# Selección de Resúmenes de Menopausia

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## Hormone replacement therapy and cancer risks in perimenopausal women: A retrospective cohort study using a Japanese claims database

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Aim: Hormone replacement therapy (HRT) relieves menopausal syndromes but concerns regarding certain cancer risks remain. This study aimed to investigate cancer risks in perimenopausal women using HRT. Methods: Using a health care database in Japan, we compared breast cancer and other cancer risks in perimenopausal women who started HRT between January 2011 and October 2021 at age 45-54 years with that of women who did not use HRT. Women in the control group were selected by 1:4 exact matching on birth year, and followed from the same index time as their counterparts. Results: Data from 12 207 women in the exposure group and 48 828 age-matched women in the control group were analyzed. The median HRT duration was 16.1 (interquartile range, 9.9-28.0) months. Breast cancer risk was lower in the HRT group (adjusted hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.54-0.82). When stratified by age, breast cancer risk was lower in the HRT group who started HRT at age 45-49 years (adjusted HR, 0.54; 95% CI, 0.40-0.72). Estrogen-major HRT accounted for approximately one-third of HRT and uterine corpus cancer risk was increased in estrogen-major HRT (adjusted HR, 2.44; 95% CI, 1.56-3.81). Conclusions: Breast cancer risk in women starting HRT between 45 and 49 years is lower than that in the average population; this finding might be susceptible to unmeasured factors such as early menopause among HRT recipients. Unopposed estrogen therapy accounts for considerable proportion of HRT in Japan and it increases uterine corpus cancer.

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## The risk of long-term cardiometabolic disease in women with premature or early menopause: A systematic review and meta-analysis

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Background: Transition into menopause is associated with an increased risk of cardiovascular disease (CVD). However, it is unclear whether the association exists between premature menopause (defined as age at menopause 40 years) or early menopause (defined as age at menopause 40-45 years) and CVD or cardiovascular risk factors. The aim of this review was to comprehensively evaluate and meta-analyze the most reliable evidence about the relationship between menopausal age and the risk of long-term cardiometabolic disease. Methods: A comprehensive literature search of the PubMed, Web of Science, and Embase databases from inception to October 1, 2022, for titles and abstracts with a restriction to English language papers led to the discovery of the studies. Data are expressed as the Hazard Ratio (HR) with 95% confidence intervals (CI). The degree of heterogeneity was measured using the I-square (I 2) index. Results: 921,517 participants from 20 cohort studies published between 1998 and 2022 were considered. Compared to women with menopause at age >45 years, women with premature menopause (PM) or early menopause (EM) had a higher risks of type 2 diabetes (RR: 1.32, 95% CI: 1.08-1.62; RR: 1.11, 95% CI: 0.91-1.36, respectively), hyperlipidemia (RR: 1.21, 95% CI: 1.05-1.39; RR: 1.17, 95% CI: 1.02-1.33, respectively), coronary heart disease (RR: 1.52, 95% CI: 1.22-1.91; RR: 1.19, 95% CI: 1.07-1.32, respectively), stroke (RR: 1.27, 95% CI: 1.02-1.58; RR: 1.13, 95% CI: 0.97-1.32, respectively) and total cardiovascular event (RR: 1.36, 95% CI: 1.16-1.60; RR: 1.14, 95% CI: 0.97-1.35, respectively). No difference was found for hypertension in PM or EM women (RR: 0.98, 95% CI: 0.89-1.07; RR: 0.97, 95% CI: 0.91-1.04, respectively). Additionally, we also found that PM women, but not EM women, were linked with an increased risk of ischemic and hemorrhagic stroke. However, this is not in line with the conclusion that both PM and EM had a higher risk of total stroke. Conclusion: Women with PM or EM have a higher risk of developing long-term CVD, compared to women with menopause at age >45 years. Therefore, we recommend early lifestyle interventions (e.g., maintaining a healthy lifestyle) and medical treatments (e.g., timely initiation of menopausal hormone therapy) to decrease the risk of cardiometabolic disease in early or premature menopausal women.

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## Endometrial safety of low-dose vaginal estrogens

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It is estimated that up to 50% to 90% of postmenopausal women may experience genitourinary syndrome of menopause (GSM), which may have a detrimental impact on quality of life. One of the most effective modes of treatment of GSM is low-dose vaginal estrogens. Numerous studies have addressed the safety of these estrogens using endometrial biopsy and/or endometrial thickness on ultrasound. Based on these studies, the consensus is that low-dose vaginal estrogens do not substantially increase the risk of endometrial hyperplasia or cancer; however, the data are severely limited by short duration of follow-up. Although long-term trials are warranted, they are difficult to carry out, costly, and will not yield data for years. More immediate information regarding endometrial safety may be obtained from studies measuring endometrial tissue and serum concentrations of estradiol, estrone, and relevant equine estrogens after administration of different estrogen formulations and doses. This would allow us to understand better the metabolism of estrogens by the vagina and endometrium, and how much estrogen is reaching the endometrium. Here, we discuss metabolism, receptor binding, and signaling of estrogens in vaginal and endometrial tissue, and summarize the existing studies on the endometrial impact of low-dose vaginal estrogen treatment in postmenopausal women.

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## Research advances in crosstalk between muscle and bone in osteosarcopenia

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Osteosarcopenia is a burgeoning geriatric syndrome and a familiar disease among older individuals. It is characterized by reduced skeletal muscle mass and bone mineral density due to osteoporosis and sarcopenia. Its clinical manifestations include reduced physical performance and individuals becoming prone to falls during the aging process resulting in fractures and hospitalization, which seriously affects the quality of life of patients and increases the risk of death. Due to the aging social structure of the global population, the morbidity of osteosarcopenia is expected to continue to increase. Both muscle and bone belong to the motor system and originate from the mesoderm; therefore, sarcopenia and osteoporosis also share similar pathogenical factors, which influence and regulate each other. Studying the pathogenesis and treatment of osteosarcopenia is of great significance to improve the quality of life of patients. Therefore, the present study reviewed the research progress on sarcopenia and osteoporosis in osteosarcopenia from the standpoints of its definition, epidemiology, clinical manifestations and diagnosis, prevention and treatment.

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## Thyroid Dysfunction in Peri- and Postmenopausal Women—Cumulative Risks

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Background: Menopausal estrogen depletion increases the risk of cardiovascular disease and of osteoporosis. Both of these risks can be increased by thyroid dysfunction as well. This cumulation of risks will be presented. Methods: This review is based on publications retrieved by a selective search in PubMed (publications dated January 2000 to October 2022) for clinical trials, meta-analyses, randomized controlled trials, and systematic reviews containing the keywords "menopause and thyroid disorders." Results: Hyperthyroidism and menopause have similar symptoms. Decreased levels of thyroid stimulating hormone (TSH) are found in 8-10% of women in their fifth and sixth decades. TSH is decreased in 21.6-27.2% of women treated with L-thyroxine; decreased TSH is associated with increased cardiovascular mortality (hazard ratio [HR] 3.3, 95% confidence interval [CI]: [1.3; 8.0]) and increased mortality of all causes (HR 2.1; 95% CI: [1.2; 3.8]). Menopausal estrogen depletion accelerates the risk of cardiovascular disease and causes a disproportionate loss of bone density. In hyperthyroidism, bone density is decreased, and the risk of vertebral fractures is increased (HR 3.57; 95% CI: [1.88; 6.78]). Conclusion: The risk of heart diseases and bone diseases accelerates around the time of the menopause. Early detection and treatment of hyperthyroidism, which can further elevate the risk of both of these diseases is therefore required. In perimenopausal and postmenopausal women who are being treated for hypothyroidism, TSH suppression must be avoided. Thyroid dysfunction is common in women; its manifestations are less obvious with advancing age, making clinical diagnosis more difficult, yet it can have major deleterious effects. Thus, the indications for measuring TSH in perimenopausal women should be kept broad, rather than restrictive.

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## The impacts of menopausal hormone therapy on longer-term health consequences of ovarian hormone deficiency

B-K Yoon 1

This study on the longer-term health consequences of ovarian hormone deficiency (OHD) received the Henry Burger Prize in 2022. Osteoporosis, cardiovascular disease and dementia are major degenerative diseases that are also causally associated with OHD. Two randomized controlled trials (RCTs) revealed no significant difference in bone mineral density by adding alendronate to ongoing menopausal hormone therapy (MHT) or combining alendronate at MHT initiation. Another RCT pursuing the effects on fracture recurrence and total mortality in women with hip fracture disclosed that MHT with percutaneous estradiol gel (PEG) and micronized progesterone (MP4) was comparable to risedronate. Basic studies reported that 17β-estradiol exerted direct beneficial actions on vascular smooth muscle in cell proliferation, fibrinolysis and apoptosis. A fourth RCT showed that MP4 had a neutral impact on the PEG response of blood pressure and arterial stiffness. A fifth RCT suggested that the combination therapy of conjugated equine estrogen and MP4 was superior to tacrine in preserving activities in daily living in women with Alzheimer's disease. In addition, PEG plus MP4 attenuated cognitive decline in women with mild cognitive impairment in a sixth RCT. Finally, the all-cause mortality in recently menopausal women receiving MHT was updated using an adaptive meta-analysis of four RCTs.

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## Menopause and diabetes

S Cerdas Pérez 1

In the last 20 years, the prevalence of type 2 diabetes mellitus (T2DM) has tripled in adults aged 20-79 years, affecting more than 25% of people over 50 years of age and especially women during menopause. After the menopause transition, women gain weight, increasing abdominal fat and decreasing lean body mass, with a significant reduction in energy expenditure. Increased insulin resistance and hyperinsulinism characterize this period, aggravated by an increase in plasma proinflammatory cytokines and free fatty acids, and a state of relative hyperandrogenism. Previous recommendations systematically excluded women with T2DM from menopause hormone therapy (MHT); new evidence confirms that MHT significantly reduces the diagnosis of new-onset T2DM and may be beneficial in terms of glycemic control when used for menopause symptom management in patients with pre-existing T2DM. A comprehensive and individualized approach is considered the first line of management for women during this period, especially in T2DM patients or in women at risk of developing the disease. The objectives of this presentation are to review the etiopathogenic factors involved in the increased incidence of new cases of T2DM during menopause, the impact of menopause on T2DM and the role of MHT.

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## Optimizing sleep across the menopausal transition

F C Baker 1 2

Women frequently experience sleep disturbances, particularly night-time awakenings, as they transition menopause and enter postmenopause. Sleep is essential for optimal functioning and health. Persistent and distressing sleep disturbances across menopause can negatively impact daytime functioning and productivity, and increase risk for mental and physical health conditions. While multiple factors can disturb sleep, two unique factors in the context of menopause are vasomotor symptoms and the changing reproductive hormone environment. Vasomotor symptoms are associated with sleep disturbances and contribute significantly to awakenings and amount of time spent awake during the night. Even after accounting for vasomotor and depressive symptoms, lower estradiol and higher follicle stimulating hormone levels, indicative of menopause, are associated with sleep disturbance, particularly awakenings, suggesting that the hormone environment may directly affect sleep. Management strategies for clinically significant menopausal sleep disturbances include cognitive behavioral therapy for insomnia, which is effective and durable in treating menopausal insomnia. Hormone therapy alleviates sleep disturbances, particularly in the presence of disruptive vasomotor symptoms. Sleep disturbances have a significant impact on women's functioning and health, and there is a need for further research of the underlying mechanisms to advance effective preventative and treatment strategies that ensure optimal health and well-being of midlife women.

Lancet Diabetes Endocrinol. 2023 Mar 31;S2213-8587(23)00063-3. doi: 10.1016/S2213-8587(23)00063-3.

# The effect of monthly vitamin D supplementation on fractures: a tertiary outcome from the population-based, double-blind, randomised, placebo-controlled D-Health trial

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Background: Low serum 25-hydroxy vitamin D concentration is associated with increased fracture risk. It is uncertain whether vitamin D supplementation reduces fractures, or whether intermittent doses are harmful. We aimed to investigate if supplementing adults living in Australia with monthly doses of 60 000 international units (IU) vitamin D3 for 5 years or less altered the rate of fractures. Methods: We did a population-based, double-blind, randomised, placebo-controlled trial of oral vitamin D3 supplementation (60 000 IU per month) for up to 5 years in adults aged 60-84 years living in Australia. We randomly assigned (1:1) 21 315 participants to either vitamin D or placebo. We ascertained fractures through linkage with administrative datasets. The main outcome was total fractures. Additional outcomes were non-vertebral, major osteoporotic (hip, wrist, proximal humerus, and spine), and hip fractures. We excluded participants (989 [4·6%]) without linked data, and estimated hazard ratios (HRs) and 95% CIs using flexible parametric survival models. The trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12613000743763, and the trial intervention ended in February, 2020. Findings: Between Feb 14, 2014, and June 17, 2015, we recruited 21 315 participants. For the current analysis, we included 20 326 participants (vitamin D 10 154 [50·0%]; placebo 10 172 [50·0%]). 9295 (45·7%) of 20 326 participants were women and the mean age was 69·3 years (SD 5·5). Over a median follow-up of 5·1 years (IQR 5·1-5·1), 568 (5·6%) participants in the vitamin D group and 603 (5·9%) in the placebo group had one or more fractures. There was no effect on fracture risk overall (HR 0·94 [95% CI 0·84-1·06]), and the interaction between randomisation group and time was not significant (p=0·14). However, the HR for total fractures appeared to decrease with increasing follow-up time. The overall HRs for non-vertebral, major osteoporotic, and hip fractures were 0·96 (95% CI 0·85-1·08), 1·00 (0·85-1·18), and 1·11 (0·86-1·45), respectively. Interpretation: These findings do not support concerns that bolus doses of vitamin D administered monthly increase fracture risk. Long-term supplementation might reduce the incidence of total fractures, but additional research is needed to clarify this effect.