



## Selección de Resúmenes de Menopausia

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### **Do sarcopenia and/or osteoporosis increase the risk of frailty? A 4-year observation of the second and third ROAD study surveys.**

Yoshimura N, Muraki S, Oka H, Iidaka T, Kodama R, Horii C, Kawaguchi H, Nakamura K, Akune T, Tanaka S.

In this 4-year follow-up study including 1083 subjects ( $\geq 60$  years), the prevalence of frailty was estimated to be 5.6%; osteoporosis was found to be significantly associated with frailty. Moreover, the presence of both osteoporosis and sarcopenia increased the risk of frailty compared to the presence of osteoporosis or sarcopenia alone.

**INTRODUCTION:** This study aims to examine the contribution of sarcopenia and osteoporosis to the occurrence of frailty using 4-year follow-up information of a population-based cohort study. **METHODS:** The second survey of the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study was conducted between 2008 and 2010; 1083 subjects (aged  $\geq 60$  years, 372 men, 711 women) completed all examinations on frailty, sarcopenia, and osteoporosis, which were defined using Fried's definition, Asian Working Group for Sarcopenia criteria, and WHO criteria, respectively. The third survey was conducted between 2012 and 2013; 749 of 1083 individuals enrolled from the second survey (69.2%, 248 men, 501 women) completed assessments identical to those in the second survey.

**RESULTS:** The prevalence of frailty in the second survey was 5.6% (men, 3.8%; women, 6.6%). The cumulative incidence of frailty was 1.2%/year (men, 0.8%/year; women, 1.3%/year). After adjustment for confounding factors, logistic regression analysis indicated that osteoporosis was significantly associated with the occurrence of frailty (odds ratio, 3.07; 95% confidence interval, 1.26-7.36;  $p=0.012$ ). Moreover, the occurrence of frailty significantly increased according to the presence of osteoporosis and sarcopenia (odds ratio vs. neither osteoporosis nor sarcopenia: osteoporosis alone, 2.50; osteoporosis and sarcopenia, 5.80). **CONCLUSIONS:** Preventing osteoporosis and coexistence of osteoporosis and sarcopenia may help reduce the risk of frailty.

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### **Effects of Vitamin D3 Supplementation on Muscle Strength, Mass, and Physical Performance in Women with Vitamin D Insufficiency: A Randomized Placebo-Controlled Trial.**

Bislev LS, Langagergaard Rødbro L, Rolighed L, Sikjaer T, Rejnmark L.

Vitamin D insufficiency and hyperparathyroidism have been associated with reduced muscle strength, physical performance, postural stability, well-being, and quality of life. In a double-blinded, randomized placebo-controlled trial, we aimed to investigate effects of vitamin D3 supplementation on above-mentioned outcomes in healthy community-dwelling postmenopausal women with plasma levels of 25-hydroxyvitamin D (25(OH)D) below  $< 50$  nmol/l and high parathyroid hormone (PTH) levels. Participants ( $N=81$ ) were 1:1 treated with vitamin D3, 70  $\mu\text{g}$  (2800 IU)/day or identical placebo for three months during wintertime (56°N). Vitamin D3 supplementation increased levels of 25(OH)D and 1,25(OH)2D by 230% (95% CI 189 to 272)%,  $p<0.001$  and 58% (190 to 271)%,  $p<0.001$ , respectively, and reduced PTH by 17% (-23 to -11%),  $p<0.001$ . Compared with placebo, vitamin D3 significantly reduced maximal handgrip strength by 9% (-15 to -3%;  $p<0.01$ ) and knee flexion strength by 13% (-24 to -2%;  $p=0.02$ ) and increased the time spent on performing the Timed Up and Go test by 4.4%; (0.1-8.6%;  $p<0.05$ ). Levels of physical activity, total lean body mass, appendicular lean mass index, postural stability, well-being, and quality of life did not change in response to treatment. Compared with placebo, a daily supplement with a relatively high dose of vitamin D3 had no beneficial effects on any outcomes. In some measures of muscle strength and physical performance, we even saw a small unfavorable effect. Our data call for caution on use of relatively high daily doses of vitamin D3 in the treatment of vitamin D insufficiency.

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## Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women.

Premenopausal Breast Cancer Collaborative Group. Schoemaker MJ, Nichols HB, Wright LB, Brook MN, et al.

**Importance:** The association between increasing body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and risk of breast cancer is unique in cancer epidemiology in that a crossover effect exists, with risk reduction before and risk increase after menopause. The inverse association with premenopausal breast cancer risk is poorly characterized but might be important in the understanding of breast cancer causation. **Objective:** To investigate the association of BMI with premenopausal breast cancer risk, in particular by age at BMI, attained age, risk factors for breast cancer, and tumor characteristics. **Design, Setting, and Participants:** This multicenter analysis used pooled individual-level data from 758 592 premenopausal women from 19 prospective cohorts to estimate hazard ratios (HRs) of premenopausal breast cancer in association with BMI from ages 18 through 54 years using Cox proportional hazards regression analysis. Median follow-up was 9.3 years (interquartile range, 4.9-13.5 years) per participant, with 13 082 incident cases of breast cancer. Participants were recruited from January 1, 1963, through December 31, 2013, and data were analyzed from September 1, 2013, through December 31, 2017. **Exposures:** Body mass index at ages 18 to 24, 25 to 34, 35 to 44, and 45 to 54 years. **Main Outcomes and Measures:** Invasive or in situ premenopausal breast cancer. **Results:** Among the 758 592 premenopausal women (median age, 40.6 years; interquartile range, 35.2-45.5 years) included in the analysis, inverse linear associations of BMI with breast cancer risk were found that were stronger for BMI at ages 18 to 24 years (HR per 5 kg/m<sup>2</sup> [5.0-U] difference, 0.77; 95% CI, 0.73-0.80) than for BMI at ages 45 to 54 years (HR per 5.0-U difference, 0.88; 95% CI, 0.86-0.91). The inverse associations were observed even among nonoverweight women. There was a 4.2-fold risk gradient between the highest and lowest BMI categories (BMI  $\geq$  35.0 vs <17.0) at ages 18 to 24 years (HR, 0.24; 95% CI, 0.14-0.40). Hazard ratios did not appreciably vary by attained age or between strata of other breast cancer risk factors. Associations were stronger for estrogen receptor-positive and/or progesterone receptor-positive than for hormone receptor-negative breast cancer for BMI at every age group (eg, for BMI at age 18 to 24 years: HR per 5.0-U difference for estrogen receptor-positive and progesterone receptor-positive tumors, 0.76 [95% CI, 0.70-0.81] vs hormone receptor-negative tumors, 0.85 [95% CI, 0.76-0.95]); BMI at ages 25 to 54 years was not consistently associated with triple-negative or hormone receptor-negative breast cancer overall. **Conclusions and Relevance:** The results of this study suggest that increased adiposity is associated with a reduced risk of premenopausal breast cancer at a greater magnitude than previously shown and across the entire distribution of BMI. The strongest associations of risk were observed for BMI in early adulthood. Understanding the biological mechanisms underlying these associations could have important preventive potential.

**Am J Clin Nutr. 2018 Jun 21. doi: 10.1093/ajcn/nqy073. [Epub ahead of print]**

## Chocolate intake and heart disease and stroke in the Women's Health Initiative: a prospective analysis.

Greenberg JA, Manson JE, Neuhauser ML, Tinker L, Eaton C, Johnson KC, Shikany JM.

**Background:** Three recent meta-analyses found significant prospective inverse associations between chocolate intake and cardiovascular disease risk. Evidence from these meta-analyses suggests that such inverse associations may only apply to elderly individuals or those with pre-existing major chronic disease. **Objective:** We assessed the association between habitual chocolate intake and subsequent incident coronary heart disease (CHD) and stroke, and the potential effect of modification by age. **Design:** We conducted multivariable Cox regression analyses using data from 83,310 postmenopausal women free of baseline pre-existing major chronic disease in the prospective Women's Health Initiative cohort. Chocolate intake was assessed using a food-frequency questionnaire. Physician-adjudicated events or deaths were ascertained up to 30 September 2013. **Results:** After exclusions, there were 3246 CHD and 2624 stroke events or deaths, representing incidence rates of 3.9% and 3.2% during 1,098,091 and 1,101,022 person-years (13.4 y), respectively. We found no association between consumption of chocolate and risk of CHD (P for linear trend = 0.94) or stroke (P = 0.24). The results for CHD and stroke combined were similar (P = 0.30), but were significantly modified by age (P for interaction = 0.02). For women age <65 y at baseline, those who ate 1 oz (28.35 g) of chocolate <1/mo, 1 to <1.5/mo, 1.5 to <3.5/mo, 3.5/mo to <3/wk, and  $\geq$ 3/wk had HRs (95% CIs) of 1.00 (referent), 1.17 (1.00, 1.36), 1.05 (0.90, 1.22), 1.09 (0.94, 1.25), and 1.27 (1.09, 1.49), respectively (P for linear trend = 0.005). No association was apparent for older women. **Conclusion:** We observed no association between chocolate intake and risk of CHD, stroke, or both combined in participants free of pre-existing major chronic disease. The

relation for both combined was modified by age, with a significant positive linear trend and an increased risk in the highest quintile of chocolate consumption among women age <65 y.

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### **Glucocorticoid exposure and fracture risk in a cohort of US patients with selected conditions.**

Balasubramanian A, Wade SW, Adler RA, Saag K, Pannacciulli N, Curtis JR.

**PURPOSE:** We evaluated systemic glucocorticoid exposure and fracture among patients with newly-diagnosed inflammatory and immune-modulated conditions. **METHODS:** Using administrative data, inception cohorts of RA, asthma/COPD, IBD, MS, lupus, and sarcoidosis patients age 18-64 years with benefits coverage  $\geq 12$  months before diagnosis (1/1/2005-12/31/2012) were followed to clinical fracture, cancer diagnosis, or 12/31/2012. Glucocorticoid users were new to therapy. Fracture incidence rates (IR) per 1,000 person-years were stratified by prednisone equivalent doses. Cox's proportional hazards models assessed risk by daily and cumulative dose, and by time since discontinuation, adjusted for baseline characteristics. **RESULTS:** Most patients (72% of 403,337) had glucocorticoid exposure; 52% were under age 50. IR (95% confidence intervals [CI]) of any osteoporotic fracture was elevated at doses <5 mg/day, IR: 9.33 [7.29, 11.77] versus 0 mg/day, IR: 4.87 [4.72, 5.02]). Fracture rates were elevated at doses <5 mg/day in patients <50 years and those  $\geq 50$  years. In both age groups, fracture risk increased with increasing cumulative exposure, being approximately 2.5-fold higher at cumulative dose  $\geq 5400$  mg compared to <675 mg. At  $\geq 5400$  mg, IR were 5.69 [4.32, 7.35] in patients <50 years and 17.10 [14.97, 19.46] in older patients. Fracture risk decreased significantly within months following glucocorticoid discontinuation. **CONCLUSIONS:** In patients with a variety of inflammatory conditions, fracture risk increased at doses as low as <5 mg/day. Risk increased with increasing cumulative exposure and decreased soon following glucocorticoid discontinuation. Trends were similar between patients older and younger than 50 years.

**J Bone Miner Res. 2018 Jun 19. doi: 10.1002/jbmr.3471. [Epub ahead of print]**

### **Bone Turnover Markers Are Not Associated With Hip Fracture Risk: A Case-Control Study in the Women's Health Initiative.**

Crandall CJ, Vasan S, LaCroix A, LeBoff MS, Cauley JA, Robbins JA, Jackson RD, Bauer DC.

Current guidelines recommend that serum C-terminal telopeptide of type I collagen (CTX) and serum procollagen type 1 aminoterminal propeptide (PINP), measured by standardized assays, be used as reference markers in observational and interventional studies. However, there are limited data to determine whether serum CTX and PINP are associated with hip fracture risk among postmenopausal women. We determined the associations of serum CTX and serum PINP with hip fracture risk among postmenopausal women aged 50 to 79 years at baseline. We performed a prospective case-control study (400 cases, 400 controls) nested in the Women's Health Initiative Observational Study, which enrolled participants at 40 US clinical centers. Cases were women with incident hip fracture not taking osteoporosis medication; hip fractures were confirmed using medical records. Untreated controls were matched by age, race/ethnicity, and date of blood sampling. Serum CTX and serum PINP were analyzed on 12-hour fasting blood samples. The main outcome measure was incident hip fracture risk (mean follow-up 7.13 years). After adjustment for body mass index, smoking, frequency of falls, history of fracture, calcium and vitamin D intake, and other relevant covariates, neither serum CTX level nor serum PINP level was statistically significantly associated with hip fracture risk (CTX p<sub>trend</sub> = 0.22, PINP p<sub>trend</sub> = 0.53). Our results do not support the utility of serum CTX level or PINP level to predict hip fracture risk in women in this age group. These results will inform future guidelines regarding the potential utility of these markers in fracture prediction.

**Menopause. 2018 Jun 18. doi: 10.1097/GME.0000000000001130. [Epub ahead of print]**

### **Factors associated with developing vaginal dryness symptoms in women transitioning through menopause: a longitudinal study.**

Waetjen LE, Crawford SL, Chang PY, Reed BD, et al; Study of Women's Health Across the Nation (SWAN).

**OBJECTIVE:** To evaluate factors associated with incident self-reported vaginal dryness and the consequences of this symptom across the menopausal transition in a multiracial/ethnic cohort of community-dwelling women. **METHODS:** We analyzed questionnaire and biomarker data from baseline and 13 approximately annual visits over 17 years (1996-2013) from 2,435 participants in the Study of Women's Health Across the Nation, a prospective cohort study. We used discrete-time Cox proportional-hazards regression to identify predictors of incident vaginal

dryness and to evaluate vaginal dryness as a predictor of pain during intercourse and changes in sexual intercourse frequency. **RESULTS:** The prevalence of vaginal dryness increased from 19.4% among all women at baseline (ages 42-53 years) to 34.0% at the 13th visit (ages 57-69 years). Advancing menopausal stage, surgical menopause, anxiety, and being married were positively associated with developing vaginal dryness, regardless of partnered sexual activity. For women not using hormone therapy, higher concurrent levels of endogenous estradiol were inversely associated (multivariable-adjusted hazard ratio: 0.94 per 0.5 standard deviation increase, 95% confidence interval: 0.91-0.98). Concurrent testosterone levels, concurrent dehydroepiandrosterone sulfate levels, and longitudinal change in any reproductive hormone were not associated with developing vaginal dryness. Both vaginal dryness and lubricant use were associated with subsequent reporting of pain during intercourse, but not with a decline in intercourse frequency. **CONCLUSION:** In these longitudinal analyses, our data support many clinical observations about the relationship between vaginal dryness, menopause, and pain during intercourse, and suggest that reporting of vaginal dryness is not related to androgen level or sexual intercourse frequency.

**Indian J Endocrinol Metab. 2018 Mar-Apr;22(2):223-228. doi: 10.4103/ijem.IJEM\_620\_17.**

### **Assessment of Cardiovascular Risk in Natural and Surgical Menopause.**

Abbas SZ, Sangawan V, Das A, Pandey AK.

**Background:** Menopause is associated with increased cardiovascular disease (CVD) risk. Arterial stiffness, a biomarker of vascular aging, increases the risk for CVD. **Aims and Objectives:** The study was aimed to determine whether menopause is associated with arterial stiffness amongst natural and surgical menopausal women. **Materials and Methods:** We conducted a cross-sectional study amongst natural postmenopausal women, with Surgical menopause and Premenopausal. Arterial stiffness was measured by Periscopy TM. Large artery stiffness may be an important mechanism by which hysterectomy increases the risk of cardiovascular disease in postmenopausal women. **Results:** Carotid femoral pulse wave velocity (cfPWV) and Brachial Ankle Pulse wave velocity (baPWV) were significantly higher in surgical and natural menopause compared to women with Premenopausal group.