# Selección de Resúmenes de Menopausia

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Juan Enrique Blümel. Departamento Medicina Sur. Universidad de Chile

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## Age and gender effects on the prevalence of poor sleep quality in the adult population.

Madrid-Valero JJ, Martínez-Selva JM, Ribeiro do Couto B, Sánchez-Romera JF, Ordoñana JR.

OBJECTIVE: Sleep quality has a significant impact on health and quality of life and is affected, among other factors, by age and sex. However, the prevalence of problems in this area in the general population is not well known. Therefore, our objective was to study the prevalence and main characteristics of sleep quality in an adult population sample. METHODS: 2,144 subjects aged between 43 and 71 years belonging to the Murcia (Spain) Twin Registry. Sleep quality was measured by self-report through the Pittsburgh Sleep Quality Index (PSQI). Logistic regression models were used to analyse the results. RESULTS: The prevalence of poor sleep quality stands at 38.2%. Univariate logistic regression analyses showed that women were almost twice as likely as men (OR: 1.88; 95% confidence interval [95%CI]: 1.54 to 2.28) to have poor quality of sleep. Age was directly and significantly associated with a low quality of sleep (OR: 1.05; 95%CI: 1.03 to 1.06). CONCLUSIONS: The prevalence of poor sleep quality is high among adults, especially women. There is a direct relationship between age and deterioration in the quality of sleep. This relationship also appears to be more consistent in women.

**Int J Environ Res Public Health. 2016 Jul 26;13(8). pii: E755.**

## Olives and Bone: A Green Osteoporosis Prevention Option.

Chin KY, Ima-Nirwana S.

Skeletal degeneration due to aging, also known as osteoporosis, is a major health problem worldwide. Certain dietary components confer protection to our skeletal system against osteoporosis. Consumption of olives, olive oil and olive polyphenols has been shown to improve bone health. This review aims to summarize the current evidence from cellular, animal and human studies on the skeletal protective effects of olives, olive oil and olive polyphenols. Animal studies showed that supplementation of olives, olive oil or olive polyphenols could improve skeletal health assessed via bone mineral density, bone biomechanical strength and bone turnover markers in ovariectomized rats, especially those with inflammation. The beneficial effects of olive oil and olive polyphenols could be attributed to their ability to reduce oxidative stress and inflammation. However, variations in the bone protective, antioxidant and anti-inflammatory effects between studies were noted. Cellular studies demonstrated that olive polyphenols enhanced proliferation of pre-osteoblasts, differentiation of osteoblasts and decreased the formation of osteoclast-like cells. However, the exact molecular pathways for its bone health promoting effects are yet to be clearly elucidated. Human studies revealed that daily consumption of olive oil could prevent the decline in bone mineral density and improve bone turnover markers. As a conclusion, olives, olive oil and its polyphenols are potential dietary interventions to prevent osteoporosis among the elderly.

**J Clin Endocrinol Metab. 2016 Jul 29:jc20161828. [Epub ahead of print]**

## Menopause, reproductive life, hormone replacement therapy and bone phenotype at age 60-64: a British birth cohort.

Kuh D, Muthuri S, Cooper R, Moore A, MacKinnon K, Cooper C, Adams JE, Hardy R, Ward KA.

CONTEXT: Previous studies of menopausal age and length of reproductive life on bone are limited by retrospective reproductive histories, being cross sectional, or lacking gold standard bone technologies, or information on hormone replacement therapy (HRT) or surgical treatment. OBJECTIVE: To investigate age at menopause, length of reproductive life and HRT use in relation to volumetric and areal bone mineral density (vBMD, aBMD), bone size and strength in women aged 60-64. DESIGN: A birth cohort study followed for 64 years with prospective measures of age at menarche and menopause and monthly HRT histories. SETTING: England, Scotland, Wales Participants: 848 women with known type of menopause and bone measures at 60-64 years Main outcome measures: Peripheral quantitative computed tomography (pQCT) measurements of the distal radius total and trabecular vBMD; diaphyseal

radius total and medullary cross sectional area, cortical vBMD and polar strength strain index (SSI); dual energy x-ray absorptiometry (DXA) measurments of aBMD at the lumbar spine and total hip. RESULTS: A ten year increase in age at natural (but not surgical) menopause was associated with 8.2% (95% CI: 1.3,15.1%, p=.02) greater trabecular vBMD and a 6.0% (95% CI 0.51,11.5%, p=.03) greater total vBMD; findings were similar for length of reproductive life. A ten year difference in HRT use was associated with a 6.0% (95% CI 2.6%,9.3%, p<.001) greater polar SSI and a 0.9% (95% CI 0.4%, 1.5%, p=.001) greater cortical vBMD. These estimates changed little on adjustment. Estimates for aBMD were consistent with those for pQCT. CONCLUSIONS: The positive effects on trabecular vBMD of later natural menopause and longer reproductive life persisted into early old age. HRT use was associated with greater radius cortical vBMD and polar SSI, and spine aBMD.

**J Am Heart Assoc. 2016 Jul 28;5(8). pii: e003769. doi: 10.1161/JAHA.116.003769.**

## Association of Age at Menopause With Incident Heart Failure: A Prospective Cohort Study and Meta-Analysis.

Appiah D, Schreiner PJ, Demerath EW, Loehr LR, Chang PP, Folsom AR.

Background: Early age (<45 years) at menopause has been postulated to be associated with increased cardiovascular disease risk; however, evidence of its relation with heart failure (HF) incidence is limited. We examined whether age at menopause is associated inversely with HF incidence in the Atherosclerosis Risk In Communities (ARIC) study and summarized all existing data in a meta-analysis. Methods and results: In ARIC, data were obtained from 5629 postmenopausal women (mean age 56 years, 26% with bilateral oophorectomy) without HF. During a median follow-up of 21.4 years, 965 incident HF events occurred. In a Cox regression model adjusted for reproductive health and HF risk factors, the hazard ratios for incident HF across categories of age at menopause (<45, 45-49, 50-54, and ≥55 years) were 1.32, 1.17, 1.00 (referent), and 1.12, respectively. Compared with women with later onset of menopause (aged ≥45 years), those with early menopause had elevated HF risk (hazard ratio 1.20, 95% CI 1.01-1.43). For the meta-analysis, we searched Medline and Embase for articles published through December 2015 that prospectively evaluated age at menopause and HF risk. Summarized estimates from the 3 included studies (3568 events) showed higher HF risk among women with early menopause compared with those with later menopause (hazard ratio 1.33, 95% CI 1.15-1.53). Conclusions: These results provided evidence that early age at menopause is associated with a modestly greater risk of HF. Identification of women with early menopause offers a window of opportunity to implement interventions that will improve overall cardiovascular health during the postmenopausal years.

**Menopause. 2016 Jul 25. [Epub ahead of print]**

## Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy: a Finnish nationwide comparative study.

Mikkola TS, Savolainen-Peltonen H, Tuomikoski P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O.

OBJECTIVE: Data are controversial on the impact of postmenopausal hormone therapy (HT) on breast cancer mortality. We analyzed nationwide Finnish data on breast cancer mortality risk in women using HT consisting of estradiol-only therapy (ET) or estrogen-progestogen therapy (EPT). METHODS: In total, 489,105 women using HT in 1994 to 2009, traced from the nationwide reimbursement register, were followed from the HT initiation (3.3 million cumulative exposure years) to breast cancer death (n=1,578 women). The observed deaths were compared with those in the age-standardized background population. RESULTS: The breast cancer mortality risk was reduced in all HT users with exposure for at most 5 years (standardized mortality ratio 0.56; CI 0.52-0.60), more than 5 to 10 years (0.46; 0.41-0.51), or more than 10 years (0.62; 0.56-0.68). A significantly larger risk reduction was detected in the 50 to 59 years age group (0.33; 0.29-0.37) compared with 60 to 69 (0.64; 0.59-0.70) or 70 to 79 (0.78; 0.69-0.87) years age groups. The death risk reductions in ET users tended to be larger in all age groups compared with EPT users, with a significant difference only in the 70 to 79 years age group (0.66; 0.57-0.76 vs 0.88; 0.77-1.00). The age at HT initiation, regardless whether ET or EPT, showed no association with breast cancer mortality. CONCLUSIONS: In the Finnish unselected population, breast cancer is fatal in 1 of 10 patients. Our data imply that this risk is prevalent in 1 of 20 patients with history of HT use. This is an important message for women considering or already using HT.

**Menopause. 2016 Jul 25. [Epub ahead of print]**

## Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Women's Health Initiative.

Shadyab AH, Macera CA, Shaffer RA, Jain S, Gallo LC, Gass ML, Waring ME, Stefanick ML, LaCroix AZ.

OBJECTIVE: The aim of the present study was to investigate associations between reproductive factors and survival to age 90 years. METHODS: This was a prospective study of postmenopausal women from the Women's Health Initiative recruited from 1993 to 1998 and followed until the last outcomes evaluation on August 29, 2014. Participants included 16,251 women born on or before August 29, 1924 for whom survival to age 90 during follow-up was ascertained. Women were classified as having survived to age 90 (exceptional longevity) or died before age 90. Multivariable logistic regression models were used to evaluate associations of ages at menarche and menopause (natural or surgical) and reproductive lifespan with longevity, adjusting for demographic, lifestyle, and reproductive characteristics. RESULTS: Participants were on average aged 74.7 years (range, 69-81 y) at baseline. Of 16,251 women, 8,892 (55%) survived to age 90. Women aged at least 12 years at menarche had modestly increased odds of longevity (odds ratio [OR], 1.09; 95% CI, 1.00-1.19). There was a significant trend toward increased longevity for later age at menopause (natural or surgical; Ptrend=0.01), with ORs (95% CIs) of 1.19 (1.04-1.36) and 1.18 (1.02-1.36) for 50 to 54 and at least 55 compared with less than 40 years, respectively. Later age at natural menopause as a separate exposure was also significantly associated with increased longevity (Ptrend=0.02). Longer reproductive lifespan was significantly associated with increased longevity (Ptrend=0.008). The odds of longevity were 13% (OR 1.13; 95% CI, 1.03-1.25) higher in women with more than 40 compared with less than 33 reproductive years.

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## The impact of depot medroxyprogesterone acetate on fracture risk: a case-control study from the UK.

Kyvernitakis I, Kostev K, Nassour T, Thomasius F, Hadji P.

INTRODUCTION: DMPA has been associated with impaired bone mineral acquisition during adolescence and accelerated bone loss in later life. We performed this large population-based study to assess the association between use of DMPA or combined oral contraceptives and the incident risk of fracture. METHODS: We identified 4189 women between 20 and 44 years of age with a first-time fracture diagnosis, matched them with 4189 random controls using the Disease Analyzer database and investigated the relation with DMPA exposure. RESULTS: Overall, 11 % of the fracture cases and 7.7 % of the controls had DMPA use recorded. The adjusted OR for developing a fracture in patients with current use of DMPA compared to non-users was 0.97 (95 % CI 0.51-1.86), 2.41 (95 % CI 1.42-4.08), and 1.46 (95 % CI 0.96-2.23) for 1-2, 3-9, and ≥10 prescriptions, respectively. The adjusted OR for developing a fracture in patients with past use of DMPA compared to non-users was 0.96 (95 % CI 0.73-1.26), 1.14 (95 % CI 0.86-1.51), and 1.55 (95 % CI 1.07-2.27) for 1-2, 3-9, and ≥10 prescriptions, respectively. The highest fracture risk was identified in young patients less than 30 years with longer DMPA exposure (≥10 prescriptions; OR 3.04, 95 % CI 1.36-6.81), as well as in patients in the late reproductive years with past use of DMPA (OR 1.72, 95 % CI 1.13-2.63). CONCLUSIONS: Our results indicate that DMPA exposure is associated with increased fracture risk and may have negative effects on bone metabolism, resulting in impaired bone mineral acquisition during adolescence and accelerated bone loss in adult life.

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## Menopause accelerates biological aging.

Levine ME, Lu AT, Chen BH, Hernandez DG, Singleton AB, Ferrucci L, Bandinelli S, Salfati E, Manson JE, et al.

Although epigenetic processes have been linked to aging and disease in other systems, it is not yet known whether they relate to reproductive aging. Recently, we developed a highly accurate epigenetic biomarker of age (known as the "epigenetic clock"), which is based on DNA methylation levels. Here we carry out an epigenetic clock analysis of blood, saliva, and buccal epithelium using data from four large studies: the Women's Health Initiative (n = 1,864); Invecchiare nel Chianti (n = 200); Parkinson's disease, Environment, and Genes (n = 256); and the United Kingdom Medical Research Council National Survey of Health and Development (n = 790). We find that increased epigenetic age acceleration in blood is significantly associated with earlier menopause (P = 0.00091), bilateral oophorectomy (P

= 0.0018), and a longer time since menopause (P = 0.017). Conversely, epigenetic age acceleration in buccal epithelium and saliva do not relate to age at menopause; however, a higher epigenetic age in saliva is exhibited in women who undergo bilateral oophorectomy (P = 0.0079), while a lower epigenetic age in buccal epithelium was found for women who underwent menopausal hormone therapy (P = 0.00078). Using genetic data, we find evidence of coheritability between age at menopause and epigenetic age acceleration in blood. Using Mendelian randomization analysis, we find that two SNPs that are highly associated with age at menopause exhibit a significant association with epigenetic age acceleration. Overall, our Mendelian randomization approach and other lines of evidence suggest that menopause accelerates epigenetic aging of blood, but mechanistic studies will be needed to dissect cause-and-effect relationships further.

**Syst Rev. 2016 Jul 26;5(1):121. doi: 10.1186/s13643-016-0294-5.**

## Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis.

Asi N, Mohammed K, Haydour Q, Gionfriddo MR, Vargas OL, Prokop LJ, Faubion SS, Murad MH.

BACKGROUND: Use of menopausal hormonal therapy (MHT)-containing estrogen and a synthetic progestin is associated with an increased risk of breast cancer. It is unclear if progesterone in combination with estrogen carries a lower risk of breast cancer. Limited data suggest differences between progesterone and progestins on cardiovascular risk factors, including cholesterol and glucose metabolism. Whether this translates to differences in cardiovascular outcomes is uncertain. We conducted a systematic review and meta-analysis to synthesize the existing evidence about the effect of progesterone in comparison to synthetic progestins, each in combination with estrogens, on the risk of breast cancer and cardiovascular events. METHODS: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus through 17 May 2016 for studies that enrolled postmenopausal women using progesterone vs. synthetic progestins and reported the outcomes of interest. Study selection and data extraction were performed by two independent reviewers. Meta-analysis was conducted using the random effects model. RESULTS: We included two cohort studies and one population-based case-control study out of 3410 citations identified by the search. The included studies enrolled 86,881 postmenopausal women with mean age of 59 years and follow-up range from 3 to 20 years. The overall risk of bias of the included cohort studies in the meta-analysis was moderate. There was no data on cardiovascular events. Progesterone was associated with lower breast cancer risk compared to synthetic progestins when each is given in combination with estrogen, relative risk 0.67; 95 % confidence interval 0.55-0.81.
CONCLUSIONS: Observational studies suggest that in menopausal women, estrogen and progesterone use may be associated with lower breast cancer risk compared to synthetic progestin.

**Adv Pharmacol. 2016;77:307-60. doi: 10.1016/bs.apha.2016.05.003. Epub 2016 Jun 29.**

## Estrogens and Coronary Artery Disease: New Clinical Perspectives.

Meyer MR, Barton M.

In premenopausal women, endogenous estrogens are associated with reduced prevalence of arterial hypertension, coronary artery disease, myocardial infarction, and stroke. Clinical trials conducted in the 1990s such as HERS, WHI, and WISDOM have shown that postmenopausal treatment with horse hormone mixtures (so-called conjugated equine estrogens) and synthetic progestins adversely affects female cardiovascular health. Our understanding of rapid (nongenomic) and chronic (genomic) estrogen signaling has since advanced considerably, including identification of a new G protein-coupled estrogen receptor (GPER), which like the "classical" receptors ERα and ERβ is highly abundant in the cardiovascular system. Here, we discuss the role of estrogen receptors in the pathogenesis of coronary artery disease and review natural and synthetic ligands of estrogen receptors as well as their effects in physiology, on cardiovascular risk factors, and atherosclerotic vascular disease. Data from preclinical and clinical studies using nonselective compounds activating GPER, which include selective estrogen receptor modulators such as tamoxifen or raloxifene, selective estrogen receptor downregulators such as Faslodex™ (fulvestrant/ICI 182,780), vitamin B3 (niacin), green tea catechins, and soy flavonoids such as genistein or resveratrol, strongly suggest that activation of GPER may afford therapeutic benefit for primary and secondary prevention in patients with or at risk for coronary artery disease. Evidence from preclinical studies suggest similar efficacy profiles for selective small molecule GPER agonists such as G-1 which are devoid of uterotrophic activity. Further clinical research in this area is warranted to provide opportunities for future cardiovascular drug development.