An empowerment model for managing menopause

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Menopause eventually happens to all people with typically functioning ovaries, and almost one billion women worldwide are postmenopausal. Although the biology of typical menopause is ubiquitous, the experience varies substantially. Factors contributing to the experience include not only individual factors, such as the nature and severity of symptoms, but also psychological, social, and contextual considerations, many of which are modifiable. In this first paper in the *Lancet* Series on menopause, we argue for a new approach that goes beyond the treatment of specific symptoms, to encompass a broad model to support women transitioning this life stage, using the model of empowerment. WHO defines empowerment as an active process of gaining knowledge, confidence, and self-determination to self-manage health and make informed decisions about care. Rather than focusing on menopause as an endocrine deficiency, we propose an empowerment model that recognises factors modifying the experience, in which the patient is an expert in their own condition and the health-care worker supports the patient to become an equal and active partner in managing their own care.

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This is the first in a Series of four papers about menopause. All papers in the Series are available at XXXXX

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Background

Although menopause is biologically inevitable, experiences vary considerably and are shaped by factors including symptoms, race and ethnicity, social meanings, expectations, self-esteem, life adversity, and general health. In many high-income countries (HICs), menopause is commonly described as a medical problem and sometimes as a hormone deficiency disorder with typical symptoms and long-term health risks that are best managed by hormone replacement.[1] However, this disease-based model is challenging in practice given the wide variation in experiences between women and their changing experiences over time. Also, the inevitability of menopause makes finding out whether long-term health outcomes are due to menopause or ageing difficult, particularly given the scarcity of adequate prospective data for long-term health consequences of premature or early menopause. Although management of symptoms is important, a medicalised view of menopause can be disempowering for women, leading to over-treatment and overlooking potential positive effects, such as better mental health with age and freedom from menstruation, menstrual disorders, and contraception.[2]

In this first paper in our *Lancet* Series, we consider a new approach to menopause that goes beyond the treatment of specific symptoms, based on the model of health empowerment. WHO defines empowerment as an active process of gaining knowledge, confidence, and self-determination to self-manage health and make informed decisions about care.[3] Although the principles of health empowerment have not previously been applied to menopause, in 2005 the US National Institutes of Health (NIH) identified the need to develop and disseminate information emphasising menopause as an ordinary, healthy phase of women's lives and promoting its demedicalisation.[4] Across several health domains there is growing evidence that empowerment is an effective tool to optimise self-management of health, which can also reduce health-care costs.[5]

To be empowered, women must be informed and listened to. Women have clearly stated that they want their voices heard and their experiences of menopause acknowledged and validated. Unfortunately, some women report that their concerns are dismissed, particularly those from minority groups.[6] We propose a more inclusive approach (figure 1). Key components of menopause empowerment include access to evidence-based and balanced information, preferably before the onset of menopause (panel), tools to support decision making around treatments for symptoms (eg, decision aids), and access to a supportive clinician who listens with empathy and offers treatment if needed by using a shared decision-making model (figure 1). More broadly, challenging widespread stigma about menopause as a period of decline and decay and creating a more menopause-friendly work environment might help to empower women.[8]

In this paper, we focus on empowerment in the context of typical menopause. In other papers in the Series, we consider other types of menopause which might affect the experience and we believe warrant more attention: early menopause, menopause after cancer, and mental health during the menopause transition.

Key messages

- Most women navigate menopause without the need for medical treatments
- Over-medicalisation of menopause can lead to disempowerment and over-treatment
- New tools are available to support the empowerment of women to navigate the menopause transition
- Empowerment is likely to confer benefits for women across socioeconomic and geographical locations, health services, and economies

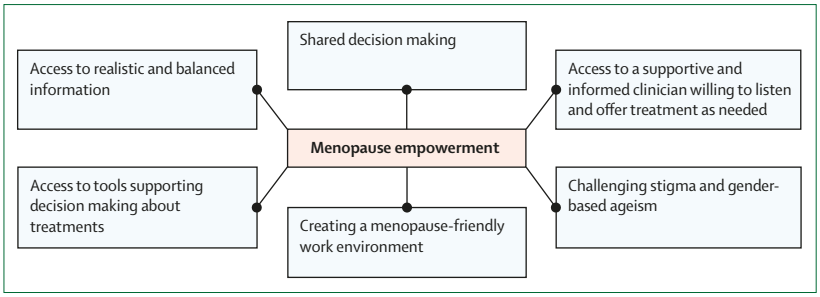

Figure 1: **Empowering women to manage menopause**

***Panel*: How clinicians can support empowerment in the management of menopause**

Before menopause

- Provide evidence-based information about what to expect
- Challenge overly negative assumptions about menopause and ageing and encourage discussion with friends and family
- Encourage routines that might reduce stress and improve mood—eg, mindfulness and exercise

During the menopause transition

- Provide reassurance and offer effective treatments for symptoms as requested
- Provide realistic information about the likely effects of treatment, the potential for residual symptoms, and the possibility that symptoms could recur when treatment stops
- Offer reassurance that vasomotor symptoms are usually time limited and might be most frequent in the year around the final menstrual period[7]
- Offer behavioural strategies that might reduce the anxiety that can accompany hot flushes, and provide advice on sleep hygiene
- Offer advice about lifestyle factors, addressing sleep, alcohol, and smoking, which can exacerbate vasomotor symptoms
- Challenge self-critical beliefs, which can increase arousal and make flushes worse
- Offer advice about management of symptoms in the workplace[8]
- Encourage connections with other women for discussion and support

After menopause

- Offer effective treatments for persistent vasomotor or genitourinary symptoms
- Encourage good general health[9]
- Offer screening as indicated for primary and secondary prevention of chronic disease

For **general health information** see https://www.nhs.uk/live-well/

Menopause as a hormone deficiency disease

Menopause became medicalised in the early 20th century, with the belief that women's identity (so-called femininity) and physical and mental health was predicated on the balance between oestrogen excess or deficiency.[1] A wide range of mental and physical disorders in women were (and still are) attributed to hormonal imbalance. Loss of oestrogen after menopause was thought to be individually and socially harmful, and to have consequences such as "untold misery of alcoholism, drug addiction, divorce and broken homes".[10] Oestrogen treatment emerged during the rejuvenation and anti-ageing movements of the early 1900s. Hormones extracted from animals were injected into humans to counter the perceived deficiencies of age.[1] In women, oestrogens were widely prescribed for menstrual and reproductive disorders, pregnancy complications (eg, diethylstilbestrol), psychoses, and depression.[10] From the 1940s, purpose-designed hormone replacement therapy (HRT), extracted from pregnant mares' urine, was widely promoted for the "unstable, estrogen-starved postmenopausal woman".[11]

Access to HRT has directly benefited many women, bringing the first effective treatment for menopausal symptoms and potential long-term benefits for younger menopausal women. However, as predicted by *The Lancet* in 1975, "The prospect of universal treatment of a large section of the female population is clearly a glittering commercial prize for the pharmaceutical industry" and uptake was rapid. By the mid-1960s around a third of UK women aged 50–64 were taking HRT, making it the most commonly prescribed medication in this population.[12] Uptake was low in low-income and middle-income countries (LMICs), where menopause is generally considered a part of the natural ageing process, bringing benefits, such as the cessation of menstruation.[13]

The use of HRT (now called menopausal hormone therapy [MHT]) plummeted in 2002, when a large randomised placebo-controlled trial (RCT) was terminated early due to its findings of an increased risk of breast cancer with combined MHT,[14] inadequate benefit in the primary outcome (coronary heart disease), and increased risk of stroke with oestrogen-only MHT.[15] This drop in MHT use was followed by a decreased incidence of breast cancer in some countries[16] and an increased risk of fracture in others.[17] Although long-term follow-up from this RCT has shown no increase in all-cause mortality after 5–7 years of MHT, uptake has never returned to previous levels in most countries. In the UK, use of MHT increased by around 60% between 2020 and 2022, particularly in women from the most affluent areas of the country.[18] The reasons for this increased use are uncertain but might reflect the subtantial increase in media attention towards menopause. We argue that additional strategies beyond medication are needed to effectively support women as they transition menopause.

Search strategy and selection criteria

We searched databases on MEDLINE, Embase, BioMed Central, Cochrane, and Google from December, 2020, to July, 2023, with key words tailored to each section of the manuscript combining "menopaus*", "psychotherapy*", "premature ovarian insufficiency", and "postmenopaus*" with "menopausal symptom*", "vasomotor symptom*", "genitourinary symptom*", "genitourinary syndrome of menopause", "hormone therap*", "hormone replacement therap*", "non-hormonal therapy*", "psychotherapy*", "empower*", "disempower*", "self confiden*", "self-determination", "self manag*", "care model", "model of care", "model of self care", "shared decision making", "menopause at work", "working", "employment", "ageism", "ageist", "age discrimination", and "age prejudice". We cross-referenced these terms with "systematic review*", "meta-analysis", "metaanalysis", "randomised/randomized controlled trial*", "clinical guideline*", "clinical practice guideline*", and "core outcomes" and websites and guidelines of menopause societies, including British Menopause Society, International Menopause Society, North American Menopause Society, Australasian Menopause Society, the United States Preventive Task Force (USPTF) recommendations on Menopause, and the National Institute of Clinical Excellence (NICE) guidelines. The Turning Research Into Practice and PubMed databases were searched for evidence-based guidelines and systematic reviews. We prioritised the most recent evidence from RCTs and recommendations from international guidelines based on systematic reviews of the evidence (eg, NICE and USPTF). Only publications in English were included.

What is menopause?

The menopause occurs with the final menstrual period; thus, the occurrence of menopause can only be determined in retrospect, and women are considered postmenopausal after 12 months with no periods.[19] The timing of menopause is thought to be predicated on the size of the primordial follicle pool (ie, ovarian reserve), which is fixed by the time of birth. When the follicle count drops below a critical threshold, ovulation becomes intermittent and eventually stops. The process of going through the menopause starts with menstrual cycle changes and ends 1 year after the final menstrual period (figure 2).[19] Women with irregular menstrual cycles, following endometrial ablation or hysterectomy, and users of hormonal contraception might be uncertain about the timing of menopause.

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in some instances, we have referred to "people" rather than "women" to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used "women" in some instances, to avoid inappropriate generalisation. Evidence on menopause in gender-diverse individuals is scarce and needs more attention.[20]

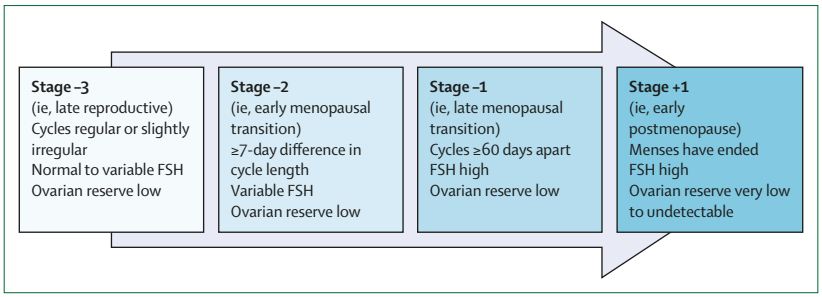

Figure 2: **Reproductive stages over time spanning the menopausal transition**[21]
FSH=follicle-stimulating hormone.

Predicting the onset of menopause

Changes in the menstrual cycle are the most reliable indicator of the menopause transition.[19] Blood tests, such as measurement of anti-mullerian hormone, are uninformative for women older than 45 years.[21] The transition usually starts at around age 47 years in HICs and lasts for 4 years on average, with the average age at menopause being 51 years.[21] Timing might be earlier in LMICs; for example, data from India indicate that the mean age at menopause is approximately 46 years.[22] Globally, around 10% of women experience premature menopause (before age 40 years) or early menopause (at age 40–44 years),[23] which can be iatrogenic (eg, following chemotherapy or radiation for cancer or bilateral oophorectomy) or spontaneous.

What symptoms are caused by menopause?

In a large US longitudinal study, during the menopausal transition, prolonged menstrual bleeding affected more than 90% of women at least once and nearly 80% of women at least three times, and about a third of women had 3 or more days of heavy bleeding on at least three occasions.[24] Heavy and irregular bleeding could affect many aspects of life, including work. Access to toilet facilities and breaks might help. The menopause transition is also when vasomotor symptoms are most likely to start.[25] More information is needed about how best to manage bleeding problems and menopausal symptoms over this period.

Apart from menstrual cycle changes, there is uncertainty about what other symptoms menopause causes, with no universal menopause syndrome.[26] In 2005, an NIH interdisciplinary expert consensus concluded that many women have few or no symptoms and that only vasomotor symptoms, vaginal dryness, and possibly sleep disturbance were clearly attributable to menopause.[4] Subsequently, prospective studies reported that depressive symptoms and disturbances in sleep and

cognition can temporarily worsen for some women.[27,28] Whether the menopause transition is associated with clinically significant increased anxiety is uncertain and prospective studies show inconsistent findings.[29]

One US prospective study of 255 women reported an increase in aches, joint pain, and stiffness.[30] The 1946 British Birth Cohort reported that psychological symptoms and discomfort with sex increase in around 10–20% of women over the menopause transition.[31] Less is known about menopausal symptoms in LMICs, but cross-cultural studies suggest that sleep disturbance and muscle and joint pain are more common than vasomotor symptoms,[32,33] although findings are conflicting.[34]

Vasomotor symptoms

In HICs, about 40% of women report vasomotor symptoms in the early menopause transition, peaking at 60–80% in the 2 years after the final menstrual period.[19,31] These can continue for 4–7 years on average but usually decrease over time.[7] Predicting individual symptoms is difficult but prospective studies show that vasomotor symptoms starting in the early menopause transition are more likely to be persistent.[35] Symptom severity can contribute to women seeking treatment for vasomotor symptoms. A pooled analysis of eight cohort studies of more than 21000 women reported that 38% had moderate or severe vasomotor symptoms.[36] A prospective US study (n=255) found that a third of women recruited before menopause had persistent moderate or severe symptoms for 10 years.[37]

Vasomotor symptoms seem to differ between ethnic and racial groups. For example, Black and Hispanic women report more severe vasomotor symptoms and Asian American women less severe vasomotor symptoms compared with White women,[26] but less is known about minoritised racial and ethnic groups in other multicultural countries, such as the UK. Within the USA there might be sub-variations in the menopausal symptom experience of Asian women.[38] As well as frequency and severity, other factors influence the experience of vasomotor symptoms, such as attitudes towards menopause and ageing, religion, socioeconomic status, lifestyle (eg, diet and exercise), and methodological limitations of individual studies.[34] However, it is important not to make assumptions about women's experience of menopause based on ethnicity or race.

The degree of interference from vasomotor symptoms, which is strongly influenced by psychological, social, and biological factors, is a priority for menopausal women.[39] There is a bi-directional association between vasomotor symptoms and stress, making stress a potentially modifiable factor. There is also a two-way association between vasomotor symptoms and depressed mood. Women with more severe vasomotor symptoms tend to report more depressive symptoms, and women who are depressed can find vasomotor symptoms hard to manage.[40,41] Other potentially modifiable factors include smoking, high BMI, depressed mood, anxiety, and negative beliefs about menopause. Lifestyle and behavioural changes have shown some success in reducing troublesome symptoms, although findings are mixed (panel).[36,42,43]

Muscle and joint pains

Most studies of menopausal symptoms were conducted in White women from HICs or in racial subgroups within these countries. Women in LMICs report substantial differences in the experience of menopause. Southeast Asian women in LMICs might be less troubled by vasomotor symptoms and more likely to report muscle and joint pains than women in HICs.[44] MHT can modestly improve joint pain but the effect on muscle aches is unknown.[45]

Sleep disturbance

Sleep disturbances are more common in women than in men across the life course and can increase over the menopause transition.[46] Night-time awakenings due to vasomotor symptoms are common, but sleep can be disturbed for other reasons over this period, and conditions such as obstructive sleep apnoea or depression can contribute.[46] Menopausal symptoms that disturb sleep can affect daytime function, including mood and concentration. An international, consumer-driven process to find out what outcomes should be measured in menopause clinical trials concluded that the effect of treatments on sleep was a priority area.[47]

Genitourinary symptoms

Between 10% and 40% of postmenopausal women report symptoms such as vaginal dryness, vulvovaginal irritation or itching, and dyspareunia.[48] Unlike vasomotor symptoms, these genitourinary symptoms tend to start after menopause and can persist into older age. Genitourinary changes, such as vaginal dryness, can also be secondary to ageing.

Other symptoms

The effects of hormone changes can be difficult to differentiate from concurrent life events such as caring for children at home, managing paid and unpaid employment, taking responsibility for ageing parents, and balancing conflicting life roles.[49] In particular, changes in mood and cognition and sexual difficulties commonly ascribed to menopause can be caused or exacerbated by these life stressors.[50] Similarly, although subjective changes in concentration and memory are common over the menopause transition, these have not been clearly linked to long-term cognitive decline. Prospective studies of objective measures of cognition over the menopause transition show only small and mostly temporary memory changes in a minority of women, an observation that many find reassuring.[51,52] Subjective changes in memory and concentration can be more common, but whether

these changes are secondary to factors such as sleep disturbance is uncertain.[53]

Menopause and long-term health

Natural menopause at the average age is associated with an increased incidence of some health problems and a reduced incidence of others. Although bone density is known to decline after menopause, whether menopause at the average age increases other chronic conditions such as diabetes, dementia, or cardiovascular disease is uncertain. Prospective studies of body composition and weight have shown mixed findings, but the Study of Women's Health Across the Nation showed a small increase in weight gain of 0·25 kg per year over the menopause transition, which stabilised postmenopause. The average absolute weight gain associated with menopause was 1·6 kg.[54]

Managing menopausal symptoms

Although there is uncertainty about the symptoms menopause causes, vasomotor symptoms are consistently reported and are the leading patient priority for treatment, followed by sleep, concentration, and fatigue.[55]

Psychological therapies

The most troublesome aspects of vasomotor symptoms are frequency, severity, bother, and impact on sleep.[55] Effective non-pharmacological treatments for vasomotor symptoms include purpose-designed cognitive behaviour therapy (CBT) and hypnosis.[56] In 2022, a systematic review and meta-analysis including 14 RCTs reported that CBT was superior to control groups in reducing hot flushes, night sweats, sleep disturbance, depression, anxiety, and fatigue and significantly improved quality of life, although effects were generally small to moderate.[57] CBT also reduces problematic vasomotor symptoms at work and after breast cancer.[58] CBT can be delivered in groups by health professionals, with the use of self-help books, online, or by telephone.[58] Clinicians should advise patients that RCTs of acupuncture, plant-based therapies, and exercise have largely not shown benefit over placebo or sham procedure for vasomotor symptoms.[59] Clinicans should offer advice about lifestyle factors, addressing sleep, alcohol, and smoking, which can exacerbate vasomotor symptoms (panel).

The North American Menopause Society recommends clinical hypnosis for vasomotor symptoms. This recommendation is based on two RCTs showing a statistically significant improvement in the frequency and severity of vasomotor symptoms.[60,61] At 12 weeks the reduction in subjective hot flushes with hypnosis was 74·2% versus 17·1% in controls. Clinical hypnosis also reduced interference due to vasomotor symptoms and improved sleep quality. Hypnosis can be delivered by a trained provider or accessed on a smartphone app.

Medical therapies

The North American Menopause Society recommends specific MHT, gabapentin, and oxybutynin, which have mild to moderate efficacy and reduce hot flushes by 1–2 per day with no clinically significant improvement in menopause-related quality of life.[60] Targeted therapy with the neurokinin B receptor antagonist fezolinetant is available in the USA and some European countries. Two large RCTs have compared the efficacy of fezolinetant versus placebo for vasomotor symptoms over 12 weeks, with a 40-week open label extension.[62,63] With 45 mg per day (the dose now marketed), there was a statistically significant reduction in hot flush frequency and severity up to 1 year and serious adverse events were infrequent. Fezolinetant also improved menopause-related quality of life.[64] Although clinical trials of neurokinin B receptor antagonists in patients with cancer have not yet been published, breast cancer is not a contraindication to fezolinetant use in the USA. However, improvements in vasomotor symptoms with fezolinetant are modest and do not meet the minimally important clinical difference[65] for hot flush frequency or menopause-related quality of life. A meta-analysis published in 2024,[66] which included 2168 patients from five RCTs, reported a 22·5% mean improvement in frequency of vasomotor symptoms, with small improvements in menopause-related quality of life. In 2023, the independent US Institute for Clinical and Economic Review concluded that fezolinetant was less effective than MHT for vasomotor symptoms, and that MHT might provide additional benefits for sleep, vaginal dryness, and fracture prevention.[67]

Help-seeking for menopausal symptoms is highly contextual, but 13% of women in HICs are given MHT.[36] In the UK, NICE recommends MHT after discussion of the short-term and long-term risks and benefits, which are likely to differ according to patient's age and type of MHT.[68] For those with problematic symptoms, MHT generally leads to statistically and clinically significant reductions in vasomotor symptom frequency and severity, along with improvements in menopause-related quality of life.[67] For standard (1 mg) and low (0·5 mg) dose estradiol, this improvement equates to around 2–4 fewer hot flushes per day versus placebo, which might not be clinically meaningful for those with very frequent symptoms.[67] Vasomotor symptoms can co-occur with sleep and mood disturbance[69,70] and a 2022 systematic review reported that MHT led to small improvements in sleep.[71] However, the primary indication for MHT is the treatment of problematic vasomotor symptoms.[72] MHT might improve sleep, memory, and concentration in women taking it for vasomotor symptoms but it is unlikely to have any effect in women without vasomotor symptoms.[73] For symptom clusters such as hot flushes, disturbed sleep, and depressed mood, RCTs show that CBT is effective.[57]

Systemic MHT improves vaginal dryness, but a 2023 systematic review of ten RCTs reported that MHT can worsen or cause urinary incontinence.[74] Hence, vaginal

For more on **CBT delivered in groups by health professions** see https://thebms.org.uk/

dryness is best managaed with vaginal oestrogen. Patients' priorities for symptom control should inform shared decision making around treatment.

Although combined and oestrogen-only MHT preparations have similar efficacy, their risk profile differs. For example, a 2004 RCT of more than 27 000 women showed that combined MHT increased breast cancer risk, but oestrogen-only MHT did not.[15] More recently, large observational studies including individual participant meta-analyses from over 108 000 patients with breast cancer found that all types of systemic MHT increased risk of breast cancer; risk was substantially greater with combined MHT compared with oestrogen alone. The authors estimated that about one in 50 users of combined MHT will develop breast cancer after 5 years of continued use.[75] Combined MHT is the most frequently prescribed form of MHT. In the UK, an estimated 80% of MHT users take a combined preparation because adequate dose and duration of progestogen is needed to prevent endometrial hyperplasia.[68]

The mode of delivery of MHT also affects the risk to benefit ratio. Transdermal MHT is as effective as oral MHT for vasomotor symptoms[76] but a systematic review in 2018 found that transdermal MHT did not increase venous thromboembolic disease, although evidence quality was low to moderate.[15,77,78] Decisions about how to take MHT should be shared, although patients should be made aware that transdermal preparations appear safer regarding venous thromboembolic risk.

The Monthly Index of Medical Specialities lists contraindications to MHT including oestrogen-sensitive cancer, history of venous thromboembolism or pulmonary embolism, active or recent arterial thromboembolic disease (eg, angina and myocardial infarction), acute liver disease, unexplained genital bleeding, pregnancy, elevated triglycerides, untreated hypertension, porphyria, and previous stroke or transient ischaemic attack. Recommendations on the duration of MHT use vary, but in their 2022 guidelines, the North American Menopause Society cautions against starting MHT after age 60 years or beyond 10 years since menopause.[56] However, the relative risks versus benefits of continuing MHT beyond age 60 years are uncertain and require a shared decision-making approach. Stopping MHT commonly leads to resurgent vasomotor symptoms in up to 50% of patients, and whether this resurgence reflects ongoing menopausal symptoms or a withdrawal effect from MHT is uncertain.[79] Neither stopping MHT slowly nor stopping gradually have been shown to prevent resurgent symptoms.[80] Shared decision making about treatment should consider the degree of symptom bother, personal preferences, cardiovascular disease and breast cancer risk, and uterine status (ie, having had a hysterectomy or not).[72]

Fracture risk increases after menopause and NICE indicates that 5 years of MHT reduces risk by 25 fractures per 1000 women on average (range nine to 37 fewer fractures per 1000 women).[68] However, benefits dissipate by 5 years after MHT is discontinued.[68,81] Therefore, 10 years of MHT from age 50 years to 60 years will not appreciably reduce fracture risk because fractures are uncommon at this age. Although MHT is approved in some countries for the prevention of osteoporosis, the US Preventive Services Task Force recommended in 2022 that MHT should not be used for the primary prevention of any chronic conditions solely because of the unfavourable risk versus benefit balance.[82] In 2023, the Endocrine Society recommended that MHT only be used to prevent osteoporosis in those at substantial risk for whom other therapies are not tolerated or appropriate.[72]

For women with predominantly genitourinary symptoms, a 2021 meta-analysis reported that vaginal (topical) oestrogens can reduce dryness and prevent recurrent urinary tract infection.[83] An RCT of daily intravaginal dehydroepiandrosterone showed significantly reduced dyspareunia and vaginal dryness at 12 weeks.[84] Placebo-controlled RCTs have shown that ospemifene, a selective oestrogen receptor modulator, improves vaginal dryness and dyspareunia.[85] However, there are no clinical trials directly comparing ospemifene with vaginal oestrogen, and published trials have focused on objective outcomes such as vaginal pH and the appearance of vaginal cells on microscopy, which are not priorities for symptomatic women or clinicians.[71] Information about vaginal laser is still emerging, but RCTs in participants with and without breast cancer have shown no benefit over sham procedure for genitourinary symptom severity,[86,87] stress incontinence,[88] or sexual function.[89] Shared decision making for genitourinary symptoms should include discussion of over-the-counter moisturisers and lubricants, vaginal oestrogen or dehydroepiandrosterone, and oral ospemifene.[72]

Interventions to support empowerment

Many women navigate menopause without the need for medical intervention, but some experience symptoms that affect function and quality of life. Those seeking medical care are often looking for information rather than drug treatment unless their symptoms are severe.[90] Women need easy access to unbiased, accurate information in a form they can understand, created without industry influence and without any hidden agendas to sell a drug or service.[91] Accessing credible information can be challenging, particularly for women in LMICs where home remedies, ayurvedic, and homoeopathic therapies are often preferred to medical treatments for menopausal symptoms.[33] Clinicians caring for patients with menopausal symptoms can empower and support them by listening with empathy, validating their experiences, and being aware of the social and cultural differences that can underlie those experiences (figure 1). Normalising menopause and providing realistic and balanced information about the likely nature, severity, and duration of symptoms can be empowering for women and help them to make decisions

about management (panel).

For those seeking treatment, clinicians should offer evidence-based information about the range of effective interventions for problematic symptoms, including non-pharmacological and non-hormonal methods, with a model of shared decision making (figure 1).[92] However, MHT is the only treatment that benefits both vasomotor and genitourinary symptoms and reduces fracture risk. Menopausal symptoms commonly cluster, and patients experiencing clusters of hot flushes, disturbed sleep, and depressed mood might benefit from interventions that improve multiple symptoms, such as CBT, or non-hormonal treatments that benefit both vasomotor symptoms and depressed mood.[58,93] A qualitative study of CBT for vasomotor symptoms reported that women felt empowered by learning to self-manage their symptoms, including greater knowledge about menopause, acceptance of their symptoms, and new coping strategies leading to greater confidence and a sense of control.[94] Empowerment can directly improve the experience of menopause. A UK qualitative study reported the complex narrative of menopause as a normal event, a struggle, a loss of identity, and as a time of liberation and transformation.[95] Unfortunately, many women seeking treatment for menopausal symptoms report feeling dismissed and receiving inaccurate information and ineffective treatments.[96]

Provision of realistic and impartial information is essential. For example, My Meno Plan was funded by the US NIH and developed without commercial input. It provides evidence-based information about typical changes over the menopause transition and postmenopause and options for self-management and treatment. No treatments are 100% effective, and counselling should be realistic about what improvements to expect and what side-effects can occur (for example, improvement of sleep, memory, and concentration with MHT only for those with problematic vasomotor symptoms[73]). Also, postmenopausal women considering combined MHT should be aware that up to 50% develop bleeding in the initial months, which might require investigation to rule out endometrial hyperplasia or cancer with ultrasound and potentially lead to hysteroscopy and biopsy.[97] The effect of MHT on bleeding patterns in the perimenopause are not well understood, but intrauterine progestogen might offer better control of heavy bleeding compared with combined MHT.[98]

Women aged 45–55 years represent a highly productive group making an essential contribution to society and social structures. Women older than 40 years are the fastest growing sector of the paid workforce in HICs, and most essential and voluntary workers are women.[99] Many are working during the menopause transition, and symptoms at work can be particularly problematic due to embarrassment and concerns about the reactions of other people. This situation can be particularly challenging for those working in informal economies and in LMICs. According to the UK Health and Safety Executive, women aged 45–54 years report more work-related stress than men or women of any other age group, associated with high job demands and inadequate control and support at work.[100] These women have clearly indicated how things could improve. A qualitative study with 137 participants reported that women want their managers to be informed and empathetic about menopause and how symptoms might be exacerbated by the work environment.[101] They also wanted their workplace to offer open and supportive communication and helpful work policies including flexible work hours. Many health and social care workers are women. Uniforms that are heavy or made of non-breathable fabric are an avoidable source of discomfort for menopausal women.[102] Practical adjustments to support and empower menopausal women at work include informed and empathetic managers, fans, control of ambient air temperature, and uniforms made from breathable fabrics.[8,100]

Evidence from the UN (in 2023) and WHO (in 2021) reports that around 90% of people hold gender biases[103] and more than 50% hold ageist attitudes.[104] For older women experiencing menopause, these biases can intersect to reinforce negative attitudes and experiences. Clinicians can help by recognising these biases in themselves and avoiding framing menopause as a period of decay and decline (panel). Negative attitudes towards menopause can directly affect personal experiences. In 2010, a systematic review reported that women with neutral or positive attitudes towards menopause tended to have a greater sense of control than women with more negative attitudes.[105] On the basis of a systematic review of qualitative studies, clinicians can offer reassurance that many women experience growing confidence and assertiveness, freedom from some responsibilities, shifts in family relationships, and accepting and embracing age.[95,105]

For more on **My Meno Plan** see https://mymenoplan.org/

Future developments

There is considerable variation between women in their experience of menopause and few ways to predict who might have symptoms and for how long. Predictive models using genetic and environmental data can inform tools for individual use. Similarly, future studies might be able to identify personalised treatments for those with specific clusters of symptoms or those identified by digital health measures. There is clearly a need for more evidence-based strategies to relieve menopausal symptoms, which requires a skilled workforce to provide clinical care.

Ageism is a powerful social determinant of health, and in countries where menopause is equated with physical and mental decline, it is not surprising that many find this transition daunting. Actively challenging ageism and encouraging a more positive discourse can help reduce anxiety for women approaching menopause.[92] The social

value of older women can affect this experience. In contexts in which women's value is predicated on reproduction, menopause tends to reduce social status. By contrast, in societies in which ageing confers respect, such as in Indigenous communities in Australia, menopause is considered less problematic.[106] Growing public discourse about menopause in some settings (eg, the UK) is raising awareness and could help change the culture by reducing stigma and shame and encouraging open discussion. Women have indicated that they want this topic to come out of the shadows and be more openly discussed, particularly in the workplace. They want their experiences heard by each other and their health-care providers.[91] Public initiatives aiming to empower women by dispelling myths, sharing realistic experiences, and promoting positive images include Menopause Café, and arts initiatives such as Flesh after Fifty directly challenge negative beliefs and create new positive role models.

For **Menopause Cafe** see https://www.menopausecafe.net/

For **Flesh after Fifty** see https://www.fleshafterfifty.com/

Digital health, including use of mobile health apps, telemedicine, and data analytics to improve health systems, surged during the COVID-19 pandemic. New tools are emerging that are designed to empower women to recognise, understand, and manage their own menopausal symptoms through digital technology. For example, Henpicked menopause hub and Women Living Better provide evidence-based, realistic, and clear information about the menopause transition and its symptoms, including stories from women with lived experience and information about treatment options. Women can use the My Meno Plan tool to compare treatments and develop their own management approach in consultation with their health-care provider. Much information about menopause available online is driven by commercial interests. The National Library of Medicine tool can be used for evaluating the quality of online health information. People in LMICs can benefit from proactive information from health-care providers about what to expect at menopause.

For **Henpicked** see https://henpicked.net/

For **Women Living Better** see https://womenlivingbetter.org

For the **Global Coalition on Aging** see https://globalcoalitiononaging.com/

For more on the **National Library of Medicine tool** see https://medlineplus.gov/webeval/webeval.html

In 2021, a European consensus recommended that workplaces should create an open, inclusive, and supportive culture around menopause, with occupational health professionals and human resource managers working together.[8] To enable employers to make these changes, online resources such as Menopause at Work provide evidence-based and practical information for employers to support their employees, including education, communication, and flexible work policies. However, more information is needed about what workplace interventions are effective.

For **Menopause at Work** see https://www.menopauseatwork.org/

Despite substantial gaps in knowledge about menopause, research has largely focused on developing new drugs for vasomotor symptoms, although most women do not choose to take medication. Interpretation of these clinical trials has been hindered by inadequate agreed patient-reported outcome measures and inconsistent measures for the same symptom,[107] which limits comparisons between treatments and precludes data pooling. To standardise these measures, the Core Outcomes in Menopause initiative reached global consensus among clinicians, researchers, and women with lived experience of menopause across 28 countries to find out which outcomes should be measured in future clinical trials for menopausal symptoms.[47,108]

Most research in menopause is from HICs. Little is known about the diversity of experience across LMICs, and what is known suggests that the differences are greater than the similarities.[109] In addition, women have not been widely consulted about their priorities for menopause research. A Menopause Priority Setting Partnership is underway with the James Lind Alliance[110] to find out the research priorities of affected women and their health-care providers for menopause research.

In her 2023 book *Period*, Kate Clancy described how menstruation is routinely stigmatised as an unruly pathology requiring medical management and as a lamentable curse of womanhood.[111] Perceptions of menopause are similar and contribute to disempowerment and negative experiences. Women are shamed for menstruating, and then shamed for not menstruating. 2020 was the start of the WHO and UN decade of healthy ageing. Priority areas of the Global Coalition on Aging include women's lifelong health needs and risks and how best to deliver integrated, person-centred care across the life course. Health literacy, access to quality health care, and economic participation are inextricably linked. By connecting healthy ageing with women's rights, global and national policy leaders can help to empower women to live long, healthy lives.

Contributors

MH conceived and designed the paper, wrote the initial draft, and was responsible for revising this draft on the basis of comments from the other authors. AZL, JD, GDM, MS, DG, and MSH made substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of data for the work. AZL, JD, GDM, MS, DG, and MSH contributed towards drafting the work or revising it critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MH is responsible for the final approval of this manuscript and agrees to be accountable.

Declaration of interests

MH declares salary funding from the Australian National Health and Medical Research Council, support for meeting attendance from the UK National Institute for Health and Care Excellence, and the following roles: principal investigator for a clinical trial of salpingectomy vs salpingo-oophorectomy for prevention of ovarian cancer (TUBA-WISP II); board member for Breastscreen Victoria; editor for the Cochrane Collaboration; recipient of a fellowship from the Lundbeck Foundation (2022-23); site investigator for a clinical trial of a non-hormonal agent (Q-122) for vasomotor symptoms in patients with breast cancer (QUE Oncology, 2020-22); and site investigator for a clinical trial of a medical device for treating vaginal dryness (Madorra). AZL has grant funding for research on menopause from the National Institute on Aging of the National Institutes of Health in the USA. MSH has worked in collaboration with Rightsteps UK to develop CBT solutions for menopausal symptoms 2020–25 and is author of two books on CBT for menopausal symptoms with Melanie Smith. All other authors declare no conflicts of interest.

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Optimising health after early menopause

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The typical age at menopause is 50–51 years in high-income countries. However, early menopause is common, with around 8% of women in high-income countries and 12% of women globally experiencing menopause between the ages of 40 years and 44 years. Menopause before age 40 years (premature ovarian insufficiency) affects an additional 2–4% of women. Both early menopause and premature ovarian insufficiency can herald an increased risk of chronic disease, including osteoporosis and cardiovascular disease. People who enter menopause at younger ages might also experience distress and feel less supported than those who reach menopause at the average age. Clinical practice guidelines are available for the diagnosis and management of premature ovarian insufficiency, but there is a gap in clinical guidance for early menopause. We argue that instead of distinct age thresholds being applied, early menopause should be seen on a spectrum between premature ovarian insufficiency and menopause at the average age. This Series paper presents evidence for the short-term and long-term consequences of early menopause. We offer a practical framework for clinicians to guide diagnosis and management of early menopause, which considers the nature and severity of symptoms, age and medical history, and the individual's wishes and priorities to optimise their quality of life and short-term and long-term health. We conclude with recommendations for future research to address key gaps in the current evidence.

Introduction

Menopause marks the permanent cessation of menstrual cycles, usually confirmed after 12 consecutive months of amenorrhoea. Natural menopause typically occurs at around age 50–51 years in high-income countries (HICs).[1,2] In clinical practice, the onset of menstrual changes and menopausal symptoms generally indicates the start of perimenopause or menopausal transition. While the menopause is marked by the final menstrual period, symptoms can persist for years into the postmenopause.[3] Early menopause is usually defined as occurring between the ages of 40 years and 44 years, whereas premature ovarian insufficiency indicates menopause before age 40 years. Both can be either spontaneous or iatrogenic, with iatrogenic causes including bilateral oophorectomy and chemotherapy or pelvic radiation treatment for cancer.

In this Series paper, we outline the evidence suggesting that both premature ovarian insufficiency and early menopause are linked with increased risk of chronic conditions in later life, such as cardiovascular disease and osteoporosis, although data are generally scarce around early menopause. Similarly, although consensus guidance exists for diagnosing and managing premature ovarian insufficiency, no guidance is available for early menopause. Given the scarcity of specific evidence regarding the long-term health implications of early menopause, we argue that early menopause should be considered as being on a spectrum between premature ovarian insufficiency and the typical age of menopause. To prevent patients from falling through this gap in care, we offer a practical framework to guide diagnosis and management of early menopause and identify evidence-based approaches for individuals either with or at risk of early menopause to optimise their health and quality of life in the short and long term. This process has identified key evidence gaps for further research and areas where people with early menopause require greater support.

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in some instances, we have referred to "people" rather than "women" in order to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used "women" in some instances, to avoid inappropriate generalisation. More information is needed about the experience of menopause in transgender men and gender-diverse people.[4]

Search strategy and selection criteria

We conducted a review of published articles up to July, 2023, on the PubMed, Embase, Scopus, and Cochrane

Key messages

- Early menopause, defined as menopause between ages 40 years and 44 years, affects approximately 12% of women globally.
- Diagnosis of early menopause is often delayed and can cause emotional distress, particularly in individuals hoping to become pregnant.
- We propose that early menopause should be considered as being on a spectrum between premature ovarian insufficiency and menopause at the average age.
- We present a framework for the diagnosis and evaluation of early menopause for use in clinical practice.

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databases. The search was restricted to studies published in English with the following keywords and medical subject heading terms in PubMed (MeSH) and Embase (Emtree): "menopause"; "premature menopause"; "premature ovarian insufficiency"; "early menopause"; "menopausal symptoms"; "vasomotor symptoms"; "menopausal hormone therapy"; "hormone therapy"; "hormone replacement therapy"; and "non-hormonal therapy". For long-term health outcomes, we combined these terms with "chronic disease", "non-communicable disease", "osteoporosis", "fracture", "cardiovascular disease", "heart disease", "stroke", "depression", "dementia", "cancer", and "mortality". We prioritised the most robust evidence from clinical trials, systematic reviews, meta-analyses, and pooled studies. We also reviewed guidelines and position statements from the period 2010–23 on menopause management.

Background

Biology

The pool of primordial follicles is established in utero, with a peak of 6–7 million oocytes at 16–20 weeks' gestation.[5] Most follicles undergo atresia and decline to approximately 700 000 normal oocytes at birth, approximately 300 000 oocytes by menarche, and fewer than 1000 oocytes at menopause.[5–7] Both the size of the pool of primordial follicles and the rate of follicular atresia probably determine the timing of menopause, but the underlying mechanisms regulating these factors are poorly understood.[8–10]

Prevalence of early menopause and premature ovarian insufficiency

Estimates for the prevalence of spontaneous early menopause and premature ovarian insufficiency vary substantially according to the population studied. The International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) pooled individual data from over 50 000 women with spontaneous menopause from nine studies in HICs to show that 7·6% of women had early menopause and 2% had premature ovarian insufficiency.[11] Global estimates, from a meta-analysis of 31 studies including over 150 000 women with spontaneous menopause, show a higher prevalence of 12·2% (95% CI 10·5–14) for early menopause, and 3·7% (3·1–4·3) for premature ovarian insufficiency, potentially reflecting a lower mean age at menopause in low-income and middle-income countries (LMICs).[12] A national study from China found a prevalence of 10·9% for spontaneous early menopause and a prevalence of 3·2% for premature ovarian insufficiency.[13] The prevalence in India is even higher at 20·2% for early menopause, with two prevalence estimates for premature ovarian insufficiency of 1·5% and 2·1%,[14,15] and an average age at menopause of 46 years.[16] Another reason for differences in prevalence might be the age limits used for observational studies on menopause (eg, arbitrarily setting a minimum age of 35 years for inclusion in a study will exclude some individuals who had premature ovarian insufficiency at an earlier age).[17] Although secular trends in many countries show an increase in the age at menopause is evident in many countries,[18–20] global evidence is scarce regarding trends in the prevalence of premature ovarian insufficiency and early menopause.[12]

A substantial proportion of cases of premature ovarian insufficiency and early menopause have iatrogenic causes, with wide variations according to gynaecological surgical practices in different countries. A national study in India reported that the prevalence of iatrogenic premature ovarian insufficiency was 1·7%, solely due to bilateral oophorectomy.[14] By contrast, a registry-based study (n=1 036 918) from Sweden reported an overall prevalence of 1·9% for spontaneous and iatrogenic premature ovarian insufficiency and, of these women, 10·7% had iatrogenic premature ovarian insufficiency.[21] As survival rates for young patients with cancer increase, iatrogenic premature ovarian insufficiency and early menopause will probably increase secondary to chemotherapy and radiotherapy.[22]

Risk factors for spontaneous early menopause and premature ovarian insufficiency

Bilateral oophorectomy in premenopausal individuals will induce surgical menopause. Unilateral oophorectomy is also associated with a younger age at menopause, on average 1·8 years younger compared with people with intact ovaries.[23] Hysterectomy alone with ovarian preservation is associated with menopause 1·9 years earlier than in women who do not have this procedure.[24]

The mechanisms underlying spontaneous early menopause and premature ovarian insufficiency are poorly understood. Studies in HICs indicate that genetic factors account for roughly half of the variation in age at natural menopause, estimated at 42% of variation in the UK, 44% in the Netherlands, and 52% in the USA.[25–27] These data are supported by retrospective studies reporting a six-fold to eight-fold increase in the risk of menopause before age 45 years for women with a maternal history of early menopause or premature ovarian insufficiency.[28,29] Recent genome-wide association studies have also identified specific genetic factors linked with the timing of menopause that provide insights on potential causal pathways for ovarian ageing.[30]

Nulliparity is associated with early menopause and premature ovarian insufficiency, although the direction of this relationship is uncertain since there could be shared factors that affect both nulliparity and age at menopause. The InterLACE consortium found (in a pooled analysis of 51 450 women in nine studies) that nulliparous women were twice as likely to have premature ovarian insufficiency and 30% more likely to have early menopause than women with two or more children.[11] Nulliparous women who also had early

menarche (before age 12 years) had a five-fold increased risk of premature ovarian insufficiency and double the risk of early menopause, compared with women who had menarche at 12 years or older with two or more children.[11] In studies from LMICs, women in India[31] and China[13] with premature ovarian insufficiency were more likely to have had an earlier age when first giving birth and a shorter duration of breastfeeding, although again the causal pathways at work remain unclear.

Globally, cigarette smoking is a well established risk factor for early menopause.[13,14,32,33] InterLACE reported that participants who currently smoked were twice as likely to have premature ovarian insufficiency as those who had never smoked, and 80% more likely to have early menopause.[34] There was a consistent dose–response relationship for participants who currently smoked and those who formerly smoked (duration and cumulative dose), but those who stopped smoking at least 10 years before menopause had a similar risk of early menopause to individuals who had never smoked. The prevalence of smoking has declined markedly in many HICs over recent decades, but the effect of this decline on rates of early menopause and premature ovarian insufficiency has yet to be documented.

Implications of early menopause and premature ovarian insufficiency

Menopausal symptoms

The effect of menopause and its symptoms on individuals will be highly contextual.[35] Common symptoms directly attributable to menopause include vasomotor symptoms (including hot flushes and night sweats), sleep disturbance, and vaginal dryness.[36–38] In addition, some studies have identified depressed mood and aches and joint pain,[39] with south Asian and Chinese women (living in HICs) more likely to report joint pain.[40,41] The prevalence of moderate-to-severe vasomotor symptoms in natural menopause also varies considerably across populations, with prevalence findings from an international survey ranging from 40% in Europe and 34% in the USA to 16% in Japan.[42] Whether menopausal symptoms following early menopause and premature ovarian insufficiency differ in nature, severity, or duration compared with symptoms following menopause at the average age is unknown. For iatrogenic early menopause and premature ovarian insufficiency, the abrupt cessation of oestrogen is thought to lead to more severe symptoms.[43] However, in the only prospective controlled study of surgical menopause, vasomotor symptoms at 12 months affected 82% of individuals who did not take menopausal hormone therapy (MHT), including 68% who reported mild symptoms, suggesting that severe vasomotor symptoms are not inevitable after surgical menopause.[44]

The diagnosis of menopause from 5 years to a decade or more earlier than expected can carry stigma and might affect self-esteem.[45] Symptoms in the years leading up to menopause can affect intimate relationships and, for some people, the loss of fertility can be especially distressing. The experience of menopausal symptoms can affect not only an individual's quality of life but also their effectiveness in the workplace, with economic consequences due to lower workforce participation rates.[46–48] For example, a 2022 study from the UK found that women with early menopause had lower labour market participation at age 50 years than other women.[47]

For individuals with iatrogenic early menopause or premature ovarian insufficiency, the change in circulating sex steroid concentrations occurs suddenly, and often in the context of treatment burden (eg, from chemotherapy) for a recent disease diagnosis, such as breast cancer. Some studies of women with iatrogenic premature ovarian insufficiency report low social support,[49] moderate-to-severe emotional distress,[50] and high rates of depression.[51] Although studies are scarce, some of these adverse outcomes could plausibly apply to people with menopause in their early 40s.

Longer-term health implications

Bone health

Oestrogens contribute to the regulation of bone resorption and formation.[10] Women with premature ovarian insufficiency and early menopause are at increased risk of fragility fractures. A cross-sectional study of 4725 women from the Netherlands found that those with spontaneous early menopause or premature ovarian insufficiency had a 50% higher overall fracture rate up to age 80 years compared with those with menopause at the average age.[52] Similar findings are reported in prospective studies from Sweden (osteoporosis and fragility fracture by age 77 years)[53] and the Netherlands (vertebral fractures at age 62 years).[54]

Cardiovascular disease

Since the late 1980s, cardiovascular risk has been thought to be influenced by oestrogen exposure, contributing to gender differences in the incidence of cardiovascular disease. People with early menopause or premature ovarian insufficiency are at increased risk of coronary heart disease, stroke, and cardiovascular disease-related mortality.[55–57] Pooled data from 15 studies (from Australia, Japan, Scandinavia, the UK, and the USA) show that women with spontaneous early menopause had a 30% increased risk (and women with premature ovarian insufficiency had a 55% increased risk) of a cardiovascular disease event compared with individuals with menopause at age 50–54 years, although these risks attenuated over time, with no difference found by age 70 years.[58] Women with surgical early menopause or premature ovarian insufficiency were at an even higher relative risk (60% and 90%, respectively) for cardiovascular disease events.[59] Findings from the UK Biobank study show both spontaneous and iatrogenic premature ovarian insufficiency are associated with increased risk of hyper-

lipidaemia, hypertension, and type 2 diabetes, compared with menopause at the average age.[60]

Mental health and neurological conditions

Unfortunately, little is known about early menopause and mental health. Premature ovarian insufficiency might negatively affect mental health in the short and long term. A meta-analysis of four studies with 3033 women with spontaneous premature ovarian insufficiency found that they were twice as likely to develop depression compared with women with menopause at age 40 years or older.[61] In a retrospective UK study of 136 women with premature ovarian insufficiency, 78% reported a negative effect on their self-image and confidence and lower general health, mental wellbeing, and sexual satisfaction compared with before their diagnosis.[62] No evidence for the mental health effects of early menopause was identified in our review of the literature.

Surgical menopause at or before age 45 years has been associated with higher risk of dementia and faster overall cognitive decline,[63] but the specific relationship between early menopause and premature ovarian insufficiency and neurological conditions is less clear. A cohort study based on the Korean National Health Insurance System database (with prospective data on 4·7 million post-menopausal women) reported that early menopause or premature ovarian insufficiency was associated with all-cause dementia, with the risk declining as age at menopause increased.[64] In a French population cohort study (n=4868), however, no association was found between early menopause and a decline in cognitive function in later life (tested across multiple domains), whereas both surgical and spontaneous premature ovarian insufficiency were linked with a decline in verbal fluency and visual memory.[65]

Oestrogen-sensitive cancers

Breast cancer is the most common cancer in HICs, and most breast cancers are oestrogen-sensitive. Women with menopause before age 45 years are at lower relative risk of breast cancer (by 27% for early menopause and 33% for premature ovarian insufficiency),[66,67] and at lower risk for endometrial and ovarian cancers compared with women with menopause at age 50–54 years.[10,66]

Life expectancy

Overall the evidence indicates that earlier natural menopause is associated with higher all-cause mortality,[68] and this risk is greater with premature ovarian insufficiency than with early menopause. A meta-analysis of seven studies found that premature ovarian insufficiency was linked with a 40% increased relative risk (RR; 95% CI 1·10–1·77) of all-cause mortality, whereas for women with early menopause the association was limited to a small increased risk of ischaemic heart disease (RR 1·09, 1·00–1·18).[69] A large US study of women with natural menopause who did not smoke and had not had MHT[70] found that early menopause was linked with a 9% increased relative risk of death due to coronary heart disease and a 19% increased risk for respiratory disease, which were the two main contributors to a small but identifiable increased risk of all-cause mortality (RR 1·04, 95% CI 1·00–1·08). Similarly, a large Canadian study of prophylactic bilateral oophorectomy[71] found that women with iatrogenic early menopause had a higher likelihood of all-cause mortality (hazard ratio 1·16, 95% CI 1·04–1·30) and this association increased further for those with iatrogenic premature ovarian insufficiency (1·31, 1·18–1·45) compared with women who had this surgery at age 50–55 years. This study included women both with and without hormone therapy, and for both the early menopause and premature ovarian insufficiency groups the association with all-cause mortality was largely driven by deaths from causes other than cancer.[71]

Diagnosis and management of early menopause

The initial challenge for health professionals is to make the diagnosis of early menopause and to explain the condition and potential consequences. Most international guidelines advise offering MHT to individuals without contraindications following early menopause.[72–74] MHT is highly effective for short-term symptoms, but it has not been shown to improve long-term health outcomes. Early menopause has implications for fertility, contraception, and potentially for sexual function. Addressing the psychological needs of people with early menopause and offering long-term follow-up and support is crucial.[45,50,75]

Diagnosis

The diagnosis of early menopause might not be straightforward unless a clear iatrogenic cause is identified. In individuals with spontaneous early menopause presenting with secondary amenorrhoea, vasomotor symptoms, or both, investigations are indicated to establish the diagnosis.[76] Some people will be amenorrhoeic after hysterectomy with ovarian conservation, or while taking long-acting progestogen contraception, so the diagnosis is made on the basis of symptoms and biochemistry. There are no consensus criteria for diagnosing early menopause after cancer treatment, which can cause transient or fluctuating symptoms.

Although evidence on early menopause diagnoses is scarce, some studies report that people with premature ovarian insufficiency might experience delayed diagnosis. In a US study,[77] more than half of women with spontaneous premature ovarian insufficiency reported seeing three different clinicians, and for 25% of the women, establishing a diagnosis took over 5 years. Similarly, for 25% of Australian women with premature ovarian insufficiency, diagnosis was delayed for more than 2 years and most saw at least two clinicians.[51] As a result, some individuals might be categorised as having early menopause rather than premature ovarian insufficiency. Most women receiving a diagnosis of spontaneous premature ovarian insufficiency

are dissatisfied with the clinical interaction,[50] but we do not know the views of people diagnosed with early menopause. For both groups, navigating treatment entails further complexity as patients grapple with the risks and efficacy of hormonal and non-hormonal therapies.[78]

Treatment options

Lifestyle interventions

Advice on healthy lifestyles should be a routine part of clinical interactions with health professionals and is particularly relevant for people experiencing early menopause or premature ovarian insufficiency. In these patients, the aims should be reducing cardiovascular risk (eg, through smoking cessation) and promoting bone health (eg, through weight-bearing exercise and a calcium-rich diet).[2]

Non-hormonal treatments

Complementary and alternative remedies are widely marketed and used for vasomotor symptoms.[79] There is a lack of evidence for the efficacy of herbal treatments and dietary supplements to relieve vasomotor symptoms, with the possible exception of isoflavones and black cohosh, and findings of studies might not translate into clinical practice, as preparations vary considerably.[76,80] Psychological interventions, particularly cognitive behavioural therapy, reduce the effects of vasomotor symptoms and improve sleep and mood disturbance generally associated with menopause.[76,81] A randomised control trial (RCT) has shown the efficacy of mindfulness for reducing hot flashes and improving quality of life for women with premature ovarian insufficiency.[82]

Non-hormonal pharmacological treatments[83] are offered to people who have contraindications to oestrogen treatment (eg, individuals with oestrogen-sensitive breast cancer).[84] For vasomotor symptoms, the most widely used treatments are selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors.[83] Gabapentinoids and oxybutynin are less widely used, but neurokinin-3 receptor antagonists, such as fezolinetant, show promise in reducing moderate-to-severe vasomotor symptoms associated with menopause.[85,86]

Pharmacological treatments for women with low bone mineral density include vitamin D and calcium supplements,[87,88] but the value of these interventions has not been explored in young women and is likely to vary in different populations according to ethnicity and dietary habits. Bisphosphonates are not generally used in spontaneous early menopause but can be given in oncology practice, particularly when oestrogen is contraindicated.[89]

Hormonal treatments

In the general population, MHT is highly effective in relieving some symptoms of menopause with a dose-dependent response, and it is generally prescribed as physiological oestradiol-based preparations.[80] Oestrogen is given in combination with progestogen to avoid unscheduled bleeding and the risk of endometrial hyperplasia, unless individuals have undergone hysterectomy. A combined oral contraceptive might be a convenient and acceptable preparation for young people with premature ovarian insufficiency, although the relative efficacy of this treatment compared with MHT, for both short-term and long-term outcomes, is unclear. Serious adverse effects from a combined oral contraceptive are rare but increase with age,[75,90] so MHT is preferred for early menopause. Systemic treatment can be given orally or transdermally, the latter having metabolic advantages. Topical (intravaginal) treatment is effective in relieving urogenital symptoms and might be required in addition to MHT;[75] endometrial protection is not required with topical oestrogen.

Oestrogen replacement is recommended following both premature ovarian insufficiency and early menopause until the typical age of menopause,[74,91] but the optimum duration of use is uncertain. Although oestrogen treatment is often initiated for symptom control, longer-term use is advised in the expectation of improved health outcomes. The adverse health effects of early menopause are less severe than those of premature ovarian insufficiency, as would be expected given the relative duration and degree of oestrogen loss.[58,68,92] There might, therefore, be fewer potential health benefits from MHT for early menopause than for premature ovarian insufficiency. Moreover, these treatment benefits need to be set against the risks of adverse effects, which are related to age.

Prevention of osteoporosis and the maintenance of bone health is a major rationale for the use of MHT following premature ovarian insufficiency.[2] Clinical guidance is extrapolated from the Women's Health Initiative (WHI) data, which showed that MHT in older postmenopausal women improves bone mineral density and reduces vertebral and hip fracture risk.[93,94] However, fractures are uncommon in women younger than 45 years (the association between low bone mineral density and fracture is age-dependent, mediated by falls).[95] There are a few small prospective studies showing the benefit of MHT on bone health in premature ovarian insufficiency.[2] However, bone health in early menopause specifically has not been sufficiently studied.

Early cohort studies suggested that MHT might have a role in the prevention of cardiovascular disease in postmenopausal women but this role was not confirmed by large randomised trials.[96,97] The largest trial (the WHI) showed an increase in the risk of ischaemic heart disease and stroke in people taking oestrogen.[97,98] However, a subgroup analysis of women aged 50–59 years showed some risk reduction in coronary heart disease and mortality with MHT.[99,100] Although a Cochrane review found reduced risk for coronary heart disease for women who started MHT less than 10 years after the menopause (RR 0·52, 95% CI 0·29–0·96), it confirmed an increased risk of venous thromboembolism (1·74, 1·11–2·73), and

was unable to support the use of MHT for primary or secondary prevention of coronary heart disease.[99] Findings from the analysis of pooled data from InterLACE[59] only detected a reduction in risk in cardiovascular disease for women with MHT after surgical early menopause or premature ovarian insufficiency, but not for those with spontaneous early menopause and premature ovarian insufficiency. A study of women in the USA with bilateral oophorectomy before age 45 years[101] found that those receiving MHT had no evidence of increased mortality from cardiovascular disease compared with women from the same age group who did not have bilateral oophorectomy, whereas those who had not taken MHT were at increased risk (hazard ratio [HR] 1·84, 95% CI 1·27–2·68), compared with women from the same age group who did not have bilateral oophorectomy.[101] There are no RCTs of MHT, however, in women with early menopause or premature ovarian insufficiency.

Concern was raised by the Women's Health Initiative study's findings of an increased risk of dementia in older users of MHT, which might reflect the thrombotic risk of MHT.[102] There is very little information, however, on the effect of oestrogen treatment on cognitive function in younger people with early menopause or premature ovarian insufficiency. A population-based cohort study of women aged at least 65 years found that both spontaneous and surgical premature ovarian insufficiency were associated with poorer cognitive function in later life,[65] but found no evidence of a cognitive benefit from MHT.

Risk of breast cancer is slightly increased in healthy premenopausal women with long-term use of a combined oral contraceptive[103,104] and is increased in older postmenopausal women taking combined MHT.[105,106] However, the type of MHT is important: long-term follow-up from participants in the Women's Health Initiative study showed a reduction in breast cancer risk with previous use of oestrogen alone, but an increased risk with previous use of combined MHT.[107] Whether the type of progestogen affects breast cancer risk is uncertain.[108] Breast cancer risk increases with both age and the duration of MHT use. For women with early menopause starting MHT aged 40–44 years, observational data suggest that the increase in breast cancer risk is similar to that in women with menopause at the average age.[106] Few women in long-term observational studies started MHT before the age of 40 years, although these women are at increased risk after more than 15 years of MHT use.[106] There are no randomised data relating to breast cancer risk in early menopause or premature ovarian insufficiency.

Optimising health outcomes for women with early menopause

Clinical guidelines

Existing clinical practice guidelines for menopause management rarely address early menopause. A systematic review of 22 current guidelines[109] found that some include premature ovarian insufficiency but have little advice in relation to early menopause. For example, the UK National Institute for Health and Care Excellence guidelines on the diagnosis and management of menopause include some recommendations on premature ovarian insufficiency and address the diagnosis of early menopause but not its management.[76] The European Society of Human Reproduction and Embryology published specific premature ovarian insufficiency guidelines in 2015, but has no clinical guidelines for early menopause.[2]

In 2014, Jane and Davis[110] produced a practitioner toolkit for managing menopause in women aged 40 years and older on the basis of recommendations in position statements and practice guidelines. Building on this model, we have, in turn, developed a practical clinical framework to assist with diagnosis and management of early menopause (figure).

Management recommendations are limited by the scarcity of evidence relating specifically to early menopause. However, the boundaries between typical menopause, early menopause, and premature ovarian insufficiency are arbitrary, and age cutoffs are often crossed in clinical practice during the lengthy process of menopause transition. Early menopause occupies a zone between premature ovarian insufficiency and menopause at the typical age, so extrapolating from existing studies in these groups while awaiting further targeted studies seems reasonable.

People with early menopause should be aware of the potential long-term risks, including osteoporosis, fractures, and cardiovascular disease. Ensuring this awareness provides an opportunity for a broader discussion on the key role of health behaviours (eg, smoking cessation, healthy diet, healthy bodyweight, and exercise) for cardiometabolic health and maintenance of bone density. Clinicians might also see opportunities to address specific risk factors.

Individualised care

Considerable scope exists to provide a more holistic and individualised approach to the management of early menopause. This approach could be part of a broader attitude to reproductive health that ideally engages with individuals, especially those at risk of early menopause, well before the menopausal transition.[111] For example, discussion of early menopause should be part of consultations with individuals with *BRCA1/2* mutations, which place them at high risk of breast and ovarian cancer, who might be planning the timing of risk-reducing bilateral salpingo-oophorectomy.

Improving community information on early menopause and premature ovarian insufficiency and natural menopause could aid prompt diagnoses. Social media is often a primary source of health information for women[112] and there is a need for objective and evidence-based online resources. For example, a co-designed digital health resource for women with early menopause or premature ovarian insufficiency and health practitioners targets these unmet needs for information

and support management.[113] Clinical guidelines should now routinely be translated into lay terms, allowing patients direct access to high-quality information.

Future recommendations

Reducing the risk of early menopause

The incidence of iatrogenic early menopause can be reduced by changes in the management of benign gynaecological conditions (eg, hysterectomy rates have reduced since the introduction of intrauterine progestogen devices), and by modifications in oncology practice (eg, the use of less gonadotoxic chemotherapy regimens).

Research priorities

There are substantial gaps in our knowledge of the cause, natural history, and optimal management of early

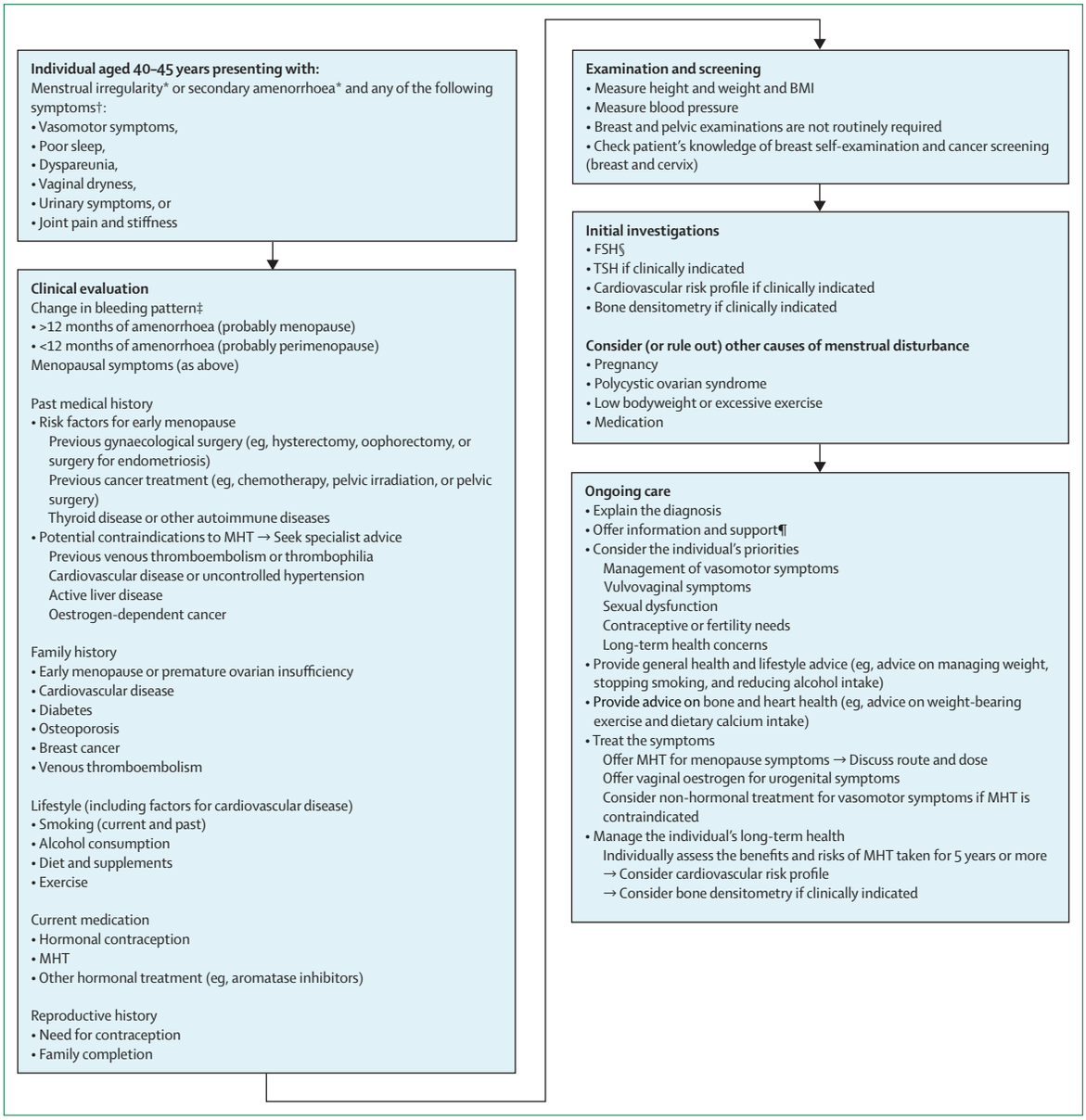

Figure: **Practical framework for diagnosis, evaluation, and management of early menopause**
FSH=follicle-stimulating hormone. MHT=menopausal hormone therapy. TSH=thyroid-stimulating hormone. *Might not be apparent if the individual is taking hormonal contraception or has had a previous hysterectomy. †Symptoms of menopause can vary between individuals and in the same individual over time. Some people have no symptoms apart from cessation of menstruation. Symptoms such as mood disturbances, anxiety, brain fog, palpitations, and low libido are common but might not be attributable to menopause. ‡Intermenstrual or post-coital bleeding needs further investigation; also consider further investigation for heavier bleeding. §A raised FSH concentration is confirmation of a diagnosis, but a typical FSH concentration does not rule out perimenopause. If uncertain, repeat testing might be needed. This test can guide contraceptive needs. FSH is of no value while the individual is taking combined oral contraception, and of limited value if they are taking any hormonal treatment. ¶For example, Healthtalk Australia's digital resource on early menopause and the Daisy Network

For more on **Healthtalk Australia's digital resource on early menopause** see https://www.healthtalkaustralia.org/early-menopause-experiences-and-perspectives-of-women-and-health-professionals/

For more on the **Daisy Network** see https://www.daisynetwork.org/

menopause (panel). There are also important evidence gaps for both premature ovarian insufficiency and early menopause in LMICs, particular around under-reporting.[114,115] Governments should be encouraged to look beyond reproductive and child health programmes and consider the health consequences of ageing and management of associated conditions, such as menopause.

With the shift to routine digital health management, there might be new opportunities to collect detailed data on the diagnosis and management of early menopause. Similarly, the rise of digital health hubs on early menopause and premature ovarian insufficiency provides considerable research opportunities to engage with people on their menopausal experiences and evaluate the effect of information strategies on subsequent treatment choices.

In summary, approximately 8–10% of women globally experience early menopause, but the causes, natural history, and potential long-term health outcomes are poorly understood. In particular, whether MHT confers long-term health benefits for people with early menopause is unclear. Information on early menopause is largely extrapolated from existing evidence on premature ovarian insufficiency or from studies of menopause at the average age. Interpretation of this evidence assumes a spectrum of age at menopause, with consequences reflecting the timing and duration of oestrogen withdrawal. Unfortunately, there is insufficient evidence for current guidance advising MHT until the average age at menopause (ie, 50 years) and so treatment should be considered on an individualised basis. Clinicians and researchers should work with people experiencing early menopause to establish their personal priorities for research and wishes for treatment.

Panel: Research priorities to improve our knowledge of early menopause

More information is needed on:

- People's experiences of early menopause diagnoses, particularly how to reduce diagnostic delay to inform effective interventions
- The priorities of people who experience the menopause transition for research gaps in early menopause to guide the future research agenda; in collaboration with the James Lind Alliance, a Menopause Priority Setting Partnership is underway, including people with premature ovarian insufficiency and early menopause
- The views of patients on the optimal management of early menopause, including unmet needs around diagnosis and treatment
- The causes and natural history of early menopause to establish who is at risk
- Long-term health outcomes following early menopause, which need to be assessed in prospective studies to inform prevention and early diagnosis of adverse outcomes
- Early menopause across diverse populations, including in low-income and middle-income countries
- The safety and effectiveness of treatment options (including but not limited to menopausal hormone therapy) following early menopause, in particular in managing menopausal symptoms, improving quality of life, and reducing chronic disease risks in both the short and long term
- The effectiveness of interventions for people with early menopause in improving health behaviours that reduce the potential risk of cardiovascular disease and poor bone health

For more on the **James Lind Alliance** see https://www.jla.nihr.ac.uk/

Contributors

MH and GDM conceived and designed this Series paper. GDM wrote the initial draft and was responsible for revising this draft on the basis of comments from all other authors. MCD, SH, H-FC, SR, KM, and MH made substantial contributions to the conception or design of this Series paper; or to the acquisition, analysis, or interpretation of data. MCD, SH, H-FC, SR, KM, and MH made substantial contributions to drafting this Series paper or revising it critically for important intellectual content; and gave their final approval of the submitted version. MCD, SH, H-FC, SR, KM, and MH agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MH is responsible for the final approval of this manuscript.

Declaration of interests

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Promoting good mental health over the menopause transition

Lydia Brown, Myra S Hunter, Rong Chen, Carolyn J Crandall, Jennifer L Gordon, Gita D Mishra, Viktoria Rother, Hadine Joffe, Martha Hickey**

The potential risk for mental health conditions over the menopause transition shapes women's expectations and informs putative physiological mechanisms regulating women's mental health. We review evidence from prospective studies reporting on associations between mental health conditions and the menopause transition. Major depressive disorder and the more prevalent subthreshold depressive symptoms are the most common conditions studied. We reviewed 12 prospective studies reporting depressive symptoms, major depressive disorder, or both over the menopause transition and found no compelling evidence for a universal increased risk for either condition. However, specific subgroups of participants, primarily defined by menopause-related risk factors (ie, vasomotor symptoms that are severe or disturb sleep, a long duration of the transition, or reproductive hormone dynamics) and psychosocial risk factors (eg, stressful life events), were vulnerable to depressive symptoms. The increased risk of major depressive disorder over the menopause transition appears predominantly in individuals with previous major depressive disorder. Greater focus on recognising risk factors in primary care is warranted. On the basis of scarce data, we found no compelling evidence that risk of anxiety, bipolar disorder, or psychosis is universally elevated over the menopause transition. Potential misattribution of psychological distress and psychiatric disorders to menopause could harm women by delaying accurate diagnosis and the initiation of effective psychotropic treatments, and by creating negative expectations for people approaching menopause. A paradigm shift is needed. We conclude with recommendations for the detection and treatment of depressive symptoms or major depressive disorder and strategies to promote good mental health over the menopause transition, while responsibly preparing and supporting those at risk.

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Introduction

The menopause transition usually starts around age 47 years with the onset of menstrual changes and ends at the final menstrual period.[1] Perimenopause is a related term. Perimenopause includes the menopause transition and the 12 months following the final menstrual period (early postmenopausal stage). The attribution of psychological distress to the menopause in high-income countries is long-standing. In 1816, Charles-Pierre-Louis de Gardanne included "hysteria, or nervous affection of the uterus" as a typical symptom of the menopause.[2] In 1959, Kupperman, Wetchler, and Blatt described the menopause as a "rather unpleasant and possibly dangerous"[3] period of life, and developed the first widely used menopause symptom checklist.[4] Notably, this scale, the 11-item Blatt–Kupperman Index, includes psychological symptoms such as melancholia and nervousness, informing the inclusion of psychological symptoms in contemporary menopause rating scales.[5,6] Although this approach has raised the profile of mental health conditions requiring care, it might also have contributed to the widespread belief that the menopause transition is universally associated with poor mental health. Anxiety,[7,8] paranoid thinking,[9] schizophrenic psychosis,[10] and even suicidality[11,12] have been attributed to the menopause, yet the empirical evidence to support these claims has not been subject to rigorous scientific review.

This Series paper has three objectives. First, we review findings from prospective studies investigating the association between the menopause transition and risk of mental health symptoms and disorders, including depression, anxiety, bipolar disorder, psychosis, and suicide risk. Second, since most research has focused on the relationship between the menopause transition and the risk of depressive symptoms and major depressive disorder, we contextualise these findings and explore

Key messages

- Concerns about increased risks of anxiety and depression may shape expectations and experiences of menopause.
- However, women are not universally or uniformly at risk of psychological symptoms over the menopause transition.
- Risk factors for depressive symptoms at this time include severe and prolonged vasomotor symptoms, chronic sleep disturbance, and stressful life events, and women with previous depressive disorder might be at increased risk of recurrence of a new depressive episode during the menopause transition.
- The menopause transition often coincides with important life stressors, health conditions, and role transitions that increase vulnerability to depression.
- Clinicians should not assume that psychological symptoms during the menopause transition are always attributable to hormonal changes and should offer evidence-based treatments; menopausal hormone therapy can improve concurrent depressive symptoms for patients with troublesome vasomotor symptoms.

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vulnerability factors that help explain why some subgroups of people are at risk of depressive symptoms or major depressive disorder over the menopause transition. Third, we conclude with recommendations for the detection and treatment of depressive symptoms or major depressive disorder and strategies to promote mental health over the menopause transition.

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in this Series, we sometimes refer to "people" rather than "women" in order to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used "women" in some instances, to avoid inappropriate generalisation. More information is needed about the experience of menopause in transgender men and gender-diverse people.[13]

Search strategy and selection criteria

We searched the databases MEDLINE, Embase, and PsycInfo from Jan 1, 1990, to July 1, 2023. Key terms were customised for individual sections and included "menopaus*", "perimenopause*", and "postmenopaus*" combined with "depression", "depressive disorder*", "anxiety", "bipolar", "bi-polar", "psychosis", "psychotic", "schizophren*", and "suicid*". For sections reporting on the absolute and relative risk of mental health symptoms or disorders over the menopause transition, we limited our review a priori to cohort studies with more than 100 participants for whom prospective data on the risk of mental health symptoms or disorders in the menopause transition compared with before the menopause transition (ie, premenopause) were available. When a prospective study reported data in more than one paper, we have reported findings from the most comprehensive study with the largest sample size or longest follow-up period. Findings were cross-checked against relevant meta-analyses, systematic reviews, and clinical guidelines. In sections reporting on risk factors and recommendations, we prioritised findings from prospective studies, clinical guidelines, and recent randomised controlled trials (RCTs).

Findings from prospective studies

Depression

An association between the menopause and depression is widely promoted. Highly cited papers state a doubled to quadrupled risk of depressive symptoms or depressive disorders over the menopause transition.[7,14,15] However, most papers report the relative risk rather than the absolute risk. Furthermore, studies have often not adequately distinguished between depressive symptoms and depressive disorder. Generally, depressive symptoms are more prevalent, less debilitating, and do not constitute a clinical depressive disorder, the most common and burdensome of which is major depressive disorder (table 1).[18] The presence of depressive symptoms does not necessarily imply that a person is experiencing a depressive episode.[19] Self-report scales typically include generic symptoms, such as sleep problems, appetite disturbance, and fatigue, that have a range of physical, psychological, and social causes that are not limited to depression. For example, during the menopause transition, vasomotor symptoms (hot flushes and night sweats) might cause sleep disturbance, which could elevate scores on a depressive symptom

	Major depressive disorder	Depressive symptoms
Method of assessment	Typically assessed by a trained health professional through a clinical interview	Assessed through a self-administered questionnaire
Prevalence	Global 12-month prevalence of approximately 6%[16]	Prevalence is established with a cutoff score to represent the presence or absence of clinically significant symptoms; on the 20-item CES-D, a cutoff score of ≥16 is commonly used to indicate the presence of clinically significant depressive symptoms
Symptoms	Nine symptoms including two core symptoms of depressed mood and anhedonia; symptoms can be remembered with the SIGECAPS mnemonic: depressed mood and sleep changes (insomnia or hypersomnia), interest (markedly diminished pleasure in all or almost all activities), guilt (excessive guilt or feelings of worthlessness), energy loss or fatigue, concentration disturbance, appetite or weight changes, psychomotor retardation or agitation, and suicidal ideation or thoughts of death that are recurrent	The CES-D measures symptoms of depression on a frequency scale ranging from 0 (rarely or none of the time) to 3 (most or all the time)
Diagnosis	Requires co-occurrence of at least five of the nine symptoms, including at least one core symptom; symptoms must be sustained and clearly present nearly every day and must represent a change from previous functioning; symptoms must cause clinically significant distress or impairment in daily life functioning	The CES-D is not diagnostic of major depressive disorder; meta-analysis[17] indicates that a cutoff of ≥16 on the CES-D has a specificity of only 0·70 for major depressive disorder in the general population or primary care settings
Timeframe	Symptoms must persist over at least 2 weeks	Symptoms can ebb and flow and might not be sustained; the CES-D measures symptoms over the past week

CES-D=Center for Epidemiologic Studies Depression Scale.

Table 1: **Differences between major depressive disorder and depressive symptoms**

	Country	Participants (n)	Ethnicity	Inclusion criteria	Duration of follow-up	Outcome measure	Effect of the menopause transition on risk of depressive symptoms
Major depressive disorder*							
Study of Women's Health Across the Nation (SWAN)†[20–22]	USA	443	47% White; 28% African American; 25% Chinese, Hispanic, or Japanese	Premenopausal or perimenopausal women aged 42–52 years at baseline with an intact uterus and no use of MHT	13 years and 13 assessments	SCID	The most recent publication (13 years of follow-up) with the largest sample size[20] found that the menopause transition was associated with an increased risk of recurrence of major depressive disorder (HR 2·67, 95% CI 1·04–6·86, p=0·04 in perimenopause; 4·03, 1·15–14·15, p=0·03 in early postmenopause) but not new onset major depressive disorder
Zurich Study‡[23]	Switzerland	168	Not reported	Women aged 21 years at baseline	29 years and seven assessments (menopause data measured at two timepoints)	SPIKE	Women who transitioned to perimenopause (OR 0·71, 95% CI 0·34–1·51) or postmenopause (0·57, 0·24–1·37) were not at increased risk of major depressive disorder
Depressive symptoms							
Penn Ovarian Aging Study (POAS)§[15,24,25]	USA	436	Stratified sample: 50% African American and 50% White	Premenopausal women aged 35–47 years at baseline	8 years and ten assessments	CES-D (cutoff of 16)	At 8-year follow-up, the menopause transition was associated with a quadrupled risk of new onset depressive symptoms in a subsample without a personal history (n=231) relative to the premenopausal baseline (OR 4·29, 95% CI 2·39–7·72), and the effect was stronger (5·44, 2·56–11·59) when adjusting for covariates; however, data at 14 years of follow-up[24] show evidence of declining depressive symptom prevalence from 10 years before to 7 years after the menopause
Study of Women's Health Across the Nation (SWAN)§[26,27]	USA	3302	47% White; 28% African American; and 25% Chinese, Hispanic,or Japanese	Premenopausal or perimenopausal women aged 42–52 years at baseline with an intact uterus and no use of MHT	13 years and 13 assessments	CES-D (cutoff of 16)	The early and late menopause transitions were associated with elevated risk of depressive symptoms, with the highest risk in the late menopause transition (adjusted OR 1·68, 95% CI 1·28–2·20) and early postmenopause (1·83, 1·40–2·42)
Australian Longitudinal Study of Women's Health (ALSWH)†[28]	Australia	5895	73% Australian-born; 17% from another English-speaking background; 6% European; and 3·5% Asian or other	Women aged 45–50 years at baseline; women reporting use of an oral contraceptive pill were excluded from analysis	15 years and seven assessments	CES-D (continuous)	In longitudinal analyses, entering the menopause transition did not increase the risk of depressive symptoms (adjusted B 0·03, 95% CI −0·29 to 0·35); remaining in the menopause transition at consecutive study timepoints was associated with increased depressive symptoms: women in the menopause transition scored 0·29 points higher on the CES-D 10 compared with women remaining in postmenopause (95% CI 0·02 to 0·61); overall, women in the menopause transition scored 0·19 points higher on the CES-D compared with those in postmenopause (−0·02 to 0·31)
Eindhoven Perimenopausal Osteoporosis Study†[29]	Netherlands	2103	100% Dutch	Women aged between approximately 47 years and 54 years; women who used hormone therapy or who had undergone hysterectomy or oophorectomy were excluded from analyses	3·5 years and two assessments	EDS (cutoff of 12)	Entering the menopause transition was potentially a risk factor for depressive symptoms in multivariate modelling, but the effect was sensitive to the statistical methodology used; with the step-wise method of logistic regression, transition from premenopause to perimenopause (OR 1·80, 95% CI 1·12–3·33) and perimenopause to postmenopause (1·81, 1·25–2·26) were associated with a significantly increased risk of depressive symptoms; with the enter method of logistic regression, the transition from premenopause to perimenopause did not increase the risk of depressive symptoms (1·14, 0·64–2·02)

(Table 2 continues on next page)

	Country	Participants (n)	Ethnicity	Inclusion criteria	Duration of follow-up	Outcome measure	Effect of the menopause transition on risk of depressive symptoms
(Continued from previous page)							
Harvard Study of Mood and Cycles[114]	USA	460	Not reported	Premenopausal women aged 36–45 years at baseline with no lifetime diagnosis of major depressive disorder	6 years and seven assessments (six assessments in the first 3 years, and the seventh at 6 years)	CES-D (cutoff of 16), SCID, or at least one positive response to three questions about mood symptoms	Overall, the menopause transition was associated with increased risk of depressive symptoms at borderline statistical significance (OR 1·8, 95% CI 1·0–3·2); women with both vasomotor symptoms and stressful life events were at increased risk of depressive symptoms during the menopause transition (adjusted OR 2·5, 95% CI 1·2–5·2); for women with one or neither of these risk factors, risk of depressive symptoms was not increased over the menopause transition
Massachusetts Women's Health Study†[30]	USA	2565	Not reported	Premenopausal and perimenopausal women aged 45–55 years at baseline with a uterus and at least one ovary intact	5 years and six assessments	CES-D (cutoff of 16)	Risk of depressive symptoms was independent of reproductive stage, but women experiencing a long menopause transition (>27 months) were twice as likely to report depressive symptoms; this effect was accounted for by including vasomotor symptoms and the presence of menstrual problems in multivariate modelling
Personality and Total Health Through Life (PATH)†[31]	Australia	711	Not reported	Premenopausal women aged 40–44 years at baseline; women using MHT and women who had had an oophorectomy or hysterectomy were excluded from analyses	8 years and two assessments	GDS (symptom count)	Women in the menopause transition at follow-up were at greater risk of experiencing depressive symptoms relative to women who remained premenopausal (IRR 1·29, 95% CI 1·10–1·52); in subgroup analyses, the effect was only seen in women without a probable history of major depressive disorder (1·35, 1·08–1·68); depressive symptoms were independent of reproductive stage among women with a personal history of probable major depressive disorder
Seattle Midlife Women's Health Study†[32]	USA	302	77% White; 11% African American; and 8·3% Asian American, or Pacific Islander	Women aged 35–55 years at baseline; women taking hormones were excluded from analyses	9 years and annual assessments	CES-D	Risk of depressive symptoms was independent of reproductive stage; reproductive stages were not significant predictors of depressive symptoms when entered simultaneously in a multivariable model but were included in the final model because they were the major research focus of the paper; in the final model, the late menopause transition was associated with elevated depressive symptoms (β 1·37, p=0·03)
The Manitoba Project†[33]	Canada	477	Not reported	Women aged 45–55 years who had either menstruated in the past 3 months or had previously had a hysterectomy	3 years and six assessments (depressive symptoms measured at five timepoints)	CES-D (cutoff of 16)	The menopause transition was not associated with an increased risk of depressive symptoms compared with remaining premenopausal; however, among women without depressive symptoms at baseline, women who had a hysterectomy were more likely to develop depressive symptoms than premenopausal women (OR 1·7, 95% CI 1·15–2·6)
Midlife Women's Health Study‡[34]	USA	264	51% White; 26% African American; and 23% Latina	Regularly menstruating individuals aged 40–50 years; women taking hormone therapy or antidepressants, or who had a history of major chronic illness were excluded from enrolment	3 years and six assessments	CES-D	At 36 months, only 64 women (24%) had transitioned to being in the menopause transition; menopausal stage was not a significant predictor of CES-D scores or risk of depression (score ≥16); women who were in the menopause transition had a non-significantly higher mean score on the CESD (mean 12·6) compared with women who remained premenopausal (10·9)

(Table 2 continues on next page)

	Country	Participants (n)	Ethnicity	Inclusion criteria	Duration of follow-up	Outcome measure	Effect of the menopause transition on risk of depressive symptoms
(Continued from previous page)							
PALM Study‡[35]	China	430	Not reported	Women aged 35–64 years with an intact uterus and at least one ovary; women who had had a hysterectomy or were taking hormone therapies were excluded from analyses	9 years and annual assessments	HADS-D (cutoff of ≥8)	There was no evidence of increased risk of depressive symptoms during the menopause transition; the prevalence of depressive symptoms was 14·5% in women with premenopause, 18·2% during the menopause transition, and 19·6% in postmenopause; these differences were not statistically significant
Zurich Study‡[23]	Switzerland	168	Not reported	Women aged 21 years at baseline	29 years and seven assessments (menopause data measured at two timepoints when women were aged 41 years and 50 years)	SCL-90-R	The transition to perimenopause or postmenopause was not associated with increased risk of depressive symptoms (transition to perimenopause: b 0·090, 95% CI −0·13 to 0·31; transition to postmenopause: 0·00, −0·22 to 0·22)

The self-report tools were either not valid measures of major depressive disorder[24] or used the Patient Health Questionnaire, which has been found to greatly overestimate the prevalence of major depressive disorder.[36] CES-D=Centre for Epidemiologic Studies Depression Scale. DSM=Diagnostic and Statistical Manual of Mental Disorders. EDS=Edinburgh Depression Scale. GDS=Goldberg Depression Scale. HADS-D=Hospital Anxiety and Depression Scale–depression subscale. HR=hazard ratio. IRR=incidence rate ratio. MHT=menopausal hormone therapy. OR=odds ratio. SCID=Structured Clinical Interview for DSM-IV. SCL-90-R=Symptom Checklist-90-Revised. SPIKE=Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology. *Major depressive disorder is uniformly diagnosed with a structured clinical interview. The Harvard Study of Mood and Cycles and the Penn Ovarian Aging Study were excluded from this section because they used a combination of clinical interviews and self-report screening tools to assess for major depressive disorder. †The study reported mixed findings or evidence of an effect limited to some women with risk factors. ‡The study did not find evidence of increased risk of depressive symptoms or disorders over the menopause transition compared with the premenopausal baseline. §The study found uniform increased risk of depressive symptoms or disorders over the menopause transition compared with the premenopausal baseline.

Table 2: **Findings from prospective studies investigating the relationship between reproductive stage and depressive symptoms and disorders**

scale even without core depressive symptoms (ie, low mood and anhedonia). Definitive diagnosis of major depressive disorder requires clinician-rated interviews. Of the 12 prospective studies investigating the association between the menopause transition and depression (table 2), only two[20,23] have uniformly diagnosed major depressive disorder with clinician-rated interviews, probably due to the expense of implementing this assessment. Hence, our understanding of the risk of major depressive disorder over the menopause transition assessed uniformly by clinical interviews is limited to data from 600 women globally.

Major depressive disorder

Major depressive disorder affects approximately 6% of the global population each year and is diagnosed twice as often in women as in men.[16] The mechanisms underlying this sex difference are poorly understood, but changes in endogenous sex steroid hormones have been identified as a contributory factor.[1] The menopause transition is marked by changes in circulating sex steroids compared with before the menopause transition (premenopause).[37] Specifically, oestradiol variability is more marked during the early menopause transition, and then progesterone production reduces then stops as ovulation ceases in the late menopause transition.[1] The menopause transition often coincides with substantial midlife stresses, health conditions, and role transitions, which increase individuals' vulnerability to depression.[20]

One prospective study suggests that women with a previous history of major depressive disorder are at increased risk of recurrence over the menopause transition. The Study of Women's Health Across the Nation (SWAN) Mental Health substudy (n=425)[20] reported a 2·67-fold increased risk of major depressive disorder recurrence over the menopause transition (95% CI 1·04–6·86; p=0·04).[20] However, there was no increased risk of first lifetime episodes of major depressive disorder. First-onset major depressive disorder was predicted by risk factors unrelated to the menopause transition, such as trait anxiety, low physical functioning, and physical illness. Over 30 years, the longitudinal Zurich Study (n=168)[23] measured the prevalence of major depressive disorder at age 41 years and again at age 50 years. They found no increase in major depressive disorder in people who became perimenopausal or postmenopausal over this period, although only 27% of the sample group had reached postmenopause at follow-up and, unlike SWAN, this study did not include annual assessments of reproductive stage and mood.

In summary, the few available prospective data suggest that the menopause transition might be a vulnerable period for the recurrence of major depressive disorder but not for first lifetime onset of this condition. Future

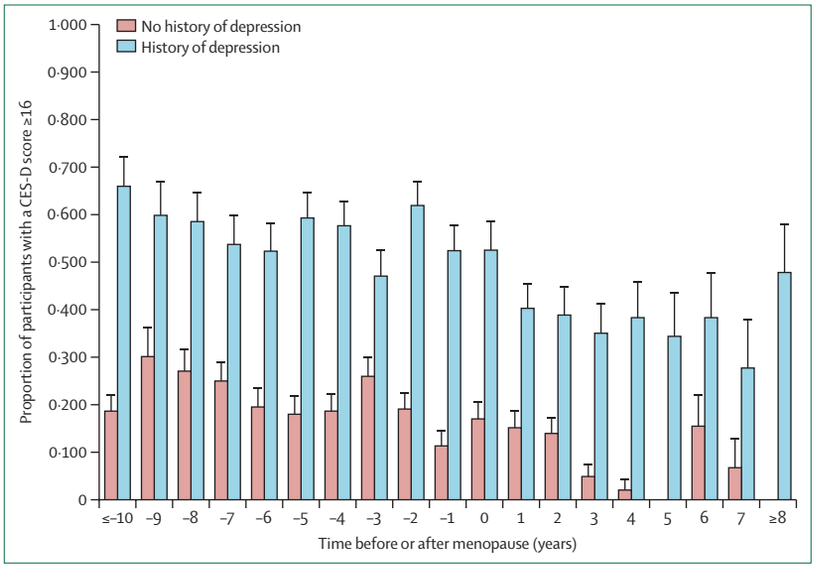

Figure 1: **Proportion of participants with a score of 16 or higher on the CES-D in each study year, grouped by history of depression at study enrolment**
Reproduced from Freeman and colleagues,[24] by permission of the American Medical Association. Error bars indicate SE. CES-D=Center for Epidemiologic Studies Depression Scale.

research is needed to clarify menopause-related factors that might increase the risk of first lifetime onset major depressive disorder during the menopause transition.

Depressive symptoms

Four prospective studies have measured the prevalence of depressive symptoms over the menopause transition for groups with and without previous major depressive disorder.[28,29,35,38] These studies report prevalences of between 16·5%[29] and 27·8%,[38] which are slightly higher than those seen in the late premenopause (between 14·3%[29] and 20·9%).[38] However, a 13-year prospective study over the menopause transition reported that depressive symptoms were much higher (50–65%) in people with previous major depressive disorder.[24] These data suggest that for people without previous major depressive disorder, the absolute risk of depressive symptoms is not markedly elevated over the menopause transition.

Less is known about the prevalence of depressive symptoms during the menopause transition in low-income and middle-income countries. Of the 12 prospective studies tracking changes in depressive symptoms across the menopause transition, only one, the PALM study from China,[35] was not conducted in a high-income country. The remaining studies were conducted in the USA (n=6), Europe (n=2), Australia (n=2), and Canada (n=1). The PALM study found a prevalence of depressive symptoms of 14·5% in the premenopause (baseline), which rose slightly to 18·2% during the menopause transition and to 19·6% in the postmenopause. These differences were not statistically significant.

Of the 12 prospective studies that have considered the relative risk of depressive symptoms during the menopause transition compared with the premenopause, two[15,26] reported increased depressive symptoms, and three[23,34,35] found no association. The remaining seven studies reported mixed results. Four identified specific subgroups as being at risk of depressive symptoms, including people with a combination of vasomotor symptoms and adverse life events in the 6 months before assessment,[14] people with a hysterectomy,[33] people without a history of probable major depressive disorder,[31] and people with a longer duration of the menopause transition.[30] One study found an association contingent on time spent in the menopause transition.[28] Women who remained perimenopausal across recurrent surveys had a higher risk of depressive symptoms. Two studies found evidence of a possible association between depressive symptoms and the menopause, but this association was sensitive to the statistical approach used (table 2).[29,32]

SWAN[26,27] and the Penn Ovarian Aging Study (POAS)[15,25] reported an increased risk of depressive symptoms over the menopause transition compared with the premenopause. SWAN[26,27] followed over 3000 women in the USA for more than 13 years and found an increase in depressive symptoms during the menopause transition (adjusted odds ratio [OR] 1·68, 95% CI 1·28–2·20).[26] At the 8-year follow-up in women who were aged 35–47 years and premenopausal at baseline,[15] POAS[15,25] found that the menopause transition more than quadrupled the risk of depressive symptoms (OR 4·29, 95% CI 2·39– 7·72). Taken in isolation, this result suggests a substantial risk of depressive symptoms that could be alarming for women and their clinicians. However, in women with no previous depressive disorder, a minority (10–30%) reported clinically significant depressive symptoms across both the late premenopause and menopause transition, with no obvious increase in depressive symptoms in the years preceding the final menstrual period (figure 1).[24] By contrast, 45–65% of women with previous major depressive disorder reported depressive symptoms over late premenopause and the menopause transition. POAS found the risk of depressive symptoms reduced after menopause,[24] whereas SWAN found evidence of ongoing risk, especially in women with a history of depressive symptoms.[39]

Five prospective studies did not find a universally increased risk of depressive symptoms over the menopause transition, but their findings offer clarification about at-risk subgroups.[14,28,30] The Harvard Study of Mood and Cycles[14] in the USA found a marginally significant association overall (OR 1·8, 95% CI 1·00–3·20), but subgroup analyses showed that only women with both vasomotor symptoms and stressful life events in the 6 months before assessment were at risk of depressive symptoms (adjusted OR 2·5, 95% CI 1·20–5·20). The duration of the menopause transition

varies substantially between individuals. Both the Massachusetts Women's Health Study (n=2565, USA)[30] and the Australian Longitudinal Study of Women's Health (ALSWH; n=5,895)[28] reported that longer time spent in the menopause transition was associated with significantly increased risk of depressive symptoms. In the Massachusetts Study, increasing depressive symptoms associated with a long menopause transition were explained by vasomotor symptoms and menstrual symptoms in multivariable modelling.[30] In agreement, ALSWH found that women who remained perimenopausal across recurrent surveys had a higher risk of depressive symptoms (a Center for Epidemiologic Studies Depression Scale [CES-D] score of 0·29 points higher, 95% CI 0·02–0·61) than those who remained postmenopausal. PATH[31] found an association overall, but in subgroup analyses only individuals without a history of probable major depressive disorder were at increased risk of more symptoms of depression during the menopause transition (incidence rate ratio 1·35, 95% CI 1·08–1·68). The Manitoba Project[33] found no association between reproductive stage and risk of depressive symptoms overall, but participants with a hysterectomy who did not have depressive symptoms at baseline were more likely to develop depressive symptoms than those who were premenopausal (OR 1·7, 95% CI 1·15–2·6).

The Eindhoven Perimenopausal Osteoporosis Study (EPOS)[29] and Seattle Midlife Women's Health Study[32] found a possible increased risk of depressive symptoms over the menopause transition, but the association was sensitive to the statistical analysis used (table 2). For example, EPOS found evidence of increased symptoms of depression during the menopause transition with the stepwise method but not with the enter method of logistic regression.[29]

The Zurich study,[23] PALM study,[35] and Midlife Women's Health study[34] found no increased risk of depressive symptoms over the menopause transition. In the Midlife Women's Health study, just 64 participants (24%) had entered the menopause transition at the endpoint of the study, which limited the study's statistical power to detect an association.

In summary, on the basis of mixed findings from prospective studies, we found no compelling evidence for a universal or uniform increased risk of depressive symptoms over the menopause transition. Greater awareness of risk factors might inform an understanding of the mechanisms underlying depressive symptoms in subgroups of women and provide new opportunities for prevention and treatment.

Anxiety

Associations between the menopause transition and anxiety are poorly understood.[40] One prospective study measuring anxiety disorders found no increase over the menopause transition.[23] Four prospective studies have measured changes in anxiety symptoms over the menopause transition, with mixed results (appendix p 1). Two studies found no increase in anxiety symptoms over the menopause transition.[23,35] In contrast, the SWAN[41] and PATH[31] studies found that people with low anxiety in the premenopause were at risk of increased anxiety symptoms during the menopause transition. The SWAN study controlled for vasomotor symptoms, which is important since symptoms of menopause can overlap with symptoms of anxiety, such as sweating, a racing heart, and rapid breathing.

Findings from POAS suggest that anxiety exacerbates vasomotor symptoms. Women with physical symptoms of anxiety were at increased risk of developing moderate or severe vasomotor symptoms over the menopause transition.[42] In China, the PALM study[43] found a bidirectional longitudinal relationship between symptoms of anxiety and bother due to vasomotor symptoms, suggesting that anxiety could be both a cause and consequence of vasomotor symptoms.

In summary, there is no consistent evidence that anxiety increases over the menopause transition. However, somatic anxiety might predict moderate or severe vasomotor symptoms, suggesting that reducing anxiety might reduce bother from vasomotor symptoms and is a potential target for intervention.

Other mental health disorders

Bipolar disorder

No prospective studies have investigated psychiatric symptoms over the menopause transition in people with bipolar disorder. One small study (n=47) found that depressive episodes (but not mood elevation) measured prospectively over the menopause transition were increased compared with retrospective self-reports of premenopausal depressive episode frequency.[44] A systematic review of nine cross-sectional or retrospective studies reported an increase in symptoms of bipolar disorder over the menopause transition, largely on the basis of retrospective self-reports.[45] The largest of these studies found that 25·9% (57 of 220) of participants with bipolar 1 disorder retrospectively self-reported having "perimenopausal mood symptoms", compared with 12·5% (7 of 56) of their relatives without a diagnosed mood disorder.[46]

Schizophrenia spectrum and other psychotic disorders

It has been widely suggested that the menopause transition is a vulnerable period for new onset or recurrent episodes of schizophrenic psychosis,[10] however empirical evidence supporting this claim is scarce. We found no prospective studies investigating rates of psychotic symptoms or disorders over the menopause transition.

A meta-analysis of 83 studies found that women but not men experience a small increase in first lifetime onset psychosis after age 45 years.[47] These data

See Online for appendix

informed the oestrogen hypothesis, which suggests that a decline in oestrogens across the menopause transition might trigger psychosis in women.[10] A large (n=61 889) Finnish study[48] found that women with schizophrenia-spectrum disorders were more often hospitalised for psychosis after age 45 years than men were.[48] However, oestrogen withdrawal does not occur uniformly at this age and circulating oestradiol concentrations in the early menopause transition can be markedly elevated in a woman's late 40s.[49] The mean age of onset of schizophrenic psychosis is 20–40 years when oestradiol concentrations are generally high (appendix p 4).

Suicidality and the menopause transition

The risk of suicide is higher in men than in women across the lifespan, and midlife is a time of elevated suicide risk for both sexes.[50,51] Recent media reports have suggested that women are at elevated risk of suicide over the menopause transition.[11,12] However, there is no substantive evidence of an association between attempted or completed suicide and the menopause transition. One cross-sectional study from Korea (n=45 177)[52] showed increased suicidal ideation (thoughts about wanting to die in the past year) during the menopause transition (prevalence of 7·2% compared with a premenopause prevalence of 5·73%). Although the study measured self-reported rates of suicide attempts, no relationship between these rates and reproductive stage was reported.[52] A US study of 298 women in treatment for mood disorders found no association between reproductive stage and suicidal ideation or attempts.[53]

One longitudinal study (n=291 709) in US veterans[54] found that use of menopausal hormone therapy (MHT) was associated with significantly increased risk of attempted and completed suicide over the next 4·5 years. These associations with death by suicide remained significant after accounting for psychiatric comorbidity and psychoactive medications.[54]

In summary, despite claims that the menopause transition is associated with increased risk of suicide, empirical data to support these claims are scarce. However, some evidence suggests that use of MHT is associated with suicide attempts and completion. The reasons for this association are uncertain.

Who is at risk of experiencing depressive symptoms or disorders over the menopause transition?

Large prospective studies report that a small subgroup of about 5–9%[28,55] of women experience increasing depressive symptoms over midlife, whereas a similar proportion (8·5–11%)[28,55] report decreasing depressive symptoms. Menopause-specific and general risk and resilience factors might help explain why a subgroup of women could be at risk of depressive symptoms or disorders over the menopause transition.

Established psychosocial risk factors for depressive symptoms

Prospective studies confirm that established psychosocial stressors such as financial problems,[29] unemployment,[29] poor social support,[26] and stressful life events[29,32] are important predictors of depressive symptoms during the menopause transition.[23,29,26] Similarly, adverse childhood experiences,[56] being from a minority ethnic group,[25] higher BMI,[15,29] neuroticism,[23] and lifestyle behaviours (eg, smoking and lack of physical activity)[26] are also associated with increased risk of depressive symptoms.

Emerging evidence suggests that psychosocial factors can interact with sex steroid hormones to modify mood. A prospective study (n=52)[57] found that greater variability in serially measured oestradiol over 14 months predicted greater depressive symptoms, but only in individuals with very stressful life events in the 6 months before baseline assessment, suggesting an interaction between established risk factors for depression and endocrine changes over the menopause transition.

Menopause-related factors

Type and timing of menopause

The type (natural or surgical) and timing of menopause might influence the risk of depressive symptoms. Prospective studies show that surgical menopause (ie, from bilateral oophorectomy before natural menopause) confers greater risk[58–60] than hysterectomy alone.[58,59] However, the effects might be transitory. A prospective controlled study of depressive symptoms and anxiety following surgical menopause showed a doubling in new-onset depressive symptoms at 12 months, which had resolved by 24 months.[61] Abrupt changes in sex steroid hormones following oophorectomy might contribute to this effect. However, women undergoing surgical menopause commonly have other risk factors for depression, such as adverse childhood experiences, abuse, and chronic pelvic pain.[62] Similarly, women with spontaneous premature[63] or early[64] menopause are at increased risk of depressive symptoms, but are more likely to have experienced cancer treatment, infertility, and gynaecological pathology than women who have menopause at the average age. Hence, factors other than endocrine changes might influence mood for these subgroups. Longer duration of the menopause transition has also been associated with increased risk of depressive symptoms,[28,30,60] potentially explained by extended time with vasomotor symptoms.[30]

Vasomotor symptoms and sleep disturbance

A systematic review of 33 publications[65] reported that the presence and frequency of vasomotor symptoms were bidirectionally associated with depressive symptoms.[65] Some women are more bothered by vasomotor symptoms than others and this variability might relate to mood,

stress, and the degree of sleep disturbance. The extent to which vasomotor symptoms are problematic or interfere with daily life predicts mood disturbance and quality of life more than vasomotor symptom frequency does.[66] A pooled analysis of longitudinal data from over 20 000 women found that sleep disturbance largely accounted for the association between vasomotor symptoms and depressed mood.[67] In an experimental ovarian suppression model of menopause, vasomotor symptoms at night but not during the day contributed to depressed mood independent of their effect on sleep.[68] Effective management of nocturnal vasomotor symptoms and sleep disturbance might play an important part in the prevention and management of mood disturbances over the menopause transition.

Sex steroids

Oestradiol variability,[15,57,69,70] low progesterone concentration,[70] and change in the ratio of testosterone concentration to oestradiol concentration[71] have been associated with an increased risk of depressive symptoms, but findings vary and these associations have not been consistently replicated.[26,32,72,73] Prospective studies with annual measures of oestradiol concentration and mood found no associations with depressive symptoms,[26,32,73] and cross-sectional studies report no differences in oestradiol concentrations in perimenopausal women with a depressive disorder compared with those without.[74] However, epidemiological[15,57] and repeated-measures[69,70] studies with more frequent assessments report that greater oestradiol variability is associated with worse mood. Circulating progesterone is reduced over the menopause transition. One study found that low progesterone concentrations were associated with worse mood.[70] Some women might be more mood-sensitive to changes in oestradiol concentrations than others,[75,76] as was shown for women with previous major depressive disorder during the menopause transition who experienced a relapse of symptoms when MHT was withdrawn.[75] Together, these data suggest that greater oestradiol variability and possibly a decline in progesterone might increase the risk of depressive symptoms, especially in vulnerable women. However, there are no established ways of predicting vulnerability to depressed mood following fluctuations in ovarian sex steroids.

Psychosocial and cultural aspects of menopause

Psychosocial and cultural factors shape mental health over the menopause transition. Negative expectations and attitudes towards menopause (eg, "[d]uring the menopause or the change of life, I became, or expect to become, irritable or depressed")[27] and ageing[60] (eg, worry about physical decline) predict subsequent depressive symptoms. Most women experience vasomotor symptoms. Together with predisposing factors such as anxiety, people with more negative attitudes towards menopause might have unhelpful cognitive appraisals of vasomotor symptoms (eg, thinking that people will notice their hot flashes or that their symptoms will never end), which might increase their distress and amplify the effects of these symptoms on their mood and functioning.[77] By contrast, positive coping strategies might minimise the effect of vasomotor symptoms on mood. There are marked global differences in attitudes towards menopause, which might help to explain the variation in attributed symptoms across different cultures.[78] For example, White Australians report higher rates of depressive symptoms together with fears of ageing than Laotian women, who position menopause as a positive event.[79]

Optimising mental health at menopause

Identifying modifiable factors is essential to inform preventive interventions. Managing troublesome vasomotor symptoms and sleep disturbance might reduce the risk of depressive symptoms and possibly major depressive disorder. Effective pharmacological and non-pharmacological interventions for vasomotor symptoms are widely available.[80] Evidence-based information promoting more positive or neutral attitudes towards ageing and menopause might be helpful (panel). Increasing social support and physical activity are other potentially modifiable targets.[55] Furthermore, a systematic review has identified psychological resources including optimism, healthy self-image, and perceived control as being protective of mental health across the menopause transition.[81] Cognitive behaviour therapy (CBT) is a proven intervention for depression and anxiety across life stages and is effective for sleep disturbance and for vasomotor symptoms. CBT is specifically recommended by UK National Institute for Health and Care Excellence (NICE) guidelines for depressed mood during menopause.[82] The North American Menopause Society 2023 guidelines also recommend CBT for bothersome vasomotor symptoms.[83]

In summary, women with previous major depressive disorder might be at elevated risk of recurrence over the menopause transition. Vulnerability to depressive symptoms includes both established psychosocial risk factors and menopause-specific factors, which might interact (figure 2).

Detection and treatment of depressive symptoms and major depressive disorder over the menopause transition

A US survey of trainee physicians[84] found that only 6·8% felt adequately prepared to address menopause, despite recognising the importance of this life stage.[84] Understanding the associations between menopause and mental health and evaluating and managing mental health disorders and symptoms are essential aspects of midlife care.

Detection

***Panel*: Promoting mental health over the menopause transition**

Key findings from prospective data

Depressive symptoms or depressive disorder

- Risk of first lifetime major depressive disorder is not increased over the menopause transition, but individuals with previous major depressive disorder might be at increased risk of recurrence
- Women are not universally or uniformly at risk of depressive symptoms over the menopause transition; only a minority experience depressive symptoms, and these symptoms are more common in people with previous major depressive disorder
- Vulnerability to depressive symptoms over the menopause transition is due to established and menopause-related risk factors (figure 2)
- The type and timing of menopause might contribute to risk; surgical menopause might be more likely than natural menopause to increase depressive symptoms
- Frequent, severe, or nocturnal vasomotor symptoms can be associated with increased risk of depressive symptoms
- Fluctuations in oestradiol concentrations might contribute to vulnerability to depressive symptoms in some individuals, especially those who are mood-sensitive to oestradiol; however, findings are mixed and there are no established biomarkers

Other symptoms or disorders

- Scarce evidence suggests that the risk of anxiety disorders does not increase over the menopause transition;[17] women are not universally or uniformly at risk of experiencing symptoms of anxiety over the menopause
- The onset or trajectory of psychosis has not been shown to be affected by the menopause transition
- No studies have found that the menopause transition increases risk of suicide attempt or completion

Recommendations for clinicians

- Provide individuals with evidence-based information about menopause, including clear statements that most individuals are not at risk of mental health problems
- Be aware of who is at risk of depressive symptoms and major depressive disorder; consider treating modifiable risk factors such as severe vasomotor symptoms and sleep problems when these are present
- Do not automatically assume that psychological symptoms over the menopause transition are attributable to menopause; investigate and manage these symptoms as at any other life stage
- Be cautious about discontinuing active treatments for major depressive disorder (eg, antidepressants or psychotherapy) over the menopause transition due to the possible increased risk of recurrence

Social change to improve mental health over the menopause transition

- Challenge assumptions that the menopause transition confers universal risk for depression, anxiety, and other mental health symptoms or disorders, since these assumptions are inaccurate and potentially harmful
- Learn from societies in which ageing in women confers status and in which views of menopause are more affirming
- Model empowered views of the menopause and women's ageing to cultivate more positive attitudes at the societal level
- Promote gender equity and safety across the lifespan since early adversity increases the risk of poor mental health at midlife

The approach to diagnosis and management of depressive symptoms and major depressive disorder over the menopause transition should mirror that at other life stages.[85] Because the menopause transition is a risk period for recurrence of major depressive disorder, women with previous experience of this condition require vigilant monitoring during this life stage. Although the menopause transition is not a risk period for first lifetime onset major depressive disorder, UK guidelines[86] recommend being alert to depression across adulthood and considering screening. During the menopause transition, clinicians should consider risk factors for mental illness, including previous history, and both established psychosocial and menopause-related risk factors (figure 2).

Prevention

RCTs have considered psychosocial[87,88] and hormonal interventions[76] for the primary prevention of depressive symptoms or disorders over the menopause transition. Mindfulness based stress reduction (MBSR) is an 8-week group intervention designed to ameliorate stress through mindfulness meditation and yoga techniques. Two RCTs investigated the efficacy of MBSR to prevent depressive symptoms[88] and cope with severe vasomotor symptoms.[89] In 104 euthymic women in menopause, MBSR effectively prevented the development of depressive symptoms while also promoting higher levels of resilience and lower levels of stress and anxiety relative to participants who were on the waiting list for treatment.[88] These benefits were particularly evident in participants with previous major depressive disorder, stressful life events in the 6 months before assessment, and increased mood sensitivity to oestradiol fluctuations.

In an RCT of 172 euthymic women in perimenopause and early postmenopause,[76] high-dose MHT (100 µg transdermal oestradiol with progesterone every 3 months) halved the risk of emergent depressive

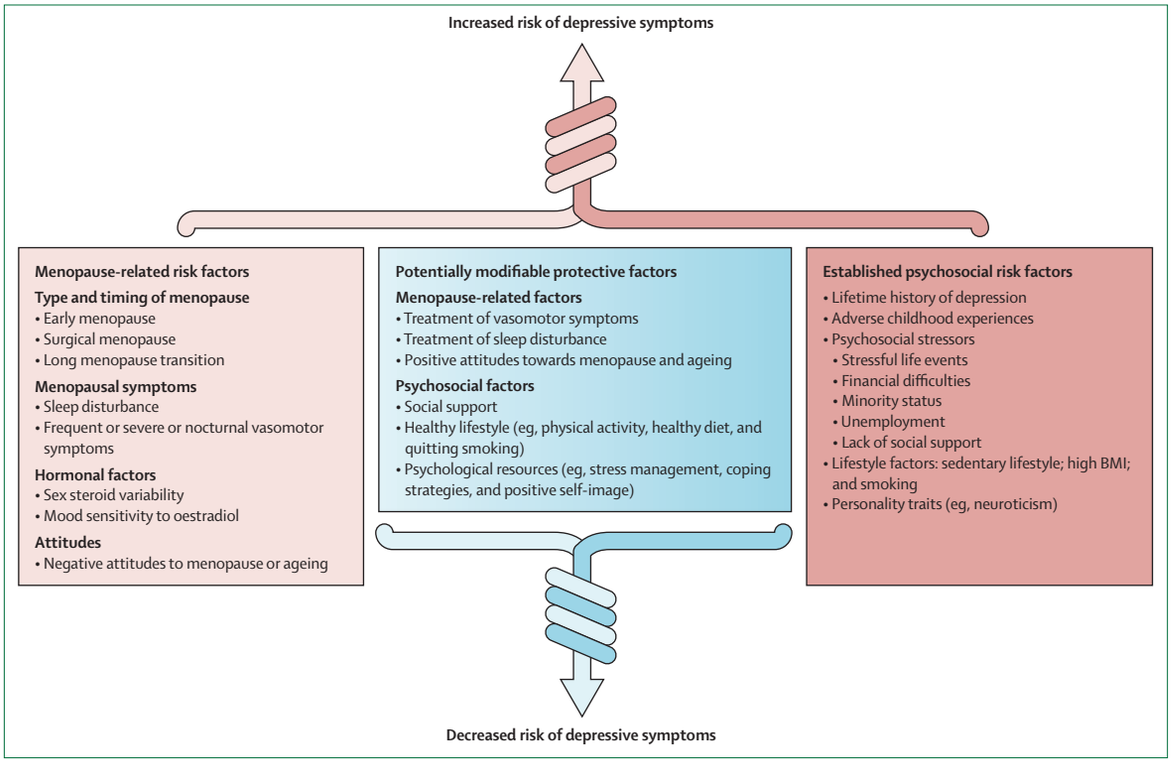

Figure 2: **Interactions between menopause-specific and established psychosocial risk factors for depression and potentially modifiable protective factors that predict increased risk or resilience to depressive symptoms during the menopause transition**
The intertwined arrows indicate that risk and resilience factors can interact with each other to elevate or reduce the overall risk of depressive symptoms.

symptoms compared with placebo over 12 months (incidence 17·3% *vs* 32·3%), particularly in those with stressful life events in the 6 months before assessment. However, MHT was not specifically effective in preventing major depressive disorder in women who had already experienced this condition, who are a group more at risk of depression over the menopause transition. Also, this regimen did not contain adequate dose and duration of progesterone to prevent endometrial hyperplasia.[90]

In summary, emerging evidence suggests that, among women at elevated risk, psychosocial interventions might prevent depressive symptoms over the menopause transition. Overall, the evidence does not support MHT to prevent depressive symptoms or major depressive disorder over the menopause transition.

Treatment

Depressive disorders over the menopause transition should be treated as at any other life stage, within a personalised framework that considers previous history, hormone sensitivity, and psychosocial and menopause-related factors in the cause, recurrence, and maintenance of symptoms.[91] Effective options for major depressive disorder include psychotherapy, antidepressants, and interventional psychiatric approaches. Psychotherapy might be particularly helpful when symptoms are caused or exacerbated by exogenous stressors, including life events and role transitions common in midlife women. Selected antidepressants including selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors might confer additional benefits by treating both depression and vasomotor symptoms.[92] The duration of antidepressant treatment for major depressive disorder during the menopause transition has not been studied and standard treatment duration guidelines are therefore advised. For people experiencing major depressive disorder as they approach the menopause transition, consideration should be given to continuing antidepressants due to the increased risk of recurrence.[93]

MHT is not an approved treatment for depressive symptoms or major depressive disorder by regulatory agencies in Europe or the USA due to insufficient evidence for efficacy. Trials of MHT as a treatment for major depressive disorder have had small sample sizes (combined n=222 on MHT and a placebo) and shown mixed results.[94–97] Two RCTs (combined n=84) found that transdermal oestradiol was superior to a placebo in women with perimenopause and early postmenopause over 3 weeks[94] and 12 weeks[95] of administration. Two other RCTs (combined n=138) of transdermal oestradiol for major depressive disorder and other unipolar depressive disorders in women in perimenopause[96] or a

mixed cohort of women in perimenopause and postmenopause[97] reported no benefits over a placebo.

MHT improves concurrent depressive symptoms for patients with bothersome vasomotor symptoms,[98] but it is not a primary approach for depressive symptoms in the absense of vasomotor symptoms. A meta-analysis of 12 RCTs found that bioidentical oestrogen was ineffective in reducing depressive symptoms in women in perimenopause and postmenopause.[99] Despite this result, some organisations suggest considering MHT to treat depressive symptoms during the menopause transition.[100]

Promoting good mental health over the menopause transition

WHO defines health promotion as a "process of enabling people to increase control over, and to improve, their health".[101] Information resources for people transitioning the menopause might contain mixed messages about what to expect and fail to identify at-risk groups. For example, the UK National Health Service and Mayo Clinic websites list mood changes as symptoms of menopause, whereas Johns Hopkins University emphasises that the association between menopause and mental health is inconclusive. Our findings support enhanced awareness of groups and individuals at risk for poor mental health over the menopause transition and caution against automatically attributing depressed mood or other mental health symptoms or disorders to menopause. This assumption is potentially harmful, as it creates negative expectations that reinforce stereotypes about the menopause and ageing. A survey of more than 7000 European and Australian midlife women[102] found that about half (48% of European respondents and 56% of Australian respondents) were concerned about managing menopause and that most did not feel "very well supported" in terms of their symptoms during the menopause transition.[102] Women and their clinicians need access to accurate and consistent information about what to expect, who is at risk for poor mental health, and when to seek help (panel).

For more on the **UK National Health Service overview of menopause** see https://www.nhs.uk/conditions/menopause/

For more on the **Mayo Clinic overview of menopause** see https://www.mayoclinic.org/diseases-conditions/menopause/symptoms-causes/syc-20353397

For more on the **Johns Hopkins Introduction to Menopause** see https://www.hopkinsmedicine.org/health/conditions-and-diseases/introduction-to-menopause

For people at risk of depressive symptoms over the menopause transition (figure 2), addressing modifiable risk factors, such as sleep disturbance, troublesome vasomotor symptoms, and stress exposures, while promoting more positive attitudes towards menopause and ageing, might be beneficial. According to UN data, 90% of people hold gender biases against women.[103] Outdated views about menopause might be both a cause and a consequence of gender bias. Promoting gender equity and safety across the lifespan is relevant, since early life adversity is a powerful predictor of midlife mental health.[56] Midlife is often a period of low wellbeing for both men and women,[104] and, therefore, a potential window of opportunity to prioritise mental health optimisation. Psychological interventions such as MBSR show promise for prevention,[88] and CBT can reduce anxiety and depressed mood, together with vasomotor symptoms.[82]

Primary care providers and community health educators can contribute to improving care with helpful health messaging and evidence-based practices that empower women and promote mental health over the menopause transition.

Contributors

MH and LB conceived and designed this Series paper. LB wrote the initial draft and was responsible for revising this draft on the basis of comments from all other authors. MSH, RC, CJC, JLG, GDM, VR, HJ, and MH made substantial contributions to the conception or design of this Series paper; or to the acquisition, analysis, or interpretation of data. MSH, RC, CJC, JLG, GDM, VR, HJ, and MH made substantial contributions to drafting this Series paper or revising it critically for important intellectual content; and gave their final approval of the submitted version. MSH, RC, CJC, JLG, GDM, VR, HJ, and MH agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

MSH declares consultation for Rightsteps UK. HJ declares grant funding from the National Institutes of Health, Pfizer, and Merck; and consulting for Bayer, Merck, and Hello Therapeutics. MH declares salary funding from the Australian National Health and Medical Research Council, support for meeting attendance from the UK National Institute for Health and Care Excellence, and the following roles: principal investigator for a clinical trial of salpingectomy vs salpingo-oophorectomy for prevention of ovarian cancer (TUBA-WISP II); board member for Breastscreen Victoria; editor for the Cochrane Collaboration; recipient of a fellowship from the Lundbeck Foundation (2022-23); site investigator for a clinical trial of a non-hormonal agent (Q-122) for vasomotor symptoms in patients with breast cancer (QUE Oncology, 2020-22); and site investigator for a clinical trial of a medical device for treating vaginal dryness (Madorra). All other authors declare no competing interests.

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Menopause 4

Managing menopause after cancer

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Globally, 9 million women are diagnosed with cancer each year. Breast cancer is the most commonly diagnosed cancer worldwide, followed by colorectal cancer in high-income countries and cervical cancer in low-income countries. Survival from cancer is improving and more women are experiencing long-term effects of cancer treatment, such as premature ovarian insufficiency or early menopause. Managing menopausal symptoms after cancer can be challenging, and more severe than at natural menopause. Menopausal symptoms can extend beyond hot flushes and night sweats (vasomotor symptoms). Treatment-induced symptoms might include sexual dysfunction and impairment of sleep, mood, and quality of life. In the long term, premature ovarian insufficiency might increase the risk of chronic conditions such as osteoporosis and cardiovascular disease. Diagnosing menopause after cancer can be challenging as menopausal symptoms can overlap with other common symptoms in patients with cancer, such as fatigue and sexual dysfunction. Menopausal hormone therapy is an effective treatment for vasomotor symptoms and seems to be safe for many patients with cancer. When hormone therapy is contraindicated or avoided, emerging evidence supports the efficacy of non-pharmacological and non-hormonal treatments, although most evidence is based on women older than 50 years with breast cancer. Vaginal oestrogen seems safe for most patients with genitourinary symptoms, but there are few non-hormonal options. Many patients have inadequate centralised care for managing menopausal symptoms after cancer treatment, and more information is needed about cost-effective and patient-focused models of care for this growing population.

Introduction

The average age at natural menopause is 51 years in high-income countries (HICs).[1] A systematic review and meta-analysis in 2014 showed an earlier age at menopause in low-income and middle-income countries (LMICs) across Asia, India, Latin America, and the Middle East.[2] Menopause is more likely to be premature (ie, occurring before age 40 years) or early (ie, at age 41–44 years) after cancer and burgeoning evidence indicates that young age at menopause can be a risk factor for chronic disease.[3] A 2017 meta-analysis of 45 studies in female patients who had survived cancer found a median age at menopause of 44 years.[4] Guidelines from the UK National Institute for Health and Care Excellence (NICE) recommend menopausal hormone therapy (MHT) for younger postmenopausal women without contraindications,[5] but often the safety and efficacy of MHT after cancer is uncertain. Crucially, most patients who have troublesome menopausal symptoms after cancer do not have access to effective treatments, even in HICs.[6] This Series paper will address the prevention and management of menopausal symptoms after cancer, including evidence about health disparities if available.[7]

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in some instances, we have referred to "people" rather than "women" to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used "women" in some instances, to avoid inappropriate generalisation. More information is needed about the experience of menopause in transgender men and gender-diverse people. Evidence on menopause in gender-diverse people is scarce and this area needs more attention.[8]

Search strategy and selection criteria

The recommendations in this Series paper are based on a review of the published literature and appraisal of professional guidelines. We searched databases on MEDLINE, Embase, BioMed Central, Cochrane, and Google from Dec 7, 2020, to Jan 8, 2024, with keywords tailored to each section of the manuscript including "cancer", "neoplasm*", "cancer survivor*", "menopause", "postmenopause", "perimenopause", "menopausal symptom*", "vasomotor symptom*", "hot flush*", "hot flash*", "night sweat*", "sleep disturbance*", "sleep disorder*", "vaginal dryness", "genitourinary syndrome of menopause", "dyspareunia", "sexual dysfunction", "quality of life", "menopausal hormone therapy", "hormone therapy", "hormone replacement therapy", "cognitive behaviour therapy", "cognitive behavioral therapy", "non-hormonal treatment*" , "nonhormonal treatment*", "low and middle income countr*", "high income countr*", "cancer", "BRCA1", "BRCA2", "risk reducing salpingo-oophorectomy", "RRSO", "osteoporosis", "premature ovarian failure", "premature ovarian insufficiency", "chemotherapy", "radiation", "venous thrombo-embolic disease", "multidisciplinary care". We cross-referenced these terms with "systematic review*", "meta-analysis", "metaanalysis", "randomised/randomized controlled

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Key messages

- More than 9 million women are diagnosed with cancer each year and treatments commonly induce early menopause and menopausal symptoms
- Many patients do not have access to effective treatments, even in high-income countries, with an even greater impairment of quality of life and psychological distress in low-income settings
- Diagnosing menopause after cancer can be challenging and many women resume menstruation within 2 years of chemotherapy completion; undetectable anti-Müllerian hormone at 30 months predicts menopause after chemotherapy for breast cancer and menopause is almost universal after ovarian radiation
- Women younger than 45 years without contraindications should be offered an individualised treatment plan including menopausal hormone therapy after cancer treatment
- If menopausal hormone therapy is contraindicated, non-pharmacological and non-hormonal treatments are available for vasomotor symptoms; vaginal oestrogen seems to be safe for most patients with cancer and growing evidence supports safety after breast cancer
- Multidisciplinary management of menopause after cancer is essential and should include primary care and, if appropriate, allied health practitioners
- Reaching the population who need treatment is a global problem and online platforms are being developed to better support and empower patients with cancer to make shared, evidenced-based decisions with their local health-care provider

trial*", "clinical guideline*", "clinical practice guideline*". We also searched websites and guidelines of menopause societies including the British Menopause Society, International Menopause Society, North American Menopause Society, Australasian Menopause Society, and the NICE guidelines. The Turning Research into Practice and PubMed databases were searched for evidence-based guidelines and systematic reviews. We prioritised the most recent evidence from randomised controlled trials and recommendations from international guidelines based on systematic reviews of the evidence (eg, WHO, International Agency for Research on Cancer, NICE, US Preventive Task Force, National Comprehensive Cancer Network, and American Society of Clinical Oncology). Only publications in English were included.

The growing burden of menopausal symptoms after cancer treatment

In premenopausal women, treatment for common cancers such as breast, gynaecological, haematological, and some low colorectal cancers will often cause ovarian damage, potentially inducing permanent menopause.[9] Perimenopausal or postmenopausal women diagnosed with oestrogen-receptor-positive cancers while taking MHT will be advised to stop, which can cause resurgent vasomotor symptoms that are further exacerbated by anti-oestrogen therapy.[10]

The standard of care for premenopausal high-risk oestrogen-receptor-positive breast cancer includes gonadotoxic chemotherapy followed by ovarian suppression plus oral endocrine therapy. This treatment can lead to more severe vasomotor symptoms (ie, hot flushes and night sweats) compared with natural menopause, particularly in younger women.[11,12] Patients with oestrogen-receptor-positive postmenopausal breast cancer are advised to take third-generation aromatase inhibitors (eg, anastrozole, letrozole, and exemestane), which can induce or aggravate menopausal symptoms including hot flushes, night sweats, and vaginal dryness.[13] Menopausal symptoms are a common reason for not starting or prematurely stopping endocrine therapy, which directly increases morbidity and mortality from breast cancer.[11] Newer protocols extending endocrine therapy from 5 years to 10 years in oestrogen-receptor-positive or progesterone-receptor-positive cancer are likely to increase the burden of symptoms. In a 2021 community-based survey (n=385), the prevalence of menopausal symptoms in survivors of breast cancer 6 years after diagnosis was high: 346 (90%) had vasomotor symptoms or sleep disturbance, 289 (75%) had vaginal dryness, 240 (62%) had mood swings, and 229 (59%) had sexual difficulties.[6] Severity of hot flushes and sleep disturbance predicted their inability to resume everyday activities. Less than a third were offered treatment and less than half found this to be effective. These symptoms can cause distress and impair quality of life, and managing these symptoms is a leading priority for patients with cancer.[14] Around a third of patients with breast cancer are dissatisfied with the information provided about the effects of cancer treatment on reproductive outcomes such as menopause.[15]

Around one in 400 women are at elevated risk of ovarian cancer due to pathogenic gene variants such as *BRCA1* or *BRCA2*.[16,17] International guidelines advise risk-reducing bilateral salpingo-oophorectomy by age 35–40 years, which will induce surgical menopause.[18] Patients' concerns about managing menopausal symptoms after bilateral salpingo-oophorectomy are a leading barrier to this potentially life-saving surgery[19] and many clinicians are uncertain how best to manage surgical menopause in this population.[20] The clinical case in panel 1 emphasises the importance of pre-operative counselling about the probable consequences of surgical menopause in these patients and of postoperative symptom management. In 2023, new international consensus guidelines provided recommendations for symptom management and prevention of chronic disease following risk-reducing salpingo-oophorectomy in premenopausal women with the *BRCA1* or *BRCA2* pathogenic variant.[21]

***Panel 1*: Fictional clinical case study**

- A 37-year-old woman with a male partner and two children aged 5 years and 3 years visited her primary care provider because of sleeping difficulties. The primary care provider knows her well. The patient previously had imaging to investigate right-sided pain, which revealed a complex ovarian mass. This mass was subsequently found to be stage 1C1 high-grade serous ovarian cancer. She had a total abdominal hysterectomy and removal of both ovaries, staging laparotomy, and adjuvant systemic chemotherapy. Genetic testing showed that she carried the *BRCA1* pathogenic variant, so both ovaries were removed. She also decided to undergo risk-reducing bilateral mastectomy with informed consent.
- When the primary care provider asked more about her sleeping problems, the patient started to cry. She was frustrated by this show of emotion and said that she was not herself anymore. She found that minor problems were harder to deal with and she easily became emotional, which had caused arguments with her partner and her parents. Her family members were concerned about her health during her cancer treatment, but now that she was cured, they did not understand why she was always angry or sad. When she tried to make up with her partner, he often wanted to initiate sex. However, sexual intercourse was painful. Also, she was self-conscious about her appearance after mastectomy.
- She was concerned about these changes and the effect they had on her life, especially at night. When she eventually fell asleep, she sometimes suddenly woke up feeling very hot, sweaty, and anxious. Sometimes these sensations also occurred during the day. After telling her story, she felt relieved to have told someone about her problems and was hopeful that the primary care provider could help to solve them.
- The primary care provider discussed with the patient that her symptoms (mood changes, vaginal dryness, hot flushes, and sleep disturbance) are all common after surgical menopause. This information gave great relief to the patient, who did not realise that removing her ovaries might have this effect. Previously she was blaming herself for feeling angry or sad, felt guilty about being unwilling to have penetrative intercourse, and was concerned about her relationship. She was also fearful that night sweats were a sign of brain metastases from her ovarian cancer. The primary care provider gave her information about symptoms after surgical menopause and possible treatments and made another appointment.
- When she returned a week later, the patient felt somewhat better. However, she continued to experience troublesome hot flushes, sleep disturbance, and vaginal dryness. The primary care provider had contacted the gynaecological oncologist to discuss treatment options. They advised that there were no contraindications to menopausal hormone therapy (MHT) in women with a history of high-grade serous ovarian cancer; however, the relevant studies had small sample sizes and short follow-up. Although the patient had a *BRCA1* pathogenic variant, there were no substantial concerns about breast cancer because she had undergone bilateral mastectomy and would be receiving oestrogen-only MHT.
- Together, the patient and the primary care provider discussed the treatment options. Initially, the patient was reluctant to consider pharmacological therapies because she had taken so much medication in the previous year. During an individualised discussion of the risks and benefits, the primary care provider explained that MHT was the most effective treatment for hot flushes and night sweats and would also prevent bone loss. The patient and the primary care provider made a joint decision that she should try MHT.
- A month later, the patient reported that her vasomotor symptoms were greatly improved and her sleep was much better. Her relationship with her family had improved and she had returned to work. She had recommenced sexual activity but continued to experience vaginal dryness, so the primary care provider offered vaginal topical oestrogen. However, the patient continued to experience anxiety, particularly a fear of cancer recurrence. Together, they agreed that help from a psychologist was needed, and the patient was referred for cognitive behavioural therapy.

Around 1·8 million women are diagnosed with gynaecological cancers every year and treatments such as bilateral oophorectomy, pelvic radiation, and gonadotoxic chemotherapy commonly induce premature ovarian insufficiency (POI) or early menopause.[22] In 2020, around 10% of cancers diagnosed in women were colorectal.[23] Colorectal cancer rates are increasing in younger women, particularly rectal and anal cancer, which are commonly treated with pelvic irradiation that will induce menopause.[24]

Leukaemia and lymphomas comprise about 4% of all cancers in women younger than 50 years and are commonly treated with a stem-cell transplant.[24] Gonadotoxic chemotherapy before stem-cell transplantation will induce menopause in around 80% of premenopausal women, depending on their age and nature of the conditioning regimen.[25,26]

Unmet needs of women with cancer in LMICs

Survivors of cancer who are socioeconomically disadvantaged have poor health-related quality of life, in both low-income and high-income settings, due to underdiagnosis of menopausal symptoms and barriers to timely and appropriate care.[27] Multiple studies have shown that general physical health declines during midlife (age 35–65 years) in women from LMICs.[28] Impaired quality of life and psychological distress after cancer treatment is more severe in survivors from LMICs compared with survivors in HICs. Longitudinal studies reported young age and late cancer stage at diagnosis, low education and health literacy, financial hardships, and inadequate availability of supportive care as the primary reasons for continued distress of the people who survived cancer in LMICs.[29]

Menopause-related symptoms and their consequences often receive little attention, as follow-up care is focused predominantly on surveillance for cancer recurrence. Minimising the health consequences of menopausal symptoms induced or exacerbated by cancer treatment and offering resource-appropriate solutions will substantially improve the quality of life of thousands of women every year.

***Panel 2*: Circumstances in which ovarian function can be preserved in gynaecological cancer**

Consider ovarian preservation in premenopausal women with:

- Cervical cancer—stage 1 or 2A human papillomavirus-associated adenocarcinoma and squamous carcinoma of the cervix undergoing radical hysterectomy
- Endometrial cancer—stage 1 low grade (not associated with Lynch syndrome or *TP53* mutated); future molecular subtyping of endometrial cancer might improve stratification of care
- Ovarian cancer—stage 1 (A) low grade, contralateral ovary could be preserved after explaining the 6–13% risk of recurrence in the preserved ovary; germ cell tumours with early unilateral disease

Consider elective transposition in women younger than 40 years with:

- Cervical cancer—locally advanced, if primary chemoradiation is planned
- Rectal cancer—requiring neo-adjuvant chemoradiation
- Cancer requiring pelvic radiation (eg, anal, vulval, sarcoma)

Consider intra-operative transposition in women with:

- Cervical cancer—if radical hysterectomy is abandoned due to positive node or if adjuvant radiation is likely
- Rectal cancer—if adjuvant radiation is likely to be needed due to close margins or intra-operative complications

Preservation of ovarian function before cancer treatment

Cancer treatments, including oophorectomy, gonadotoxic chemotherapy, and pelvic radiation, can induce menopause. Recognising the potential short-term and long-term value of preserving ovarian function, the European Society of Medical Oncology has produced guidelines recommending strategies to preserve fertility and ovarian function after cancer (panel 2).[30] Gonadotoxic chemotherapy, particularly regimens containing alkylating agents, commonly damage ovarian function and can induce permanent menopause.[31] The effect of new targeted therapies and immunotherapy on ovarian function is uncertain, but in mice, immunotherapy is gonadotoxic and reduces ovarian reserve.[32] In 2018, a systematic review found that ovarian suppression with gonadotropin-hormone-releasing hormone analogues before chemotherapy for breast cancer reduced chemotherapy-induced ovarian failure by around 50%.[33] A randomised trial is underway to determine if gonadotropin-releasing hormone agonists provide ovarian protection in young women and adolescents undergoing chemotherapy for cancer (eg, breast, lymphoma, leukaemia, and sarcoma),[34] but evidence to date shows little benefit for patients with haematological cancer.[35] The effect of pre-chemotherapy gonadotropin-hormone-releasing hormone analogues on age at menopause and long-term ovarian function is unknown.

Pelvic radiation for locally advanced colorectal and cervical cancers will induce menopause in around 94·1% of premenopausal women.[36] There are few effective options for preventing ovarian damage due to chemotherapy. Preclinical data suggest that modification of pathways to primordial follicle apoptosis can protect the ovaries during chemoradiation.[37] However, this approach has not yet been trialled in women. Moving the ovaries outside the field of radiation (transposition) can be protective and should be discussed as part of shared decision making. A 2019 systematic review of ovarian transposition before external beam pelvic radiation (n=765) concluded that ovarian function could be preserved in 20–100% of cases,[38] with efficacy primarily dependent on age. In a small series of 22 women with low rectal (n=20) or anal (n=2) cancer, transposition preserved ovarian function in 90% of participants younger than 40 years but only in 38% of those older than 40 years[39] (panel 2).

Diagnosing and managing menopause after cancer

There are no consensus criteria for diagnosing menopause after cancer. General diagnostic criteria, such as more than 12 months of amenorrhoea and elevated follicle stimulating hormone, cannot reliably be used, as ovarian function can resume many years after treatment. Although circulating anti-Müllerian hormone can indicate reduced ovarian reserve after chemotherapy, it does not reliably predict fertility, duration of reproductive life-span, or ovarian function.[40] A cross-sectional study of 1043 women aged 20–35 years found that 31·6% had amenorrhoea after cancer treatment, with risk factors including chemotherapy, older age at diagnosis, and never having been pregnant. Overall, 70% resumed menstruation, with almost all (90%) resuming menstruation within 2 years of treatment.[41]

Women younger than 45 years with prolonged amenorrhoea after gonadotoxic cancer treatment should be offered MHT, provided they do not have contra-indications. Management should be tailored to the individual, taking into account the patient's age, cancer type, time since diagnosis (competing risks change over time), quality of life (menopausal symptoms), comorbidities (eg, venous thromboembolism, poly-pharmacy, and the potential for drug interactions), risk factors for chronic disease (eg, osteoporosis and ischaemic heart disease), and views and preferences. Evidence of moderate-to-low quality from the general population suggests that transdermal MHT does not increase venous thromboembolism rates.[42] Since patients with cancer are at elevated risk of venous thromboembolism, we recommend offering transdermal rather than oral MHT. Testing of ovarian function after 12 months can be considered, depending on the cancer treatment. For example, ovarian function is unlikely to resume after pelvic radiation without ovarian transposition but might

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resume after chemotherapy for breast cancer, particularly in young women. In patients aged 40–45 years with breast cancer and secondary amenorrhoea after chemotherapy, an undetectable anti-mullerian hormone at 30 months is a reliable predictor of permanent menopause.[43]

In addition to MHT, there is growing evidence supporting the efficacy of non-hormonal and non-pharmacological therapies for menopausal symptoms, which has substantially increased treatment options for the management of vasomotor symptoms and (to a lesser extent) genitourinary symptoms associated with menopause.[44]

MHT

In the general population, MHT reduces vasomotor symptoms by around 85% and treating vasomotor symptoms can also improve sleep and quality of life.[45] Less is known about the efficacy and safety of MHT after cancer, but a systematic review reported an increased risk of recurrence following oestrogen-receptor-positive (but not negative) breast cancer.[46] Much of the evidence informing this systematic review came from a large randomised controlled trial (RCT) of tibolone (LIBERATE), which reported a significantly increased risk of new breast cancers and breast cancer recurrence with tibolone compared with placebo.[47] When the findings from LIBERATE were removed from the systematic review, there was no longer a statistically significant harm for patients with breast cancer. However, given concerns for an increased risk of breast cancer recurrence, especially in patients who might benefit from low circulating oestrogen concentrations, we generally recommend against MHT in survivors of breast cancer, particularly those with oestrogen-receptor-positive disease. However, exceptions can be made if quality of life is substantially affected or disease risks are low after careful discussion and shared decision making (figure 1).

For patients with cancer and POI or early menopause who are eligible to take MHT, the optimal duration of use is uncertain but should be considered until the average age of menopause (≥45 years) depending on symptoms and other health indices such as bone density. Figure 1 summarises available evidence regarding the safety of MHT after cancer. Figure 2 summarises advice about MHT use in female-specific cancer, and figure 3 provides specific advice for MHT after cancers that affect both men and women. Decisions about MHT after cancer should use a shared decision-making approach, including the patient and the treating oncologist.

	Effect of MHT on cancer outcomes	Level of evidence	MHT use
Breast cancer: overall	Systematic review and meta-analysis (n=4050) found increased risk of recurrence with tibolone or MHT (HR 1·46)[46]	Moderate	Avoid MHT
Breast cancer: oestrogen-receptor-negative	Subgroup analysis found no increased risk of recurrence with tibolone or MHT (HR 1·19)[46]	Moderate	Consider MHT in specific patients*
Breast cancer: oestrogen-receptor-positive	Subgroup analysis found increased risk of recurrence (HR 1·80) with tibolone or MHT[46]	Moderate	Avoid MHT
Uterine sarcomas	European guidelines suggest avoiding MHT, might be oestrogen sensitive[48]	Very low	Avoid MHT
Ovarian cancer: low-grade serous and granulosa cell	European guidelines suggest avoiding MHT, might be oestrogen sensistive[48]	Very low	Avoid MHT
Low-grade, early-stage endometrial cancer	Systematic review found no effect on cancer outcomes[49]	Moderate	Consider MHT
Cervical cancer	One small retrospective study (n=120) found no effect on cancer outcomes;[50] European guidelines suggest offering MHT[51]	Very low	Consider MHT
Haematological cancer	One small study (n=130) showed no effect on cancer outcomes[52]	Very low	Consider MHT
Early cutaneous malignant melanoma	One small study (n=206) showed no effect on cancer outcomes[53]	Very low	Consider MHT
Colorectal cancer	One large prospective study (n=834)[54] and one national cohort study[55] reported improved cancer outcomes	Low	Consider MHT
Hepatocellular cancer	One case–control study (n=244) reported improved cancer outcomes[56]	Very low	Consider MHT
Ovarian germ cell tumours	European guidelines suggest offering on an individualised basis[48]	Very low	Consider MHT
Epithelial ovarian cancer	Systematic review found uncertain evidence for efficacy or safety of MHT[57]	Moderate	Consider MHT
Vaginal, vulval, and anal squamous cell carcinoma	Do not express oestrogen receptors, MHT thought to be safe[58]	Very low	Consider MHT
Kidney cancer	Meta-analysis suggests better cancer outcomes with MHT[59]	Low	Consider MHT
Lung cancer	Mixed evidence: prospective cohort study (n=727)[60] and SEER data (n=485)[61] showed improved cancer outcomes; retrospective study (n=498)[62] and RCT[63] showed increased mortality	Moderate	Consider MHT

Figure 1: **Use of systemic MHT (or tibolone) by cancer type**
Red indicates that MHT should be avoided; orange indicates that MHT should be considered. Grading uses the Grading of Recommendations, Assessment, Development, and Evaluation approach.[64] MHT=menopausal hormone therapy. HR=hazard ratio. RCT=randomised controlled trial. *After oestrogen-receptor-negative breast cancer, consider MHT if menopausal symptoms do not respond to non-hormonal treatments, particularly following bilateral mastectomy. Discuss with the patient that evidence to inform the safety of MHT in these circumstances is limited.[65–69]

Non-pharmacological therapies for vasomotor symptoms

Non-pharmacological approaches can also reduce the effects of vasomotor symptoms after cancer. Cognitive behaviour therapy (CBT) has the strongest evidence base. After breast cancer, CBT is effective delivered to groups, individually, online, or by specialist nurses, with a sustained effect at 26 weeks versus usual care, and it improves sleep and depressive symptoms.[70] CBT reduces interference and bother due to vasomotor symptoms, which is a priority area for patients.[71]

Two small RCTs of hypnosis in patients with breast cancer showed improvements in vasomotor symptoms, mood, and sleep.[44] Stellate ganglion block involves injection of local anaesthetic into the neck for the management of conditions such as complex regional pain and peripheral vascular disease. One small, randomised sham-controlled trial (n=40) showed a reduction in moderate-to-severe vasomotor symptoms with stellate ganglion block.[72,73] However, this procedure is invasive and costly, with small but serious health risks. Acupuncture is of uncertain benefit for vasomotor symptoms but can help with fatigue and joint pain after breast cancer.[44] Small RCTs indicate that yoga, relaxation training, and mindfulness-based stress reduction reduce vasomotor symptoms, with benefits for sleep, depressive symptoms, and self-reported stress.[44] Physical exercise, supplements, and homoeopathy are ineffective.[44] Lifestyle changes, such as dressing in layers, can help and a cool pad pillow topper reduces vasomotor symptoms after breast cancer.[74]

Non-hormonal treatments for vasomotor symptoms

In patients in whom MHT is contraindicated or should be avoided after cancer (table), a burgeoning number of non-hormonal therapies are available. However, unlike MHT these therapies will not improve genitourinary symptoms or prevent fracture. Some antidepressants reduce vasomotor symptoms by 40–60%.[75] The anticonvulsants pregabalin and gabapentin have similar efficacy.[75] The antihypertensive clonidine is less effective than venlafaxine.[44] One small RCT showed that oxybutynin was effective for vasomotor symptoms after breast cancer.[76] There are few head-to-head trials of non-hormonal treatments for vasomotor symptoms, which makes knowing what works best difficult. Selecting non-hormonal treatments should follow a shared decision making approach. For example, gabapentin reduces vasomotor symptoms but can cause drowsiness and hence is often more suitable for night-time symptoms. The dose of escitalopram for vasomotor symptoms is equivalent to the antidepressant dose so can be considered for patients who also have depression. Existing medications will also guide choice. Selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors should not be used together. A suggested approach to starting non-hormonal treatments for vasomotor symptoms is oxybutynin 2·5–5 mg twice a day, escitalopram 10–20 mg, or venlafaxine 37·5 mg increasing to 75 mg controlled release. Gabapentin (300–900 mg) reduces night sweats and causes drowsiness, which might improve sleep.[44] A systematic review of the side-effects of these non-hormonal therapies in patients with breast cancer reported that 81% of patients experienced adverse effects, which were graded as mild in 67%.[77] Higher doses of gabapentin and venlafaxine were most likely to induce side-effects.[77] Antidepressants should be stopped gradually.

Targeted therapy with the neurokinin B receptor antagonist fezolinetant is available in the USA and some European countries. Two large RCTs have compared the efficacy of fezolinetant versus placebo for vasomotor symptoms over 12 weeks, with a 40-week open label extension.[78,79] With 45 mg per day (the dose now marketed), there was a statistically significant reduction in hot flush frequency and severity up to 1 year and serious adverse events were infrequent. Fezolinetant also improved menopause-related quality of life.[80] Although clinical trials of neurokinin B receptor antagonists in patients with cancer have not yet been published, breast cancer is not a contraindication to fezolinetant use in the USA. However, improvements in vasomotor symptoms with fezolinetant are modest and do not meet the minimally important clinical difference[81] for hot flush frequency or menopause-related quality of life. A meta-analysis published in 2024,[82] which included 2168 patients from five RCTs, reported a 22·5% mean improvement in frequency of vasomotor symptoms, with small improvements in menopause-related quality of life. In 2023, the independent US Institute for Clinical and Economic Review concluded that fezolinetant was less effective than MHT for vasomotor symptoms, and that MHT might provide additional benefits for sleep, vaginal dryness, and fracture prevention.[83]

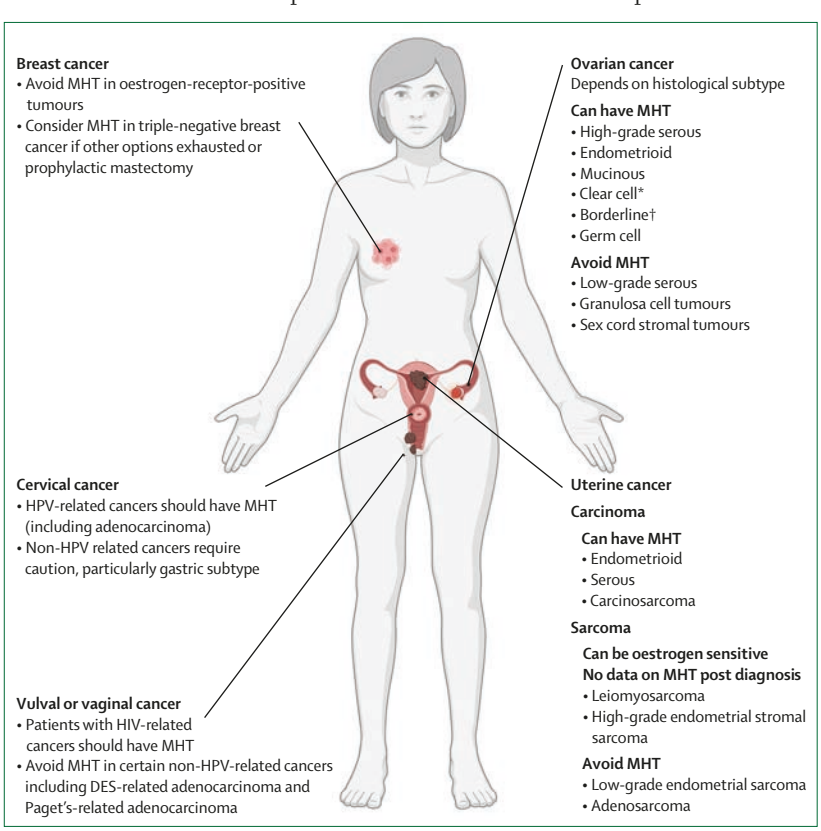

Figure 2: **Use of MHT after female-specific cancers**
MHT=menopausal hormone therapy. HPV=human papillomavirus. *Consider transdermal due to increased venous thromboembolism risk. †Fully resected, no invasive implants.

Managing sexual difficulties and dysfunction

In 2016, a systematic review reported that sexual dysfunction affected 78% of patients with gynaecological cancer and 65% of patients with breast or colorectal cancer, particularly premenopausal women.[84] Sexual dysfunction can arise from factors that are biological (eg, menopause or surgery), psychological (eg, depression, anxiety, or body image), interpersonal (eg, relationship and communication issues), and sociocultural (eg, religion or cultural). A holistic approach including partners might be best suited to address these issues. The American Society of Clinical Oncology advises that health-care professionals should initiate a discussion about sexual problems with all patients with cancer and offer psychosocial or psychosexual counselling to improve sexual response, body image, intimacy and relationship issues, and overall sexual functioning and satisfaction.[85] However, less than 25% of patients with cancer seek professional help.[86] Less is known about the psychosexual effects of cancer in LMICs, where there might be substantial cultural differences in beliefs and understanding about sex and approaches to managing sexual dysfunction compared with HICs.[87]

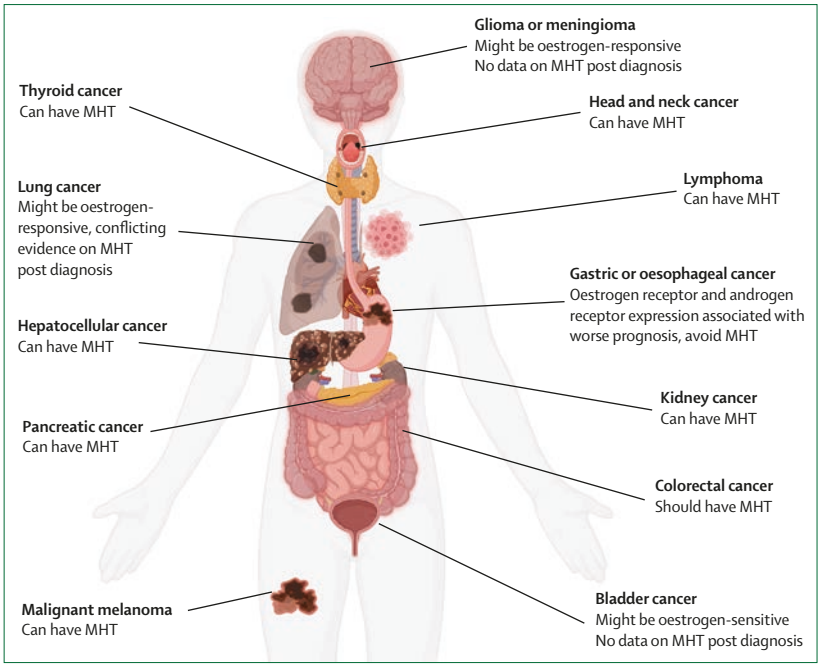

Figure 3: **Use of MHT after non-female specific cancers**
MHT=menopausal hormone therapy.

Management of genitourinary symptoms and sexual dysfunction after breast cancer

A 2018 consensus guideline from the American College of Obstetrics and Gynecology advised non-hormonal agents as first-line therapy, with vaginal oestrogens reserved for persistent symptoms after discussion with the treating oncologist.[88,89] In the general population, vaginal oestrogens improve dryness with no differences between products.[90] Although often recommended for long-term use, a 2020 systematic review reported that safety data are limited to 1 year.[91] Less is known about the efficacy and safety of vaginal oestrogen after breast cancer. In 2022, a Danish data linkage study reported a small increase in breast cancer recurrence in patients taking adjuvant aromatase inhibitors and using vaginal oestrogen, although their survival was no worse.[92] In 2024, a UK registry-based study of 49 237 patients aged 40–79 years with breast cancer showed no evidence of increased breast cancer mortality in those who used versus those who did not use vaginal oestrogen, although only 5% used vaginal oestrogen.[93] Vaginal oestrogens are systemically absorbed in small but measurable amounts, which are dose dependent, with low and ultra-low doses leading to low or no measurable absorption.[94] In the general population, an RCT of daily vaginal prasterone for 12 weeks showed a reduction in pain during sexual activity and an improvement in vaginal dryness.[95] However, one RCT (n=464) of vaginal prasterone after breast cancer showed no benefit compared with vaginal moisturiser at 8 weeks.[96]

Ospemifene is an oral treatment for vaginal dryness that is approved for use after breast cancer in the UK and the USA. In the general population, ospemifene is superior to placebo for vaginal dryness and improves sexual function at 12 weeks.[97] However, there are no direct comparator trials with vaginal oestrogen, and efficacy and safety of ospemifene after cancer are unknown.[96] There is little evidence to support the efficacy of lubricants and moisturisers. One small RCT comparing silicone with water-based lubricants in patients with breast cancer taking aromatase inhibitors found that silicone lubricants were more effective for sexual pain but more than 80% of

	Vasomotor symptoms	Sexual dysfunction	Vaginal dryness
Selected SSRIs and SNRIs	Likely	Unlikely*	Unlikely
Specific anticonvulsants	Likely	Unlikely	Unlikely
Oxybutynin	Likely	Unlikely	Unlikely
Clonidine	Likely	Unlikely	Unlikely
Vaginal lubricants or moisturisers	Unlikely	Possible	Possible
Vaginal carbon dioxide laser	Unlikely	Unlikely	Unlikely
Stellate ganglion block	Possible	Unlikely	Unlikely
Cognitive behavioural therapy	Likely	Likely	Unlikely
Physical exercise	Unlikely	Unlikely	Unlikely
Acupuncture	Possible	Unlikely	Unlikely
Hypnosis	Likely	Unlikely	Unlikely
Yoga and mindfulness-based stress reduction	Possible	Unlikely	Unlikely

Effectiveness is defined as likely (evidence from randomised controlled trials), possible (evidence from single-arm studies), or unlikely (no evidence of effectiveness). SNRIs=serotonin norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors. All trials are in patients with breast cancer. Adapted from Franzoi and colleagues with permission.[44] *Does not worsen sexual function when used for vasomotor symptoms.

Table: **Effectiveness of non-hormonal treatments for vasomotor symptoms, sexual difficulties, and vaginal dryness**

patients still had sexual pain despite lubricant use.[98] One RCT of vulval anaesthetic (lignocaine) after breast cancer showed reduced pain with intercourse.[99]

Cancer and its treatment might also reduce libido and sexual satisfaction. One RCT showed that intravaginal testosterone reduced pain and dryness and increased satisfaction in patients with breast cancer taking aromatase inhibitors.[100] However, the safety of testosterone after breast cancer is uncertain. Psychosexual interventions including CBT, education, and counselling might be helpful.[101] An RCT showed that CBT improved overall sexual function and desire, arousal and vaginal lubrication, and sexual pleasure and reduced discomfort and distress after breast cancer.[102] Brief sexual counselling by telephone or in person might also be effective.[103]

Management of genitourinary symptoms and sexual dysfunction after pelvic radiotherapy

The vaginal effects of external beam radiotherapy or brachytherapy, particularly vaginal dryness, fibrosis, and shortening, which can present as pain with sexual activity and impaired sexual function, can be more severe than those of chemotherapy.[101] Vaginal dilators are recommended to maintain vaginal capacity after pelvic radiation, but uptake is low at less than 25% of patients and the evidence base is scant.[101] In 2014, a systematic review found no reliable evidence that routine regular vaginal dilation during radiotherapy prevents stenosis or improves quality of life.[104] Vaginal oestrogen is commonly offered with little evidence to support efficacy. Pelvic floor dysfunction, including urinary and faecal incontinence, dyspareunia, and vaginismus, are common after gynaecological cancer treatment. A small RCT (n=34) showed that pelvic floor physiotherapy improved sexual function after gynaecological cancer.[105]

Integrative oncology

Integrative oncology describes the use of complementary treatments alongside conventional cancer therapies. This approach takes a patient-centred, evidence-informed perspective and uses mind–body practices, natural products, and lifestyle modifications alongside conventional treatments. Integrative oncology might include therapies such as CBT, mindfulness, and hypnosis for vasomotor symptoms, mood, and sleep.[106] Patients with cancer in many settings rely on traditional, complementary, and integrative treatments that are culturally appropriate and more accessible than conventional therapies.[107] Although there is very little evidence to support the use of traditional and complementary therapies in cancer treatment, several randomised controlled trials have shown benefits for reducing symptoms such as fatigue, depression, anxiety, and insomnia, which could improve quality of life.[108]

Multidisciplinary care

Managing menopause after cancer requires a multidisciplinary clinical team and the use of an evidence base to inform practice, optimal models for service delivery, and investment in sectors such as primary care and allied health. Tertiary-based care cannot meet the needs of the growing number of people who survive cancer. Since menopausal symptoms affect a wide range of these patients, siloed care within tumour streams could lead to duplication of precious services.

In Australia, the multidisciplinary Menopausal Service after Cancer (MSAC) provided by gynaecologists, endocrinologists, and primary care and allied health providers manages vasomotor and genitourinary symptoms, sleep and mood disturbance, and sexual difficulties across cancer types and in one place.[109] A 2021 study showed statistically significant improvements in the four most troublesome symptoms (ie, hot flushes, fatigue, sleep difficulties, and loss of interest in sex) in patients whose care was managed through MSAC.[110] To minimise cost and reduce waste, clear guidelines are needed to support the management of menopausal symptoms after cancer. This approach should include high-quality information for patients about hormonal, non-hormonal, and psychological treatment options that stratify risk according to cancer type. Involving patients in decisions about their care and enabling them to make informed choices is key and is likely to lead to better outcomes.

COVID-19 changed how medical care is delivered. Telemedicine can extend the reach of care and increase convenience for patients. In 2021, a systematic review reported that digital health interventions were helpful and effective for supportive care in patients with cancer. Most studies reported positive outcomes for symptoms such as fatigue and pain, health-related quality of life, functional capacity, and mood compared with usual care, although most studies were in breast cancer.[111] Telehealth is also accessible and effective for managing menopausal symptoms after cancer and could reduce the burden of hospital appointments. Patients with cancer often prefer video telehealth when physical examination is not needed.[112] Telehealth can also be delivered directly to the primary care provider who has reviewed and examined the patient, which can reduce the need for tertiary referral.[113]

Tertiary care should be multidisciplinary, inclusive of all symptomatic patients, and should aim to manage all common symptoms.[114] In-person visits are needed for vulval and vaginal examination to manage chronic genital graft versus host disease, which affects around 30% of allograft patients in whom effective management can prevent severe complications such as vaginal stenosis.[115]

In breast cancer, RCT evidence supports the role of nurse practitioners in patient counselling and education and to assess symptoms.[116] Allied health professionals such as primary care providers are well placed to provide ongoing psychological support, monitor for short-term and long-term complications of cancer treatment, modify risk factors, and make timely onward referral as needed. Care delivered by allied health-care professionals and

their peers in discussion with cancer specialists might be more sustainable than ongoing tertiary care.

Health disparities in LMICs

Rates of treatment-induced menopause are elevated in LMICs, where the average age at cancer diagnosis is 40–50 years compared with 66 years in HICs.[24] In these settings, more women are diagnosed with cancer when they are still premenopausal and are exposed to treatments that are likely to induce POI or early menopause. Prevention and management of treatment-induced menopause is an unmet need in LMICs. Supportive care should be integrated into the comprehensive cancer care model through the training of primary and tertiary health-care providers and the provision of essential and affordable medication to manage symptoms. Education for patients and their carers should include identification of symptoms, self-management approaches, and pathways for seeking care. Scarcity of evidence from high-quality research is commonly cited as the key reason for not integrating traditional and complementary medicine into cancer survivorship care.[117]

Evidence gaps

Almost all published studies of menopause and cancer are in early breast cancer, and less is known about advanced breast cancer or other cancers in women. There are no reliable ways of predicting who will experience severe or prolonged menopausal symptoms following cancer treatment. In breast cancer, vaginal dryness is more common with aromatase inhibitors than tamoxifen, and some evidence suggests that switching between tamoxifen and aromatase inhibitors can improve vasomotor symptoms in postmenopausal women.[13,118] Among premenopausal women, switching to tamoxifen plus ovarian function suppression or tamoxifen alone might improve vaginal dryness, and this treatment can be considered by the treating oncologist when weighing the advantages and disadvantages of disease risks and tolerance of therapy.[119] Decisions regarding the necessity and type of hormonal therapy used for breast cancer treatment depend on menopausal status, evolving literature, disease risk, and patients' comorbidities, tolerance over time, and preferences.

Although aromatase inhibitors have become the standard of care for many patients with oestrogen-positive breast cancer (with ovarian suppression in premenopausal women), there are commonly issues with access and cost for women in LMICs. Tamoxifen is widely used for premenopausal and postmenopausal women in these settings, and it is included in WHO's list of essential cancer medicines. More information is needed about the effect of long-term tamoxifen use on menopausal symptoms and quality of life for patients from LMICs, especially when they transition from premenopausal to postmenopausal. Most clinical trials of treatments for menopausal symptoms were done in older women but younger patients with cancer can experience severe symptoms and worse quality of life.[120] Little is known about the effects of cancer treatment in lesbian, gay, bisexual, transgender, queer or questioning, and intersex (LGBTQI+) individuals, but some people report hostility and prejudice from health-care providers and anxiety about disclosing their sexual orientation and gender identity.[121] In Australia, these data have informed a new information resource for LGBTQI+ people with cancer.

For more on the **resource for LGBTQI+ people with cancer** see https://www.cancercouncil.com.au/cancer-information/lgbtqi/

Although new non-hormonal and non-pharmacological treatments are needed for patients with contraindications to MHT, young patients with cancer who are eligible to take MHT might not be offered it. New MHT preparations are emerging, including selective oestrogen receptor modulators and non-hormonal therapies targeting the neurokinin B receptor. One targeted therapy (Q-122) has shown moderate efficacy for vasomotor symptoms in patients with breast cancer taking endocrine therapy.[122] Fezolinetant is available in some countries for vasomotor symptoms, with efficacy, safety, and tolerability shown up to 1 year in the general population.[78,123] However, efficacy and safety of this agent after cancer are not clear.

Safe and effective non-hormonal treatments for managing genitourinary symptoms after cancer are needed. The efficacy of vaginal laser is uncertain. A 2021 randomised sham-controlled trial of vaginal laser for genitourinary symptoms in postmenopausal women, of whom around half had previous breast cancer, found no difference between the sham and laser groups.[124] In 2023, a randomised trial of carbon dioxide laser on sexual function in survivors of breast cancer showed no benefit over sham laser.[125]

Reaching the population who need treatment is a global problem. Novel online information and treatment resources based on stepped care aim to increase knowledge and improve access to treatment. In gynaecological cancer, new personalised online resources co-developed with patients provide much-needed information and symptomatic support.

For more on the **personalised online resources** see https://thisisgo.ie/

Contributors

MH conceived and designed the paper, wrote the initial draft, and was responsible for revising this draft based on comments from the other authors. PB, JS, MES, EW, KNC, C-HY, AHP, and DJB made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MH is responsible for the final approval of this manuscript and agrees to be accountable. PB and EW are personnel of the International Agency for Research on Cancer or WHO. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer or WHO.

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