



## Selección de Resúmenes de Menopausia

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### Association of Estradiol and Visceral Fat with Structural Brain Networks and Memory Performance in Adults.

Zsido RG<sup>1,2</sup>, Heinrich M<sup>1,2</sup>, Slavich GM<sup>3</sup>, Beyer F<sup>1,4</sup>, Kharabian Masouleh S<sup>1</sup>, Kratzsch J<sup>5</sup>, Raschpichler , et al. Changes in estradiol during aging are associated with increased dementia risk. It remains unclear how estradiol supports cognitive health and whether risk factors, such as midlife obesity, are exacerbated by estrogen loss. Objectives: To assess whether visceral adipose tissue (VAT) moderates the association between age and brain network structure and to investigate whether estradiol moderates the association between VAT and brain network structure. Design, Setting, and Participants: Cross-sectional study of data from 974 cognitively healthy adults in Germany who participated in the Health Study of the Leipzig Research Centre for Civilization Diseases, a previously described population-based cohort study. Two moderation analyses were performed, including VAT as the moderator variable between age and brain network structure and estradiol as the moderator variable between VAT and brain network structure. The study was conducted from August 1, 2011, to November 23, 2014. Analyses were conducted from August 2017 to September 2018. Exposures: Serum estradiol levels from fasting blood and visceral adipose tissue volume from T1-weighted magnetic resonance imaging (MRI). Main Outcomes and Measures: Brain network covariance (individual loading on structural network derived from T1-weighted MRI) and memory performance (composite score from the Consortium to Establish a Registry for Alzheimer Disease [CERAD] verbal episodic memory test on learning [score range, 0-30], recall [score range, 0-10], and recognition [score range, 0-20]). Results: Final analyses included data from 473 women (mean [SD] age, 50.10 [15.63] years) and 501 men (mean [SD] age, 51.24 [15.67] years). Visceral adipose tissue was associated with an exacerbation of the negative association of aging with network covariance for women (interaction term  $\beta = -0.02$ ; 95% bias-corrected bootstrap CI, -0.03 to -0.01;  $P = .001$ ) and men (interaction term  $\beta = -0.02$ ; 95% bias-corrected bootstrap CI, -0.03 to -0.01;  $P < .001$ ). Estradiol level was associated with a reduction in the negative association of VAT with network covariance in women (interaction term  $\beta = 0.63$ ; 95% bias-corrected bootstrap CI, 0.14-1.12;  $P = .01$ ), with no significant association in men. In the female midlife subgroup (age range, 35-55 years, when menopause transition occurs), low estradiol levels were associated with lower memory network covariance (Cohen  $d = 0.61$ ;  $t_{80} = 2.76$ ;  $P = .007$ ) and worse memory performance (Cohen  $d = 0.63$ ;  $t_{76} = 2.76$ ;  $P = .007$ ). Conclusions and Relevance: This study reports a novel association between VAT, estradiol, and structural brain networks as a potential mechanism underlying cognitive decline in women. These findings appear to highlight the need for sex-specific strategies, including VAT and hormonal screening during midlife, to support healthy cognitive aging.

**Curr Dev Nutr. 2019 Jun 13;3(Suppl 1). doi: 10.1093/cdn/nzz039.P18-049-19. eCollection 2019 Jun.**

### Premenopausal Calcium with or Without Vitamin D Supplementation: A Critical Window of Opportunity for Preventing Bone Loss Across Menopause Transition.

Bailey R<sup>1</sup>, Wallace T<sup>2</sup>, Weaver C<sup>3</sup>, Zou P<sup>3</sup>.

Objectives: To estimate the annualized BMD changes of the lumbar spine and femoral neck by the use of calcium with or without vitamin D supplements in the Study of Women's Health Across the Nation (SWAN), a multi-center, multi-ethnic, community-based longitudinal cohort across the menopause transition. Methods: Mixed model regression was used to estimate the 10 year annualized BMD change between the calcium with or without vitamin D supplements in SWAN women ( $n = 1564$ ; aged 42 to 52 years at baseline) unadjusted and adjusted for time-varying covariates (age, menopausal status [pre-, early peri-, late peri- and post- menopausal], smoking, physical activity) and time-constant covariates (height, baseline alcohol). Models were also stratified by menopausal status at baseline. Results: When combined by menopausal status, calcium with or without vitamin D supplement use was associated with less femoral neck BMD annualized loss across in all models (beta = 0.0038 vs -0.0048;  $P = 0.003$ ). When stratified by pre- and peri- menopause at baseline, calcium with or without vitamin D supplement use was only significant in pre-menopausal women for both the lumbar spine (beta = 0.0067 vs -0.0082;  $P = 0.02$ ) and femoral neck (beta = -0.0037 vs -0.0052;  $P$

= 0.002). Conclusions: The use of calcium with or without vitamin D supplements is associated with less BMD loss of the lumbar spine and femoral neck, especially in premenopausal women.

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### **Intensive screening for osteoporosis in patients with hip fracture.**

Amar AOS1, Hyldstrup L2, Nielsen J2, Palm H3, Jensen JB2.

Opportunities to evaluate, treat, and prevent future osteoporotic fractures are often being overlooked, especially in patients with a prior osteoporotic fracture. We find that an intensive outreach osteoporosis investigation strategy can help increase the number of patients investigated and treated for osteoporosis following a hip fracture. **PURPOSE:** Patients experiencing a hip fracture are subject to an increased risk of subsequent fractures. This suggests an urgent need to develop strategies that will allow a higher number of patients with fragility hip fractures to be investigated and treated for osteoporosis. In accordance, we developed a secondary osteoporosis prevention program and evaluated the results of the program. **METHODS:** In the study period, 1071 patients with a hip fracture were admitted to Hvidovre University Hospital. Eligible patients were offered an osteoporosis investigation program, which included a DXA-scan with vertebral fracture assessment and a medical consultation. The data retrieved from this program were registered and analyzed. The primary goal of the study was to describe the number of subjects, who completed the program, and to characterize the initiated osteoporosis treatment. Secondary outcomes evaluated were prevalence of DXA-verified osteoporosis, changes in T-score due to treatment, and 1-year mortality rate. **RESULTS:** In total, 557 patients were offered participation of which 333 patients completed the full program. Among these, 159 patients had DXA-verified osteoporosis and 192 patients were started treatment. This resulted in a significant higher T-score at the lumbar spine and femoral neck compared with subjects not treated. Additionally, we report a 1-year mortality rate of 27.7% among all patients with hip fracture. **CONCLUSION:** We report that an intensive outreach osteoporosis investigation program can help increase the number of hip fracture patients being tested and treated for osteoporosis. Further, the initiation of treatment can significantly increase the T-score.

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### **Estradiol Protects Neuropeptide Y/Agouti-related Peptide Neurons against Insulin Resistance in Females.**

Qiu J, Bosch MA, Zhang C, Rønnekleiv OK, Kelly MJ.

With obesity men exhibit a higher incidence of metabolic syndrome than women in early adult life, but this sex advantage wanes in postmenopausal women. A key diagnostic of the metabolic syndrome is insulin resistance in both peripheral tissues and brain, especially in the hypothalamus. Since the anorexigenic hormone 17 $\beta$ -estradiol (E2) regulates food intake in part by inhibiting the excitability of the hypothalamic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons, we hypothesized that E2 would protect against insulin resistance in NPY/AgRP neurons with diet-induced obesity (DIO). Therefore, we did whole-cell recordings and single cell qPCR in arcuate NPYGFP neurons from both female and male mice to test the efficacy of insulin with DIO. The resting membrane potential and input resistance of NPY/AgRP neurons was significantly increased in DIO versus control-diet fed males. Most notably, the efficacy of insulin to activate KATP channels in NPY/AgRP neurons was significantly attenuated, although the KATP channel opener diazoxide was fully effective in NPY/AgRP neurons from DIO males, indicating that the KATP channels were expressed and functional. In contrast, insulin was fully efficacious to activate KATP channels in DIO females, and the response was reversed by the KATP channel blocker tolbutamide. However, the ability of insulin to activate KATP channels was abrogated with ovariectomy but fully restored with E2 replacement. The insulin resistance in obese males was likely mediated by an increase in suppressor of cytokine signaling-3 (SOCS-3), protein tyrosine phosphatase B (PTP1B) and T cell protein tyrosine phosphatase (TCPTP) activity since the expression of all three mRNAs were upregulated in the obese males but not in females. As proof of principle, pre-incubation of hypothalamic slices from DIO males with the PTP1B/TCPTP inhibitor CX08005 completely rescued the effects of insulin. Therefore, E2 protects NPY/AgRP neurons in females against insulin resistance through, at least in part, attenuating phosphatase activity. The neuroprotective effects of E2 may explain sex differences in the expression of metabolic syndrome with aging.

**J Bone Miner Res. 2019 Jun 18. doi: 10.1002/jbmr.3813. [Epub ahead of print]**

## Association of Bone Density Monitoring in Routine Clinical Practice with Anti-Osteoporosis Medication Use and Incident Fractures: A Matched Cohort Study.

Leslie WD1, Morin SN2, Martineau P1,3, Bryanton M1, Lix LM1.

Routine bone mineral density (BMD) monitoring of individuals during the initial 5 years of anti-osteoporosis treatment is controversial. Using a registry-based cohort from the Province of Manitoba, Canada, we compared anti-osteoporosis medication use and fracture outcomes in women with versus without BMD monitoring receiving anti-osteoporosis medication. We identified 4,559 women age 40 years and older receiving anti-osteoporosis therapy with serial BMD testing (monitoring) within 5 years (mean interval 3.2 years) and 4,559 propensity-score matched women without BMD monitoring. We assessed anti-osteoporosis medication use over 5 years from a population-based retail pharmacy database. Incident fractures to 10 years from health services data. During median 10 years observation, 1223 (13.4%) women developed major osteoporotic fracture including 382 (4.2%) with hip fractures. Monitored women had significantly better fracture-free survival for major osteoporotic fracture ( $P=0.040$ ; 10 year cumulative risk 1.9% lower, 95% CI 0.3-3.6%) and hip fracture ( $P=0.001$ ; 10 year cumulative risk 1.8% lower, 95% CI 0.7-2.8%) compared with women who were not monitored. Hazard ratios (HRs) were significantly lower in monitored vs not monitored women for major osteoporotic fracture (HR 0.89, 95% confidence interval 0.80-0.98) and hip fracture (0.74, 0.63-0.87). Days of medication use, medication persistence ratio and treatment switching over 5 years were greater in monitored vs not monitored women. At the end of 5 years, more women in the monitored group persisted on treatment and more switched treatment, with switching behavior associated with an observed interval reduction in BMD. In conclusion, our findings suggest a possible role for BMD monitoring after initiating anti-osteoporosis therapy in the routine clinical practice setting.

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## The Effect of Sprint Interval Training on Body Composition of Postmenopausal Women.

Boutcher YN1, Boutcher SH1, Yoo HY1, Meerkin JD2.

**INTRODUCTION:** Menopause is accompanied by body composition changes that include a decrease in lean mass and aerobic fitness and an increase in fat mass. Sprint interval training (SIT) may be able to reverse these changes. **PURPOSE:** To examine the effect of an 8-wk SIT program on body composition and aerobic fitness of overweight postmenopausal women. **METHODS:** Forty postmenopausal women were randomized into SIT ( $n = 20$ ) or control ( $n = 20$ ) groups. The SIT group completed three SIT sessions a week for 8 wk with each session consisting of 20 min of alternating 8-s sprints and 12-s of light pedaling. Total mass, regional lean mass, and fat mass were assessed using dual-energy x-ray absorptiometry. Maximal oxygen uptake ( $\dot{V}O_{2max}$ ) was predicted using a submaximal test. **RESULTS:** Total lean mass was significantly increased from pretest ( $48.1 \pm 5.81$  kg) to posttest ( $48.8 \pm 5.96$  kg) and fat mass was significantly reduced (pre,  $29.5 \pm 7.29$  kg; post,  $29.1 \pm 7.61$  kg) for the SIT group. Lean mass was mostly increased in the trunk (pre,  $24.4 \pm 2.79$  kg; post,  $24.8 \pm 2.93$  kg) and legs (pre,  $15.6 \pm 2.31$  kg; post,  $15.9 \pm 2.34$  kg).  $\dot{V}O_{2max}$  was significantly increased from pretest ( $21.7 \pm 4.89$  mL·kg<sup>-1</sup>·min<sup>-1</sup>) to posttest ( $24.4 \pm 5.96$  mL·kg<sup>-1</sup>·min<sup>-1</sup>) for the SIT group only. **CONCLUSIONS:** The SIT intervention increased total lean mass, decreased fat mass, and increased aerobic fitness of postmenopausal women after only 8 h of actual exercise over 8 wk.

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## Cigarette Smoke Induces the Risk of Metabolic Bone Diseases: Transforming Growth Factor Beta Signaling Impairment via Dysfunctional Primary Cilia Affects Migration, Proliferation, and Differentiation of Human Mesenchymal Stem Cells.

Aspera-Werz RH1, Chen T2, Ehnert S3, Zhu S4, Fröhlich T5, Nussler AK6.

It is well established that smoking has detrimental effects on bone integrity and is a preventable risk factor for metabolic bone disorders. Following orthopedic surgeries, smokers frequently show delayed fracture healing associated with many complications, which results in prolonged hospital stays. One crucial factor responsible for fracture repair is the recruitment and differentiation of mesenchymal stem cells (MSCs) at early stages, a mechanism mediated by transforming growth factor  $\beta$  (TGF- $\beta$ ). Although it is known that smokers frequently have decreased TGF- $\beta$  levels, little is known about the actual signaling occurring in these patients. We investigated the effect of cigarette smoke on

TGF- $\beta$  signaling in MSCs to evaluate which step in the pathway is affected by cigarette smoke extract (CSE). Single-cell-derived human mesenchymal stem cell line (SCP-1 cells) were treated with CSE concentrations associated with smoking up to 20 cigarettes a day. TGF- $\beta$  signaling was analyzed using an adenovirus-based reporter assay system. Primary cilia structure and downstream TGF- $\beta$  signaling modulators (Smad2, Smad3, and Smad4) were analyzed by Western blot and immunofluorescence staining. CSE exposure significantly reduced TGF- $\beta$  signaling. Intriguingly, we observed that protein levels of phospho-Smad2/3 (active forms) as well as nuclear translocation of the phospho-Smad3/4 complex decreased after CSE exposure, phenomena that affected signal propagation. CSE exposure reduced the activation of TGF- $\beta$  modulators under constitutive activation of TGF- $\beta$  receptor type I (ALK5), evidencing that CSE affects signaling downstream of the ALK5 receptor but not the binding of the cytokine to the receptor itself. CSE-mediated TGF- $\beta$  signaling impaired MSC migration, proliferation, and differentiation and ultimately affected endochondral ossification. Thus, we conclude that CSE-mediated disruption of TGF- $\beta$  signaling in MSCs is partially responsible for delayed fracture healing in smokers.