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The menopause and hormone replacement therapy

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The menopause: the background

Introduction

The menopause is the transition from the reproductive to the non-reproductive stage of life in women and is characterized clinically by permanent cessation of menstruation and biologically by loss of ovarian function. The menopause occurs around a mean age of 50 years; virtually all women by the age of 55 years or so will have experienced the menopause. The changes in birth and mortality rates over the last century and, in particular, the profound decline in maternal mortality in developed countries have resulted in an average life expectancy of women of about 75 years; thus, most women will be postmenopausal for one third of their lifetime. Such women (9 million in England and Wales) now comprise about 18% of the total population. The aim of this review is to highlight current issues concerning the menopause and hormone replacement therapy, hence literature cited is not intended to be comprehensive but indicative. This article will briefly describe the epidemiology of the menopause, summarize the epidemiological data concerning hormone replacement therapy, the questions these raise and the implications these have concerning health in postmenopausal women.

Definitions of the menopause

A World Health Organization report on the menopause¹ suggested the following definitions.

1. The *menopause* should be defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity.
2. The *perimenopause* (or climacteric) should be used to include the period immediately prior to the menopause with endocrinological, biological and clinical features of approaching menopause, and at least the first year after the menopause.

3. The *postmenopause* should be defined as dating from the menopause, although it cannot be determined until after a period of 12 months of spontaneous amenorrhoea has been observed.

Though the diagnosis of menopause is based on clinical signs and symptoms, primarily amenorrhoea, and confirmed when necessary with assays for steroid hormones or gonadotrophins, the loss of ovarian function is the essential characteristic of menopause. Thus, a surgical menopause occurs after bilateral oophorectomy with or without hysterectomy, but would not include cessation of menstruation following a simple hysterectomy.

Age at menopause

The median age at menopause in most Western industrialized societies has been shown to be remarkably constant, around 50 years, though there is a wide range between 35–59 years or so around a slightly skewed normal distribution.^{2–4} Premature ovarian failure is associated with some rare clinical conditions such as galactosaemia or can be induced by radiation therapy or cytotoxic chemotherapy. Some exogenous factors can affect menopausal age: notably, women cigarette smokers have a menopause on average 1–2 years earlier than non-smokers; poor nutritional status is another.^{5–12}

Endocrine changes

During reproductive years, the preovulatory follicle and corpus luteum are the major source of sex steroids: oestradiol predominates, with smaller amounts of oestrone. Androgens, mainly androstenedione and testosterone, are also produced by stroma and theca. The most marked hormonal change following the menopause, with the loss of follicular units, is the 10–20-fold reduction in oestradiol levels. Other hormones, notably oestrone, androstenedione, testosterone and dehydroepiandrosterone also decrease markedly.^{13–15} Levels of follicle stimulating hormone (FSH) increase to 10–15 times the early follicular phase levels in

young women, while luteinizing hormone (LH) reaches a maximum three times higher about 2 years after the menopause. After the menopause, the major source of oestrogens is from peripheral conversion in adipose tissue of adrenal androgen precursors, notably androstenedione, to oestrogens, mainly oestrone: the amount of body fat is hence a major determinant of oestrogen levels in postmenopausal women.¹⁶⁻¹⁸

Hormone replacement therapy

The background

While the menopause can be viewed simply as part of normal ageing, others have argued that in the past most women did not live until menopausal age. Fertility generally decreases with age in mammals, but the evolutionary significance of the menopause is unclear. Thus, it has been suggested that the menopause is an oestrogen-deficient state which can be remedied by oestrogen replacement therapy, exemplified by such statements as those by Wilson below:

'The unpalatable truth must be faced that all postmenopausal women are castrates.'¹⁹

'... estrogen deficiency is as much a disease as thyroid, pancreatic or adrenal deficiency. No attempt will be made here to detail all of the unwholesome effects of this deficiency disease; a few will suffice, e.g. thinning of bones, dowager's hump, ugly body contours, flaccidity of the breast, and atrophy of the genitalia ... The estrogenic treatment of older women will inhibit osteoporosis and thus help to prevent fractures, as long as they continue healthful activities and appropriate diets. Breasts and genital organs will not shrivel. Such women will be much more pleasant to live with and will not become dull and unattractive.'²⁰

In contrast, others have argued that many of the conditions associated with the menopause largely reflect age-related changes which may be potentially modifiable by behavioural factors.^{21,22} The original indications for oestrogen replacement therapy were to treat clinical symptoms associated with the menopause such as hot flushes and sweats. However, with such enthusiastic early proponents of oestrogen replacement therapy as Wilson and others, by the early 1970s in the United States, large proportions of postmenopausal women (50% of women aged 55-64 and 30% of women aged 65-74 years in one population study²³) were using oestrogens, not just for symptomatic relief, but with the idea that oestrogen use promoted maintenance of youthfulness and health.

While animal and clinical data on the biological effects of oestrogens have long been available, the large numbers of postmenopausal women taking oestrogens enabled the conduct of epidemiological studies on the associations between oestrogen use and various conditions such as reproductive cancers, osteoporosis and cardiovascular disease in women in the general population. These studies, predominantly from the United States, have been appearing since the mid-1970s to the present, and findings have in turn stimulated more clinical and experimental studies to identify possible biological mechanisms.

Hormone replacement therapy and endometrial cancer

Of all the effects of oestrogen therapy, perhaps the best known is the increased risk of endometrial cancer. The first reports from case control studies of increased endometrial cancer associated with exogenous use appeared in the mid-1970s and there is little doubt from both numerous case control and more recently, prospective studies, that oestrogen use increases risk of endometrial cancer by three to over six fold.²⁴⁻²⁹ Significantly increased risk appears with a duration of around 3 years' use and its magnitude appears to be related to dose and duration of use. However, this risk seems to be more or less abolished by adding progestogen;³⁰⁻³² this has led to the widespread use of combined oestrogen and progestogen preparations.

Hormone replacement therapy and breast cancer

Oophorectomy has long been recognized to produce regression of breast cancer in women. However, the evidence for an increased risk of breast cancer associated with exogenous oestrogen use is much more equivocal.³³⁻³⁸ Early case control studies provided no consistent indication that exogenous oestrogen use increased breast cancer risk though some more recent studies have suggested increased breast cancer risk. Several reviews have examined this issue.³³⁻³⁵ Two possible explanations have been hypothesized for the inconsistent findings. Firstly, risk may be related to duration of use and early studies were more likely to have women who had taken oestrogen for shorter periods than later studies. It is likely that short duration oestrogen use does not increase risk of breast cancer: recent meta-analyses have indicated relative risks of around 1.00 associated with short-term use.³⁴ However, a meta-analysis which examined risk by duration of oestrogen use indicated a summary relative risk of 1.3 for women using oestrogens for 15 years or more compared to non-users.³⁵ Secondly, early studies included women who used mainly unopposed conjugated

oestrogens, but in later studies, women were more likely to be using a variety of different formulations including oestradiol compounds as well as opposed therapy. It is possible that such formulations may be associated with different risks of breast cancer.^{36–40} Notably, Bergkvist *et al.* reported from a prospective study of 23,244 women in Sweden that while overall, long-term use of oestrogens appeared to be associated with a slightly increased risk of breast cancer, no increase in risk was found after the use of conjugated oestrogens; oestradiol was associated with 1.8-fold increase in risk after more than 6 years use and risk of breast cancer was highest (4.4 after 6 years use or more) among women who took oestrogen and progestogen in combination for extended periods.³⁶ This observation is consistent with a hypothesis advanced by Key and Pike that progestogens may potentiate the effects of oestrogen in inducing breast cell mitosis and hence, increasing breast cancer risk.³⁹

If it is the case that risk of breast cancer associated with hormone replacement therapy is related to duration of use and/or is increased with oestradiol compounds or the addition of progestogens, this raises issues of concern about optimal formulations or duration of therapy. The current trend is towards increasing duration of hormone replacement therapy since the benefits in terms of fracture prevention would seem to require long term (at least 6–10 years' use), and there has been a proliferation of different hormonal formulations. Even a small increase in risk is possibly of greater concern since breast cancer is substantially commoner than endometrial cancer and generally perceived as a worse disease to suffer.

Hormone replacement therapy and osteoporosis

Numerous observational studies as well as controlled trials have indicated that oestrogen therapy in women can prevent bone mineral loss not only around the menopause, but even in women several years after menopause.^{41–46} This benefit for bone mineral density appears to be dose related and only seems to last for the duration of oestrogen therapy. The potential value that perimenopausal oestrogen use may have for preventing osteoporotic fractures, most of which occur after age 75 years, is still debatable since there are no long-term primary prevention trials. It has been argued that postponing bone loss even for a few years would be of value in reducing lifetime fracture risk. This would seem to be borne out by observational studies which do indicate up to a halving of fracture risk associated with oestrogen use.^{47–50} How long therapy needs to be continued in perimenopausal women to have a substantial impact on fractures is unclear but at least two case control studies of women with fracture indicate that duration of 5 years' use or

more is required before fracture risk is significantly decreased. It is not clear whether adding progestogens influences fracture risk.

Hormone replacement therapy and cardiovascular disease

The biggest potential public health impact of hormone replacement therapy is for cardiovascular disease, which is overwhelmingly the leading cause of mortality in women. Numerous case control and prospective studies have been reported, most recently reviewed by Meade and Berra.⁵¹ Only a few studies have suggested an adverse effect: of these the most notable are the data from the Framingham prospective study reported by Wilson documenting 1.9 relative risk for ischaemic heart disease and 2.3 for stroke.⁵² Most studies have consistently documented substantially reduced risks of coronary heart disease, of up to 60% in women who use oestrogen replacement therapy compared to non-users.^{53–60} Explanations for the inconsistencies include the unusual use of angina as an endpoint in the Framingham study, or the use of different preparations. Interestingly, where data are available, most notably from the largest prospective study, based on US nurses, reduction of risk appears to be more marked in current users compared to past users, and is not related to duration of therapy.⁵⁴ It is not clear how much the observed reduced risk in these studies is due to the selection bias of healthier women being more likely to be users of hormone replacement therapy, but the general consensus from the available evidence is that the cardioprotective effect of oestrogens is real.

The most plausible biological mechanism for the apparent protective effect of oestrogens on coronary heart disease risk is via lipid levels. Both observational and trial data have shown that oestrogens increase high density lipoprotein (HDL) cholesterol levels, which are beneficial for coronary heart disease;^{23,61–63} indeed, it has been suggested that oestrogen therapy might be first line treatment for hypercholesterolaemia. Little is known about the long-term effect of combined (oestrogen plus progestogen) therapy on coronary heart disease risk. Of concern, however, are observations that the addition of progestogens, in particular the more androgenic formulations such as norethisterone, reduces the HDL-cholesterol raising effect of oestrogens.⁶³ How much the suggested protective effect of oestrogen may be mediated through the effect on lipids and how much through other mechanisms, such as clotting factors,^{51,64} or vascular reactivity⁶⁵ is undetermined. The major uncertainty concerning the impact of hormone replacement therapy on coronary heart disease is what effect adding progestogen has.

The evidence for stroke is more equivocal;^{66–70}

this might be related to the fact that raised blood pressure rather than lipid profile is the main risk factor for stroke.

Long-term risks and benefits of hormone replacement therapy

Hormone replacement therapy is associated with considerable effects on conditions with major impact on the health of women: namely cardiovascular disease, cancer and osteoporosis. It is not surprising that, given the plethora of data about the various potential risks and benefits of hormone replacement therapy, that there has been little agreement about whom should be advised to take it, what sort of formulation and for how long. Several authors have argued that, as with any other medical intervention it is recognized that recommendations for use depend on an evaluation of the overall balance of adverse effects and benefits.^{69,70} This implies understanding not just the qualitative relationship between the intervention and various outcomes but also a quantitative assessment.

This can be illustrated by an example using data on British women to estimate the effect of hormone replacement therapy and based on the simplest assumptions. For this analysis, annual disease rates by 10 year age groups for women, were obtained from the Office of Population Censuses and

Surveys statistics for England and Wales. Breast, endometrial, coronary heart disease and stroke mortality rates were obtained from mortality statistics;⁷¹ since hip fracture mortality figures are unreliable, incidence rates were estimated using the Hospital Inpatient Enquiry;⁷² these hip fracture incidence rates are of the same order as those estimated by Boyce and Vessey.⁷³ Assuming that all women had been using hormone replacement therapy for 10 years, relative risks for each disease associated with hormone replacement therapy, either unopposed oestrogen or oestrogen plus progestogen were derived from data reviewed earlier.

Table I shows the estimated changes in annual rates by 10 year age category for various disease endpoints associated with hormone replacement therapy, either unopposed oestrogen or oestrogen with progestogen. This demonstrates how the overall impact of an intervention on any disease depends not just on the relative risk, but on the absolute rates of that disease; thus, a small percentage reduction in a common condition such as cardiovascular disease has a much greater numerical impact in the population than a large percentage change in risk for a rare condition such as endometrial cancer. In this model, we assume that adding progestogen to oestrogen abolishes the excess risk from endometrial cancer completely,

Table I Illustrative estimated changes in annual rates* by 10 year age group, England and Wales associated with hormone replacement therapy (HRT) unopposed oestrogen or combined with progestogen for 10 days a month, for 10 years.

	<i>IHD</i>	<i>Stroke</i>	<i>Breast cancer</i>	<i>Uterus cancer</i>	<i>Hip fracture</i>	<i>Net balance of events</i>
Estimated annual rates per 100,000 by age group						
45–54 years	30	17	62	2	18	
55–64 years	171	60	101	8	66	
65–74 years	600	243	135	16	231	
75+ years	2,419	1,938	259	34	1,480	
Unopposed oestrogen						
Relative risk	0.6	0.8	1.2	4.0	0.5	
Change in annual rate per 100,000 by age group						
45–54 years	–12	–3	+12	+8	–9	–4
55–64 years	–68	–12	+20	+32	–33	–61
65–74 years	–240	–49	+27	+64	–126	–324
75+ years	–968	–388	+52	+136	–740	–1908
Oestrogen with progestogen						
Relative risk	0.8	0.9	1.3	1.0	0.5	
Change in annual rate per 100,000 by age group						
45–54 years	–6	–2	+18	0	–9	–1
55–64 years	–34	–6	+30	0	–33	–43
65–74 years	–120	–24	+41	0	–126	–229
75+ years	–484	–194	+78	0	–740	–1340

*Ischaemic heart disease, cerebrovascular disease, breast cancer, endometrial cancer mortality rates from OPCS;⁷¹ hip fracture estimated incidence rates from HIPE data.⁷²

but reduces the cardiovascular benefit. Because cardiovascular disease contributes a much greater number of events compared to endometrial cancer, the effect of adding progestogen to oestrogen is to reduce the overall net benefit, since abolishing the excess risk from endometrial cancer is more than counterbalanced by the reduction of the benefit for cardiovascular disease which is small in relative, but large in absolute terms. The age categories illustrate how, even with fixed relative risk, the overall risk–benefit balance changes depending on the absolute rates of the various conditions. At younger ages, where rates of cardiovascular disease and fracture are low, overall the risk–benefit ratio is neutral; cardiovascular disease and fracture rates but not cancer rates rise exponentially with age such that at older ages, the risk–benefit ratio overwhelmingly favours hormone replacement therapy.

The estimates shown are compatible with observations from several epidemiological studies indicating lower all cause mortality in hormone replacement therapy users compared to non-users.^{56,60} However, this simple model is meant only to be illustrative, not definitive. Detailed cost–benefit analyses have been conducted elsewhere.^{74–76} This model is intended only to show how overall risk–benefit ratios depend on the absolute rates of the disease and are sensitive to small changes and hence cannot be universally applied: for example, in populations where absolute rates of cardiovascular disease and hip fracture may be low or reproductive cancer high, such as in certain age or ethnic groups, the balance of risk, and also the cost, to benefit will change substantially.

Hormone replacement therapy: current issues

The clinical use of hormone replacement therapy for specific relief of menopausal symptoms such as vaginitis or hot flushes is well accepted. The major debate concerning hormone replacement therapy is whether widespread general use should be encouraged as a policy in asymptomatic healthy postmenopausal women for prevention of osteoporosis and cardiovascular disease. While short-term trials indicate beneficial effects of oestrogens on intermediate variables such as bone mineral density and on lipid profiles, the assumption of longer term benefits for clinical endpoints such as fractures, heart attacks or strokes rest upon observational studies which may suffer from selection bias for healthy users. There are some anxieties about increased risk of reproductive cancers which may not entirely be resolved by the addition of progestogens. The major uncertainties are in the quantification of the overall long-term benefits and risks associated with prolonged use.

Questions concerning these uncertainties include the following:

1. *The type of hormone* There are now dozens of different preparations available but it is notable that the bulk of the epidemiological data indicating benefits and risks of oestrogens was based on preparations using conjugated equine oestrogens. Different oestrogen and progestogen formulations do not necessarily have identical actions, and it is not known how far these effects can be generalized to other oestrogens now being marketed. In at least one study, oestradiol compounds appeared to be more strongly associated with breast cancer risk. The major question concerns the addition of progestogens. The benefit of progestogens is to reduce the endometrial cancer risk. Progestogens do not appear to affect the benefits of oestrogens for osteoporosis. However, there is some evidence that some progestogens, particularly the androgenic formulations currently most commonly used, may negate the high density lipoprotein–cholesterol raising effect, and hence, cardiovascular protective effect of oestrogen therapy. There is also some concern that the addition of progestogens may potentiate breast cancer risk.

2. *Method of application* Different modes of hormonal application such as transdermal or depot preparations are now available. The resultant blood levels, as well as metabolic consequences of these may be quite different from the oral preparations on which the epidemiological data were based. While such preparations may be more effective for symptomatic treatment, there are only limited clinical studies with respect to the long-term effects, beneficial and otherwise, of these on osteoporosis, cardiovascular disease, and cancer.

3. *Duration of use* If the main aim is relief of perimenopausal symptoms, women are likely to continue for the length of time that provides such relief. However, if the main indication is to prevent osteoporosis, therapy may need to be continued for longer periods, possibly 6 years or substantially more to prevent fractures. The dilemma is that such long-term use may be associated with increasing risk of breast cancer.

Several prospective population studies, mostly in the United States, are continuing surveillance of women on postmenopausal hormone replacement therapy. A multicentre trial to compare the effects of different hormone formulations including unopposed oestrogens versus combined oestrogen and progestogen preparation on lipid profiles (PEPI) is currently under way in the United States. However, it is argued that long-term randomized controlled trials of hormone replacement therapy which have the capacity to examine the effects on clinical endpoints including mortality are required before we can feel entirely comfortable about recommending its use as a universal prophylactic therapy in asymptomatic women.

Currently, the bulk of the evidence indicates hormone replacement therapy appears to have considerable general benefits and few would argue that every postmenopausal woman should have the opportunity at least to consider hormone replacement therapy. However, individual women and their medical practitioners need to be clear about their main reasons for the use of hormone replacement therapy: whether for short term relief of symptoms or for longer term prophylaxis since the optimal formulations, mode of administration and duration of use may differ according to the main indication for therapy; as Barrett-Connor³³ suggests, ... 'choices must consider more than the possible prevention of one specific disease, but also issues of the individual woman's risk pattern, fears and quality of life.'

The menopause: epidemiological aspects

Despite abundant research on hormone replacement therapy, current knowledge about many questions concerning the menopause is still sparse. These questions include the incidence and frequency of menopause-related conditions in different populations, the role of endogenous sex hormones in the aetiology of symptoms and chronic diseases associated with the menopause and the role of exogenous factors which might influence either hormonal levels or the incidence of such menopause-related conditions. Hormone replacement therapy is only one dimension in a large range of factors which are only just beginning to be explored.

Epidemiological data suggest that the incidence of many of the conditions that we associate with the menopause, including both symptomatology and chronic diseases such as osteoporosis, vary widely between different populations and hence are not

necessarily inevitable consequences of the menopause. While comparisons of the frequency of vasomotor, psychological and gynaecological symptoms in different studies are difficult, due to different definitions and study methods, some researchers have attempted to use standardized ascertainment and criteria enabling cross-cultural comparisons. Night sweats, hot flushes and palpitations have been attributed to vasomotor instability, and are reported to affect approximately 75% of menopausal women.⁷⁷⁻⁷⁹ A Canadian study indicated a frequency of 65% of perimenopausal women reporting hot flushes at some time in the past.²² However, using identical methodology to the Canadian study, only 20% of the women in a Japanese survey reported hot flushes.⁸⁰ Psychological symptoms such as depression and tiredness reported affect 25% of perimenopausal women in the Netherlands⁸¹ but were documented only by 5-10% of Japanese women.⁸⁰ We do not know why such wide variation in symptoms occur, nor do we understand the specific mechanisms; in particular, the role of oestrogen deficiency is still debated.⁸²

Similarly, the importance of endogenous oestrogen levels in the aetiology of chronic disease is also unclear. Within populations, changing from pre- to postmenopausal status is associated with increased cardiovascular risk, independent of age.^{83,84} This suggests that low levels of oestrogens are associated with increased cardiovascular disease risk. However, data from the World Health Organisation⁸⁵ in Table II, which shows age-specific death rates for women by age group by selected causes of death in England and Wales, and Japan, also indicate that considerable variation exists in chronic diseases thought to be oestrogen related such as breast cancer and cardiovascular disease. Since Japanese women have generally lower oestrogen levels than Caucasian women,⁸⁶ the considerably lower cardio-

Table II Death rates per million, for women in England and Wales (E & W) 1989 and Japan 1988^{71,85}

Cause		Ages in years					
		25-34	35-44	45-54	55-64	65-74	75+
All causes	E & W	446	1,123	2,978	8,783	22,611	111,332
	Japan	432	918	2,147	4,859	13,504	66,758
All cancers (ICD 140-239)	E & W	149	612	1,705	4,221	7,677	15,138
	Japan	128	426	1,009	2,174	4,458	9,381
Breast (ICD 174)	E & W	36	234	617	1,012	1,345	2,593
	Japan	18	84	170	217	190	212
Cardiovascular disease (ICD 390-459)	E & W	43	159	599	2,723	9,969	57,486
	Japan	64	167	507	1,346	5,219	33,893
Ischaemic heart disease (ICD 410-414)	E & W	7	54	299	1,711	5,999	24,192
	Japan	4	12	50	198	961	5,019
Stroke (ICD 430-438)	E & W	19	66	165	601	2,431	19,380
	Japan	19	75	272	634	2,292	14,411

vascular disease rates in the Japanese cannot be explained by differences in oestrogen levels. Even within England and Wales, there have been large secular changes over the last 30 years⁸⁷ including a doubling of age-specific hip fracture rates.⁷³ These geographic and secular variations in many of the conditions traditionally associated with the menopause cannot be attributed to differences in use of hormone replacement therapy or endogenous oestrogen levels and suggest that, while the menopause may be a risk factor, there are other determinants which are likely to have a more profound influence.

Numerous exogenous factors such as diet, cigarette smoking habit and physical activity, which affect risk of chronic disease also influence endogenous sex hormone levels, but little is understood about the possible mechanisms. For example, high fat intakes have been associated with higher endogenous androgens or oestrogen levels, while a diet high in plant foods or increased physical activity is associated with lower oestrogen and increased sex hormone-binding globulin levels.^{86,88-90} Cigarette smoking habit has been shown to reduce oestrogen and increase androgen levels in postmenopausal women.⁹¹⁻⁹³ Oestrogen therapy not only, as expected, increases levels of circulating oestrogens but also has effects on other hormones including a decrease in endogenous androgens and increase in sex hormone-binding globulin and cortisol levels.⁹⁴

The work on tamoxifen provides an illustration of potential new areas for exploration. Tamoxifen is a competitive oestrogen inhibitor, initially used

in therapy of established breast cancer; trials of tamoxifen therapy for primary prevention of breast cancer in high-risk women are underway or being planned.⁹⁵ However, tamoxifen has also been documented to have some oestrogen-like agonistic activity, and is associated both with increasing high-density lipoprotein levels as well as increasing bone density.

While issues such as the long-term effects of tamoxifen are still debated, this has raised the possibility of other partial oestrogen agonists, which may have advantages without the disadvantages of oestrogen therapy. For example, phytoestrogens, found in plant foods, appear to have weak oestrogenic agonist as well as antagonist effects,⁹⁶ which may explain the observation that high soya bean intake is not only protective for breast cancer,⁹⁷ possibly through an anti-oestrogenic effect at the breast site, but also appears beneficial for cardiovascular risk through influencing lipids.

Optimum management of the menopause and the postmenopausal years will depend on identifying factors which influence the incidence of conditions associated with the menopause and their possible mechanisms. It is still not clear how far these conditions are due to oestrogen deficiency and can be remedied by hormone replacement therapy. However, the variations in postmenopausal health between different populations and profound changes over time indicate the potential for improvement, as well as several promising directions for research.

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