# MENOPAUSE MATTERS
# SEPTEMBER 2025

## The Women's Health Initiative study revisited

An article has appeared giving a secondary analysis of the Women's Health Initiative trial that was published more than 25 years ago. That initial research examined cardiovascular risks of menopausal hormone therapy in more than 25,000 women aged 50-79 years. The study compared conjugated equine estrogens (CEE) alone or with medroxyprogesterone acetate versus placebo over 6-7 years (Rossouw et al. *JAMA Intern Med.* 2025; doi:10.1001/jamainternmed.2025.4510).

Key findings showed that hormone therapy reduced moderate to severe vasomotor symptoms across all ages, especially in younger women. Cardiovascular disease risk varied significantly by age: women aged 50-59 showed neutral cardiovascular effects from both treatments, while those 60-69 had uncertain but potentially elevated risks. Women 70+ experienced substantially increased atherosclerotic cardiovascular disease risks, most markedly with combination therapy.

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

*Editorial comment. These deductions are not surprising and given the diligence of the work, they are without question, accurate. However, these medications are no longer used and modern hormone therapy (in terms of what is prescribed and the method of delivery) may have different cardiovascular effects from those presented here which are based on a study a quarter of a century old (Grady et al. JAMA Intern Med. 2025; doi:10.1001/jamainternmed.2025.4521).*

*In my opinion, this work is of important historical interest, but it is dubious whether it should be used to support or refute modern hormone therapy guidelines.*

**Reflections on the WHI trial itself.**
*The trial was sponsored by the United States National Institutes of Health although the products were provided by the makers of the particular estrogens and progestogens used. The total cost exceeded $625 million and it focused on disease prevention. The trial was stopped early in 2002 because risks exceeded benefits for chronic disease prevention.*

*However, subsequent analyses revealed important nuances:*

- *Timing hypothesis: Younger women (50-59) or those closer to menopause onset showed different risk profiles than older participants*
- *Absolute risks: While relative risks were elevated, absolute risk increases were relatively small for many outcomes.*

*The announcements of the trials' outcomes, and how these were presented, drew considerable comment, with a resultant drop in the menopausal hormone treatment market of 80%. Subsequent trials of more detailed aspects of perimenopausal symptom relief failed to establish an appropriate place for products of a different nature. Newer studies of modern medications have shown similar outcomes (Johansson et al. BMJ 2024;387:e078784). This study was commented on by Dr Nicole Jaff (Contemporary menopausal hormone therapy and risk of cardiovascular disease: Swedish nationwide register based emulated target trial. IMS updates, Menopause Live, e-letter commentary. 2025 April 28) So, has this information moved us forward clinically? I will leave it to the experts to profess on*

*this matter. Please see Schweitzer. JAMA. 2025; doi: 10.1001/jama.2025.14187 or Grady et al. JAMA Intern Med. 2025; doi: 10.1001/jamainternmed.2025.4521.*

## U S politics & Women's Health

In the United States, the status of women's health on the political stage shows marked variations. During the previous administration a $12 billion women's health initiative was proposed with a $16 billion investment, including a new institute focused on female biology and physiology. This has not materialised, and the NIH continues to spend less than 10% of the overall budget on women's health research and this is declining (Temkin. *JAMA.* 2025; doi:10.1001/jama.2025.14446).

In fact, the present NIH budget proposals will decrease by 43% next year (the equivalent of $20 billion) which will stall research into all aspects of medical care (*Cutting the NIH—The $8 Trillion Health Care Catastrophe.* Cutler et al. *JAMA Health Forum.* 2025; doi:10.1001/jamahealthforum.2025.2791). These financial manoeuvres plus misogynistic legislation indicate a reversal of wise investment in the health of the nation which, in both the long and short term, is best improved by investment in women's health (Edlow et al. *JAMA Health Forum.* 2025; doi:10.1001/jamahealthforum.2025.1226).

## Women's mental health

The world journal literature on **mental health** seems to be expanding exponentially. Women's mental health seems particularly in focus, and this starts in pregnancy and moves through to postmenopausal brain health. From the "allostatic load" in pregnancy to dementia in old age, women's cognitive function is attracting research attention.

**Pregnancy**. The allostatic load in pregnancy explores the stress faced by women throughout gestation and its effects on fetal and maternal outcomes. It has been recognised for more than a decade (Wallace et al., *Matern Child Health J.* 2013; doi:10.1007/s10995-012-1083-y), but now is being investigated as an epigenetic factor that women can pass on to their offspring (Press et al. *JAMA Netw Open.* 2025; doi:10.1001/jamanetworkopen.2024.53128).

**Children.** A prospective study examined more than 5,000 Canadian children to explore whether there are links between childhood screen time and academic performance (Li et al. *JAMA Netw Open*. 2025; doi:10.1001/jamanetworkopen.2025.37092). It was found that teenagers spend an average of 8.5 hours per day engaged with screen-based media (Christakis et al. *JAMA Pediatr.* 2025; doi:10.1001/jamapediatrics.2024.6627). Researchers calculated that each additional hour of screen time was associated with 10% lower odds of achieving high academic levels in standardised tests. TV and digital media time showed similar negative associations with achievement in reading and mathematics. Video gaming was linked to lower reading scores, particularly among girls. The findings suggest that reducing screen time exposure in young children may help enhance academic achievement in school. One-third of 10-year-old adolescent participants in a large US survey had an increasing addictive use trajectory for social media or mobile phones. Such behaviours are associated with "worse mental health." (Xiao et al. *JAMA*. 2025; doi:10.1001/jama.2025.7829).

**Adolescence.** Adolescents – especially girls – are at risk from mental ill-health issues from excessive social media use. A study examined social media engagement patterns from ages 9-13 and cognitive performance (Nagata et al. *JAMA.* 2025; doi:10.1001/jama.2025.16613). Increasing usage showed significantly lower scores on language and memory tests compared to minimal users, which suggests even low social media exposure in early adolescence may impact cognitive performance, potentially supporting stricter age restrictions. For example, a ban on social media is due to be implemented in

Australia next month. Other countries such as the United States are producing national statistics reflecting a young population "at risk' (Verlenden et al. *CDC Report MMWR*. 2024).

High-income countries are introducing legislation to reduce or ban smartphone screentime in schools as mental health services – in the UK in particular – are being overwhelmed by the demand for mental health support.

**Adults**. Of all the aspects of mental ill health, depression is the most common and women are more at risk than men. The reasons for this imbalance may be hormonal, pregnancy related, social, cultural and political, and symptoms may become more apparent during the perimenopause transition. All menopause-related consultations should include an enquiry into the person's emotional well-being as a specific question. It is a concern that psychological changes that accompany the physiological changes can be harbingers to more serious ageing conditions, so patients often welcome the opportunity to openly discuss what is "on their mind".

The condition of "brain fog" has been addressed in previous iterations of *Menopause Matters*, so for convenience the reference is repeated here being the International Menopause Society's offering being a guide by Maki and Jaff: "Brain fog in menopause: a health-care professional's guide for decision-making and counselling on cognition." An accompanying patient information leaflet is available in English and 12 other languages.

**Cognitive function, menopause & MHT**
Cognitive performance during the perimenopause and menopausal hormone therapy have been diligently researched. The outcomes show that estradiol decline does effect cognitive function and treatment with different products with varying means of delivery give different outcomes.
Some overarching features are that early menopause is associated with poorer performances across all cognitive domains measured, as is multiparity and in those who carry the APOEe4 gene variant.

In cognitive research the following abilities are investigated:
**Episodic Memory:** This is a person's ability to remember specific personal episodes and experiences. It is the ability to recall events.

**Prospective Memory:** The ability to remember to do things in the future. This involves what to do next – not what has already happened. It is crucial for daily functioning and independence.

**Executive Functions:** These are higher-level cognitive skills that help people manage their lives. They include planning, organising, working memory, adapting to new situations or switching between tasks plus problem-solving and decision-making.

The effects of hormone therapy depend on which preparation is being used, and its route of administration (Puri et al. *Neurology*. 2025; doi:10.1212/WNL.0000000000213995 & Hogervorst et al *Neurology*. 2025 & Yasgur. *Medscape*. 2024).

**Dementia**. The most topical subject in the journals over the last year was dementia, so it will be the feature of this reflection on Women's Mental Health. The prevalence of dementia was estimated at 50 million at the beginning of this decade and is anticipated to rise to 115 million in 2050. This increase is in part due to the ageing of the population but also an absolute incidence plus improvements in diagnostic modalities.

Good social relationships are known to correlate with good mental health, and the opposite is also well documented. However, the underlying mechanisms for these connections are unknown, but scientists have recently identified biomarkers that reflect "proteomic signatures" which characterise poor social

interactions such as loneliness and social isolation (Shen et al. *Nature Human Behaviour*. 2025; doi:10.1038/s41562-024-02078-1).

These proteins, found in peripheral blood of people suffering from social isolation and loneliness (which feed stress), are similar to biomarkers of inflammation, antiviral responses and complement systems. Many of the markers also appear linked to cardiovascular disease, type 2 diabetes, stroke and mortality, so a cross-over effect is likely. The science is sophisticated whereby these facts are connected but are clearly demonstrable using the UK Biobank data and Mendelian randomisation techniques backed up by MRI scan images.

The diagnosis of dementia has been a clinical one for decades, but now imaging tools such as the DunedinPACE-NI scans can act diagnostically (Brooks. *Medscape*. 2025) and bio-physical speech tests can accurately tell if a patient is struggling with word selection and allow recordings of a person talking to predict dementia (Freeman. *Medscape*. 2024).

Now tau immunoassays can diagnose dementia by blood biomarkers (Ashton et al. *JAMA Neurol.* 2024; doi:10.1001/jamaneurol.2023.5319). But before these tests can be used freely, consideration must be given by the person ordering them as to the consequences of a positive result. This goes beyond the decision to refer someone who tests positive to a neurologist.

What are the responsibilities of conveying mild cognitive impairment? What about driving or other social tasks? Will insurance or work repercussions arise? ( O'Brien et al. JAMA. 2025; doi: 10.1001/jama.2025.13006). "Forward reflection" before screening seems wise advice.

Being the first consultant of a menopausal patient does carry the obligation of assessing the person's cognitive abilities and give the prevalence of cognitive aberrations – this is a responsible task.

**Associated factors.**
**Age and sex.** The greatest association with dementia is age. Sex is also a major factor and two thirds of all patients suffering from dementia are female. The reasons for this are the subject of intense interest and it is much more nuanced than longevity explanations since males have higher mortality rates than females from dementia (Lusk et al. *JAMA Neurol*. 2025; doi:10.1001/jamaneurol.2025.2236). The sex ratio differential is, as yet not explained.

**Comorbidities** such as cardiovascular disorders cause perfusion issues that lead to the entire domain of cardiovascular dementia, so basic assessments are required at routine menopausal consultations.

**Alcoho**l. A study has examined alcohol consumption and dementia risk in US and UK populations which shows a U-shaped pattern where light drinkers had lower dementia risk than non-drinkers or heavy drinkers (Topiwala et al. *BMJ Evid-Based Med.* 2025; doi:10.1136/bmjebm-2025-113913).
However, further analysis revealed that all levels of alcohol consumption increase dementia risk by about a 15% per standard deviation of alcohol intake. The apparent protective effect of light drinking likely reflects reverse causation, where early cognitive decline causes people to reduce drinking. The findings suggest no safe alcohol level for dementia prevention, and reducing the number of alcohol use disorders could lower the overall dementia incidence.

**Environment.** A person's environment, be it social or physical is crucial to the development – or not – of dementia (Splete. *Medscape.* 2024).

**Falls**. In older adults, falls with traumatic brain injury are associated with higher rates of dementia, especially in females – again exposing postmenopausal women to risk and poorer outcomes (Huang et

al. *CMAJ*. 2025; doi:10.1503/cmaj.250361 & Ordoobadi et al. *JAMA Netw Open*. 2024; doi:10.1001/jamanetworkopen.2024.36606).
Repetitive head trauma in male soccer players has been shown to be detrimental to mental health, but with the sport's increasing popularity with females, this risk factor must be added to the preventive list for everyone (Russell et al. *JAMA Netw Open*. 2024. doi:10.1001/jamanetworkopen.2024.49742 ).

**Stroke**. A stroke is significantly associated with an acute decline in cerebral function and in all cognitive domains (Sadigh et al. *JAMA Netw Open.* 2024; doi:10.1001/jamanetworkopen.2024.37145).

**Insomnia**. Insomnia, whether associated with the menopausal transition or not, has an effect on cognitive decline and is worthy of active investigation and treatment (Brooks. *Medscape*. 2022).

**Prevention**. On a more positive note there are publications linking dementia prevention to healthy lifestyles even in patients with neuropathies (Dhana et al. *JAMA Neurol*. 2024; doi:10.1001/jamaneurol.2023.5491).

Healthy seniors should also follow the advice of the doyens of women's health research who have published on the topic of mental health, being Sabia et al (*BMJ* 2023;380:p117) and Manson (*Medscape.* 2024) as well as a detailed report (Livingston et al. *The Lancet*. 2024;404:572-628). The modifiable risk factors are cigarette smoking, diet, physical activity, excessive alcohol intake and maintaining a healthy weight.

## MHT & gastro-intestinal cancer risk

Interesting data were delivered at the European GIT Congress this year (Wocalewski et al. *United European Gastroenterology Congress.* Berlin 2025).

A paper presented indicates that menopause hormone therapy (MHT) may have a protective effect against upper GIT cancers (McCall. *Medscape*. 2025). It appears from a Nordic study of 20,000 women with oesophageal or gastric cancers, that hormone therapy offers a decrease in the risk of developing such lesions. Compared to non-users, those taking MHT were protected in a dose-responsive fashion. Those classified as "high users" had a one third reduction in oesophageal or cardia adenocarcinoma malignancies and the association was stronger for systemic combined estrogen and progestogen medications.

*Editorial comment. The data were collected prospectively with meticulous exclusion and control diligence, so the outcomes are likely to be corroborated in future studies. This opens the possibility for other cancers to be investigated with regard to the effects of MHT.*
*Another point was that topical vaginal estrogen use appears to convey cancer protection suggesting, again, that locally used products do not have the same spectrum of alternate effects as systemic preparations.*

## Weight loss & the menopause

Weight loss during the perimenopause transition presents unique challenges due to hormonal shifts. Declining estrogen levels create a "triple effect": increased insulin resistance promoting fat storage, accelerated muscle loss reducing metabolism, and elevated cortisol levels from sleep disruption driving further fat accumulation. Calorie restriction becomes counterproductive, causing low energy and increased hunger (Larkin. *Medscape.* 2025).

Additionally, the "musculoskeletal syndrome of menopause" affects 70% of women, causing joint pain and muscle/bone loss that impedes physical activity. Emotional challenges from life transitions and ageism compound these difficulties.

Evidence-based strategies to counter these effects include menopausal hormone therapy (Hurtado et al. *Menopause*. 2024; doi:10.1097/GME.0000000000002310), anti-obesity medications paired with strength training, adequate protein intake, and addressing sleep issues. Clinicians should validate symptoms, track body composition rather than scale weight, and help patients identify personal motivations. Breaking goals into small, manageable steps while providing encouragement helps maintain focus and prevents relapse during this challenging time.

**Athol Kent** **Email address atholkent@mweb.co.za**