



# Menopause

The Journal of The North American Menopause Society

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**Articles**

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**683****Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative**

JoAnn E. Manson, MD, DrPH, Matthew A. Allison, MD, MPH, J. Jeffrey Carr, MD, Robert D. Langer, MD, MPH, Barbara B. Cochrane, PhD, RN, Susan L. Hendrix, DO, Judith Hsia, MD, Julie R. Hunt, PhD, Cora E. Lewis, MD, MSPH, Karen L. Margolis, MD, MPH, Jennifer G. Robinson, MD, MPH, Rebecca J. Rodabough, MS, and Asha M. Thomas, MD, for the Women's Health Initiative and Women's Health Initiative-Coronary Artery Calcium Study Investigators

*Coronary artery–calcified plaque burden is a marker for future risk of cardiovascular events. In the Women's Health Initiative, an intervention including calcium and vitamin D did not seem to alter coronary artery calcification among postmenopausal women.*

**692****Early menopausal hormone use influences brain regions used for visual working memory**

Alison Berent-Spillson, PhD, Carol C. Persad, PhD, Tiffany Love, PhD, Anne Tkaczyk, MS, Heng Wang, MS, Nancy K. Reame, MSN, PhD, Kirk A. Frey, MD, PhD, Jon-Kar Zubieta, MD, PhD, and Yolanda R. Smith, MD, MS

*Long-term postmenopausal hormone use, begun close to the time of menopause, is associated with increased activation of brain regions used for visual working memory while performing a visual memory task. A positive correlation between activation in these regions and performance on the visual task suggests a potential benefit of early-initiation hormone use on visual working memory processes.*

**700****Desvenlafaxine and escitalopram for the treatment of postmenopausal women with major depressive disorder**

Claudio N. Soares, MD, PhD, FRCPC, Michael E. Thase, MD, Anita Clayton, MD, Christine J. Guico-Pabia, MD, MBA, MPH, Kristen Focht, Qin Jiang, MS, Susan G. Kornstein, MD, Phil Ninan, MD, Cecelia P. Kane, MD, and Lee S. Cohen, MD

*Previous studies suggest that menopause status may exert an influence on the efficacy of certain classes of antidepressants. In this randomized, double-blind study for the treatment of postmenopausal women with depression, there were no significant differences between desvenlafaxine (serotonin-norepinephrine reuptake inhibitor) and escitalopram (selective serotonin reuptake inhibitor) with respect to efficacy, safety, or tolerability.*

**712****Effects of exercise training on autonomic dysfunction management in an experimental model of menopause and myocardial infarction**

Lucinar J. Flores, MS, Diego Figueroa, MS, Iris C. Sanches, MS, Luciana Jorge, MS, Maria-Cláudia Irigoyen, MD, PhD, Bruno Rodrigues, PhD, and Kátia De Angelis, PhD

*Results indicate that exercise training in ovariectomized rats submitted to myocardial infarction improves resting hemodynamic status and reflex control of the circulation, which may be caused by an increase in the vagal component, suggesting a homeostatic role for exercise training in reducing cardiovascular risk after an ischemic event in postmenopausal women.*

718

**Obesity and reproductive hormone levels in the transition to menopause**

Ellen W. Freeman, PhD, Mary D. Sammel, ScD, Hui Lin, MS,  
and Clarisa R. Gracia, MD

*Obesity is an important factor in hormone changes of the menopausal transition, independent of age, race, and smoking. Premenopausal associations between obesity and reproductive hormones reversed after menopause.*

727

**The multidisciplinary management of menopausal symptoms after breast cancer: a unique model of care**

Martha Hickey, MD, Laura I. Emery, BSci, Jane Gregson, BA,  
Dorota A. Doherty, PhD, and Christobel M. Saunders, MD

*This article describes a unique model of multidisciplinary care for women with menopausal symptoms after breast cancer and presents preliminary data on the nature and severity of menopausal symptoms. This multidisciplinary approach ensures that women are given the opportunity to make informed and evidence-based treatment choices and are not given conflicting messages from different healthcare providers.*

734

**Hormone therapy discontinuation: physician practices after the Women's Health Initiative**

Katherine M. Newton, PhD, Susan D. Reed, MD, MPH, Louis C. Grothaus, MS,  
Andrea Z. La Croix, PhD, Larissa Nekhlyudov, MD, MPH, Kelly Ehrlich, MS,  
and Evette J. Ludman, PhD

*Most physicians advised tapering dose and days per week to discontinue menopausal hormone therapy, and they most often suggest behavioral changes and increased exercise to assist women in coping with symptoms if they return. Evidence is needed to support the efficacy of these recommendations.*

741

**The effect of diet and cardiovascular risk on ovarian aging in cynomolgus monkeys (*Macaca fascicularis*)**

Susan E. Appt, DVM, Haiying Chen, MD, PhD, Amanda K. Goode, MA,  
Patricia B. Hoyer, PhD, Thomas B. Clarkson, DVM, Michael R. Adams, DVM,  
Mark E. Wilson, PhD, Adrian A. Franke, PhD, and Jay R. Kaplan, PhD

*The present study provides evidence that the source of dietary protein, or isoflavones, affects ovarian reserve in cynomolgus monkeys. These results highlight the importance of nutrition with respect to ovarian aging, although the mechanism underlying this relationship remains to be determined.*

749

**Endothelial-mediated microcirculatory responses to an acute estradiol test are influenced by time since menopause, cumulative hormone exposure, and vasomotor symptoms**

Ruth Clapauch, MD, PhD, Anete S. Mecnas, BSc, Priscila A. Maranhão, BSc, and Eliete Bouskela, MD, PhD

*Time since menopause, cumulative exposure to oral contraceptives and hormone therapy, and triglyceride levels influenced endothelial vasodilatory response to estradiol, whereas past smoking and current vasomotor symptom intensity were associated to microcirculatory stiffness.*

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**Similar phenotype characteristics comparing familial and sporadic premature ovarian failure**

Femi Janse, MD, Erik A.H. Knauff, MD, PhD, Martinus F. Niermeijer, MD, PhD, Marinus J. Eijkemans, PhD, Joop S.E. Laven, MD, PhD, Cornelius B. Lambalk, MD, PhD, Bart C.J.M. Fauser, MD, PhD, Angelique J. Goverde, MD, PhD, on behalf of the Dutch Premature Ovarian Failure Consortium

*This study compared phenotypical characteristics, such as gonadotropins, lipids, and the incidence of known etiological factors in women with premature ovarian failure. Besides maternal age at menopause and sex hormone-binding globulin concentrations, familial and sporadic premature ovarian failure cases do not differ in phenotype.*

766

**Differential effects of 17 $\beta$ -estradiol and raloxifene on bone and lipid metabolism in rats with chronic kidney disease and estrogen insufficiency**

Manuel Naves-Díaz, PhD, Natalia Carrillo-López, BSc, Aránzazu Rodríguez-Rodríguez, PhD, Socorro Braga, MD, Teresa Fernández-Coto, MD, Jose Miguel Lopez-Novoa, MD, PhD, Francisco López-Hernández, PhD, and Jorge B. Cannata-Andía, MD, PhD

*This experimental study in rats with estrogen insufficiency and nephrectomy demonstrates the advantages of replacing sexual hormone and calcitriol deficiencies. Replacement with raloxifene offers additional benefits to the use of 17 $\beta$ -estradiol owing to the best results observed in bone, uterus, breast, and in lipid profile, a subject of great potential interest in women with chronic kidney disease.*

772

**Breast density changes associated with postmenopausal hormone therapy: post hoc radiologist- and computer-based analyses**

Mads Nielsen, PhD, Paola C. Pettersen, MD, Peter Alexandersen, MD, Gopal Karemore, MSc, Jakob Raundahl, PhD, Marco Loog, PhD, and Claus Christiansen, MD

*To compare the utility of computer-based automated approaches for assessment of breast density with reference to traditional methods, the impact of oral hormone therapy on breast density in postmenopausal women was evaluated. The computer-based approaches may be comparable with and offer advantages over traditional methods.*

779

**Insulin resistance independently influences arterial stiffness in normoglycemic normotensive postmenopausal women**

Jong Suk Park, MD, Ji Sun Nam, MD, Min Ho Cho, MD, Jeong Seon Yoo, MD, Chul Woo Ahn, MD, Sun Ha Jee, PhD, Hong Soo Lee, MD, Bong Soo Cha, MD, Kyung Rae Kim, MD, and Hyun Chul Lee, MD

*Insulin resistance was independently associated with pulse wave velocity in normoglycemic normotensive postmenopausal women.*

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**Associations between markers of inflammation and physiological and pharmacological levels of circulating sex hormones in postmenopausal women**

Roksana Karim, MBBS, PhD, Frank Z. Stanczyk, PhD, Howard N. Hodis, MD, Mary Cushman, MD, MSc, Roger A. Lobo, MD, Juliana Hwang, PhD, and Wendy J. Mack, PhD

*The inverse association of estrogens with soluble intercellular adhesion molecule-1 and homocysteine support an anti-inflammatory property of estrogen.*

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**Effect of exercise and *Cimicifuga racemosa* (CR BNO 1055) on bone mineral density, 10-year coronary heart disease risk, and menopausal complaints: the randomized controlled Training and *Cimicifuga racemosa* Erlangen (TRACE) study**

Michael Bebenek, MA, Wolfgang Kemmler, PhD, Simon von Stengel, PhD, Klaus Engelke, PhD, and Willi A. Kalender, PhD, MD

*Results indicate that the suggested training regimen may affect bone, menopausal symptoms, lean body mass, and to a smaller extent 10-year coronary heart disease risk. The application of *Cimicifuga racemosa* does not show any additional health benefits.*

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**Review Article**

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**Human breast cancer stem cells and sex hormones—a narrative review**

John A. Eden, MB, BS, MD, FRCOG, FRANZCOG, CREI

*This narrative review examines the role of breast cancer stem cells in the pathogenesis of human breast cancer. Breast cancer stem cells are mostly sex-hormone insensitive but are highly regulated by their microenvironment and peptide growth factors.*

**Special Section: Menopause, Cognition and Mental Health**

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**811**

**Introducing a special section on menopause, cognition, and mental health**

Claudio N. Soares, MD, PhD, FRCPC and Pauline M. Maki, PhD

**812**

**Menopausal transition, mood, and cognition: an integrated view to close the gaps**

Claudio N. Soares, MD, PhD, FRCPC and Pauline M. Maki, PhD

*Menopausal transition may not only be a “window of vulnerability” for depression and cognitive impairment but also a critical “window of opportunity” for the success of hormone-based treatments. This personal perspective challenges clinicians and researchers to pursue a more comprehensive approach and to tailor treatment strategies while managing symptomatic midlife women.*

**815**

**Summary of the National Institute on Aging–sponsored conference on depressive symptoms and cognitive complaints in the menopausal transition**

Pauline M. Maki, PhD, Ellen W. Freeman, PhD, Gail A. Greendale, MD, Victor W. Henderson, MD, MS, Paul A. Newhouse, MD, Peter J. Schmidt, MD, Nelda F. Scott, MD, Carol A. Shively, PhD, and Claudio N. Soares, MD, PhD, FRCPC

*This article summarizes the proceedings from the National Institutes of Health–sponsored presymposium entitled “Depressive Symptoms and Cognitive Complaints in the Menopausal Transition.” The presymposium was aimed at understanding the impact of the menopausal transition on mood, symptoms, and cognitive disorders and identifying research priorities for further investigation.*

**823**

**Associations of depression with the transition to menopause**

Ellen W. Freeman, PhD

*Recent population-based studies indicate that women are more probable to report depressed mood in the menopausal transition compared with the premenopause status. In some studies, the changing hormonal milieu is significantly associated with depressive symptoms in the transition period.*

**828**

**The influence of menopause status and postmenopausal use of hormone therapy on presentation of major depression in women**

Susan G. Kornstein, MD, Elizabeth A. Young, MD, Annie T. Harvey, PhD, Stephen R. Wisniewski, PhD, Jennifer L. Barkin, PhD, Michael E. Thase, MD, Madhukar H. Trivedi, MD, Andrew A. Nierenberg, MD, and A. John Rush, MD

*This study compares depression characteristics among premenopausal, perimenopausal, and postmenopausal women with major depressive disorder as well as between postmenopausal women with major depressive disorder who were taking and not taking hormone therapy. The findings indicate that menopause status and postmenopausal use of hormone therapy may influence the clinical presentation of major depressive episodes in women.*

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**Shift in the brain network of emotional regulation in midlife women: is the menopausal transition the turning point?**

Benicio N. Frey, MD, PhD, Geoffrey B. Hall, PhD, Stefanie Attard, BA, Kaan Yucel, MD, PhD, Ivan Skelin, MD, PhD, Meir Steiner, MD, PhD, FRCPC, and Claudio N. Soares, MD, PhD, FRCPC

*This study investigated brain correlates of emotional regulation in healthy peri- and postmenopausal women using functional magnetic resonance imaging. The results suggest that a shift in the brain network involved with emotional regulation in women may occur during the menopausal transition, a finding that might have potential clinical and therapeutic implications.*

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**Effect of sex and estrogen therapy on the aging brain: a voxel-based morphometry study**

Catherine Lord, PhD, Veronika Engert, PhD, Sonia J. Lupien, PhD, and Jens C. Pruessner, PhD

*This study identifies new plausible regions sensitive to estrogen exposure, such as the inferior parietal lobule, angular gyri, and precunei, which would have been difficult to assess using manual segmentation protocols. Results suggest a specific effect of estrogen exposure on frontotemporoparietal brain structures.*

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**Cholinergic modulation of hippocampal activity during episodic memory encoding in postmenopausal women: a pilot study**

Julie A. Dumas, PhD, Brenna C. McDonald, PsyD, Andrew J. Saykin, PsyD, Thomas W. McAllister, MD, Mary L. Hynes, RN, John D. West, MS, and Paul A. Newhouse, MD

*Menopause and the associated decrease in circulating estradiol may affect brain cholinergic systems and associated cognitive functioning. By modeling the effects of cholinergic decline on episodic memory performance and related brain activation in postmenopausal women, increased hippocampal activation was demonstrated after cholinergic blockade, suggesting a relationship between cholinergic system activity and menopause and age-related brain changes.*

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**Estrogen treatment impairs cognitive performance after psychosocial stress and monoamine depletion in postmenopausal women**

Paul A. Newhouse, MD, Julie Dumas, PhD, Heather Wilkins, BA, Emily Coderre, BA, Cynthia K. Sites, MD, Magdalena Naylor, MD, PhD, Chawki Benkelfat, MD, and Simon N. Young, PhD

*The effects of estrogen on cognition after menopause are complex, but the interactive effects of psychological stress have not been previously studied. In this study, estrogen treatment seems to impair cognitive functioning in postmenopausal women after experimental psychological stress and monoamine depletion.*

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**A review of estrogen receptor  $\alpha$  gene (*ESR1*) polymorphisms, mood, and cognition**

Erin E. Sundermann, MA, Pauline M. Maki, PhD, and Jeffrey R. Bishop, PharmD  
*A strong relationship between ESR1 variants and risk of cognitive impairment is evident, and preliminary evidence suggests a role of the ESR1 gene in certain mood outcomes including anxiety, depression, and premenstrual dysphoric disorder.*

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