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Postmenopausal health interventions: Time to move on from the Women's Health Initiative?

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ABSTRACT

Menopause is a critical period during which, without timely interventions, increased risks of cardiovascular and metabolic diseases, osteoporosis, sexual dysfunction and premature cognitive decline will contribute to diminished quality-of-life in women. Hormone therapy (HT) used to be the standard of care for managing vasomotor symptoms and prevention of chronic diseases until publication of the Women's Health Initiative (WHI) in 2002. Concerned about risks highlighted in WHI publications, many symptomatic women promptly ceased HT which resulted in increased vasomotor symptoms, osteoporosis-related-fractures and insomnia. Data from post-hoc WHI analyses and newer clinical trials consistently show reductions in coronary heart disease and mortality when estrogen therapy is initiated soon after menopause, whereas administration in later years and/or in combination with progesterone carries increased risks. However, no validated primary preventive strategies are available for younger postmenopausal women (< 60 years), highlighting the need to re-evaluate the use of estrogen alone for which the risk–benefit balance appears positive. In contrast, in older women (> 60 years), risks associated with oral HT exceed benefits; however transdermal estrogen may offer a safer alternative and should be further evaluated. Alternative therapies such as phytoestrogens and non-hormonal prescriptions may be beneficial for older women or those who are unsuitable for HT. Long-term head-to-head comparisons of HT with alternative interventions are warranted to confirm their efficacy for chronic disease prevention.

1. Background and aims

Women have longer life expectancy than men but are at greater risk of suffering age-related chronic diseases. The three major leading causes of death in ageing women are cerebrovascular accidents, heart disease and Alzheimer's disease (Australian Institute of Health and Welfare, 2014). Premenopausal women are partially protected against vascular diseases as their ovaries produce estrogen that keep blood vessels relaxed and maintain a healthy cholesterol profile (Barrett-Connor and Bush, 1991). However, following menopause at mid-life, their risk of vascular and other diseases escalates disproportionately. Menopause-related changes in metabolism favour central obesity, which increases the risk of diabetes, cardiovascular and metabolic diseases, sexual dysfunction and osteoporosis, all of which lead to poor quality of life. More importantly, the effects of estrogen deficiency are more profound in the brain, including poor cerebral perfusion that can lead to memory impairment, temperature dysregulation and sleep disturbances, thereby altering mood and concentration. Overtime, chronic sleep, mood dysregulation and subnormal cognitive functioning can increase the risk of premature cognitive impairment. Therefore, menopause is a crucial time for assessment of lifestyle factors which, without appropriate early intervention, can undermine the number of years spend in good health postmenopausally.

Hormone therapy (HT) with estrogen or estrogen plus progestin was the most widely studied treatment for women with moderate to severe vasomotor symptoms (VMS) and was considered the standard of care until publication of the findings of the Women's Health Initiative study (WHI) in 2002. Untreated VMS have been shown to impair endothelial function (Bechlioulis et al., 2010) and are associated with increased risks of hypertension, osteoporotic fracture, cardiovascular disease, depression and cognitive impairment (Crandall et al., 2015; Gast et al., 2008; Thurston et al., 2016; Worsley et al., 2014). Therefore, VMS represent a type of chronic condition for which hormone therapy was considered as a primary preventive strategy wherein control of hot flushes might be associated with prevention of future cardiovascular events.

The aims of this review are to 1) summarise the background leading to abandonment of HT to prevent chronic conditions in peri- and

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postmenopausal women, 2) report the current status of HT and remaining critical issues and 3) identify other potential interventions to minimise the development and/or worsening of chronic disease conditions in postmenopausal women.

2. Benefits and risks of hormone therapy

2.1. Risks exceed benefits in early women's health initiative publications

In the late 1990s, at least 40% of postmenopausal women in the United States were routinely prescribed HT for primary prevention of coronary heart disease (CHD), osteoporosis and subsequent fractures, some types of cancer and cognitive impairment in women with or without menopausal symptoms based on large bodies of observational evidence (Hersh et al., 2004). CHD had the highest case fatality rate and treatment with HT was thought to have greatest impact on CHD mortality; observational studies indicated 20–40% lower all-cause mortality with HT, however prospective randomized controlled trial data was not available (Henderson et al., 1991). WHI was the first large-scale randomized trial adequately powered to test the hypothesis that estrogen replacement can reduce rates of CHD (primary outcome) and common causes of morbidity and mortality in postmenopausal women including osteoporotic fractures, cancer and dementia (Anderson et al., 1998). The WHI was initiated in 1992 with a planned completion date in 2007. Women aged 50–79 (average 63) years and approximately 12 years postmenopausal were enrolled and effects of oral conjugated equine estrogen (CEE; 0.625 mg for women with prior hysterectomy) with or without medroxyprogesterone acetate (MPA; 2.5 mg for women with intact uterus, to diminish endometrial cancer risk), were compared with placebo. The HT trials included 27,500 women. The incidence of breast cancer, endometrial cancer and thrombotic risk were monitored during and after the trial.

Although its planned duration was 8.5 years, the combined estrogen plus progestin (CEE/MPA) trial was terminated after an average of 5.2 years due to increased risks of coronary events, invasive breast cancer, stroke, and venous thromboembolism; these outweighed benefits of reduced colorectal cancer, hip fracture and diabetes compared to placebo (Rossouw, 2002). The National Institutes of Health halted the CEE alone trial in February 2004 after an average of 6.8 years as the intervention increased stroke risk with no overall CHD benefit. However, there was a decreased risk of femoral neck fractures and a non-significant ($p = 0.06$) 23% reduction in breast cancer risk (Anderson et al., 2004). Fig. 1 summarizes the results of early WHI publications.

Regarding cognitive benefits, the Women's Health Initiative Memory Study (WHIMS) examined the effect of HT on probable dementia, mild cognitive impairment (MCI) and global cognitive function using the Modified Mini-mental State Examination in a subgroup of WHI women (n = 8300, aged 65 and older) with normal cognition (Shumaker et al., 1998). Neither CEE alone nor CEE/MPA therapy reduced MCI or incidence of dementia. Instead, they even adversely affected global cognitive function after a mean follow-up of 4.2 years (Espeland et al., 2004; Rapp et al., 2003; Shumaker et al., 2004) (Fig. 1). Importantly, the CEE/MPA therapy was associated with a higher risk of dementia compared to placebo, which began to appear as early as one year after randomization (Shumaker et al., 2003). An ancillary study, the Women's Health Initiative Study for Cognitive Ageing (WHISCA), evaluated longitudinal age-related changes using an annual detailed neuropsychological assessment for memory and other specific cognitive functions in 1416 women (mean age = 74 years) (Resnick et al., 2004). WHISCA results showed that verbal memory declined (mean ± SD = −0.52 ± 0.20 units per year, $p = 0.009$) with CEE/MPA combined therapy compared to placebo (Resnick et al., 2006); however, CEE alone did not have any influence on cognitive function (Resnick et al., 2009).

Due to these unexpected findings of the WHI trials, the rates of use of HT dropped by 40–80% within the first 5 months of initial publication (Burger et al., 2012). The United States Preventive Services Task Force (USPSTF) issued a recommendation against the use of estrogen with or without progestin for women considering HT for primary prevention of chronic conditions (Moyer, 2013). However, HT was still approved for relieving hot flushes and vulvovaginal atrophy symptoms as well as prevention of osteoporosis in symptomatic women (North American Menopause Society, 2012). It was recommended to start with the lowest effective dose (0.3 mg) followed by subsequent dosage adjustment based on individual patient response and for the healthcare provider to reassess periodically. Nevertheless, many women, even those with refractory symptoms, ceased taking HT due to concerns raised by the media.

Another casualty following the first reports of WHI was the premature termination of the Women's International Study of long Oestrogen after Menopause (WISDOM) study after only one year of randomised treatment; it was designed to assess the same HT regimen for 15 years in younger women (50–69 years) (Burger et al., 2012). Likewise, the open-label Danish Osteoporosis Prevention Study (DOPS),

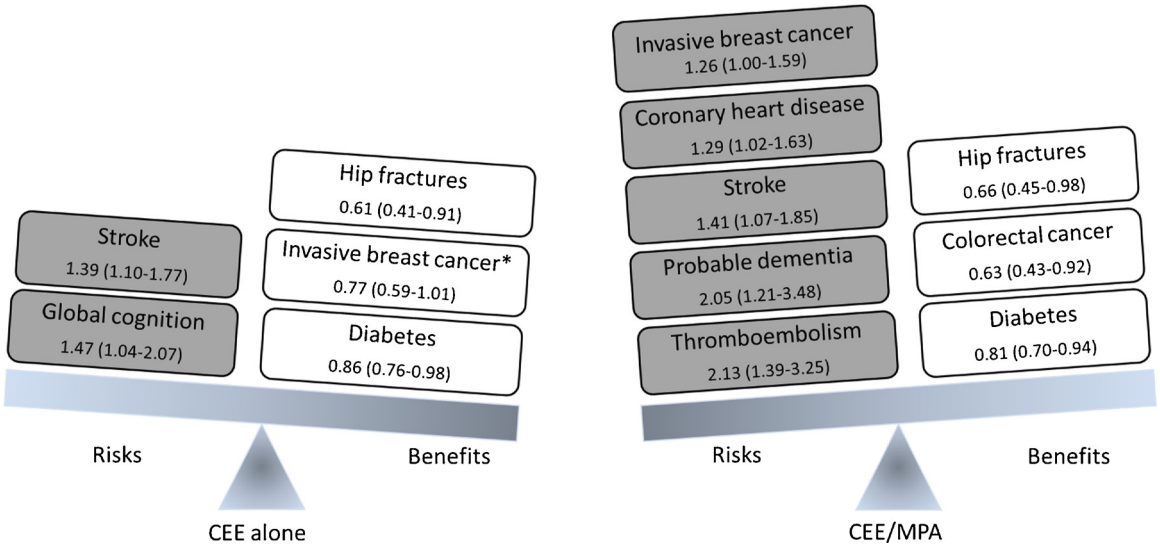

Fig. 1. Risk and benefit balance of CEE alone and CEE/MPA therapy based on early Women's Health Initiative publications (Rossouv et al., 2002; Rapp et al., 2003; Shumaker et al., 2003; Anderson et al., 2004; Espeland et al., 2004); Hazard ratios are shown with 95% confidence intervals; *, near significant trend; CEE, conjugated equine estrogen; CEE/MPA, conjugated equine estrogen plus medroxyprogesterone acetate.

initially planned for 20 years, was terminated after only 10 years of therapy (synthetic 17β-estradiol and norethisterone acetate) in 45–58 year old postmenopausal women (Schierbeck et al., 2012). Thus, the WHI findings initiated concerns that were inappropriately generalized to all postmenopausal women regardless of age and health status; they prompted faulty conclusions and effectively rescinded concomitant clinical trials, even those using different regimens, causing science and symptomatic women to suffer.

2.2. Potential determinants of the risk/benefit imbalance

Earlier observational studies demonstrated benefits of long-term exposure to HT in major age-related diseases in newly menopausal women. WHI however, overlooked perimenopausal and early postmenopausal women requiring HT primarily for the relief of menopausal symptoms (Langer et al., 2017) and enrolled a contrasting population of older women with more vascular risk factors and pre-existing disease conditions. After the discontinuation of WHI, multiple post-hoc analyses were performed to address potential health profile differences and showed that the risk of CHD might depend on an individual's age as well as the time of initiating HT (Rossouw et al., 2007). In the CEE-alone arm, there was a non-significant reduction of CHD risk in women aged 50–59 years ($p = 0.08$), but a decreased risk of CHD in combined CEE/MPA users who were ≤10 years since the onset of menopause was observed. In addition, the risks of stroke and colorectal cancer were greater when CEE therapy was started during late menopause (LaCroix et al., 2011). In addition, the DOPS study observed that women receiving HT shortly after menopause (averaged 7 months) had a significantly reduced risk of mortality, heart failure or myocardial infarction without apparent increases in risks of cancer, venous thromboembolism or stroke. Importantly, this benefit lasted even after 10 years of randomised treatment (Schierbeck et al., 2012). These findings identified that age and time since menopause as the critical determinants of the net benefit versus harm relating to HT initiation and use.

Regarding HT regimen, the dose of oral CEE (0.625 mg) used in the WHI was criticised as excessive with respect to increased risk of blood coagulation. There are three major naturally occurring estrogens in women: estrone (E1), estradiol (E2) and estriol (E3), where E2 is the predominant estrogen during reproductive years. Oral CEE, comprised mainly of E1 and at least 10 other hormones, is metabolized by the liver, which alters the physiological E1:E2 ratio, introducing risk of thromboembolic complications (Laliberté et al., 2011). In the Nurses' Health Study, there was a 44% increase in the risk of stroke in the group of women taking 0.625 mg CEE, whereas the risk of stroke disappeared with a lower dose (0.3 mg), suggesting a dose-risk relationship between oral CEE therapy and risks of thromboembolic disease and stroke (Grodstein et al., 2000). In contrast, transdermal estrogens, which avoid hepatic first-pass mechanism, may be advantageous for women at risk of venous thrombo-embolism, such as those with heightened vascular risk factors or advancing age. Moreover, recent data has shown that natural E2 may be safer for the vasculature than CEE (Smith et al., 2014). The significantly reduced risk of mortality and cardiovascular events with E2-based therapies was supported by the long-term follow up DOPS study (Schierbeck et al., 2012) and observational Finnish study (Mikkola et al., 2015).

Regarding progestin, non-physiological, continuous MPA used in the combined WHI regimen may have increased the incidence of breast cancer and dementia risk in women treated with combined CEE/MPA therapy, but not in the CEE alone arm (Ross et al., 2000; Resnick et al., 2006). MPA is a synthetic progestin derived from 17α-hydroxyprogesterone and the most commonly used progestin in HT regimens. The role of progestin in combination therapy is to antagonize the risks of unopposed estrogen. For instance, the potential for endometrial cancer in women with uterus, which estrogen would otherwise facilitate. Both MPA and progesterone might equally confer uterine protection; MPA has other pharmacological differences from natural progesterone produced in the ovaries. Studies have shown that although progesterone was neuroprotective, MPA was not and it might actually have adverse consequences and block beneficial effects of estrogen on brain function (Singh and Su, 2013). Other studies also agreed that natural micronized progesterone conferred endometrial protection, decreased vaginal bleeding and minimised risk of breast cancer compared to synthetic preparations (Gompel, 2012; L'Hermite, 2013). As a result of the suboptimal study design, no reduction of major chronic diseases was observed in WHI (outcomes were worse with CEE/MPA), raising the question of whether a different dose regimen for HT in younger, recently postmenopausal women would reduce risks of cardiovascular disease, dementia and osteoporosis.

2.3. Are there any benefits in early initiation of hormone therapy?

The Kronos Early Estrogen Prevention Study (KEEPS) was designed to address whether early initiation of a lower dose and different formulation of HT would benefit cardiovascular, metabolic, bone and cognitive outcomes in non-hysterectomized peri-menopausal women (42–58 years old, 6–36 months from menopause onset) (Wharton et al., 2013). Study medications included oral CEE (0.45 mg/day) and transdermal 17-β estradiol (t-E2; 50 μg/day), each with cyclic oral, micronized progesterone (200 mg/day for 12 days per month), or matched placebos for 48 months. KEEPS was the first trial to compare effects of long-term use of oral versus transdermal HT in women without prior preclinical vascular disease ($n = 728$).

Results from the KEEPS revealed that early HT did not affect carotid intima-media thickness progression, but improved bone mineral density, insulin sensitivity and intermediate markers of cardiovascular disease risk, including a significant reduction of low-density lipoprotein and an increase in high-density lipoprotein with CEE (Harman et al., 2014). It also provided convincing evidence that HT for recently menopausal women with low cardiovascular risk profiles was not associated with serious adverse events by treatment. This rebuilt confidence in the safety of using HT for 4 years in women with similar health profiles to improve bone health and metabolic markers but not atherosclerosis. The ancillary KEEPS Cognitive and Affective study (KEEPS-Cog) found neither beneficial nor deleterious effects of HT on cognition. This was consistent with findings from the Women's Health Initiative Memory Study of Younger Women (WHIMSY, aged 50–55 years at the time of WHI randomisation), which also observed no advantageous or harmful effects of HT on measures of memory or other cognitive domains. (Espeland et al., 2013). Compared to placebo or t-E2, KEEPS-Cog women treated with CEE showed significant reductions in depression and anxiety symptoms, corresponding to medium and small to medium effect sizes, respectively (Gleason et al., 2015).

Following KEEPS in 2014, the Early versus Late Intervention Trial with Estradiol (ELITE), was designed specifically to test the timing hypothesis of HT in 643 healthy women who were < 6 years (early) or > 10 years (late) postmenopausal without cardiovascular disease. Both early (mean age = 55 years) and late (mean age = 65 years) postmenopausal women were randomized to oral micronized 17β-estradiol 1 mg/day with vaginal micronized progesterone gel 4% (45 mg/day) for 10 days each month (for women with a uterus) or matched placebos. The primary outcome was the progression of subclinical atherosclerosis by carotid intima-media thickness; secondary endpoints included degree of coronary artery calcification measured with computed tomography and cognitive change (ELITE-Cog) (Hodis et al., 2016). After the 5-year intervention, the rate of progression of carotid intima-media thickness was significantly lower (−0.0034 mm per year, $p = 0.008$) in early postmenopausal women treated with estradiol compared to placebo, whereas there was no significant difference between groups in the late postmenopausal stratum. However, estradiol had no significant effect on cardiac computed tomography measures of atherosclerosis in either postmenopausal stratum. Similarly, ELITE-Cog

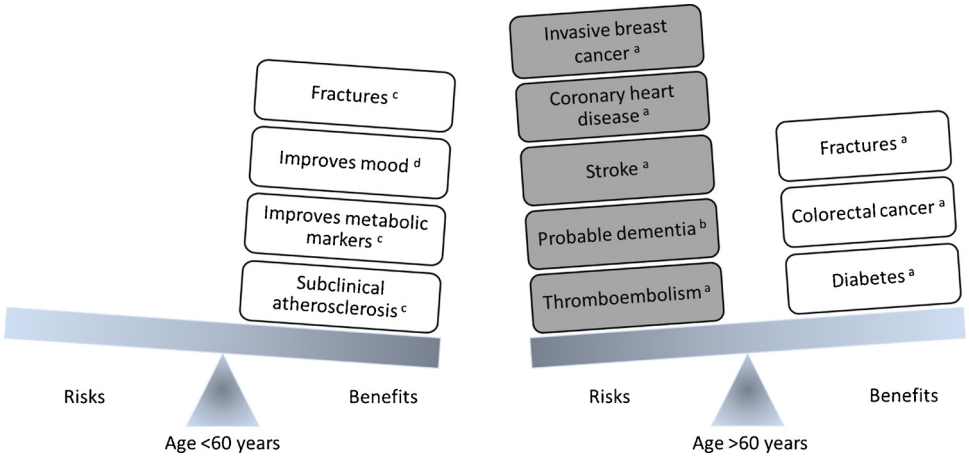

Fig. 2. Overall risks and benefits of hormone therapy stratified by age.
a, Rossouw et al., 2002; b, Shumaker et al., 2003; c, Harman et al., 2014; d, Gleason et al., 201.

results for both cognition and mood did not differ significantly between early or late groups indicating that estradiol did not harm or benefit cognitive abilities regardless of time since menopause (Henderson et al., 2016). KEEPS and ELITE indicated that in younger women close to menopause, there was a clear benefit of HT on cardiovascular outcomes, bone health, mood and metabolic markers (Fig. 2). Although the lack of cognitive benefit in these trials was disappointing, the absence of short and long-term harm to cognitive function should reassure women who choose to use HT for treatment of menopausal symptoms.

2.4. Risks and benefits of hormone therapy after cessation of intervention

Although treatment was stopped in the WHI trials in 2002 and 2004, extended assessments of outcomes were made in surviving participants who gave additional consent for a cumulative follow-up analysis. During the 13-year cumulative follow-up, most of the harmful effects of CEE/MPA, i.e., increased risks of stroke, thromboembolism and dementia, dissipated; however, invasive breast cancer risk remained significantly increased [Hazard ratio (HR) with 95% confidence interval = 1.28 (1.11–1.48)] and CHD remained non-significantly elevated [HR = 1.09 (0.96–1.24)]. In contrast, invasive breast cancer risk declined with CEE alone [HR = 0.79 (0.65–0.97)] and the increased risks of stroke and cognitive decline seen during the WHI intervention did not persist after stopping CEE alone (Manson et al., 2013). Reductions in hip fractures [HR = 0.81 (0.68–0.97)] and colorectal cancer [HR = 0.80 (0.63–1.01)] persisted with CEE/MPA. In the age-stratified analyses, younger women aged 50–59 years had significantly favourable results for all-cause mortality ($p = 0.04$), myocardial infarction ($p = 0.02$) and global index ($p = 0.02$) with CEE therapy alone during intervention. In addition, women who were > 20 years postmenopausal had a non-significantly elevated risk of CHD when supplemented with CEE/MPA therapy compared to placebo group ($p = 0.08$). Moreover, the more recent 18-year cumulative follow-up data showed that exposure to HT during the WHI intervention was not associated with increased risks of all-cause, cardiovascular or cancer mortality (Manson et al., 2017).

To summarize, the cardiovascular benefit of oral estradiol therapy was evident in women closer to menopause (< 6 years). Both estrogen (CEE, oral/transdermal E2) and micronized progesterone were found to be safe and even beneficial for subclinical atherosclerosis, mood, fractures and metabolic markers in women < 60 years old (see Fig. 2). For young women without uterus, oral CEE therapy appeared to have favourable cardiovascular outcomes compared to older women. This provides a clear indication that age and early initiation of hormone therapy are critical in reducing cardiovascular disease risk, which in turn translates to reduced mortality in postmenopausal women. For cognition, CEE/t-E2 and micronized progesterone were not deleterious to cognitive performance in women < 60 years old and oral CEE therapy could improve mood (Gleason et al., 2015); however, HT might be deleterious for cognition in older women. KEEPS-Cog study followed up with positron imaging tomography for imaging amyloid-β deposition after 3 years of stopping treatment in 118 participants. It observed reduced amyloid-β deposition particularly in APOEε4 carriers treated with t-E2 therapy, which may reflect important implications for the prevention of Alzheimer's disease in recently postmenopausal women (Kantarci et al., 2016). Interestingly, the Research into Memory, Brain function and Estrogen Replacement (REMEMBER) study involving 428 women in Australia found that women who initiated HT before 56 years of age or within 5 years of hysterectomy resulted in better performance on the Mini-Mental State Examination than those initiated HT after these times (MacLennan et al., 2006). Moreover, compared with non-HT users, better information processing and verbal fluency were observed with estrogen-only users and combined estrogen/progestin users respectively. These findings need to be confirmed with longitudinal follow-up to see whether HT might be favourable for delaying dementia in younger, recently postmenopausal women. Taken together, early HT commencement was not detrimental on cognition and might even be beneficial for some specific cognitive domains and/or mood, in contrast to late commencement.

2.5. Implications of past lessons for on-going hormone trials

To gain an appreciation of future insights into the effects of HT on women's health, we identified ongoing clinical trials in the ClinicalTrials.gov registry. Drawing upon the lessons learnt from earlier studies, current hormone trials are targeting younger postmenopausal women, who specifically require HT for symptom relief and for other potential benefits. A prospective, open-label, randomized controlled trial from China (NCT03436303) has recruited younger postmenopausal women with intact uterus (n = 120, 40–60 years within 5 years of menopause who were seeking treatment for menopausal symptoms. They were randomized into 3 treatment groups, CEE 0.3 mg/MP 100 mg group; CEE 0.625 mg/MP 100 mg group; CEE 0.625 mg/dydrogesterone 10 mg group for two years. The risks and benefits for metabolic parameters, global cognition, body composition, bone mineral density, breast cancer and quality of life measures were assessed at baseline and after one and two years of intervention. This study is expected to finish by late 2018. A larger (n = 1200) two-year randomized, multi-centre trial in a similar population in China (NCT01698164) is comparing effects of estradiol plus MPA, estradiol plus progesterone and Ximingting (contains a phytoestrogen cohosh; cimicifuga rhizome extract 100 mg/day) on similar outcome measures.

The final status and outcomes of this study are yet to be published, although it was scheduled for completion by 2012. Combination of different types and doses of estrogen and safer progestogens are being compared directly to shed light on their pros and cons for important age-related outcomes.

3. Remaining critical issues for hormone therapy

The most recent systematic review by USPSTF (Gartlehner et al., 2017) concluded that the importance of the time of initiating HT treatment remains uncertain, despite existing clinical trials (ELITE, DOPS) demonstrating significant benefits in the prevention of chronic disease events following early initiation. The authors further reported that HT for primary prevention of chronic conditions in postmenopausal women was associated with substantially increased harms, although evidence existed for clear benefits of HT for younger postmenopausal women (Manson et al., 2013). This review primarily relied on a population of WHI women (averaging 63 years of age and 12 years postmenopausal) for guidance on a treatment clinically relevant to a population that is on average 12 years younger, who have clear differences in organ system status, risk factors and clinical needs. Moreover, strong evidence existed for the effects of type, dose or mode of delivery of HT on its benefit-to-harm profile; for example, an increased risk of venous thromboembolic events was not observed with transdermal estradiol; however, inconclusive results were reported and thus provided no further clarification.

As noted earlier, prescriptions for HT have decreased substantially since 2002 and this decline has affected women of all ages, with HT now prescribed to only 5% of women over 40 years of age in the United States (Sprague et al., 2012). Currently, HT is not recommended for primary or secondary prevention of CHD at any age, despite randomized clinical trials showing that young healthy women (< 60 years) within 10 years of menopause onset do not have increased coronary risk with hormone therapy. It has been calculated from the WHI CEE-alone trial that more than 40,000 hysterectomized women aged 50–59 years have died because women who would have used estrogen in the past ceased therapy after the initial release of the WHI reports (Sarrel et al., 2013). Moreover, women who experienced surgical menopause with bilateral oophorectomy before 45 years of age and were not treated with HT showed an increased risk of all-cause mortality (27%), coronary heart disease (33%), stroke (62%), cognitive impairment (60%), osteoporosis and fractures (50%) and sexual dysfunction (40–110%) compared to treated women (Faubion et al., 2015; Shuster et al., 2010). Therefore updated comprehensive recommendations are necessary to promote understanding of the benefits and harms of HT in specific populations of women, especially in healthy women beginning treatment before 50 years old who may gain cardioprotective benefits.

In older women, particularly those with established coronary disease, additional coronary events could be observed as early as one year after initiation of HT. As atherosclerosis progresses with age, many women in the previous clinical trials (e.g., WHI and the Heart and Estrogen Replacement Study) were considered to have established or heightened risk factors for coronary disease. When atherosclerotic plaques appear in coronary arteries, *oral* estrogen treatment can induce levels of matrix metalloproteinases (MMPs) that dissolve a portion of the plaque to cause plaque instability and subsequent rupture and thrombosis. *Transdermal* estrogen, on the other hand, does not increase levels of MMPs and the consequent risk of venous thrombosis and is therefore considered a safe alternative for older women as well as younger women with existing risk factors for stroke and venous thrombosis (Canonico et al., 2016). Moreover, a recent systematic review suggested a protective cardiovascular benefit of transdermal estrogen therapy in 50–79-year-old postmenopausal women with decreased risk of stroke and no increase in the risk of CHD death or myocardial infarction (Prema et al., 2017). However, the safety and long-term effectiveness of transdermal HT on cardiovascular outcomes, especially in older women, should be determined before clinical recommendations.

In general, initiation of HT by postmenopausal women older than 65 years requires careful consideration of an individual's health benefits and risks (The NAMS, 2017 Hormone Therapy Position Statement Advisory Panel, 2017). There is an upsurge in the trajectories for stroke and Alzheimer's disease in women over the age of 65 years that increase exponentially after 85 years. Unfortunately, no effective menopause management strategy is available for elderly women above 65 years old to slow the progression of age-associated comorbidities including CHD and osteoporotic fractures. Concerns about the adverse effects of HT have led middle age and older women to explore alternative therapies for improving menopausal symptoms and other age-associated chronic conditions. Due to easy accessibility and availability of over-the-counter supplements, use of alternatives to HT including phytoestrogens and homeopathic medicines has grown dramatically in recent years. These non-hormonal options are assumed to be safer alternatives than traditional hormone therapies and might be beneficial for women who are older or deemed not suitable or reluctant to pursue a HT regimen. However, few have been evaluated comprehensively in randomized clinical trials.

4. Non-hormonal therapies to manage menopause-related health issues

4.1. Phytoestrogens

Over the last decade, there has been increasing interest in the potential for selected plant-derived bioactive compounds to relieve menopause-associated problems. These include phytoestrogens, viz. resveratrol, catechins, isoflavones and coumestans, which occur naturally in plants. They are structurally similar to human hormone 17β-estradiol and possess estrogenic and/or anti-estrogenic effects. Phytoestrogens are regarded as powerful antioxidants and anti-inflammatory agents and are found in a variety of plant products including soy, berries, legumes, seeds and nuts. Isoflavones (especially genistein) and coumestans are the most widely researched groups of phytoestrogens but the circulatory benefits of resveratrol (a stilbenoid) have gained attention in the recent years. Numerous studies have shown that phytoestrogen exposure may be associated with lower risk of coronary artery disease (Food and Drug Administration, 1999), metabolic syndrome (Jungbauer and Medjakovic, 2014), obesity and type 2 diabetes mellitus (Bhathena and Velasquez, 2002), bone density loss (Ma et al., 2008) and cognitive decline (Soni et al., 2016).

In healthy postmenopausal women, soy isoflavones showed favourable long-term overall safety profiles with no treatment effects on endometrial thickness, circulating hormone concentrations or other adverse events (Alekel et al., 2015). The Women's Isoflavone Soy Health (WISH) study examined cardiovascular and cognitive effects of soy isoflavone supplementation (91 mg/day for 3 years) in 350 healthy post-menopausal women aged 45–92 years. Although isoflavones did not significantly slow atherosclerosis progression, subgroup analyses showed a 68% reduction of subclinical atherosclerosis (measured by carotid intima media thickness) with isoflavone supplementation in healthy younger women (median age 53 years) who were < 5 years postmenopausal (Hodis et al., 2011). As for cognitive outcomes, women who were 5–10 years postmenopausal were more likely to show improvements than those who had been postmenopausal for a longer period, suggesting the importance of age and timing of initiation of supplementation with phytoestrogens.

We recently conducted a systematic review to examine whether phytoestrogens are beneficial for cognition in humans (Thaung Zaw et al., 2017). Supplementation with either soy isoflavone or resveratrol was found to improve executive function and working memory in humans with small to moderate effect sizes; however no benefits were seen with red clover isoflavones. Most of the studies with soy

isoflavones were conducted in postmenopausal women; they tended to enhance cognition in women who were less than 10 years post-menopausal (Casini et al., 2006; Duffy et al., 2003; Kritz-Silverstein et al., 2003) but not in others (Basaria et al., 2009; Maki et al., 2009). However, the phytoestrogenic nature of resveratrol has been overlooked in most of the reviewed studies. Evans et al was the only study conducted in postmenopausal women (n = 80, average 65 years old). It observed benefits for cognitive performance, pain and total well-being with 75 mg of resveratrol twice daily for 14 weeks (Evans et al., 2017; Wong et al., 2017). Other studies observed small-to-medium effect-size cognitive benefits of resveratrol in older adults of mixed gender (Witte et al., 2014; Wong et al., 2016). Compared to the more popular soy isoflavones, evidence for effects of resveratrol on other health outcomes including cardiometabolic and bone health and long-term sustained benefits in postmenopausal women are lacking. It is also worthwhile exploring the critical window hypothesis for phytoestrogen supplementation on major health outcomes in future studies.

4.2. Other non-hormonal medications and procedures for menopausal symptoms

Non-hormonal pharmaceuticals are available for the management of menopause-associated vasomotor symptoms according to the NAMS position statement in 2015. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), some antiepileptic and centrally acting drugs are effective in reducing the severity and frequency of VMS in postmenopausal women compared to placebo. Studies demonstrated that paroxetine, citalopram and escitolapram are the most effective SSRIs while venlafaxine and desvenlafaxine are efficacious SNRIs (Stubbs et al., 2017). A low dose paroxetine salt (7.5 mg/day) is the only FDA-approved non-hormonal pharmacologic therapy for management of VMS (North American Menopause Society, 2015). Gabapentin (an anticonvulsant) was also shown to reduce hot flushes similar to 0.625 mg estrogen but with significant side effects (Reddy et al., 2006). Clonidine, a centrally acting alpha-2 adrenergic agonist (antihypertensive) was found to be efficacious for treating mild menopausal symptoms. Other therapies with favourable safety profiles for HT-contraindicated women include ospemifene (a selective estrogen receptor modulator derived from toremifene) (Nappi et al., 2015) and intravaginal dehydroepiandrosterone (DHEA) for genitourinary symptoms (Archer et al., 2015). Recently, stellate ganglion blockade, which is a minimally invasive approach in the neck to control temperature regulation, has been shown to reduce 45–90% of hot flushes and cold sweat symptoms with effects lasting from 6 weeks to several months after blockade (van Gastel et al., 2012; Walega et al., 2014).

4.3. Ongoing non-pharmacological trials targeting postmenopausal women's health

We are currently conducting the Resveratrol for Healthy Ageing in postmenopausal Women: RESHAW study (ACTRN12616000679482p) at the University of Newcastle, Australia to extend our existing body of knowledge on benefits of resveratrol in women's health. RESHAW is a 2-year double blind, randomised, placebo-controlled crossover clinical trial of 140 postmenopausal women who are between 45–85 years old, at least 12 months postmenopausal, non-smokers and non-HT users. The effects of 75 mg resveratrol twice daily on cognition (primary outcome), cerebrovascular function, mood and other aspects of well-being, cardiometabolic and bone health and physical function are being evaluated. We are also exploring the critical window hypothesis on major health outcomes such as cardiovascular and cognition between early and late menopausal women. We anticipate completing the study by June 2019 and the expected benefits of long-term resveratrol supplementation include counteracting accelerated cognitive, cerebrovascular and physical decline and improving overall well-being, cardiometabolic health and bone mineral density in postmenopausal women.

Another clinical trial from the University of Salamanca in Spain (NCT03492983) is currently recruiting 140 postmenopausal women aged 50–64 years to assess effects of high cocoa chocolate (10 g/day for 6 months) on blood pressure, vascular function, body composition, quality of life and cognitive performance with an anticipated completion by the end of 2019. Other approaches in the clinical trials register to improve postmenopausal women's health include Mona Lisa Touch (MLT) therapy, which is a non-hormonal (fractional carbon dioxide) treatment of the vaginal lining, applying pinpoint laser energy aiming to restore the tissues before going through menopause and providing relief for vulvovaginal symptoms. A randomised, double blind study from the University of New South Wales in Australia (ACTRN12616001403426) is recruiting symptomatic postmenopausal women until May 2018. The enrolled women will undergo MLT treatments over a 12-month follow up period for the treatment of postmenopausal vulvovaginal symptoms including symptom intensity, Vaginal Health Index scores, Quality of Life scores, vaginal skin histology, treatment acceptability, discomfort and complications. Findings from these non-hormonal trials will allow patients and practitioners to acknowledge different treatment options and generate a more informed decision regarding management of menopause-related conditions. Although there are alternative options available, head-to-head comparisons between HT and these non-hormonal interventions are limited and larger studies are warranted to confirm safety, efficacy, optimal dose, duration and drug interactions with these interventions.

5. Conclusion

Cardiovascular disease, particularly CHD, remains the leading cause of death in all women. Interventions such as the use of statins and aspirin are not indicated for primary prevention of CHD or reduced mortality in women in contrast to their effectiveness for prevention of CHD in men (Berger et al., 2006; Petretta et al., 2010). Lifestyle interventions have been shown to modestly reduce 10-year coronary risk by only 12–14% (Maruthur et al., 2009). Further consideration should be given to the prescription of HT, especially estradiol, in specific populations of women; estrogen therapy has been shown to decrease CHD by up to 40% and mortality by 20–40% in younger women (aged < 60 years). Menopause management with oral estrogen therapy in younger, recently postmenopausal women may be appropriate for cardiovascular protection, osteoporotic fractures and reduced incidence of breast cancer. However, prescription of HT for cardioprotective benefits in younger women is still hampered by unwarranted concerns about risks; updated recommendations are required for younger women at the onset of menopause.

So far, HT is only approved for four conditions according to the NAMS, 2017 statement: management of VMS, menopausal bone loss, vulvovaginal and genitourinary symptoms in women < 60 years old who are within 10 years of menopause without contraindications. Other than that, the role of HT for primary prevention of other chronic conditions such as CHD, breast cancer and dementia remains controversial. Regarding cognitive benefits, available evidence to support the hypothesis that estrogen therapy with temporal proximity to menopause can delay cognitive impairment remains inconclusive. Nevertheless, estrogen therapy is neither detrimental nor useful for cognition in younger, recently postmenopausal women; however, beneficial effects of HT on some cognitive domains were observed in the REMEMBER pilot study, which warrants further confirmation with larger clinical trials with appropriate follow up periods. Confirmation of cognitive benefits of resveratrol might offer alternative approaches to counteract accelerated cognitive decline after menopause.

Following CHD, stroke and dementia are major public health problems in older women, which start to appear around 65 years and escalate alarmingly after 85 years of age. Unfortunately, HT had greater

risks than benefits when administered to older women. Continued investigation of other viable alternatives is essential, especially for women over 65 years with a longer period since menopause during which no effective postmenopausal strategy has been established. Transdermal estrogen therapy appears to be a promising choice until definitive findings are obtained from future randomised controlled trials of oral estrogen in older women to weigh benefits against risks of stroke and thromboembolism. Future studies of the effectiveness and safety of non-hormonal medications and procedures to reduce the burden of menopause-related chronic conditions should be conducted in head-to-head comparisons with traditional hormonal therapies. Long-term clinical trials with non-hormonal/non-pharmaceutical interventions would largely impact on the public health burden by identifying viable alternatives to conventional HT and confirming their efficacy for menopause management, especially in women who are deemed unsuitable for HT.

Competing interests

The authors declare no competing interests.

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