# Selección de Resúmenes de Menopausia

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## Age at Menopause and Trajectories of Multimorbidity Progression to Mortality: A Multi-State Analysis of UK Biobank Data

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Objective: To investigate whether age at menopause is associated with the trajectory of multimorbidity progression. Design: A retrospective cohort study. Setting: The UK Biobank. Population: 121 017 postmenopausal women aged 40-69 years with complete baseline and menopausal data. Methods: Cox proportional hazards models were used to explore the associations between menopausal age and both multimorbidity and mortality. Multi-state models were further employed to evaluate the association of menopausal age with transitions from a health state to the first chronic disease (FCD), to multimorbidity, and to mortality from each state. Main outcome measures: Multimorbidity (defined as ≥ 2 of 35 chronic conditions) and mortality. Results: Over a median follow-up period of 8.6 years, 86 821 women developed the FCD, 42237 multimorbidity, and 10 527 participants died. In the multi-state models analysis, from health to FCD, compared with women who experienced menopause after age 50 years, the risks increased by 32%, 14%, and 3% among women with premature, early, and relatively early menopause, respectively (HR = 1.32, 95% CI: 1.28-1.36; HR = 1.14, 95% CI: 1.11-1.17; HR = 1.03, 95% CI: 1.01-1.05). Similarly, for the transition from FCD to multimorbidity, the risks increased by 22% (HR = 1.22, 95% CI: 1.17-1.27), 13% (HR = 1.13, 95% CI: 1.09-1.16), and 6% (HR = 1.06, 95% CI: 1.03-1.08), respectively. Conclusions: Earlier menopause was associated with an increased risk of multimorbidity and mortality, mainly affecting two trajectories, from health to FCD and FCD to multimorbidity.

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## Migraine across the menopausal transition and beyond: A narrative review

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Background: Migraine is a neurologic disorder that disproportionately affects women and undergoes important changes across the menopausal transition. Estrogen fluctuations contribute to migraine expression and underlie the 3:1 female-to-male prevalence. Perimenopause, marked by hormonal variability and rising cardiometabolic risk, presents unique diagnostic and therapeutic challenges. Despite its high prevalence, evidence specific to perimenopausal and postmenopausal women remains limited. Objective: This review synthesizes current evidence on the epidemiology, pathophysiology, and management of migraine across the menopausal transition, with attention to hormone therapy, comorbidities, and emerging treatments. Methods: We conducted a narrative review of clinical and translational studies published within the past 5 years, supplemented by seminal mechanistic, epidemiologic, and guideline-defining studies published earlier. Relevant guideline statements from neurology, gynecology, and cardiovascular societies were also incorporated. Results: Unstable estradiol and progesterone levels during perimenopause can worsen migraine frequency and predictability. Migraine without aura often improves after menopause, whereas migraine with aura tends to persist and independently increases the risk of ischemic stroke and other vascular events. Midlife comorbidities-including vasomotor symptoms, sleep disturbance, mood disorders, and metabolic disease-further complicate management. Menopausal hormone therapy has variable effects. Oral estrogen, particularly at higher doses, may worsen migraine and elevate vascular risk, especially in women with aura. In contrast, low-dose transdermal estrogen-recommended by the North American Menopause Society-appears safer and better tolerated. Continuous progestogen regimens may reduce withdrawal-related attacks compared with cyclic regimens. Nonhormonal options, particularly selective norepinephrine reuptake inhibitors, may be considered when vasomotor symptoms coexist, whereas migraine-specific prevention should follow established evidence-based therapies. Traditional migraine therapies (triptans, NSAIDs, beta-blockers, topiramate, antidepressants) remain central but require tailoring to vascular, bone, and metabolic health. Newer agents-including calcitonin gene-related peptide monoclonal antibodies, gepants, and ditans-offer effective, non-vasoconstrictive alternatives, especially for women with cardiovascular contraindications. Conclusions: Migraine during the menopausal transition reflects the interplay between hormonal dynamics and systemic health. Management requires balancing efficacy with vascular and metabolic safety while incorporating patient preferences. Evidence gaps include

the lack of trials stratified by menopausal stage or migraine subtype. Multidisciplinary, menopause-informed care and prospective studies are needed to optimize outcomes in this population.

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## Loss of ovarian function and estrogen therapy remodel the brain's synaptic and metabolic proteome

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Menopause is linked to cognitive decline and reduced brain metabolism, while estrogen (E2) therapy has been shown to mitigate these effects. Understanding the molecular mechanisms by which ovarian hormones and E2 influence neuroprotection is essential for developing strategies to maintain brain health in women. In this study, we examined how the loss of ovarian hormones, with or without E2 treatment, affects the brain proteome and mitochondrial energy production in aged female C57BL/6J mice (36-40 weeks). The mice underwent sham or ovariectomy (OVX) surgery and were fed a high-fat diet for 10 weeks; six weeks after surgery, OVX mice received either sesame oil or E2 treatment for four weeks. Proteomic analysis of brain homogenates revealed 4,992 proteins regulated by E2, with pathway analysis showing increased signaling proteins related to synaptogenesis. OVX reduced proteins involved in synaptic function, branched-chain amino acid and ketone metabolism, the TCA cycle, and oxidative phosphorylation (Complexes I, IV, and V), while E2 restored protein expression within these pathways. Despite alterations in OxPhos proteins, basal and state 3 mitochondrial respiration remained unchanged, although notable impairments in Complex IV enzymatic activity were apparent in OVX, which were partially reversed by E2 treatment. Overall, these results indicate that E2 supports brain health by maintaining proteins crucial for synaptic integrity and metabolism, while partially offsetting the functional decline in mitochondrial bioenergetics associated with menopause.

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## Menopausal hormone therapy in breast cancer survivors: A review

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The use of menopausal hormone therapy (MHT) by breast cancer survivors remains controversial. While MHT is effective for the management of menopausal symptoms in the general population, its safety after breast cancer is uncertain due to limited and heterogeneous data. Menopausal symptoms, including vasomotor and genitourinary complaints, can significantly impair quality of life and adherence to therapy. Non-hormonal treatments are the first-line option but are often insufficient. Evidence suggests that low-dose vaginal estrogen can relieve genitourinary symptoms with minimal systemic absorption and without clear evidence of increased recurrence risk. In contrast, systemic MHT remains highly debated, with conflicting data confounded by differences in study design, hormone formulation, and patient selection. Management should therefore be individualized, balancing symptom severity, recurrence risk, and patient preferences. Until more definitive data are available, multidisciplinary collaboration and shared decision-making remain essential in optimizing quality of life while minimizing oncologic risk.

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## Menopausal hormone use after hysterectomy in endometriosis: a Finnish register-based study

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Objective: This study aimed to examine the frequency and type of menopausal hormone therapy (MHT) use after hysterectomy among women with surgically diagnosed endometriosis. Method: A retrospective register-based cohort study identified women with a first surgical diagnosis of endometriosis and a reference cohort using Finnish national registries. This study included women aged ≤45 years with hysterectomy and bilateral oophorectomy, and women >45 years with hysterectomy performed between 1996 and 2018. Women with a history of thrombosis, breast cancer or gynecological cancer were excluded. MHT use was identified from national reimbursement registry until the end of 2019. Results: Altogether 11,365 women were included: 1748 women aged ≤45 years and 9617 aged >45 years. Among women with endometriosis, 94.3% (aged ≤45 years) and 73.1% (aged >45 years) used MHT postoperatively, compared with 81.8% and 51.5% in the reference cohort ($p < 0.001$). Estrogen-only therapy was the most commonly used MHT, but the use of combined estrogen-progestin therapy increased significantly ($p < 0.001$). Conclusion: MHT use was very common in women with endometriosis. The shift toward combined therapy reflects evolving international guidance.

The high rate of MHT use underscores the need for studies assessing its long-term outcomes in women with endometriosis.

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## Gonadotropins Across the Lifespan: Their role in the Neurodevelopment-Neurodegeneration Continuum

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Gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), mediate critical reproductive functions via the hypothalamus-pituitary-gonadal axis. Their levels fluctuate across the lifespan, particularly during puberty and menopause, and across the menstrual cycle. In addition to peripheral expression, gonadotropin receptors are widely expressed in the brain, notably in memory-associated regions such as the hippocampus and cortex. Alterations in FSH and LH during reproductive transitions correlate with structural and functional brain changes. Puberty disorders, including central precocious puberty (CPP) and congenital hypogonadotropic hypogonadism (CHH), show altered gray and white matter and functional connectivity in the default mode network (DMN), which supports memory and is disrupted early in Alzheimer's disease (AD). Although preclinical evidence implicates gonadotropins in amyloid and tau pathology, studies of attention and memory have yielded inconsistent results. However, reproductive disorders such as primary ovarian insufficiency (POI) and polycystic ovary syndrome (PCOS) are associated with deficits in cognitive performance, altered DMN dynamics, and increased AD risk. Menopause, characterized by marked gonadotropin elevation, is also accompanied by alterations in brain structure, connectivity, amyloid and tau deposition, and cognition, with associations with FSH and LH that are underexplored. This review synthesizes a broad range of basic and clinical evidence across reproductive transitions and disorders, highlighting shared and distinct mechanisms by which gonadotropins influence brain development, aging, and AD risk, and suggesting directions for future research.

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## The Role of Collagen Supplementation in Bone Metabolism and Structure: A Scoping Review

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Objective: To evaluate the current literature on the role of collagen peptide supplementation in bone health, focusing on changes in bone turnover markers (BTMs) and bone mineral density (BMD). Data sources: A search was conducted following PRISMA guidelines in the databases Academic Search Premier, APA PsychInfo, CINAHL Plus, GreenFILE, MEDLINE, and SPORTDiscus. Keywords included "collagen supplementation," "bone turnover," and "bone structure." Studies published between January 2000 and March 2024 were included if they involved human subjects, oral collagen supplementation, and skeletal-related outcomes (BTMs or BMD). Risk of bias was assessed using the modified Physiotherapy Evidence Database (PEDro) scale. Main results: Fifteen studies met the inclusion criteria. Collagen supplementation was associated with improvements in BTMs such as procollagen type I N-terminal propeptide and C-terminal telopeptide of type I collagen, as well as increases in BMD at whole body, femoral neck, and lumbar spine sites, particularly in postmenopausal women. However, neutral findings and substantial heterogeneity in study design, population characteristics, and dosing protocols were also observed. Conclusions: Collagen supplementation shows promise for supporting bone health, particularly in postmenopausal women, but the evidence remains inconsistent. Future research should address these gaps by focusing on premenopausal populations, standardizing dosing protocols, and exploring broader orthopedic applications, such as reducing stress fractures and enhancing recovery from musculoskeletal injuries.

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## Oxidative Stress and Antioxidant Status in Premenopausal and Postmenopausal Women: A Comparative Cross-sectional Study

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Background: Menopause is a physiological transition associated with hormonal changes and age-related systemic alterations. Emerging evidence suggests that oxidative balance may be disrupted during this period, although the extent and pattern of oxidative stress (OS) in menopausal women remain incompletely defined.Aim: To compare OS markers and antioxidant parameters between premenopausal and postmenopausal women. Methods: This cross-sectional study

included 100 women: 50 premenopausal (aged 18-45 years) and 50 postmenopausal (aged 45-65 years). Serum levels of arylesterase (ARE), paraoxonase (PON), thiols, total antioxidant status (TAS), and total oxidant status were measured using spectrophotometric methods. The OS index was calculated from total oxidant and antioxidant status. Statistical analysis was performed using SPSS version 25.0, with $P < 0.05$ considered statistically significant. Results: Total oxidant status and OS index were significantly higher in postmenopausal women compared with premenopausal women. In contrast, antioxidant parameters-including PON, ARE, TAS, and thiol levels-were significantly lower in the postmenopausal group ($P < 0.05$). Conclusion: Menopause is associated with increased OS and reduced antioxidant capacity. This altered redox balance may contribute to the heightened risk of age-related conditions observed in postmenopausal women and highlights the potential value of monitoring OS markers during the menopausal transition.