95% CI 1.10-1.77)
Overview of WHI studies, 2013 [6]	CHD HR 1.18, 95% CI 0.95-1.45)	CHD HR 0.94 (95% CI 0.78-1.14)
Secondary analysis of WHI studies, 2025 [25]	ASCVD aged 50-59 years HR 0.84 (95% CI 0.44-1.57) ASCVD aged 60-69 years HR 0.84 (95% CI 0.51-1.39) ASCVD aged ≥70 years HR 3.22 (95% CI 1.36-7.63)	ASCVD aged 50-59 years HR 0.85 (95% CI 0.53-1.35) ASCVD aged 60-69 years HR 1.31 (95% CI 0.90-1.90) ASCVD aged ≥70 years HR 1.95 (95% CI 1.06-3.59)
Study	**Overall (vs. placebo)**	
Cochrane review, 2015 [22]	Death (all cause) RR 1.00 (95% CI 0.89-1.12) Death (CV) RR 0.81 (95% CI 0.47-1.40) Stroke RR 1.32 (95% CI 1.12-1.56) VTE RR 1.92 (95% CI 1.24-2.99)	
Study	**RCTs (vs. placebo)**	**Observational (vs. non-users)**
Systematic review & meta-analysis, 2020 [23]	Death (all cause) SE 1.00 (95% CI 0.96-1.04) Death (CV) SE 0.96 (95% CI 0.83-1.12) Stroke SE 1.14 (95% CI 1.04-1.25) VTE SE 1.70 (95% CI 1.33-2.16)	Death (all cause) SE 0.90 (95% CI 0.79-1.02) Death (CV) SE 0.81 (95% CI 0.61-1.07) Stroke SE 0.98 (95% CI 0.85-1.13) VTE SE 1.32 (95% CI 1.13-1.54)

Notes: ASCVD: atherosclerotic cardiovascular disease, CHD: coronary heart disease, CI: confidence interval, CVD: cardiovascular disease, HR: hazard ratio, RCTs: randomised controlled trials, RR: relative risk, SE: summary estimate, WHI: Women's Health Initiative

4.6 Discussion

Estrogen has a protective effect on the heart. During menopause when estrogen levels decrease, the risk of cardiovascular disease (CVD) increases. Therefore, it was thought that the use of MHT may reduce the risk of CVD due to the cardioprotective effects of estrogen.

In the WHI studies, there was an increased risk of CVD in women using estrogen-progestogen MHT (HR 1.22, 95% CI 1.09-1.36) and in women using estrogen-only MHT (HR 1.12, 95% CI 1.01-1.24) compared to placebo. These increases, particularly for MHT containing estrogen alone, are modest.

The Cochrane review that was updated in 2015 found there was no difference in the risks of all cause death and cardiovascular death in women using MHT vs. placebo (RR 1.00, 95% CI 0.89-1.12; RR 0.81, 95% CI 0.47-1.40, respectively). However, there was more cardiovascular benefit in women who start MHT early in

menopause (<10 years after menopause) than in women who start MHT later in menopause (>10 years after menopause).

A systematic review and meta-analysis looking at findings from RCTs vs. observational studies found RCTs had a shorter duration of follow-up, and included women who were older with more underlying medical conditions. There were no differences in the risks of all cause death or cardiovascular death in women using MHT compared to placebo or non-users in both RCTs and observational studies.

In a secondary analysis of WHI trials looking specifically at the risk of atherosclerotic cardiovascular disease (ASCVD) by age group, there were no differences in risk for women aged 50 to 59 years and 60 to 69 years using MHT compared to placebo. However, there was an increased risk of ASCVD in women aged 70 years and older.

Overall, these study findings suggest there are no differences in the risk of CVD in women using MHT compared to placebo or non-users. For younger women or those who start MHT early in menopause, there is possibly more benefit compared to women who start MHT later in menopause.

5 COGNITIVE IMPAIRMENT

Mild cognitive impairment is used to describe the stage between normal cognition and dementia. Symptoms include trouble with memory, language and judgement [26].

It is common for women to report memory or cognitive changes during the menopause transition and menopause. Cognitive changes associated with the menopause transition include reduced processing speed and reduced verbal memory. Verbal memory is defined as the ability to encode words and it is influenced by circulating estradiol [27].

Estradiol levels decline rapidly over the menopausal transition. This decline has been associated with a number of changes in the brain including cognitive changes, effects on sleep and effects on mood [27].

5.1 Risk factors

The strongest risk factors for mild cognitive impairment are [26]:

- Older age
- Having a form of the APOE e4 gene. This gene is also linked to Alzheimer's disease but having the gene doesn't guarantee a decline in thinking and memory.

Other medical conditions and lifestyle factors have been linked to a higher risk of changes in cognition, including [26]:

- Diabetes
- Smoking
- High blood pressure
- High cholesterol, especially high levels of LDL
- Obesity
- Depression
- Obstructive sleep apnoea
- Hearing loss and vision loss that are not treated
- Traumatic brain injury
- Lack of physical exercise
- Low education level
- Lack of mentally or socially stimulating activities
- Exposure to air pollution.

5.2 Epidemiology

A 2023 meta-analysis of 233 studies with more than 676,000 participants (men and women) aged 50 years and older found a global prevalence of mild cognitive impairment of 19.7% [28]. The prevalence increases with age with estimates showing a prevalence of 10.1% in individuals aged 70-74 years rising to 14.8% in people aged 75-79 years and reaching 25.2% in the 80-84-year age group [29].

The incidence of memory problems in the menopause transition is reported by up to two-thirds of women. It is thought these are transient and do not become chronic postmenopausal issues [27].

5.3 Association with MHT

The effects of MHT on cognition and dementia is uncertain. The age at menopause or initiation of MHT, or the type of MHT may modify this risk but this is unclear. Early observational studies suggest MHT might reduce the risk of dementia particularly when started early and used long-term. These findings were not replicated in RCTs due to the healthy user effect [30].

Paganini-Hill & Henderson (1996) [31] postulated that estrogen loss associated with menopause may contribute to the development of Alzheimer disease. They sought to evaluate the effects of different estrogen

preparations, varying doses and duration of estrogen replacement therapy on the risk of Alzheimer disease in postmenopausal women by conducting a case-control study nested within a prospective cohort study of residents in a retirement community in Southern California. The cohort comprised 8877 women who were first mailed a health survey in 1981. Of the 3760 female cohort members who died between 1981 and 1995, 248 women with Alzheimer's disease or other dementia diagnoses likely to represent Alzheimer's disease (senile dementia, dementia, or senility) mentioned on the death certificate were identified. Five controls were matched to each case according to year of death and year of birth (+/- 1 year). The risk of Alzheimer's disease and related dementia was significantly reduced in estrogen users compared with non-users (OR 0.65, 95% CI 0.49-0.88). The risk was reduced for both oral and non-oral (ie, injections and/or creams) routes of administration. The risk decreased significantly with both increasing doses and increasing duration of oral therapy with conjugated equine estrogen, the most commonly used estrogen preparation. Within each dose category, the risk decreased with increasing duration of therapy, with the lowest observed risk in long-term users who received high doses (OR 0.48, 95% CI 0.19-1.17).

5.4 Recent literature

5.4.1 Re-examination of RCTs (Bagger et al, 2005) [32]

Title: Early postmenopausal hormone therapy may prevent cognitive impairment later in life (Annex 2)

The authors followed a group of 343 women who had previously received MHT in one of 4 randomised, placebo-controlled trials (Table 11) and who were re-examined 5, 11, or 15 years after completion of treatment. Of these women, 261 received either MHT or placebo for 2 to 3 years during the trials with no further MHT use , and the remaining 82 women reported either prolonged or current use of MHT at re-examination. Outcome of the study was cognitive function assessed by the short Blessed test that includes tests of orientation, concentration, and memory function on a scale of 0 to 28 (score ≥6 indicates cognitive impairment).

Table 11: Study design of the four original placebo-controlled MHT trials

Source: Table 1 of Bagger et al (2005) [32]

Of the 343 participants, 70 women were originally from trial A, 101 from trial B, 94 from trial C, and 78 women from trial D, respectively. Data from the four trials were pooled into MHT users and never users.

Mean age of participants at follow-up was 65 ± 3 years. There was no difference in the mean cognitive scores between ever MHT users and never users. For women who received 2 to 3 years of MHT, the risk of cognitive impairment (score ≥6) was decreased by 64% (OR 0.36, 95% CI 0.15-0.90) (Table 12). A similar OR was found in long-term/current MHT users. Adjustment for age, alcohol intake, current smoking, and education did not alter the results.

The authors conclude results of the study suggest previous short-term MHT administered in the early phase of menopause may provide long-term protection against cognitive impairment.

Table 12: Odds ratios for cognitive impairment (cognitive score ≥6) in women treated with MHT compared with never users

[redacted]

Source: Table 3 of Bagger et al (2005) [32]

Comments:

The findings suggest that even short-term MHT administered early in menopause may confer long-term protection against cognitive impairment compared with never-users. It is worth noting that cognitive function was not tested at study entry nor at the end of the original RCTs.

5.4.2 WHIMSY study (Espeland et al, 2013) [33]

Title: Long term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50-55 years

This Women's Health Initiative Memory Study of Younger Women (WHIMSY) tested whether prescribing estrogen-based MHT to postmenopausal women aged 50-55 years had longer-term effects on cognitive function. The study was performed because although estrogen alone may adversely affect older women's cognitive function, it is unknown whether this extends to younger women.

WHIMSY participants had begun screening for WHI enrolment when aged 50-54 years (and initiated their assigned WHI treatment when aged 50-55 years). A total of 1326 women who had begun treatment in the two WHI studies when aged 50-55 years were assessed with an annual telephone-administered cognitive battery that included measures of global (primary outcome, assessed with the Telephone Interview for Cognitive Status-modified, TICS-m) and domain-specific cognitive functions (verbal memory, attention, executive function, verbal fluency, and working memory). The clinical trials in which they participated compared conjugated equine estrogen (CEE) 0.625 mg with or without medroxyprogesterone acetate (MPA) 2.5 mg over an average of 7 years. Cognitive testing was conducted an average of 7.2 years following the end of the trials when women had mean age of 67.2 years, and was repeated one year later.

Table 13 presents mean cognitive function scores averaged over time, with adjustment for age and visit year. For TICS-m, there was essentially no difference in the mean scores between women who had been assigned to active versus placebo therapy. This finding was consistent for both estrogen-progestogen and estrogen alone therapies. Similarly, there were no overall treatment differences for any other measure of cognitive function, including the composite score. This held for estrogen-progestogen and estrogen alone therapies and for all cognitive measures, except verbal fluency. Estrogen alone therapy was associated with 0.17 standard deviation worse mean scores on verbal fluency with a 95% confidence interval that excluded zero [−0.33 to −0.02]; estrogen-progestogen was associated with 0.07 standard deviation better mean scores on this test, however its confidence interval included zero [−0.06 to 0.19]. Covariate adjustment for risk factors for cognitive impairment did not materially alter findings.

Table 13: Mean cognitive function test scores averaged over time

Source: Table 2 of Espeland et al (2013) [33]

The WHIMSY protocol pre-specified three subgroup analyses to compare treatment effects for women grouped by: assignment to unopposed or opposed estrogen alone treatment (ie, hysterectomy status), self-reported age at last menstrual period, and prior use of MHT. There was little evidence of differential effects for any measure of cognitive function, with one exception. For verbal fluency, worse treatment-related performance was seen among women reporting prior hormone therapy use that had ceased before WHI enrolment. Prior hormone therapy use was associated with longer time since last menstrual period ($p<0.001$): compared to non-users, these times averaged 2.1 years longer for prior users and 0.2 years longer for current users. Because prior use of hormone therapy more often occurred among women with prior hysterectomy, the authors fitted a model that included treatment interactions with both hysterectomy status and prior use. Both interactions were independently statistically significant: women reporting prior hormone therapy use (interaction $p=0.01$) and those with prior hysterectomy (interaction $p=0.03$) appeared to have treatment-attributable deficits in verbal fluency that were not apparent, on average, in other women.

The authors were unable to address whether initiating MHT during menopause and maintaining therapy until any symptoms are passed affects cognitive function, either in the short or longer term.

The authors conclude estrogen-based treatments produced no overall sustained benefit or risk to cognitive function when administered to postmenopausal women aged 50-55 years.

Comments:

This study focused on younger postmenopausal women aged 50-55 years who were enrolled in the WHI trials. The authors found global cognitive function scores were similar in women randomised to MHT vs. placebo. The use of MHT in women earlier in the postmenopausal period doesn't appear to result in long term adverse cognitive consequences.

By the time this study was performed, women had been unmasked to their treatment assignment which could have influenced their performance on cognitive tests.

5.4.3 KEEPS-Cog study (Gleason et al, 2015) [34]

Title: Effects of hormone therapy on cognition and mood in recently postmenopausal women: Findings from the randomized controlled KEEPS-Cognitive and Affective study

The ancillary Cognitive and Affective study (KEEPS-Cog) of the Kronos Early Estrogen Prevention Study (KEEPS) examined the effects of up to 4 years of MHT on cognition and mood in recently postmenopausal women.

KEEPS was a randomised, double-blinded, placebo-controlled clinical trial conducted at 9 US academic centres. Of the 727 women enrolled in KEEPS, 693 (95.3%) participated in the ancillary KEEPS-Cog, with 220 women randomised to receive 4 years of 0.45 mg/day oral conjugated equine estrogens (o-CEE) plus 200 mg/day micronized progesterone (m-P) for the first 12 days of each month, 211 women randomised to receive 50 mcg/day transdermal estradiol (t-E2) plus 200 mg/day m-P for the first 12 days of each month, and 262 women randomised to receive placebo pills and patches. Primary outcomes included the Modified Mini-Mental State (3MS) examination; four cognitive factors: verbal learning/memory, auditory attention/working memory, visual attention/executive function, and speeded language/mental flexibility; and a mood measure, the Profile of Mood States (POMS). To examine the effect of treatment on cognition and mood throughout the study duration, MHT effects were analysed using a linear mixed-effects (LME) modelling approach.

On average, participants were 52.6 years old, and 1.4 years past their last menstrual period. By month 48, 169 (24.4%) and 158 (22.8%) of the 693 women who consented for ancillary KEEPS-Cog were lost to follow-up for cognitive assessment (3MS and cognitive factors) and mood evaluations (POMS), respectively. However, because LME models make full use all available data including data from women with missing data, 95.5% of participants were included in the final analysis (n = 662 in cognitive analyses, and n = 661 in mood analyses).

The mean length of follow-up was 2.85 years (SD = 0.49) for cognitive outcomes and 2.76 (SD = 0.57) for mood outcomes. No treatment-related benefits were found on cognitive outcomes. Similarly, models investigating MHT effects on the four cognitive factors were statistically non-significant for each active treatment arm vs. placebo. Table 14 includes the beta estimates and corresponding p-values for cognitive outcomes by treatment group.

For mood, model estimates indicated that women treated with o-CEE showed improvements in depression and anxiety symptoms over the 48 months of treatment, compared to women on placebo. The model estimate (Table 14) for the depression subscale was -5.36×10^{-2} (95% CI, -8.27×10^{-2} to -2.44×10^{-2}; ES = 0.49, $p < 0.001$) and for the anxiety subscale was -3.01×10^{-2} (95% CI, -5.09×10^{-2} to -9.34×10^{-3}; ES = 0.26, $p < 0.001$). Mood outcomes for women randomised to t-E2 were similar to those for women on placebo. Importantly, the KEEPS-Cog results cannot be extrapolated to treatment longer than 4 years.

The authors conclude the KEEPS-Cog findings suggest that for recently postmenopausal women, MHT did not alter cognition as hypothesised. However, beneficial mood effects with small to medium effect sizes were noted with 4 years of o-CEE, but not with 4 years of t-E2. The generalisability of these findings is limited to recently postmenopausal women with low cardiovascular risk profiles.

Table 14: Treatment efficacy: beta estimates and confidence intervals for cognitive outcomes and mood outcomes across treatment duration

Comments:

This study included oral estrogen as well as transdermal estrogen treatment arms. The authors found MHT did not improve cognition nor alter cognition (ie, results did not indicate adverse or beneficial effects of MHT compared with placebo).

5.4.4 Systematic review & meta-analysis (Melville et al, 2025) [30]

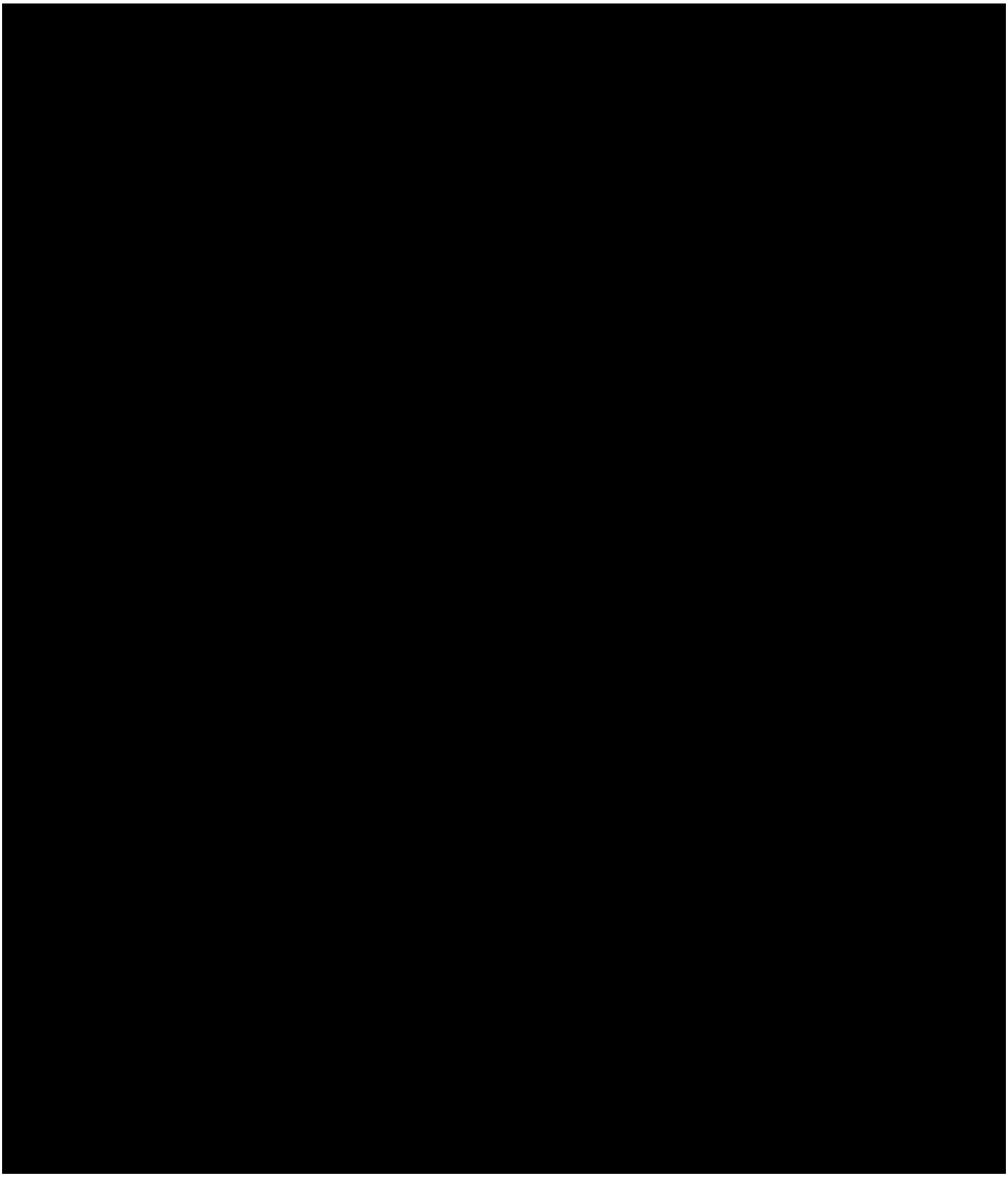
Title: Menopause hormone therapy and risk of mild cognitive impairment or dementia: a systematic review and meta-analysis (click here for full text)

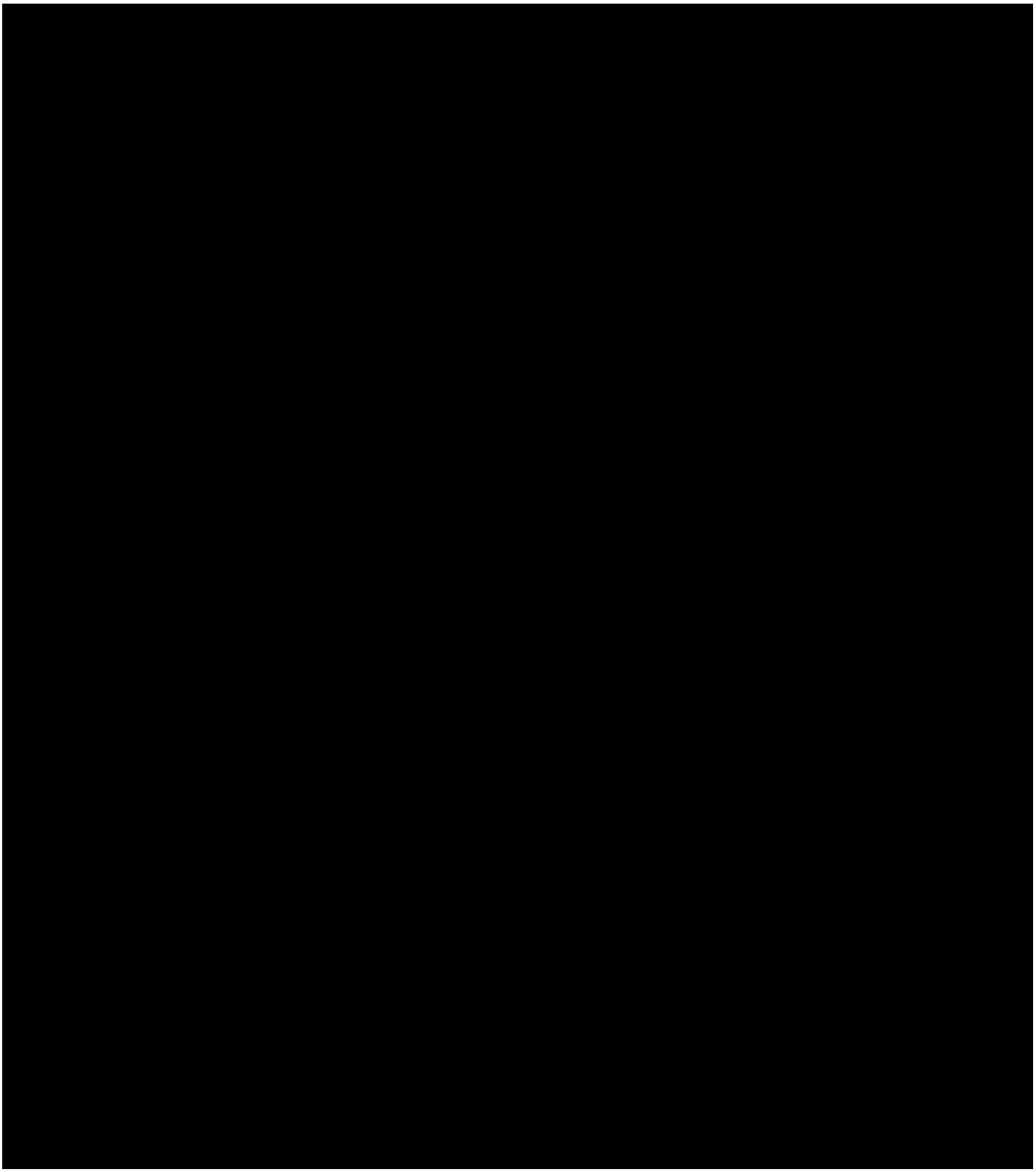
The authors systematically searched MEDLINE, Embase, Cochrane, and PsycINFO for systematic reviews published between 1 Jan 2000 and 19 Dec 2024. As no existing review met their quality or scope criteria, they conducted a systematic review and meta-analysis of primary studies published from 1 Jan 2000 to 20 Oct 2025. Eligible primary studies included RCTs, non-randomised intervention studies, and prospective observational studies examining the association between MHT and incident mild cognitive impairment or dementia.

A total of 5914 records were found. Of these, 167 articles were evaluated in full-text and 15 were included in the review. Due to overlapping datasets, the GRADE analysis included only 10 studies (1 RCT and 9 observational studies) with a total of 1,016,055 participants. Certainty of evidence ranged from moderate to very low. Outcomes assessed included incidence of all-cause dementia, Alzheimer's disease, and dementia or mild cognitive impairment.

Meta-analyses for estrogen-only are shown in Figure 8, and for estrogen-progestogen in Figure 9.

Figure 8: Random-effects meta-analyses of estrogen-only MHT and risk of dementia and Alzheimer's disease, overall and by duration and timing of use





[redacted]

No significant association was found between MHT use and risk of mild cognitive impairment or dementia. Subgroup analyses by timing, duration, and type of MHT showed no significant effects. This is consistent with previous studies but extends the uncertain to MHT and dementia following premature or early menopause.

Comments:

This systematic review and meta-analysis was not included in the FDA's review. The study included RCTs and observational studies (1 RCT and 9 observational studies in the meta-analysis). Overall, the review could not confirm whether MHT has a positive, negative, or null effect on the risk of dementia or mild cognitive impairment.

5.5 Summary of findings

A summary of the findings from various published studies discussed in this paper on the risk of cognitive impairment with MHT is shown in Table 15.

Table 15: Summary of findings from studies on the risk of cognitive impairment with MHT

Study	Estrogen-progestogen (vs. placebo)	Estrogen alone (vs. placebo)
WHIMS, 2003 [4]	Probable dementia HR 2.05 (95% CI 1.21-3.48 Mild cognitive impairment HR 1.07 (95% CI 0.74-1.55)	-
WHIMS, 2004 [5]	-	10-unit decrease in 3MSE scores RR 1.47 (95% CI 1.04-2.07)
Overview of WHI studies, 2013 [6]	Probable dementia HR 2.01 (95% CI 1.19-3.42)	Probable dementia HR 1.47 (95% CI 0.85-2.52)
Systematic review & meta-analysis, 2025 [30]	All-cause dementia RR 1.12 (95% CI 0.97-1.30) Alzheimer's RR 1.11 (95% CI 1.03-1.18)	All-cause dementia RR 1.10 (95% CI 0.93-1.31) Alzheimer's RR 0.95 (95% CI 0.82-1.11)
Study	**Overall (vs. placebo)**	
WHIMSY, 2013 [33]	Global cognitive function mean standardised difference 0.02 (95% CI -0.08 to 0.12)	

Re-examination of 4 RCTs, 2005 [32]	Cognitive impairment short-term users OR 0.36 (95% CI 0.15-0.90) Cognitive impairment long-term/current users OR 0.34 (95% CI 0.11-1.08) Cognitive impairment ever users OR 0.36 (95% CI 0.16-0.80)
KEEPS-Cog, 2015 [34]	3MSE cognition model estimate for oral estrogen 1.02×10^{-2} (95% CI -4.45×10^{-3} to 2.48×10^{-2}) 3MSE cognition model estimate for transdermal estrogen -9.40×10^{-4} (95% CI -1.57×10^{-2} to 1.38×10^{-2})

Notes: 3MSE: Modified mini-mental state examination, CI: confidence interval, HR: hazard ratio, KEEPS-Cog: Kronos early estrogen prevention study-Cognitive and affective study, OR: odds ratio, RCTs: randomised controlled trials, RR: risk ratio, WHI: Women's Health Initiative, WHIMS: Women's Health Initiative Memory Study

5.6 Discussion

The risk of mild cognitive impairment increases with age. It is common for women to experience cognitive changes during menopause.

The WHIMS studies enrolled participants from the WHI studies to evaluate the effects of MHT on probable dementia. The modified mini-mental state examination (3MSE) was used to measure outcomes. In women using estrogen-progestogen MHT, there was an increased risk of probable dementia (HR 2.05, 95% CI 1.21-3.48) compared to placebo but no difference in mild cognitive impairment (HR 1.07, 95% CI 0.74-1.55). In women using estrogen-only MHT, the 3MSE score was 0.26 units lower than placebo, though the meaning of this finding is unclear.

A study that re-examined four RCTs using the short Blessed test found that the risk of cognitive impairment (Blessed score ≥6) was decreased in short-term MHT users compared to never users (OR 0.36, 95% CI 0.15-0.90). The risk for ever users was similar (OR 0.36, 95% CI 0.16-0.80).

The WHIMSY study focused on younger postmenopausal women aged 50-55 years who were enrolled in the WHI studies. The authors found global cognitive function scores measured using TICS-m were similar in women randomised to MHT vs. placebo with a mean standardised difference of 0.02 (95% CI -0.08 to 0.12).

The KEEPS-Cog study used a few different scoring systems, including the 3MSE, and modelling to assess MHT effects on mood and cognition in recently postmenopausal women. They found that MHT did not alter cognition in women using oral or transdermal estrogen compared to placebo.

A systematic review and meta-analysis of RCTs and observational studies on the association between MHT and mild cognitive impairment or dementia could not confirm whether MHT has a positive, negative, or null effect on these risks.

In summary, more recent studies show there is a decreased risk of cognitive impairment in MHT users compared to placebo or no difference in risk.

6 OVERALL CONCLUSIONS

The WHI studies published in the early 2000s investigated oral forms of MHT (conjugated equine estrogen ± medroxyprogesterone) vs. placebo. Since then, other formulations of estrogen (eg, transdermal patch, vaginal preparations) have become available with usage data in New Zealand suggesting that these formulations are more commonly used than oral forms.

Studies since then, including re-analysis of the WHI studies, have tried to account for certain characteristics that could influence the assessment of risks, including the woman's age at MHT initiation or time since menopause when MHT was initiated, the duration of MHT use, and the route of administration or formulation of MHT.

For breast cancer, there is some agreement in the studies that using combined estrogen-progestogen MHT increases the risk of breast cancer compared to placebo or non-users. Data from studies for estrogen-only MHT are more varied with some showing an increased risk and others a lower risk compared to placebo or non-users. The Lancet 2019 meta-analysis found that the risks persisted for more than 10 years after stopping MHT use, and there was little risk with vaginal formulations.

For cardiovascular disease, study findings suggest there are no differences in the risk for women using MHT compared to placebo or non-users. For younger women or those that initiate MHT early in menopause, there is possibly more benefit compared to women who start MHT later in menopause.

For cognitive impairment, the studies show there is a decreased risk in MHT users compared to placebo or no difference in risk.

These risks of breast cancer, cardiovascular disease, and cognitive impairment must be balanced against the more tangible benefits of MHT including the relief of vasomotor symptoms to improve daily functioning and quality of life, and prevention of osteoporosis.

7 ADVICE SOUGHT

The Committee is asked to advise:

- On the recent evidence on the risks of breast cancer, cardiovascular disease, and cognitive impairment with the use of MHT. The Committee may wish to comment on the following:
    - If the risks differ for estrogen alone or estrogen-progestogen regimens, for different formulations or routes of administration, the age that MHT is initiated or time since menopause, the duration of MHT use.
    - The persistence of these risks.

8 ANNEXES

1. Rossouw et al, 2025
2. Bagger et al, 2005

9 REFERENCES

1. New Zealand Formulary. *6.4.1.1 Estrogens and management of menopausal symptoms*. 2026 [accessed 29 January 2026]; Available from: https://nzf.org.nz/nzf_3857.
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