Supplementary Online Content

Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. doi:10.1001/jama.2013.278040

This supplementary material has been provided by the authors to give readers additional information about their work.

ONLINE APPENDIX: PREVIOUS WHI PUBLICATIONS

WHI Hormone Therapy Trial Publications: References and Links to Abstracts

1. Prentice R, Rossouw JR, Johnson, SR, Freedman LS, McTiernan A. The role of randomized controlled trials in assessing the benefits and risks of long-term hormone replacement therapy: Example of the Women's Health Initiative. Menopause 1996; 3:71-76. http://journals.lww.com/menopausejournal/Fulltext/1996/03020/The_Role_of_Randomized_Controlled_Trials_in.3.aspx
2. Anderson G, Cummings S, Freedman LS, Furberg C, Henderson M, Johnson SR, Kuller L, Manson JE, Oberman A, Prentice RL, Rossouw JE for the Design Manuscript Writing Group. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials 1998; 19(1):61-109. http://www.ncbi.nlm.nih.gov/pubmed/?term=Control+Clin+Trials+1998%3B+19(1)%3A61-109.
3. Shumaker SA, Reboussin BA, Espeland MA, Rapp SR, McBee WL, Dailey M, et al. The Women's Health Initiative Memory Study (WHIMS): A trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control Clin Trials 1998; 19(6):604-621. http://www.ncbi.nlm.nih.gov/pubmed/?term=Control+Clin+Trials+1998%3B+19(6)%3A604-621.
4. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J, Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288(3):321-333. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2002%3B+288(3)%3A321-333
5. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349(6):523-534. http://www.ncbi.nlm.nih.gov/pubmed/?term=N+Engl+J+Med+2003%3B+349(6)%3A523-534
6. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: Overview and baseline characteristics of participants. Ann Epidemiol 2003; 13(9 Suppl):S78-86. http://www.ncbi.nlm.nih.gov/pubmed/?term=Ann+Epidemiol+2003%3B+13(9+Suppl)%3AS78-86.
7. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. N Engl J Med 2003; 348(7):645-650. http://www.ncbi.nlm.nih.gov/pubmed/?term=N+Engl+J+Med+2003%3B+348(7)%3A645-650.
8. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA 2003; 289(20):2673-2684. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2003%3B+289(20)%3A2673-2684.
9. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 2003; 290(13):1739-1748. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2003%3B+290(13)%3A1739-1748
10. Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, Gass ML, Stefanick ML, Lane DS, Hays J, Johnson KC, Coker LH, Dailey M, Bowen D, WHIMS Investigators. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: A randomized controlled trial. JAMA 2003; 289(20):2663-2672. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2003%3B+289(20)%3A2663-2672.
11. Hays J, Ockene JK, Brunner RL, Kotchen JM, Manson JE, Patterson RE, et al. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med 2003; 348(19):1839-1854. http://www.ncbi.nlm.nih.gov/pubmed/?term=N+Engl+J+Med+2003%3B+348(19)%3A1839-1854
12. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003; 290(13):1729-1738. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2003%3B+290(13)%3A1729-1738

13. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003; 289(24):3243-3253. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2003%3B+289(24)%3A3243-3253.
14. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JE, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003; 289(20):2651-2662. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2003%3B+289(20)%3A2651-2662.
15. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004; 291(24):2947-2958. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2004%3B+291(24)%3A2947-2958
16. Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, Hsia J, Margolis KL, Hogan PE, Wallace R, Dailey M, Freeman R, Hays J. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004; 291(24):2959-2968. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2004%3B+291(24)%3A2959-2968
17. Hsia J, Criqui MH, Rodabough RJ, Langer RD, Resnick HE, Phillips LS, et al. for the Women's Health Initiative Investigators. Estrogen plus progestin and the risk of peripheral arterial disease: the Women's Health Initiative. Circulation 2004;109(5):620-626. http://www.ncbi.nlm.nih.gov/pubmed/14769684
18. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291(14):1701-1712. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2004%3B+291(14)%3A1701-1712.
19. Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al. Estrogen plus progestin and risk of venous thrombosis. JAMA 2004; 292(13):1573-1580. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2004%3B+292(13)%3A1573-1580
20. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia 2004; 47(7):1175-1187. http://www.ncbi.nlm.nih.gov/pubmed/?term=Diabetologia+2004%3B+47(7)%3A1175-1187
21. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004; 350(10):991-1004. http://www.ncbi.nlm.nih.gov/pubmed/?term=N+Engl+J+Med+2004%3B+350(10)%3A991-1004.
22. Manson JE, Bassuk S. The menopause transition and postmenopausal hormone therapy. In: Kasper DL et al, eds. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill, 2004:2209-2213.
23. Waters DD, Gordon D, Rossouw JE, Cannon RO 3rd, Collins P, Herrington DM, et al. National Heart, Lung and Blood Institute; American College of Cardiology Foundation. Women's Ischemic Syndrome Evaluation: current status and future research directions: Report of the National Heart, Lung and Blood Institute workshop: October 2-4, 2002 : Section 4: lessons from hormone replacement trials. Circulation 2004; 109(6):e53-55. http://www.ncbi.nlm.nih.gov/pubmed/?term=Circulation+2004%3B+109(6)%3Ae53-55.
24. Resnick SM, Coker LH, Maki PM, Rapp SR, Espeland MA, Shumaker SA. The Women's Health Initiative Study of Cognitive Aging (WHISCA): A randomized clinical trial of the effects of hormone therapy on age-associated cognitive decline. Clin Trials 2004; 1(5):440-450. http://www.ncbi.nlm.nih.gov/pubmed/?term=Clin+Trials+2004%3B+1(5)%3A440-450.
25. Prentice RL, Langer R, Stefanick ML, Howard BV, Pettinger M, Anderson G, et al. for the Women's Health Initiative Investigators. Combined postmenopausal hormone therapy and cardiovascular disease: Toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. Am J Epidemiol 2005; 162(5):404-414. http://www.ncbi.nlm.nih.gov/pubmed/?term=Am+J+Epidemiol+2005%3B+162(5)%3A404-414.

26. Cirillo DJ, Wallace RB, Rodabough RJ, et al. Effect of estrogen therapy on gallbladder disease. JAMA 2005; 293(3):330-339. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2005%3B+293(3)%3A330-339.
27. Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol 2005; 105(5 Pt 1):1063-1073. http://www.ncbi.nlm.nih.gov/pubmed/?term=Obstet+Gynecol+2005%3B+105(5+Pt+1)%3A1063-1073.
28. Ockene JK, Barad DH, Cochrane BB, Larson JC, Gass M, Wassertheil-Smoller S, et al. Symptom experience after discontinuing use of estrogen plus progestin. JAMA 2005; 294(2):183-193. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2005%3B+294(2)%3A183-193.
29. McTiernan A, Martin CF, Peck JD, Aragaki AK, Chlebowski RT, Pisano ED, et al. for the Women's Health Initiative Mammogram Density Study Investigators. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. JNCI 2005; 97(18):1366-1376. http://www.ncbi.nlm.nih.gov/pubmed/?term=JNCI+2005%3B+97(18)%3A1366-1376.
30. Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA 2005; 293(8):935-948. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2005%3B+293(8)%3A935-948.
31. Brunner RL, Gass M, Aragaki A, Hays J, Granek I, Woods N, et al. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative Randomized Clinical Trial. Arch Intern Med 2005; 165(17):1976-1986. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Intern+Med+2005%3B+165(17)%3A1976-1986
32. Chen Z, Bassford T, Green SB, Cauley JA, Jackson RD, LaCroix AZ, Leboff M, Stefanick ML, Margolis KL. Postmenopausal hormone therapy and body composition--a substudy of the estrogen plus progestin trial of the Women's Health Initiative. Am J Clin Nutr 2005; 82(3):651-656. http://www.ncbi.nlm.nih.gov/pubmed/?term=Am+J+Clin+Nutr+2005%3B+82(3)%3A651-656.
33. Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. Arthritis Rheum 2006; 54(10):3194-3204. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arthritis+Rheum+2006%3B+54(10)%3A3194-3204
34. Hsia J, Manson JE, Kuller L, Pettinger M, Choe JH, Langer RD, et al. Impact of cyclooxygenase inhibitors in the Women's Health Initiative Hormone Trials: Secondary analysis of a randomized trial. PLoS Clin Trials 2006; 1(5):e26. http://www.ncbi.nlm.nih.gov/pubmed/?term=PLoS+Clin+Trials+2006%3B+1(5)%3Ae26.
35. Prentice RL, Langer RD, Stefanick ML, Howard BV, Pettinger M, Anderson GL, et al. for the Women's Health Initiative Investigators. Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. Am J Epidemiol. 2006; 163(7):589-599. http://www.ncbi.nlm.nih.gov/pubmed/?term=Am+J+Epidemiol.+2006%3B+163(7)%3A589-599.
36. Curb JD, Prentice RL, Bray PF, Langer RD, Van Horn L, Barnabei VM, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. Arch Intern Med 2006; 166(7):772-780. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Intern+Med+2006%3B+166(7)%3A772-780
37. Hsia J, Criqui MH, Herrington DM, Manson JE, Wu L, Heckbert SR, et al. for the Women's Health Initiative Research Group. Conjugated equine estrogens and peripheral arterial disease risk: The Women's Health Initiative. Am Heart J 2006; 152(1):170-176. http://www.ncbi.nlm.nih.gov/pubmed/?term=Am+Heart+J+2006%3B+152(1)%3A170-176
38. Anderson GL, Chlebowski RT, Rossouw JE, Rodabough RJ, McTiernan A, Margolis KL, Aggerwal A, Curb JD, Hendrix SL, Allan Hubbell F, Khandekar J, Lane DS, Lasser N, Lopez AM, Potter J, Ritenbaugh C. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. Maturitas 2006; 55(2):103-115. http://www.ncbi.nlm.nih.gov/pubmed/?term=Maturitas+2006%3B+55(2)%3A103-115
39. Resnick SM, Maki PM, Rapp SR, Espeland MA, Brunner R, Coker LH, et al. for the Women's Health Initiative Study of Cognitive Aging Investigators. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J Clin Endocrinol Metab 2006; 91(5):1802-1810. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Clin+Endocrinol+Metab+2006%3B+91(5)%3A1802-1810

40. Haan MN, Klein R, Klein BE, Deng Y, Blythe LK, Seddon JM, et al. Hormone therapy and age-related macular degeneration: the Women's Health Initiative Sight Exam Study. Arch Ophthalmol 2006; 124(7):988-992. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Ophthalmol+2006%3B+124(7)%3A988-992.
41. Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med 2006; 166(9):1027-1032. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Intern+Med+2006%3B+166(9)%3A1027-1032
42. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. Arch Intern Med 2006; 166(3):357-365. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Intern+Med+2006%3B+166(3)%3A357-365
43. Hendrix SL, Wassertheil-Smoller S, Johnson KC, Howard BV, Kooperberg C, Rossouw JE, et al. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. Circulation 2006; 113(20):2425-2434. http://www.ncbi.nlm.nih.gov/pubmed/?term=Circulation+2006%3B+113(20)%3A2425-2434.
44. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 2006; 295(14):1647-1657. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2006%3B+295(14)%3A1647-1657.
45. Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. J Bone Miner Res 2006; 21(6):817-828. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Bone+Miner+Res+2006%3B+21(6)%3A817-828
46. Bonds DE, Lasser N, Qi L, Brzyski R, Cann B, Heiss G, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. Diabetologia 2006; 49(3):459-468. http://www.ncbi.nlm.nih.gov/pubmed/?term=Diabetologia+2006%3B+49(3)%3A459-468.
47. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007; 297(13):1465-1477. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2007%3B+297(13)%3A1465-1477.
48. Kooperberg C, Cushman M, Hsia J, Robinson J, Aragaki A, Lynch J, et al. Can biomarkers identify women at increased stroke risk? The Women's Health Initiative hormone trials. PLoS Clin Trials 2007; 2(6): e28. http://www.ncbi.nlm.nih.gov/pubmed/?term=PLoS+Clin+Trials+2007%3B+2(6)%3A+e28.
49. Jackson RD, Shidham S. The role of hormone therapy and calcium plus vitamin D for reduction of bone loss and risk for fractures: Lessons learned from the Women's Health Initiative. Curr Osteoporos Rep 2007; 5(4):153-159. http://www.ncbi.nlm.nih.gov/pubmed/?term=Curr+Osteoporos+Rep+2007%3B+5(4)%3A153-159.
50. Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, et al. for the WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. N Engl J Med 2007; 356(25):2591-2602. http://www.ncbi.nlm.nih.gov/pubmed/?term=N+Engl+J+Med+2007%3B+356(25)%3A2591-2602
51. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007; 297(13):1465-1477. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2007%3B+297(13)%3A1465-1477.
52. Anderson GL, Kooperberg C, Geller N, Rossouw JE, Pettinger M, Prentice RL. Monitoring and reporting of the Women's Health Initiative randomized hormone therapy trials. Clin Trials 2007; 4(3):207-217. http://www.ncbi.nlm.nih.gov/pubmed/?term=Clin+Trials+2007%3B+4(3)%3A207-217
53. Allison MA, Manson JE, Langer RD, Carr JJ, Rossouw JE, Pettinger MB, et al for the Women's Health Initiative and Women's Health Initiative Coronary Artery Calcium Study Investigators. Oophorectomy, hormone therapy, and subclinical coronary artery disease in women with hysterectomy: the Women's Health Initiative coronary artery calcium study. Menopause 2008; 15(4 Pt 1):639-647. http://www.ncbi.nlm.nih.gov/pubmed/?term=Menopause+2008%3B+15(4+Pt+1)%3A639-647
54. Hsia J, Otvos JD, Rossouw JE, Wu L, Wassertheil-Smoller S, Hendrix SL, et al. for the Women's Health Initiative Research Group. Lipoprotein particle concentrations may explain the absence of coronary protection in the Women's Health Initiative Hormone Trials. Arterioscler Thromb Vasc Biol 2008;

28(9):1666-1671. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arterioscler+Thromb+Vasc+Biol+2008%3B+28(9)%3A1666-1671.
55. Rossouw JE, Cushman M, Greenland P, Lloyd-Jones DM, Bray P, Kooperberg C, et al. Inflammatory, lipid, thrombotic, and genetic markers of coronary heart disease risk in the Women's Health Initiative trials of hormone therapy. Arch Intern Med 2008; 168(20):2245-2253. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Intern+Med+2008%3B+168(20)%3A2245-2253.
56. Chen Z, Beck T, Cauley JA, Lewis CE, Lacroix A, Bassford T, e al. Hormone therapy improves femur geometry among ethnically diverse postmenopausal participants in the Women's Health Initiative Hormone Intervention Trials. J Bone Miner Res 2008; 23(12):1935-1945. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Bone+Miner+Res+2008%3B+23(12)%3A1935-1945.
57. Bray PF, Larson JC, Lacroix AZ, et al. Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. Am J Cardiol 2008; 101(11):1599-1605. http://www.ncbi.nlm.nih.gov/pubmed/?term=Am+J+Cardiol+2008%3B+101(11)%3A1599-1605.
58. Prentice RL, Chlebowski RT, Stefanick ML, Manson JE, Pettinger M, Hendrix SL, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. Am J Epidemiol 2008; 15;167(10):1207-1216. http://www.ncbi.nlm.nih.gov/pubmed/?term=Am+J+Epidemiol+2008%3B+15%3B167(10)%3A1207-1216.
59. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 2008; 299(9):1036-1045. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2008%3B+299(9)%3A1036-1045.
60. Ritenbaugh C, Stanford JL, Wu L, Shikany JM, Schoen RE, Stefanick ML, et al. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. Cancer Epidemiol Biomarkers Prev 2008; 17(10):2609-2618. http://www.ncbi.nlm.nih.gov/pubmed/?term=Cancer+Epidemiol+Biomarkers+Prev+2008%3B+17(10)%3A2609-2618.
61. Walitt B, Pettinger M, Weinstein A, et al. Effects of postmenopausal hormone therapy on rheumatoid arthritis: the women's health initiative randomized controlled trials. Arthritis Rheum 2008; 59(3):302-310. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arthritis+Rheum+2008%3B+59(3)%3A302-310.
62. Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SA, Brzyski R, Chlebowski RT, Gass M, LaCroix A, Manson JE, Prentice RL, Rossouw J, Stefanick ML; WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 2008; 299(9):1036-1045. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2008%3B+299(9)%3A1036-1045.
63. Rohan TE, Negassa A, Chlebowski RT, Habel L, McTiernan A, Ginsberg M, Wassertheil-Smoller S, Page DL. Conjugated equine estrogen and risk of benign proliferative breast disease: A randomized controlled trial. JNCI 2008; 100(8):563-571. http://www.ncbi.nlm.nih.gov/pubmed/?term=JNCI+2008%3B+100(8)%3A563-571.
64. Rohan TE, Negassa A, Chlebowski RT, Lasser NL, McTiernan A, Schenken RS, Ginsberg M, Wassertheil-Smoller S, Page DL. Estrogen plus progestin and risk of benign proliferative breast disease. Cancer Epidemiol Biomarkers Prev 2008; 17(9):2337-2343. http://www.ncbi.nlm.nih.gov/pubmed/?term=Cancer+Epidemiol+Biomarkers+Prev+2008%3B+17(9)%3A2337-2343.
65. Prentice RL, Chlebowski RT, Stefanick ML, Manson JE, Langer RD, Pettinger M, Hendrix SL, Hubbell FA, Kooperberg C, Kuller LH, Lane DS, McTiernan A, O'Sullivan MJ, Rossouw JE, Anderson GL. Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. Am J Epidemiol 2008; 167(12):1407-1415. http://www.ncbi.nlm.nih.gov/pubmed/?term=Am+J+Epidemiol+2008%3B+167(12)%3A1407-1415.
66. Chlebowski RT, Anderson G, Pettinger M, Lane D, Langer RD, Gillian MA, et al. for the Women's Health Initiative Investigators. Estrogen plus progestin and breast cancer detection by means of mammography

and breast biopsy. Arch Intern Med 2008; 168(4):370-377. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Intern+Med+2008%3B+168(4)%3A370-377
67. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet 2009; 374(9697):1243-1251. http://www.ncbi.nlm.nih.gov/pubmed/?term=Lancet+2009%3B+374(9697)%3A1243-1251
68. Prentice RL, Huang Y, Hinds DA, Peters U, Pettinger M, Cox DR, et al. Variation in the FGFR2 gene and the effects of postmenopausal hormone therapy on invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2009; 18(11):3079-3085. http://www.ncbi.nlm.nih.gov/pubmed/?term=Cancer+Epidemiol+Biomarkers+Prev+2009%3B+18(11)%3A3079-3085.
69. Coker LH, Espeland MA, Rapp SR, Legault C, Resnick SM, Hogan P, Gaussoin S, Dailey M, Shumaker SA. Postmenopausal Hormone Therapy and Cognitive Outcomes: the Women's Health Initiative Memory Study (WHIMS). J Steroid Biochem Mol Biol 2010; 118(4-5):304-310. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Steroid+Biochem+Mol+Biol+2010%3B+118(4-5)%3A304-310
70. Pitteri SJ, Hanash SM, Aragaki A, Amon LM, Chen L, Busald Buson T, Paczesny S, Katayama H, Wang H, Johnson MM, Zhang Q, McIntosh M, Wang P, Kooperberg C, Rossouw JE, Jackson R, Manson JE, Hsia J, Liu S, Martin L, Prentice RL. Postmenopausal estrogen and progestin effects on the serum proteome. Genome Med 2009; 1(12):121. http://www.ncbi.nlm.nih.gov/pubmed/?term=Genome+Med+2009%3B+1(12)%3A121
71. Crandall CJ, Aragaki AK, Chlebowski RT, McTiernan A, Anderson G, Hendrix SL, Cochrane BB, Kuller LH, Cauley JA. New-onset breast tenderness after initiation of estrogen plus progestin therapy and breast cancer risk. Arch Intern Med 2009; 169(18):1684-1691. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Intern+Med+2009%3B+169(18)%3A1684-1691.
72. Resnick SM, Espeland MA, An Y, Maki PM, Coker LH, Jackson R, Stefanick ML, Wallace R, Rapp SR; for the Women's Health Initiative Study of Cognitive Aging Investigators. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. J Clin Endocrinol Metab 2009; 94(11):4152-4161. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Clin+Endocrinol+Metab+2009%3B+94(11)%3A4152-4161.
73. Resnick SM, Espeland MA, Jaramillo SA, Hirsch C, Stefanick ML, Murray AM, Ockene J, Davatzikos C. Postmenopausal hormone therapy and regional brain volumes: The WHIMS-MRI Study. Neurology 2009; 13;72(2):135-142. http://www.ncbi.nlm.nih.gov/pubmed/?term=Neurology+2009%3B+13%3B72(2)%3A135-142.
74. Prentice RL, Manson JE, Langer RD, Anderson GL, Pettinger M, Jackson RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. Am J Epidemiol. 2009; 170(1):12-23. http://www.ncbi.nlm.nih.gov/pubmed/?term=Am+J+Epidemiol.+2009%3B+170(1)%3A12-23.
75. Katayama H, Paczesny S, Prentice R, Aragaki A, Faca VM, Pitteri SJ, Zhang Q, Wang H, Silva M, Kennedy J, Rossouw J, Jackson R, Hsia J, Chlebowski R, Manson JE, Hanash SM. Application of serum proteomics to the Women's Health Initiative conjugated equine estrogens trial reveals a multitude of effects relevant to clinical findings. Genome Med 2009; 1(4):47. http://www.ncbi.nlm.nih.gov/pubmed/?term=Genome+Med+2009%3B+1(4)%3A47
76. Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 2009; 360(6):573-587. http://www.ncbi.nlm.nih.gov/pubmed/?term=N+Engl+J+Med+2009%3B+360(6)%3A573-587.
77. Prentice RL, Pettinger M, Beresford SA, Wactawski-Wende J, Hubbell FA, et al. Colorectal cancer in relation to postmenopausal estrogen and estrogen plus progestin in the Women's Health Initiative Clinical Trial and Observational Study. Cancer Epidemiol Biomarkers Prev 2009; 18(5):1531-1537. http://www.ncbi.nlm.nih.gov/pubmed/?term=Cancer+Epidemiol+Biomarkers+Prev+2009%3B+18(5)%3A1531-1537

78. McTiernan A, Chlebowski RT, Martin C, Peck JD, Aragaki A, Pisano ED, Wang CY, Johnson KC, Manson JE, Wallace RB, Vitolins MZ, Heiss G. Conjugated equine estrogen influence on mammographic density in postmenopausal women in a substudy of the Women's Health Initiative Randomized Trial. J Clin Oncol 2009; 27(36):6135-6143. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Clin+Oncol+2009%3B+27(36)%3A6135-6143.
79. Espeland MA, Tindle HA, Bushnell CA, Jaramillo SA, Kuller LH, Margolis KL, et al. for the Women's Health Initiative Memory Study. Brain volumes, cognitive impairment, and conjugated equine estrogens. J Gerontol A Biol Sci Med Sci 2009; 64(12):1243-1250. http://www.ncbi.nlm.nih.gov/pubmed/?term=Gerontol+A+Biol+Sci+Med+Sci+2009%3B+64(12)%3A1243-1250
80. Coker LH, Hogan PE, Bryan NR, Kuller LH, Margolis KL, Bettermann K, et al. Postmenopausal hormone therapy and subclinical cerebrovascular disease: The WHIMS-MRI Study. Neurology 2009; 72(2):125-134. http://www.ncbi.nlm.nih.gov/pubmed/?term=Neurology+2009%3B+72(2)%3A125-134.
81. Edlefsen KL, Jackson RD, Prentice RL, Janssen I, Rajkovic A, O'Sullivan MJ, Anderson G. The effects of postmenopausal hormone therapy on serum estrogen, progesterone, and sex hormone-binding globulin levels in healthy postmenopausal women. Menopause 2010; 17(3):622-629. http://www.ncbi.nlm.nih.gov/pubmed/?term=Menopause+2010%3B+17(3)%3A622-629
82. Maalouf NM, Sato AH, Welch BJ, Howard BV, Cochrane BB, Sakhaee K, Robbins JA. Postmenopausal hormone use and the risk of nephrolithiasis: Results from the Women's Health Initiative hormone therapy trials. Arch Intern Med 2010; 170(18):1678-1685. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arch+Intern+Med+2010%3B+170(18)%3A1678-1685
83. Cauley JA, Lacroix AZ, Robbins JA, Larson J, Wallace R, Wactawski-Wende J, Chen Z, Bauer DC, Cummings SR, Jackson R. Baseline serum estradiol and fracture reduction during treatment with hormone therapy: The Women's Health Initiative randomized trial. Osteoporos Int 2010; 21(1):167-177. http://www.ncbi.nlm.nih.gov/pubmed/?term=Osteoporos+Int+2010%3B+21(1)%3A167-177.
84. Brunner RL, Aragaki A, Barnabei V, et al. Menopausal symptom experience before and after stopping estrogen therapy in the Women's Health Initiative randomized, placebo-controlled trial. Menopause 2010; 17(5):946-954. http://www.ncbi.nlm.nih.gov/pubmed/?term=Menopause+2010%3B+17(5)%3A946-954.
85. Chlebowski RT, Anderson G, Manson JE, Pettinger M, Yasmeen S, Lane D, Langer RD, et al. Estrogen alone in postmenopausal women and breast cancer detection by means of mammography and breast biopsy. J Clin Oncol 2010; 28(16):2690-2697. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Clin+Oncol+2010%3B+28(16)%3A2690-2697
86. Chlebowski RT, Anderson GL, Manson JE, Schwartz AG, Wakelee H, Gass M, et al. Lung cancer among postmenopausal women treated with estrogen alone in the Women's Health Initiative Randomized Trial. JNCI 2010; 102(18):1413-1421. http://www.ncbi.nlm.nih.gov/pubmed/?term=JNCI+2010%3B+102(18)%3A1413-1421.
87. Michael YL, Gold R, Manson JE, et al. Hormone therapy and physical function change among older women in the Women's Health Initiative: a randomized controlled trial. Menopause 2010; 17(2):295-302. http://www.ncbi.nlm.nih.gov/pubmed/?term=Menopause+2010%3B+17(2)%3A295-302.
88. Toh S, Hernández-Díaz S, Logan R, Rossouw JE, Hernán MA. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. Ann Intern Med 2010; 16;152(4):211-217. http://www.ncbi.nlm.nih.gov/pubmed/?term=Ann+Intern+Med+2010%3B+16%3B152(4)%3A211-217
89. Espeland ME, Brunner RL, Hogan PE, Rapp SR, Coker LH, Legault C, Granek I, and Resnick SM, for the Women's Health Initiative Study of Cognitive Aging Study Group. Long-term effects of conjugated equine estrogen therapies on domain-specific cognitive function: results from the Women's Health Initiative Study of Cognitive Aging Extension. J Am Geriatr Soc 2010; 58(7):1263-1271. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Am+Geriatr+Soc+2010%3B+58(7)%3A1263-1271
90. Brunner RL, Aragaki A, Barnabei V, Cochrane BB, Gass M, Hendrix S, et al. Menopausal symptom experience before and after stopping estrogen therapy in the Women's Health Initiative randomized,

placebo-controlled trial. Menopause 2010; 17(5):946-954. http://www.ncbi.nlm.nih.gov/pubmed/?term=Menopause+2010%3B+17(5)%3A946-954.
91. Chlebowski RT, Anderson GL, Gass M, Lane DS, Aragaki AK, Kuller LH, et al. for the WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 2010; 304(15):1684-92. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2010%3B+304(15)%3A1684-92.
92. Chlebowski RT, Anderson G, Manson JE, Pettinger M, Yasmeen S, Lane D, et al. Estrogen alone in postmenopausal women and breast cancer detection by means of mammography and breast biopsy. J Clin Onco 2010; 28(16):2690-2697. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Clin+Onco+2010%3B+28(16)%3A2690-2697.
93. Gass M, Cochrane BB, Larson JC, Manson, JE, Barnabei VM, Brzyski RG, et al. Patterns and predictors of sexual activity among women in the hormone therapy trials of the Women's Health Initiative. Menopause 2011; 18(11):1160-1171. http://www.ncbi.nlm.nih.gov/pubmed/?term=2011%3B+18(11)%3A1160-1171.
94. Bea JW, Zhao Q, Cauley JA, Lacroix AZ, Bassford T, Lewis CE, et al. Effect of hormone therapy on lean body mass, falls, and fractures: 6-year results from the Women's Health Initiative hormone trials. Menopause 2011 Jan;18(1):44-52. http://www.ncbi.nlm.nih.gov/pubmed/?term=Menopause+2011+Jan%3B18(1)%3A44-52.
95. Tang JY, Spaunhurst KM, Chlebowski RT, Wactawski-Wende J, Keiser E, et al. Menopausal hormone therapy and risks of melanoma and nonmelanoma skin cancers: Women's Health Initiative Randomized Trials. JNCI 2011; 103(19): 1469-1475. http://www.ncbi.nlm.nih.gov/pubmed/?term=JNCI+2011%3B+103(19)%3A+1469-1475.
96. Chlebowski RT, Anderson GL. The influence of time from menopause and mammography on hormone therapy–related breast cancer risk assessment. JNCI 2011; 103(4):284-285. http://www.ncbi.nlm.nih.gov/pubmed/?term=JNCI+2011%3B+103(4)%3A284-285
97. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA 2011; 305(13):1305-1314. http://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+2011%3B+305(13)%3A1305-1314.
98. Rossouw J, Bray P, Liu J, Kooperberg C, Hsia J, Lewis C, et al. Estrogen receptor polymorphisms and the vascular effects of hormone therapy. Arterioscler Thromb Vasc Biol 2011; 31(2):464-469. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arterioscler+Thromb+Vasc+Biol+2011%3B+31(2)%3A464-469.
99. Rossouw JE, Prentice RL, Manson JE, et al. Relationships of coronary heart disease with 27-hydroxycholesterol, low-density lipoprotein cholesterol, and menopausal hormone therapy. Circulation 2012; 126(13):1577-1586. http://www.ncbi.nlm.nih.gov/pubmed/?term=Circulation+2012%3B+126(13)%3A1577-1586.
100. Chlebowski RT, Anderson GL. Changing concepts: Menopausal hormone therapy and breast cancer. JNCI 2012; 104(7):517-527. http://www.ncbi.nlm.nih.gov/pubmed/?term=JNCI+2012%3B+104(7)%3A517-527.
101. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol 2012; 13(5):476-486. http://www.ncbi.nlm.nih.gov/pubmed/?term=Lancet+Oncol+2012%3B+13(5)%3A476-486.
102. Crandall CJ, Aragaki AK, Cauley JA, McTiernan A, Manson JE, Anderson G, Chlebowski RT. Breast tenderness and breast cancer risk in the estrogen plus progestin and estrogen-alone women's health initiative clinical trials. Breast Cancer Res Treat 2012; 132(1):275-285. http://www.ncbi.nlm.nih.gov/pubmed/?term=Breast+Cancer+Res+Treat+2012%3B+132(1)%3A275-285.
103. Simon MS, Chlebowski RT, Wactawski-Wende J, Johnson KC, Muskovitz A, et al. Estrogen plus progestin and colorectal cancer incidence and mortality. J Clin Oncol 2012; 30(32):3983-90. http://www.ncbi.nlm.nih.gov/pubmed/?term=J+Clin+Oncol+2012%3B+30(32)%3A3983-90.

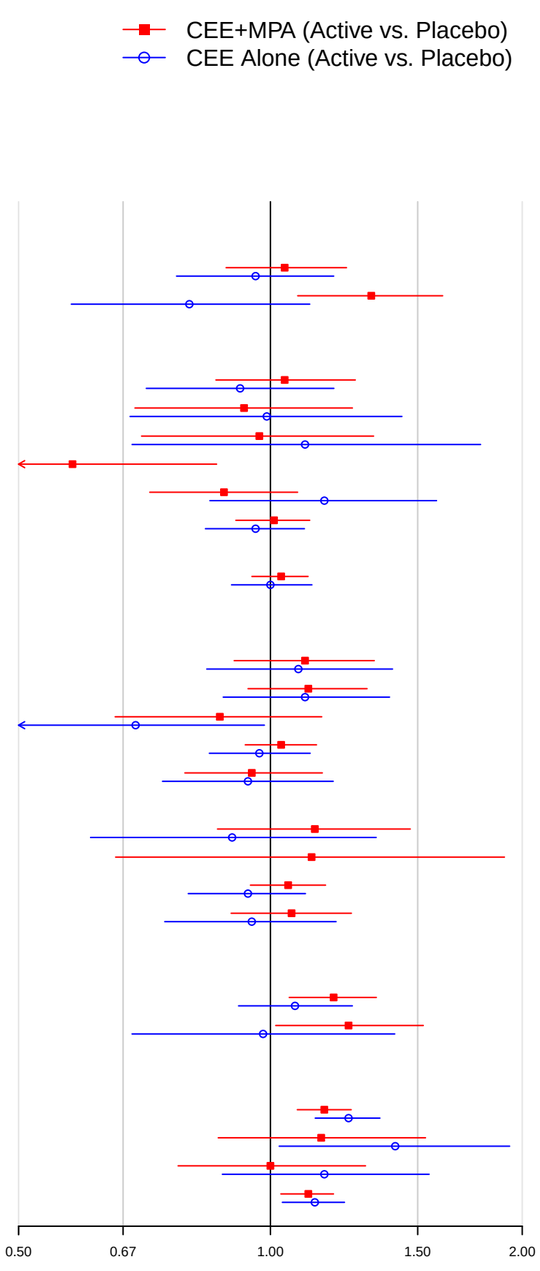
104. Crandall CJ, Aragaki AK, Cauley JA, McTiernan A, Manson JE, Anderson GL, et al. Breast tenderness after initiation of conjugated equine estrogens and mammographic density change. Breast Cancer Res Treat 2012; 131(3):969-979. http://www.ncbi.nlm.nih.gov/pubmed/?term=Breast+Cancer+Res+Treat+2012%3B+131(3)%3A969-979.
105. Perez MV, Wang PJ, Larson JC, Virnig BA, Cochrane B, Curb JD, et al. Effects of postmenopausal hormone therapy on incident atrial fibrillation: The Women's Health Initiative Randomized Controlled Trials. Circ Arrhythm Electrophysiol 2012; 5(6):1108-1116. http://www.ncbi.nlm.nih.gov/pubmed/?term=Arrhythm+Electrophysiol+2012%3B+5(6)%3A1108-1116.
106. Mackey RH, Fanelli TJ, Modugno F, Cauley JA, McTigue KM, Brooks MM, et al. Hormone therapy, estrogen metabolism, and risk of breast cancer in the Women's Health Initiative Hormone Therapy Trial. Cancer Epidemiol Biomarkers Prev 2012; 21(11):2022-2032. http://www.ncbi.nlm.nih.gov/pubmed/?term=Cancer+Epidemiol+Biomarkers+Prev+2012%3B+21(11)%3A2022-2032.
107. Huang Y, Ballinger DG, Stokowski R, Beilharz E, Robinson JG, Liu S, et al. Exploring the interaction between SNP genotype and postmenopausal hormone therapy effects on stroke risk. Genome Med 2012; 4(7):57. http://www.ncbi.nlm.nih.gov/pubmed/?term=Genome+Med+2012%3B+4(7)%3A57.
108. Rossouw JE, Johnson KC, Pettinger M, Cushman M, Sandset PM, Kuller L, et al. Tissue factor pathway inhibitor, activated protein C resistance, and risk of ischemic stroke due to postmenopausal hormone therapy. 2012; 43(4):952-957. http://www.ncbi.nlm.nih.gov/pubmed/?term=Rossouw+JE%2C+Johnson+KC%2C+Pettinger+M%2C+Cushman+M%2C+Sandset+PM%2C+Kuller+L+2012
109. Rossouw JE, Prentice RL, Manson JE, Aragaki AK, Hsia J, Martin LW, et al. Relationships of coronary heart disease with 27-hydroxycholesterol, low density lipoprotein cholesterol, and menopausal hormone therapy. Circulation 2012; 126(13):1577-1586. http://www.ncbi.nlm.nih.gov/pubmed/?term=Circulation+2012%3B+126(13)%3A1577-1586.
110. Luo J, Cochrane BB, Wactawski-Wende J, Hunt JR, Ockene JK, Margolis KL. Effects of menopausal hormone therapy on ductal carcinoma in situ of the breast. Breast Cancer Res Treat 2013; 137(3):915-925. http://www.ncbi.nlm.nih.gov/pubmed/?term=Breast+Cancer+Res+Treat+2013%3B+137(3)%3A915-925.
111. Canonico M, Plu-Bureau G, O'Sullivan MJ, Stefanick ML, Cochrane B, Scarabin PY, Manson JE. Age at menopause, reproductive history, and venous thromboembolism risk among postmenopausal women: the Women's Health Initiative hormone therapy clinical trials. Menopause 2013; in press.[e-pub 6/10/13] http://www.ncbi.nlm.nih.gov/pubmed/?term=Canonico+M%2C+Plu-Bureau+G%2C+O'Sullivan+MJ%2C+Stefanick+ML%2C+Cochrane+B%2C+Scarabin+PY2013
112. Espeland MA, Pettinger M, Falkner KL, Shumaker SA, Limacher M, Thomas F, et al. Demographic and health factors associated with enrollment in posttrial studies: The Women's Health Initiative hormone therapy trials. Clin Trials 2013; 10(3):463-472. http://www.ncbi.nlm.nih.gov/pubmed/?term=Clin+Trials+2013%3B+10(3)%3A463-472.
113. Chlebowski RT, Cirillo DJ, Eaton CB, Stefanick ML, Pettinger M, Carbone LD, et al. Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial. Menopause 2013; 20(6):600-608. http://www.ncbi.nlm.nih.gov/pubmed/?term=Menopause+2013%3B+20(6)%3A600-608
114. Wild RA, Wu C, Curb JD, Martin LW, Phillips L, Stefanick M, Trevisan M, Manson JE. Coronary heart disease events in the Women's Health Initiative hormone trials: effect modification by metabolic syndrome: A nested case-control study within the Women's Health Initiative randomized clinical trials. Menopause 2013; 20(3):254-260 http://www.ncbi.nlm.nih.gov/pubmed/?term=Wild+RA%2C+Wu+C%2C+Curb+JD%2C+Martin+LW%2C+Phillips+L%2C+Stefanick+M%2C+Trevisan+2013.
115. Robbins JA, Aragaki A, Crandall CJ, Manson JE, Carbone L, Jackson R, et al. Women's Health Initiative clinical trials: interaction of calcium and vitamin D with hormone therapy. Menopause 2013; [e-pub 6/24/13]

http://www.ncbi.nlm.nih.gov/pubmed/?term=Robbins+JA%2C+Aragaki+A%2C+Crandall+CJ%2C+Manson+JE%2C+Carbone+L%2C+Jackson+R+2013.
116. Espeland MA, Shumaker SA, Leng I, Manson JE, Brown CM, Leblanc ES, et al. for the WHIMSY Study Group. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50-55 years. JAMA Intern Med 2013; [e-pub 6/24/13] http://www.ncbi.nlm.nih.gov/pubmed/?term=Espeland+MA%2C+Shumaker+SA%2C+Leng+I%2C+Manson+JE%2C+Brown+CM%2C+Leblanc+ES+2013.

Additional publications have been developed from the publically available WHI dataset. Such manuscripts, which do not undergo review by the WHI Publications & Presentations Committee, may not reflect the views and data interpretation of the WHI research team, have not been included in the above listing.

Appendix eFigure 1. Absolute Risks and Hazard Ratios for Outcomes in the WHI Hormone Therapy Trials (PostIntervention Phase)

	CEE+MPA Trial						CEE Alone Trial					
Primary Endpoints	**Active N(%*)**	**Placebo N(%*)**	**Diff per 10K pys^**	**HR**	**95%CI**	**P**	**Active N(%*)**	**Placebo N(%*)**	**Diff per 10K pys^**	**HR**	**95%CI**	**P**
Coronary heart disease	291(0.55)	271(0.53)	+2	1.04	(0.89, 1.23)	0.61	159(0.68)	171(0.72)	−4	0.96	(0.77, 1.19)	0.70
Invasive breast cancer	228(0.43)	168(0.33)	+10	1.32	(1.08, 1.61)	0.007	64(0.27)	81(0.34)	−7	0.80	(0.58, 1.11)	0.19
Other Endpoints in the Global Index												
Stroke	217(0.40)	202(0.39)	+1	1.04	(0.86, 1.26)	0.67	109(0.46)	123(0.51)	−5	0.92	(0.71, 1.19)	0.53
Pulmonary embolism	85(0.16)	87(0.17)	−1	0.93	(0.69, 1.25)	0.63	55(0.23)	57(0.23)	0	0.99	(0.68, 1.44)	0.95
Colorectal cancer	76(0.14)	75(0.15)	−1	0.97	(0.70, 1.33)	0.83	35(0.15)	32(0.13)	+1	1.10	(0.68, 1.78)	0.69
Endometrial cancer	41(0.08)	66(0.13)	−5	0.58	(0.40, 0.86)	0.007					Not applicable	
Hip fracture	179(0.33)	195(0.38)	−5	0.88	(0.72, 1.08)	0.22	86(0.36)	74(0.31)	+6	1.16	(0.85, 1.58)	0.36
All−cause mortality	761(1.39)	728(1.39)	0	1.01	(0.91, 1.11)	0.90	403(1.66)	426(1.73)	−7	0.96	(0.84, 1.10)	0.54
Global index	1322(2.75)	1261(2.70)	+4	1.03	(0.95, 1.11)	0.50	621(2.90)	642(2.96)	−6	1.00	(0.90, 1.12)	0.95
Secondary Endpoints												
Total MI	221(0.42)	195(0.38)	+3	1.10	(0.91, 1.33)	0.34	121(0.52)	115(0.48)	+3	1.08	(0.84, 1.40)	0.54
CABG/PCI	308(0.59)	271(0.54)	+5	1.11	(0.94, 1.30)	0.22	156(0.69)	141(0.61)	+8	1.10	(0.88, 1.39)	0.40
Deep vein thrombosis	90(0.17)	101(0.20)	−3	0.87	(0.65, 1.15)	0.32	50(0.21)	74(0.31)	−10	0.69	(0.48, 0.98)	0.04
All cardiovascular events	820(1.70)	783(1.68)	+2	1.03	(0.93, 1.14)	0.57	390(1.93)	414(2.00)	−6	0.97	(0.85, 1.12)	0.68
Cardiovascular deaths	214(0.39)	216(0.41)	−2	0.95	(0.79, 1.15)	0.63	134(0.55)	145(0.59)	−4	0.94	(0.74, 1.19)	0.60
Lung cancer	120(0.22)	101(0.19)	+3	1.13	(0.86, 1.47)	0.38	47(0.20)	53(0.22)	−2	0.90	(0.61, 1.34)	0.61
Ovarian cancer	29(0.05)	25(0.05)	+1	1.12	(0.65, 1.90)	0.69						
All cancer types**	753(1.51)	690(1.45)	+7	1.05	(0.95, 1.16)	0.36	286(1.27)	308(1.36)	−9	0.94	(0.80, 1.10)	0.43
Cancer deaths	295(0.54)	268(0.51)	+3	1.06	(0.90, 1.25)	0.50	134(0.55)	143(0.58)	−3	0.95	(0.75, 1.20)	0.65
Self−Reported Endpoints^^												
Diabetes	603(1.24)	482(1.04)	+20	1.19	(1.05, 1.34)	0.005	323(1.64)	306(1.54)	+10	1.07	(0.92, 1.25)	0.39
Gallbladder disease@	213(1.27)	166(1.01)	+26	1.24	(1.01, 1.52)	0.04	57(1.65)	61(1.66)	−2	0.98	(0.68, 1.41)	0.92
Self−Reported Symptoms#												
Urinary incontinence^^	23.5%(5194)	20.3%(4879)		1.16	(1.08, 1.25)	<0.001	28.6%(2781)	23.1%(2863)		1.24	(1.13, 1.35)	<0.001
Vasomotor symptoms##	32.8%(232)	28.4%(204)		1.15	(0.87, 1.53)	0.33	41.6%(149)	29.6%(142)		1.41	(1.02, 1.93)	0.03
Breast tenderness^^	1.8%(6594)	1.8%(6334)		1.00	(0.78, 1.30)	0.98	2.6%(3811)	2.2%(3900)		1.16	(0.88, 1.55)	0.29
Joint pain^^	23.4%(5228)	21.2%(5038)		1.11	(1.03, 1.19)	0.006	29.1%(2752)	25.8%(2819)		1.13	(1.03, 1.23)	0.007

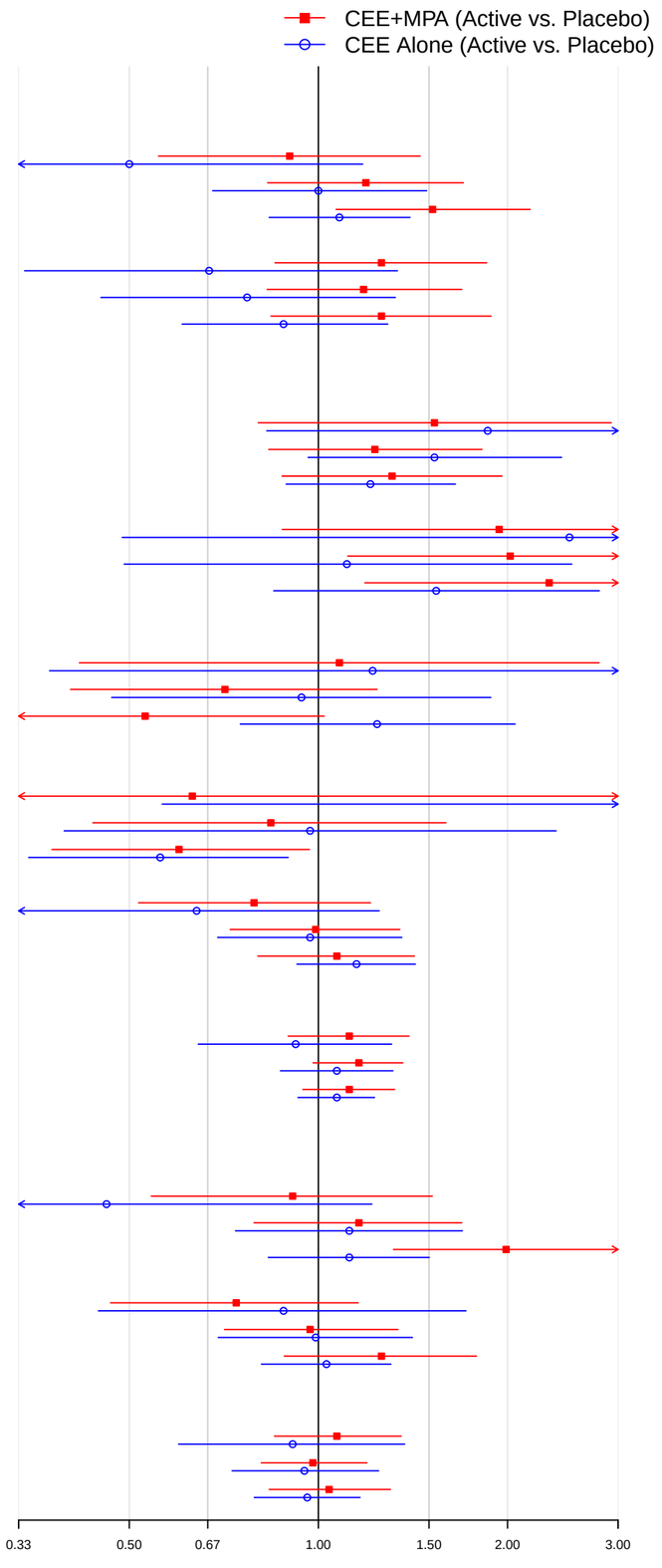


CEE indicates conjugated equine estrogens; and MPA, medroxyprogesterone acetate.

* Annualized percentage
** Excludes non−melanoma skin cancer
^Difference in estimated absolute excess risk (active minus placebo) per 10,000 person years. Numbers may not add up precisely due to rounding error.
@ Follow−up through planned close−out. Data not collected during WHI extension
^^ Includes participants who did not report a prevalent condition at baseline
# Collected at close−out. Proportion of women that reported symptom(denominator) and relative risk(95%CI) are reported
Includes symptomatic women 50−54 yrs of age

Appendix eFigure 2. Absolute Risks and Hazard Ratios for Outcomes in the Trials (Intervention Phase by Time Since Menopause)

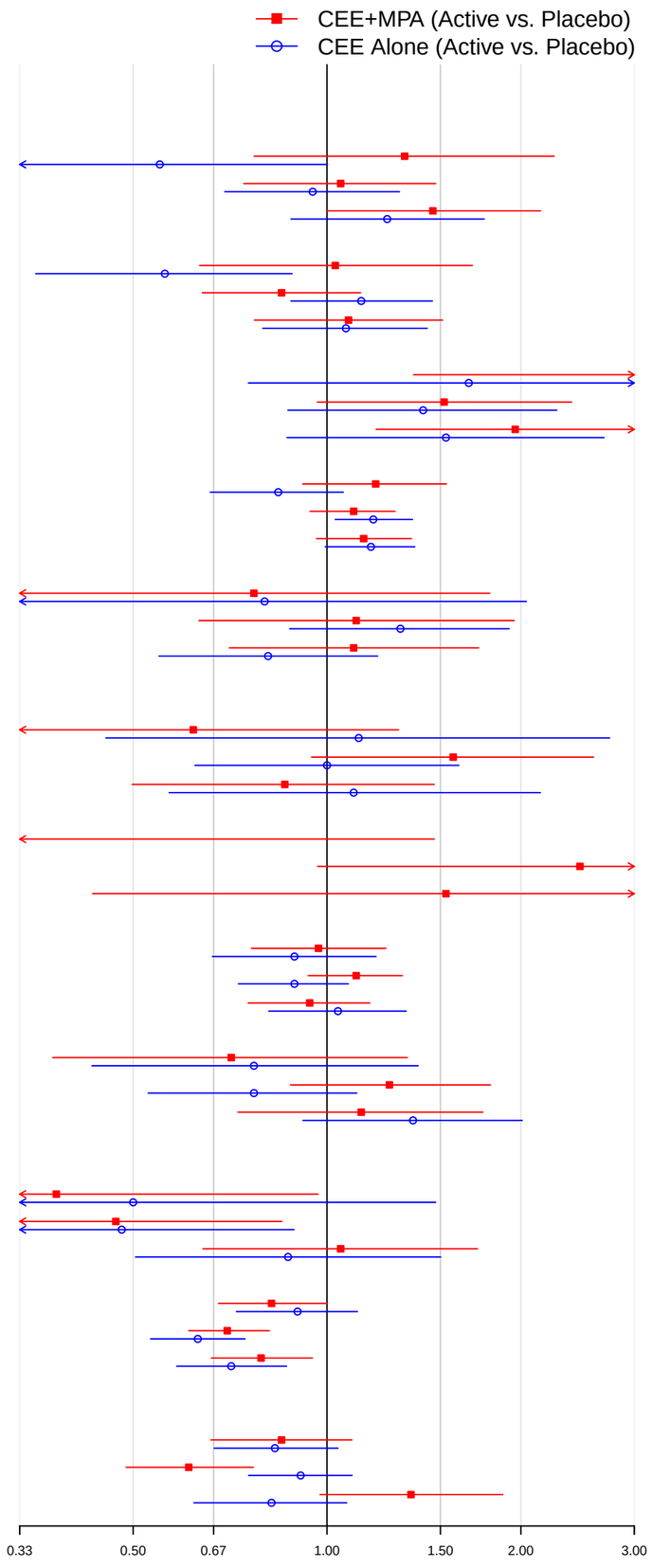
	CEE+MPA Trial						CEE Alone Trial					
Primary Endpoints	**Active N(%*)**	**Placebo N(%*)**	**Diff per 10K pys^**	**HR**	**95%CI**	**P−trend**	**Active N(%*)**	**Placebo N(%*)**	**Diff per 10K pys^**	**HR**	**95%CI**	**P−trend**
Coronary heart disease												
<10	32(0.20)	35(0.23)	−3	0.90	(0.56, 1.45)	0.08	8(0.13)	16(0.27)	−14	0.50	(0.22, 1.18)	0.16
10−<20	66(0.40)	55(0.34)	+6	1.19	(0.83, 1.70)		49(0.48)	51(0.48)	0	1.00	(0.68, 1.49)	
>=20	77(0.79)	51(0.54)	+26	1.52	(1.07, 2.17)		117(0.77)	115(0.72)	+5	1.08	(0.83, 1.40)	
Invasive breast cancer												
<10	59(0.37)	45(0.30)	+8	1.26	(0.85, 1.85)	>0.99	14(0.23)	20(0.34)	−10	0.67	(0.34, 1.34)	0.47
10−<20	67(0.41)	55(0.34)	+6	1.18	(0.83, 1.69)		23(0.23)	31(0.29)	−7	0.77	(0.45, 1.33)	
>=20	54(0.55)	42(0.44)	+11	1.26	(0.84, 1.88)		50(0.33)	59(0.37)	−4	0.88	(0.61, 1.29)	
Other Endpoints in the Global Index												
Stroke												
<10	24(0.15)	15(0.10)	+5	1.53	(0.80, 2.93)	0.79	17(0.28)	9(0.15)	+13	1.86	(0.83, 4.17)	0.25
10−<20	57(0.35)	46(0.29)	+6	1.23	(0.83, 1.82)		44(0.44)	30(0.28)	+15	1.53	(0.96, 2.44)	
>=20	56(0.57)	41(0.43)	+14	1.31	(0.88, 1.96)		86(0.56)	75(0.47)	+9	1.21	(0.89, 1.65)	
Pulmonary embolism												
<10	19(0.12)	9(0.06)	+6	1.94	(0.88, 4.30)	0.72	5(0.08)	2(0.03)	+5	2.51	(0.49, 12.97)	0.94
10−<20	33(0.20)	16(0.10)	+10	2.02	(1.11, 3.68)		12(0.12)	11(0.10)	+1	1.11	(0.49, 2.53)	
>=20	28(0.29)	12(0.13)	+16	2.33	(1.19, 4.59)		27(0.18)	18(0.11)	+6	1.54	(0.85, 2.80)	
Colorectal cancer												
<10	9(0.06)	8(0.05)	0	1.08	(0.42, 2.80)	0.23	6(0.10)	5(0.08)	+2	1.22	(0.37, 4.01)	0.74
10−<20	21(0.13)	29(0.18)	−5	0.71	(0.40, 1.24)		15(0.15)	17(0.16)	−1	0.94	(0.47, 1.88)	
>=20	14(0.14)	26(0.27)	−13	0.53	(0.28, 1.02)		33(0.21)	28(0.17)	+4	1.24	(0.75, 2.06)	
Hip fracture												
<10	2(0.01)	3(0.02)	−1	0.63	(0.11, 3.78)	0.55	5(0.08)	1(0.02)	+7	4.83	(0.56, 41.41)	0.03
10−<20	17(0.10)	20(0.12)	−2	0.84	(0.44, 1.60)		9(0.09)	10(0.09)	−1	0.97	(0.39, 2.39)	
>=20	28(0.29)	45(0.48)	−19	0.60	(0.38, 0.97)		26(0.17)	49(0.31)	−14	0.56	(0.35, 0.90)	
All−cause mortality												
<10	39(0.24)	47(0.31)	−6	0.79	(0.52, 1.21)	0.27	14(0.23)	22(0.37)	−14	0.64	(0.33, 1.25)	0.10
10−<20	80(0.48)	79(0.49)	−1	0.99	(0.72, 1.35)		65(0.64)	70(0.66)	−2	0.97	(0.69, 1.36)	
>=20	98(0.99)	89(0.93)	+7	1.07	(0.80, 1.42)		171(1.11)	156(0.97)	+14	1.15	(0.92, 1.43)	
Global index												
<10	170(1.09)	146(0.97)	+12	1.12	(0.89, 1.39)	0.96	60(1.01)	64(1.10)	−8	0.92	(0.64, 1.31)	0.56
10−<20	308(1.94)	264(1.69)	+25	1.16	(0.98, 1.36)		183(1.86)	179(1.74)	+12	1.07	(0.87, 1.31)	
>=20	291(3.12)	257(2.81)	+31	1.12	(0.94, 1.32)		393(2.68)	388(2.54)	+14	1.07	(0.93, 1.23)	
Selected Secondary Endpoints												
Total MI												
<10	28(0.18)	30(0.20)	−2	0.91	(0.54, 1.52)	0.01	6(0.10)	13(0.22)	−12	0.46	(0.18, 1.22)	0.23
10−<20	58(0.35)	49(0.31)	+5	1.16	(0.79, 1.69)		46(0.46)	43(0.41)	+5	1.12	(0.74, 1.70)	
>=20	67(0.69)	34(0.36)	+33	1.99	(1.32, 3.02)		91(0.60)	87(0.55)	+5	1.12	(0.83, 1.50)	
CABG/PCI												
<10	34(0.21)	43(0.28)	−7	0.74	(0.47, 1.16)	0.07	16(0.27)	19(0.32)	−5	0.88	(0.45, 1.72)	0.67
10−<20	75(0.46)	80(0.50)	−4	0.97	(0.71, 1.34)		60(0.60)	64(0.61)	−1	0.99	(0.69, 1.41)	
>=20	71(0.73)	55(0.58)	+15	1.26	(0.88, 1.79)		137(0.92)	138(0.88)	+4	1.03	(0.81, 1.30)	
All cancer types												
<10	151(0.97)	136(0.90)	+6	1.07	(0.85, 1.35)	0.87	43(0.72)	47(0.80)	−8	0.91	(0.60, 1.37)	0.83
10−<20	206(1.28)	204(1.30)	−2	0.98	(0.81, 1.19)		102(1.02)	112(1.08)	−6	0.95	(0.73, 1.25)	
>=20	162(1.69)	151(1.63)	+6	1.04	(0.84, 1.30)		197(1.32)	214(1.38)	−6	0.96	(0.79, 1.17)	



CEE indicates conjugated equine estrogens; and MPA, medroxyprogesterone acetate.
* Annualized percentage
^Difference in estimated absolute excess risk (active minus placebo) per 10,000 person years. Numbers may not add up precisely due to rounding error.

Appendix eFigure 3. Absolute Risks and Hazard Ratios for Secondary Outcomes in the Trials (Intervention Phase by Age Group)

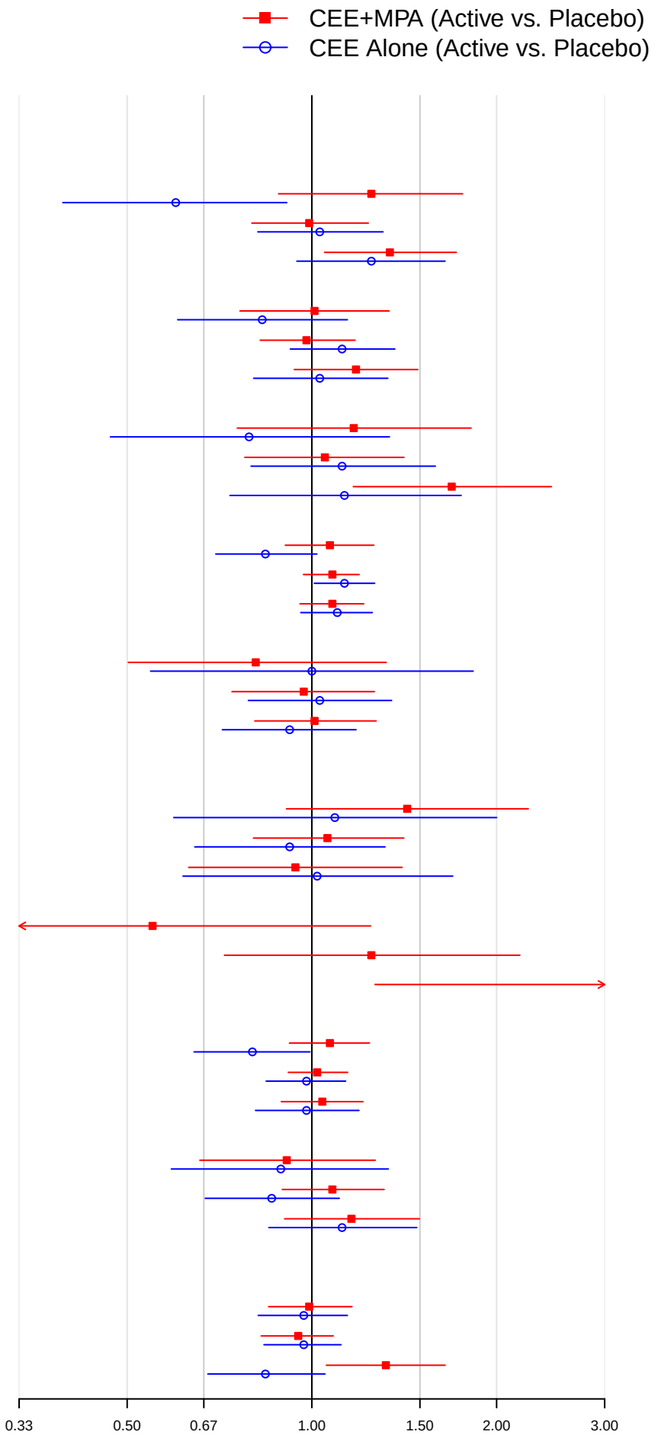
	CEE+MPA Trial						CEE Alone Trial					
Secondary Endpoints	Active N(%*)	Placebo N(%*)	Diff per 10K pys^	HR	95%CI	P−trend	Active N(%*)	Placebo N(%*)	Diff per 10K pys^	HR	95%CI	P−trend
Total MI												
50−59	32(0.19)	23(0.15)	+4	1.32	(0.77, 2.25)	0.55	17(0.14)	31(0.25)	−11	0.55	(0.31, 1.00)	0.02
60−69	70(0.33)	62(0.31)	+2	1.05	(0.74, 1.47)		76(0.46)	82(0.48)	−2	0.95	(0.69, 1.30)	
70−79	66(0.69)	44(0.47)	+21	1.46	(1.00, 2.15)		71(0.83)	60(0.69)	+14	1.24	(0.88, 1.75)	
CABG/PCI												
50−59	34(0.20)	32(0.20)	0	1.03	(0.63, 1.68)	0.67	29(0.24)	51(0.41)	−17	0.56	(0.35, 0.88)	0.06
60−69	92(0.43)	103(0.52)	−9	0.85	(0.64, 1.13)		129(0.79)	116(0.69)	+11	1.13	(0.88, 1.46)	
70−79	72(0.75)	65(0.70)	+5	1.08	(0.77, 1.51)		91(1.07)	88(1.02)	+5	1.07	(0.79, 1.43)	
Deep vein thrombosis												
50−59	26(0.15)	8(0.05)	+10	3.01	(1.36, 6.66)	0.58	16(0.13)	10(0.08)	+5	1.66	(0.75, 3.67)	0.93
60−69	49(0.23)	30(0.15)	+8	1.52	(0.97, 2.40)		39(0.23)	29(0.17)	+7	1.41	(0.87, 2.27)	
70−79	47(0.49)	23(0.25)	+24	1.96	(1.19, 3.24)		30(0.35)	20(0.23)	+12	1.53	(0.87, 2.69)	
All cardiovascular events												
50−59	135(0.82)	104(0.67)	+14	1.19	(0.92, 1.53)	0.92	127(1.08)	148(1.23)	−16	0.84	(0.66, 1.06)	0.06
60−69	361(1.76)	311(1.61)	+15	1.10	(0.94, 1.28)		430(2.80)	382(2.36)	+44	1.18	(1.03, 1.36)	
70−79	290(3.21)	248(2.80)	+41	1.14	(0.96, 1.35)		320(4.10)	283(3.50)	+60	1.17	(0.99, 1.37)	
Cardiovascular deaths												
50−59	10(0.06)	12(0.08)	−2	0.77	(0.33, 1.79)	0.55	8(0.07)	10(0.08)	−1	0.80	(0.32, 2.04)	0.35
60−69	27(0.13)	22(0.11)	+2	1.11	(0.63, 1.95)		56(0.33)	45(0.26)	+7	1.30	(0.88, 1.92)	
70−79	42(0.43)	36(0.38)	+5	1.10	(0.71, 1.72)		45(0.51)	57(0.64)	−13	0.81	(0.55, 1.20)	
Lung cancer												
50−59	12(0.07)	18(0.11)	−4	0.62	(0.30, 1.29)	0.78	10(0.08)	9(0.07)	+1	1.12	(0.45, 2.75)	0.96
60−69	41(0.19)	24(0.12)	+7	1.57	(0.95, 2.59)		34(0.20)	35(0.20)	0	1.00	(0.62, 1.60)	
70−79	25(0.26)	28(0.30)	−4	0.86	(0.50, 1.47)		18(0.21)	17(0.19)	+1	1.10	(0.57, 2.14)	
Ovarian cancer												
50−59	2(0.01)	6(0.04)	−3	0.30	(0.06, 1.47)	0.14						
60−69	16(0.07)	6(0.03)	+4	2.47	(0.97, 6.32)							
70−79	6(0.06)	4(0.04)	+2	1.53	(0.43, 5.44)							
All cancer types^^												
50−59	138(0.83)	130(0.84)	−1	0.97	(0.76, 1.23)	0.77	85(0.71)	96(0.79)	−8	0.89	(0.66, 1.19)	0.39
60−69	298(1.42)	249(1.28)	+15	1.11	(0.93, 1.31)		185(1.14)	216(1.29)	−15	0.89	(0.73, 1.08)	
70−79	162(1.71)	164(1.82)	−11	0.94	(0.75, 1.17)		129(1.52)	126(1.47)	+6	1.04	(0.81, 1.33)	
Cancer deaths												
50−59	17(0.10)	22(0.14)	−4	0.71	(0.38, 1.33)	0.37	20(0.16)	26(0.21)	−4	0.77	(0.43, 1.39)	0.05
60−69	72(0.33)	52(0.26)	+7	1.25	(0.88, 1.79)		48(0.29)	65(0.38)	−9	0.77	(0.53, 1.11)	
70−79	44(0.45)	37(0.39)	+6	1.13	(0.73, 1.75)		58(0.66)	44(0.49)	+17	1.36	(0.92, 2.01)	
Vertebral fracture												
50−59	6(0.04)	15(0.10)	−6	0.38	(0.15, 0.97)	0.02	5(0.04)	10(0.08)	−4	0.50	(0.17, 1.47)	0.20
60−69	17(0.08)	32(0.16)	−8	0.47	(0.26, 0.85)		15(0.09)	32(0.19)	−10	0.48	(0.26, 0.89)	
70−79	33(0.34)	31(0.33)	+1	1.05	(0.64, 1.71)		24(0.28)	28(0.32)	−4	0.87	(0.50, 1.50)	
All fracture												
50−59	195(1.20)	218(1.45)	−25	0.82	(0.68, 1.00)	0.83	154(1.33)	176(1.49)	−16	0.90	(0.72, 1.11)	0.15
60−69	329(1.60)	425(2.26)	−66	0.70	(0.61, 0.81)		220(1.39)	349(2.18)	−80	0.63	(0.53, 0.75)	
70−79	217(2.36)	260(3.00)	−65	0.79	(0.66, 0.95)		170(2.08)	242(2.97)	−90	0.71	(0.58, 0.87)	
Diabetes (self−report)**												
50−59	118(0.74)	125(0.85)	−11	0.85	(0.66, 1.09)	0.10	143(1.31)	174(1.58)	−26	0.83	(0.67, 1.04)	0.99
60−69	124(0.61)	186(0.99)	−38	0.61	(0.49, 0.77)		212(1.44)	239(1.59)	−15	0.91	(0.76, 1.09)	
70−79	86(0.95)	62(0.70)	+24	1.35	(0.98, 1.88)		94(1.19)	114(1.46)	−27	0.82	(0.62, 1.07)	



CEE indicates conjugated equine estrogens; and MPA, medroxyprogesterone acetate.
* Annualized percentage
^Difference in estimated absolute excess risk (active minus placebo) per 10,000 person years. Numbers may not add up precisely due to rounding error.
^^ Excludes non−melanoma skin cancer
** Includes participants that did not report a prevalent condition at baseline

Appendix eFigure 4. Absolute Risks and Hazard Ratios for Secondary Outcomes in the Trials (Overall Combined Phases, by Age Group)

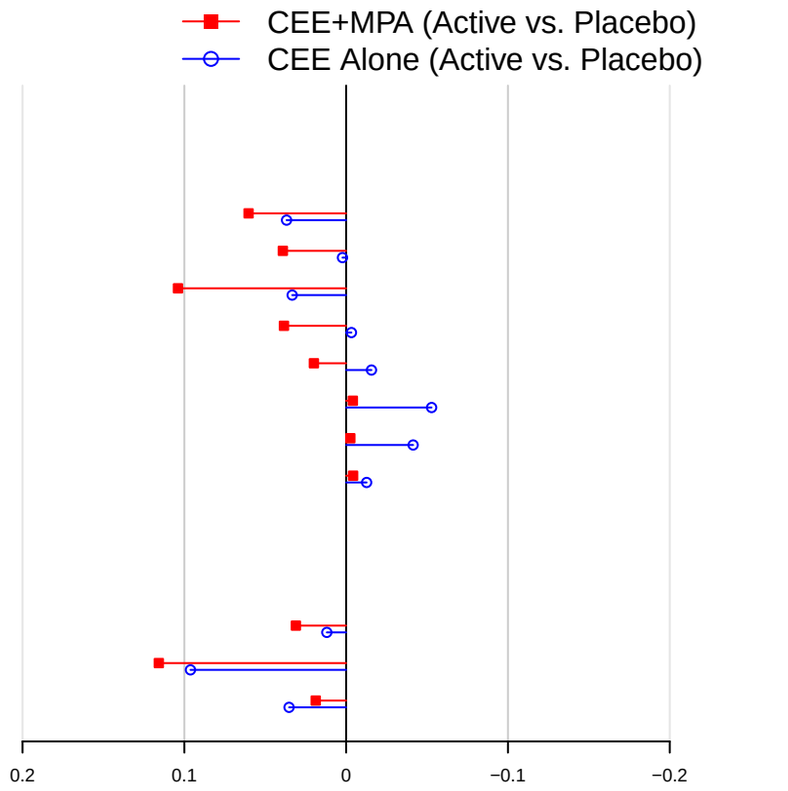
	CEE+MPA Trial						CEE Alone Trial					
Secondary Endpoints	Active N(%*)	Placebo N(%*)	Diff per 10K pys^	HR	95%CI	P−trend	Active N(%*)	Placebo N(%*)	Diff per 10K pys^	HR	95%CI	P−trend
Total MI												
50−59	75(0.21)	57(0.17)	+4	1.25	(0.88, 1.76)	0.46	35(0.17)	58(0.29)	−11	0.60	(0.39, 0.91)	0.007
60−69	165(0.36)	158(0.36)	0	0.99	(0.80, 1.24)		140(0.52)	139(0.49)	+2	1.03	(0.82, 1.31)	
70−79	149(0.76)	109(0.57)	+19	1.34	(1.05, 1.72)		110(0.82)	91(0.67)	+16	1.25	(0.95, 1.65)	
CABG/PCI												
50−59	102(0.29)	96(0.29)	0	1.01	(0.76, 1.34)	0.34	71(0.36)	83(0.42)	−6	0.83	(0.60, 1.14)	0.40
60−69	246(0.54)	244(0.57)	−3	0.98	(0.82, 1.18)		212(0.80)	192(0.69)	+10	1.12	(0.92, 1.37)	
70−79	158(0.81)	131(0.69)	+12	1.18	(0.94, 1.49)		122(0.93)	121(0.90)	+2	1.03	(0.80, 1.33)	
Deep vein thrombosis												
50−59	45(0.13)	36(0.11)	+2	1.17	(0.76, 1.82)	0.15	25(0.12)	32(0.16)	−3	0.79	(0.47, 1.34)	0.34
60−69	91(0.20)	82(0.19)	+1	1.05	(0.78, 1.41)		67(0.24)	62(0.22)	+3	1.12	(0.80, 1.59)	
70−79	76(0.38)	44(0.23)	+16	1.69	(1.17, 2.46)		43(0.31)	39(0.28)	+3	1.13	(0.74, 1.75)	
All cardiovascular events												
50−59	300(0.87)	262(0.81)	+6	1.07	(0.91, 1.26)	0.94	202(1.06)	231(1.21)	−15	0.84	(0.70, 1.02)	0.07
60−69	744(1.75)	667(1.64)	+11	1.08	(0.97, 1.19)		624(2.56)	580(2.26)	+31	1.13	(1.01, 1.27)	
70−79	562(3.22)	517(2.98)	+24	1.08	(0.96, 1.21)		441(3.76)	416(3.42)	+33	1.10	(0.96, 1.25)	
Cardiovascular deaths												
50−59	31(0.09)	35(0.10)	−2	0.81	(0.50, 1.32)	0.46	21(0.10)	21(0.10)	0	1.00	(0.55, 1.83)	0.60
60−69	110(0.24)	106(0.24)	0	0.97	(0.74, 1.26)		106(0.38)	107(0.37)	+1	1.03	(0.79, 1.35)	
70−79	152(0.75)	145(0.74)	+1	1.01	(0.81, 1.27)		116(0.84)	129(0.92)	−8	0.92	(0.71, 1.18)	
Lung cancer												
50−59	47(0.13)	31(0.09)	+4	1.43	(0.91, 2.25)	0.18	22(0.11)	20(0.10)	+1	1.09	(0.60, 2.00)	0.92
60−69	103(0.22)	91(0.21)	+1	1.06	(0.80, 1.41)		57(0.21)	64(0.22)	−2	0.92	(0.64, 1.32)	
70−79	48(0.24)	49(0.25)	−1	0.94	(0.63, 1.40)		30(0.22)	30(0.21)	0	1.02	(0.62, 1.70)	
Ovarian cancer												
50−59	9(0.03)	15(0.04)	−2	0.55	(0.24, 1.25)	0.005						
60−69	29(0.06)	22(0.05)	+1	1.25	(0.72, 2.18)							
70−79	15(0.07)	4(0.02)	+5	3.82	(1.27, 11.52)							
All cancer types**												
50−59	366(1.07)	321(1.00)	+7	1.07	(0.92, 1.24)	0.80	147(0.75)	182(0.93)	−18	0.80	(0.64, 0.99)	0.18
60−69	644(1.47)	595(1.44)	+4	1.02	(0.92, 1.14)		336(1.27)	358(1.31)	−4	0.98	(0.84, 1.14)	
70−79	341(1.81)	317(1.75)	+7	1.04	(0.89, 1.21)		202(1.53)	206(1.55)	−2	0.98	(0.81, 1.19)	
Cancer deaths												
50−59	70(0.19)	72(0.21)	−2	0.91	(0.66, 1.27)	0.27	44(0.22)	49(0.24)	−2	0.89	(0.59, 1.33)	0.24
60−69	226(0.48)	197(0.45)	+4	1.08	(0.89, 1.31)		111(0.40)	134(0.46)	−7	0.86	(0.67, 1.11)	
70−79	132(0.65)	110(0.56)	+9	1.16	(0.90, 1.50)		105(0.76)	95(0.67)	+8	1.12	(0.85, 1.48)	
Diabetes^^ (self−report)												
50−59	328(1.00)	302(0.99)	+1	0.99	(0.85, 1.16)	0.10	269(1.55)	281(1.62)	−6	0.97	(0.82, 1.14)	0.39
60−69	422(0.99)	418(1.04)	−5	0.95	(0.83, 1.08)		356(1.50)	379(1.56)	−6	0.97	(0.84, 1.12)	
70−79	181(0.99)	135(0.75)	+24	1.32	(1.06, 1.65)		147(1.21)	173(1.44)	−23	0.84	(0.68, 1.05)	



CEE indicates conjugated equine estrogen; and MPA, medroxyprogesterone acetate.
* Annualized percentage
^Difference in estimated absolute excess risk (active minus placebo) per 10,000 person years. Numbers may not add up precisely due to rounding error.
** Excludes non−melanoma skin cancer
^^ Includes participants that did not report a prevalent condition at baseline

Appendix eFigure 5. Results for Other Health−Related Quality of Life Variables in the WHI Hormone Therapy Trials (Intervention Phase)

	CEE+MPA Trial			CEE Alone Trial		
RAND−36*	**Active Mean(95%CI)**	**Placebo Mean(95%CI)**	**P−val**	**Active Mean(95%CI)**	**Placebo Mean(95%CI)**	**P−val**
Physical functioning	82.6(82.3, 82.9)	81.8(81.5, 82.1)	<0.001	76.0(75.5, 76.4)	75.4(75.0, 75.8)	0.08
Role physical	77.4(76.7, 78.0)	76.2(75.5, 76.9)	0.02	69.0(68.0, 70.0)	68.9(68.0, 69.9)	0.91
Bodily pain	77.6(77.2, 78.0)	75.6(75.2, 76.1)	<0.001	69.8(69.2, 70.4)	69.1(68.5, 69.7)	0.10
General health	76.6(76.3, 76.9)	76.1(75.8, 76.4)	0.02	72.2(71.8, 72.6)	72.2(71.9, 72.6)	0.87
Vitality	65.2(64.9, 65.6)	64.9(64.6, 65.3)	0.22	60.9(60.5, 61.3)	61.1(60.7, 61.6)	0.45
Social Functioning	89.9(89.5, 90.3)	90.0(89.6, 90.4)	0.80	85.8(85.3, 86.4)	86.9(86.3, 87.4)	0.01
Role emotional	85.3(84.7, 85.9)	85.4(84.8, 86.0)	0.87	81.0(80.2, 81.8)	82.2(81.4, 83.0)	0.04
Mental health	80.7(80.4, 80.9)	80.7(80.5, 81.0)	0.79	78.5(78.2, 78.9)	78.7(78.3, 79.0)	0.54
Other						
Self−reported health^	2.27(2.26, 2.29)	2.29(2.28, 2.31)	0.06	2.53(2.51, 2.55)	2.54(2.52, 2.55)	0.56
Sleep disturbance#	6.13(6.05, 6.20)	6.51(6.44, 6.59)	<0.001	6.92(6.81, 7.02)	7.25(7.15, 7.36)	<0.001
Depressive symptoms@	2.21(2.16, 2.26)	2.25(2.20, 2.30)	0.25	2.58(2.51, 2.65)	2.66(2.59, 2.73)	0.09

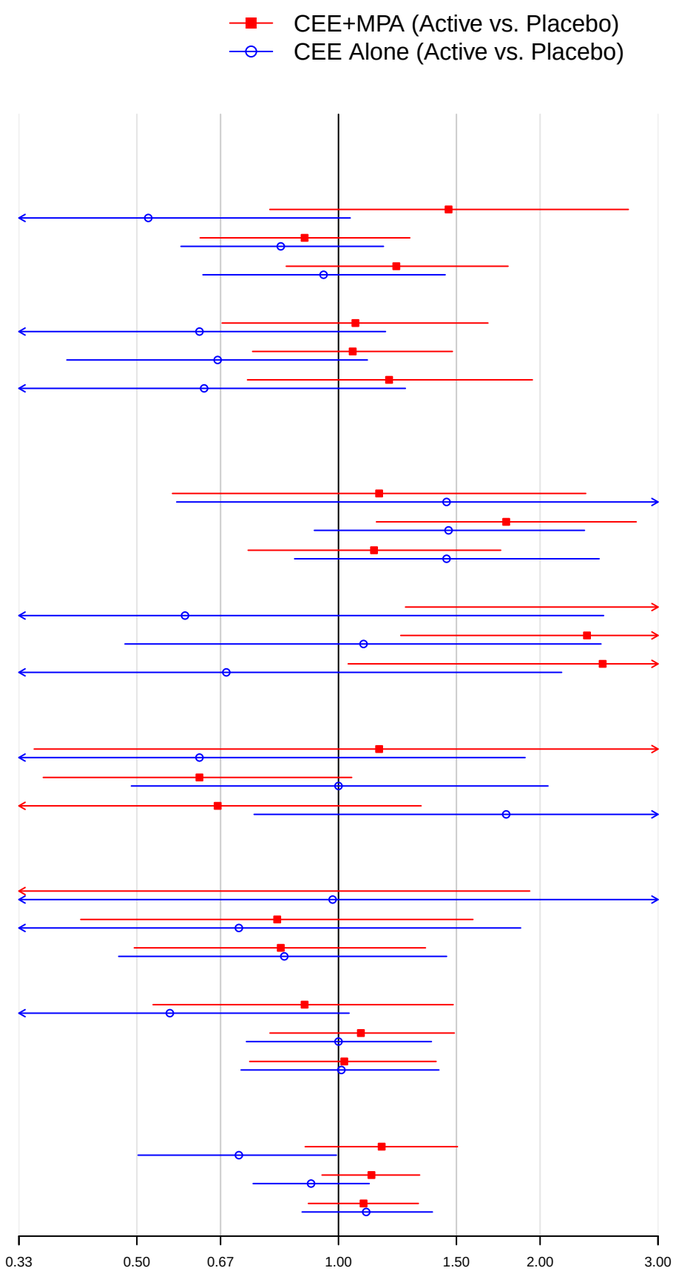


CEE indicates conjugated equine estrogens; and MPA, medroxyprogesterone acetate.
* Scored from 0 (worst) to 100 (best).
^ Scored from 1 (best) to 5 (worst).
# Scored from 0 (best) to 20 (worst).
@ Scored from 0 (best) to 18 (worst).

** Estimated Mean Difference at Year 1 , adjusting for baseline, divided by the root−mean−square error. For all measures, the sign of the effect size has been flipped (if necessary) so that adverse effects (favors placebo) extend to the right and favorable effects (favors active) extend to the left.

Appendix eFigure 6. Results Among Women in the Trials with No Prior HT Use (Intervention Phase by Age Group)

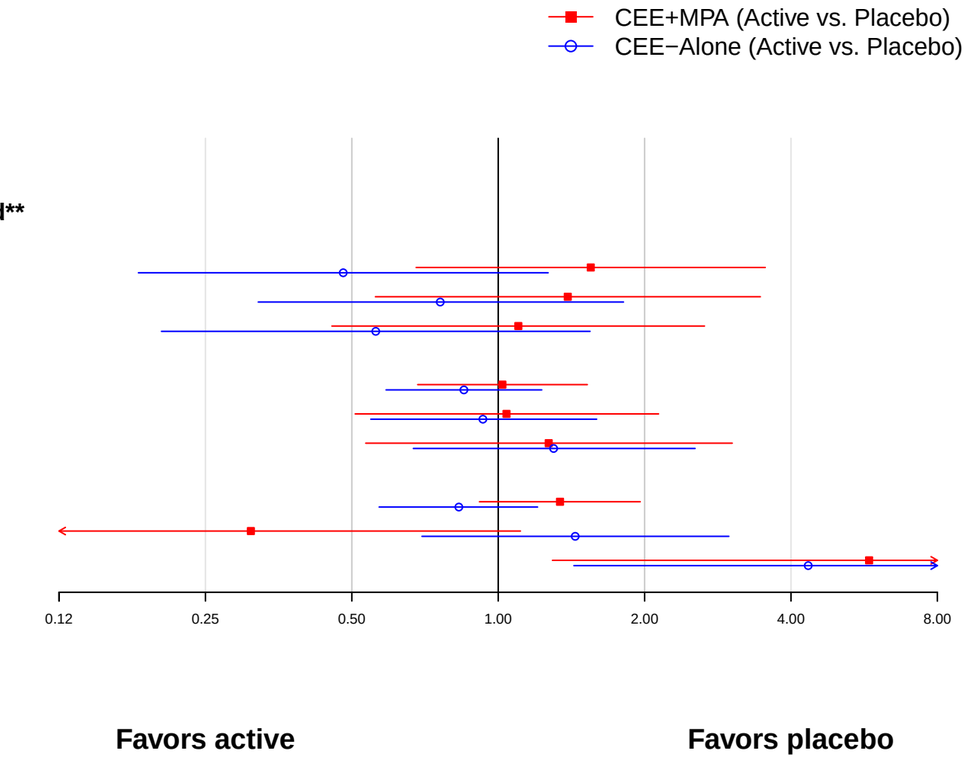
	CEE+MPA Trial						CEE Alone Trial					
Primary Endpoints	**Active N(%*)**	**Placebo N(%*)**	**Diff per 10K pys^**	**HR**	**95%CI**	**P−trend**	**Active N(%*)**	**Placebo N(%*)**	**Diff per 10K pys^**	**HR**	**95%CI**	**P−trend**
Coronary heart disease												
50−59	25(0.21)	17(0.15)	+6	1.46	(0.79, 2.71)	0.50	12(0.19)	23(0.37)	−18	0.52	(0.26, 1.04)	0.96
60−69	59(0.36)	60(0.40)	−4	0.89	(0.62, 1.28)		59(0.69)	69(0.81)	−13	0.82	(0.58, 1.17)	
70−79	59(0.83)	49(0.71)	+12	1.22	(0.84, 1.79)		43(0.95)	46(0.99)	−4	0.95	(0.63, 1.44)	
Invasive breast cancer												
50−59	39(0.33)	35(0.31)	+2	1.06	(0.67, 1.67)	0.81	15(0.24)	24(0.39)	−15	0.62	(0.32, 1.18)	0.98
60−69	70(0.43)	61(0.41)	+2	1.05	(0.74, 1.48)		24(0.28)	36(0.42)	−14	0.66	(0.39, 1.10)	
70−79	36(0.50)	29(0.42)	+9	1.19	(0.73, 1.95)		13(0.28)	21(0.45)	−17	0.63	(0.32, 1.26)	
Other Endpoints in the Global Index												
Stroke												
50−59	17(0.14)	14(0.12)	+2	1.15	(0.57, 2.34)	0.83	11(0.18)	8(0.13)	+5	1.45	(0.57, 3.67)	0.69
60−69	58(0.36)	30(0.20)	+16	1.78	(1.14, 2.78)		44(0.51)	30(0.35)	+16	1.46	(0.92, 2.33)	
70−79	44(0.62)	38(0.55)	+7	1.13	(0.73, 1.75)		34(0.75)	24(0.51)	+23	1.45	(0.86, 2.45)	
Pulmonary embolism												
50−59	16(0.14)	4(0.04)	+10	3.77	(1.26, 11.29)	0.07	3(0.05)	5(0.08)	−3	0.59	(0.14, 2.49)	0.34
60−69	33(0.20)	13(0.09)	+12	2.35	(1.24, 4.47)		12(0.14)	11(0.13)	+1	1.09	(0.48, 2.47)	
70−79	18(0.25)	7(0.10)	+15	2.48	(1.03, 5.93)		5(0.11)	7(0.15)	−4	0.68	(0.22, 2.15)	
Colorectal cancer												
50−59	6(0.05)	5(0.04)	+1	1.15	(0.35, 3.78)	0.71	5(0.08)	8(0.13)	−5	0.62	(0.20, 1.90)	0.70
60−69	23(0.14)	34(0.23)	−9	0.62	(0.36, 1.05)		15(0.17)	15(0.17)	0	1.00	(0.49, 2.06)	
70−79	13(0.18)	19(0.27)	−9	0.66	(0.32, 1.33)		14(0.30)	8(0.17)	+13	1.78	(0.75, 4.25)	
Hip fracture												
50−59	1(0.01)	4(0.04)	−3	0.21	(0.02, 1.93)	0.87	1(0.02)	1(0.02)	0	0.98	(0.06, 15.67)	0.23
60−69	16(0.10)	18(0.12)	−2	0.81	(0.41, 1.59)		7(0.08)	10(0.12)	−4	0.71	(0.27, 1.87)	
70−79	29(0.41)	34(0.49)	−9	0.82	(0.50, 1.35)		22(0.48)	27(0.58)	−10	0.83	(0.47, 1.45)	
All−cause mortality												
50−59	28(0.24)	30(0.26)	−3	0.89	(0.53, 1.48)	0.14	16(0.26)	28(0.45)	−19	0.56	(0.30, 1.04)	0.73
60−69	85(0.52)	70(0.46)	+5	1.08	(0.79, 1.49)		76(0.87)	76(0.88)	−1	1.00	(0.73, 1.38)	
70−79	77(1.07)	73(1.04)	+3	1.02	(0.74, 1.40)		66(1.42)	67(1.42)	0	1.01	(0.72, 1.41)	
Global index												
50−59	125(1.08)	103(0.92)	+16	1.16	(0.89, 1.51)	0.58	57(0.93)	80(1.33)	−40	0.71	(0.50, 0.99)	0.49
60−69	304(1.93)	249(1.70)	+22	1.12	(0.94, 1.32)		188(2.27)	200(2.45)	−18	0.91	(0.75, 1.11)	
70−79	229(3.37)	204(3.07)	+30	1.09	(0.90, 1.32)		159(3.69)	149(3.35)	+34	1.10	(0.88, 1.38)	



CEE indicates conjugated equine estrogens; and MPA, medroxyprogesterone acetate.
^ Difference in estimated absolute excess risk (active minus placebo) per 10,000 person years. Numbers may not add up precisely due to rounding error.
* Three−way trend test between randomizaton assignment, age group, and prior HT use

Appendix eFigure 7. CHD Results Among Women in the Trials (Intervention Phase, According to Vasomotor Symptoms and Age Group)

	CEE+MPA Trial					CEE−Alone Trial				
10−year age groups / Vasomotor symptoms	**Active N(%*)**	**Placebo N(%*)**	**HR**	**95%CI**	**P−trend****	**Active N(%*)**	**Placebo N(%*)**	**HR**	**95%CI**	**P−trend****
50−59 / None	15(0.21)	9(0.14)	1.55	(0.68, 3.54)	0.42	6(0.13)	13(0.28)	0.48	(0.18, 1.27)	0.04
Mild	11(0.19)	8(0.14)	1.39	(0.56, 3.46)		9(0.21)	12(0.28)	0.76	(0.32, 1.81)	
Moderate or severe	11(0.29)	9(0.27)	1.10	(0.46, 2.66)		6(0.18)	10(0.3)	0.56	(0.20, 1.55)	
60−69 / None	50(0.35)	46(0.35)	1.02	(0.68, 1.53)		52(0.53)	62(0.61)	0.85	(0.59, 1.23)	
Mild	16(0.31)	14(0.29)	1.04	(0.51, 2.14)		26(0.62)	28(0.64)	0.93	(0.55, 1.59)	
Moderate or severe	12(0.64)	9(0.55)	1.27	(0.53, 3.03)		19(0.82)	16(0.66)	1.30	(0.67, 2.54)	
70−79 / None	64(0.84)	46(0.63)	1.34	(0.92, 1.96)		50(0.79)	61(0.97)	0.83	(0.57, 1.21)	
Mild	3(0.19)	10(0.7)	0.31	(0.08, 1.11)		17(1.23)	13(0.83)	1.44	(0.70, 2.98)	
Moderate or severe	12(2.87)	2(0.45)	5.79	(1.29, 25.97)		15(2.1)	4(0.53)	4.34	(1.43, 13.14)	



CEE indicates conjugated equine estrogens; and MPA, medroxyprogesterone acetate.
* Annualized percentage
** Three−way trend test between randomizaton assignment, age group, and vasomotor symptoms

APPENDIX (SUPPLEMENTAL ONLINE MATERIALS)

Secondary and Patient-Reported Outcomes in the Two Trials

***Other symptoms and health-related quality of life outcomes*:** Several other symptoms have been examined in the WHI HT trials and results have been previously reported. Changes in menopausal symptoms and treatment-related effects were analyzed after 1 year (estrogen-progestin[1] and estrogen alone[2]), at trial closure (treatment-compliant women in the estrogen-alone trial[2]), and after stopping HT (treatment-compliant women in the estrogen-progestin[3] and estrogen-alone trials[2]). In addition to the effects on vasomotor symptoms and other endpoints reported in the main text, CEE+MPA provided significantly greater relief than placebo at 1 year for vaginal or genital dryness (74.1 *v*. 54.6%; RR=2.40 [1.90-3.02]), joint pain or stiffness (47.1 *v*. 38.4%; RR=1.43 [1.24-1.64]), and general aches or pains (49.3 *v*. 43.7%; RR=1.25 [1.08-1.44]). However, it also raised the risk for vaginal or genital discharge (4.1 *v*. 1.0%; RR=4.47 [3.44-5.81]), vaginal or genital irritation (4.2 *v*. 2.8%; RR=1.52 [1.27-1.81]), headaches (5.8 *v*. 4.7%; RR=1.26 [1.08-1.46]), and breast tenderness (9.3 *v*. 2.4%; RR=4.26 [3.59-5.04]). Vaginal bleeding, mostly spotting, was commonly reported in the estrogen-progestin trial, occurring in 51% of women in the treatment group at month 6 and declining to 13% at year 5. Among women in the placebo group, 86.6% never reported bleeding. CEE+MPA also increased the risk for hysterectomy (3.1% *v*. 2.5%; RR=1.26 [1.03-1.48]) and dilation and curettage procedures (5.4 *v*. 2.4%; RR=2.23 [1.88-2.63]).

At 1 year, CEE alone, compared with placebo, improved vaginal dryness (34.3 *v*. 42.9%; RR=0.80 [0.68-0.93]), but increased the risk for breast tenderness (8.4 *v*. 3.4%; RR=2.48 [2.08-2.97]) CEE alone was also associated with a small but significant (p=0.04) reduction in joint pain in an analysis that combined women with and without joint pain at baseline. Assignment to CEE alone was associated with a reduced risk for knee or hip replacement by the end of the intervention period (RR=0.84 [0.70-1.00]; p=0.05),[4] suggesting a favorable influence on joint health. Such a reduction was not seen for CEE+MPA.[4]

Among a subgroup of nondisabled participants aged ≥65 who completed performance-based assessments of physical function (grip strength, chair stands, and timed walk) at baseline and at 1, 3, and 6 years, neither CEE+MPA nor CEE alone reduced the risk for decline in physical function.[5]

Additional Analyses Addressing Risk Stratification

A detailed presentation of biomarker findings and analyses stratified by baseline risk factor status and other clinical characteristics is beyond the scope of this manuscript. However, three sets of analyses are highlighted in this section due to their potential relevance to clinical decision making about HT. Women with more favorable baseline CHD risk factor status (lower LDL-cholesterol levels, lower ratios of total cholesterol:HDL-C, and absence of metabolic syndrome criteria) tended to have more favorable CHD outcomes on HT than women at higher baseline risk of CHD.[6-9] For breast cancer, women closer to the onset of menopause or with shorter gap times (interval between menopause and start of HT use) tended to have higher breast cancer risk on estrogen-progestin than women with longer gaps times.[10] Finally, because some clinicians prescribe HT for fracture prevention, analyses stratifying women by their baseline risk of fracture (low, moderate, and high) were conducted, to assess the global index for each group. No group had a favorable global index in either trial (HRs were 1.20, 1.23, and 1.03, respectively, for CEE+MPA and 0.81, 1.09, 1.04, respectively, for CEE alone), indicating that the benefit in reducing fracture risk was offset or exceeded by other risks associated with HT, even among women at the highest risk for fracture.[11, 12]

Additional Discussion of the Breast Cancer Findings

Breast cancer results differed between the two trials. Women on CEE+MPA had more abnormal mammograms and required more breast biopsies.[13] CEE+MPA interfered with breast cancer detection,[13] increased breast

cancer incidence, with cancers diagnosed at a more advanced stage, likely reflecting diagnostic delay.[14] As women closer to menopause may have higher risk with estrogen plus progestin use,[10, 15-17] the slightly elevated HRs seen with CEE+MPA in WHI may underestimate breast cancer in this group. In addition, deaths from breast cancer were significantly increased after 11 years of follow-up.[14, 18] Analyses adjusting for time from menopause, mammography patterns, and prior HT use before enrollment can reconcile many of the discrepancies between observational and clinical trial findings for breast cancer.[15] While the post-intervention findings for CEE+MPA on breast cancer show some persistent elevation in risk, the year-to year reductions in HRs after stopping suggests possible influence of a carry over effect due to reduced diagnostic interference on mammography once HT ended. In contrast to the findings with CEE+MPA, the significant reduction in breast cancer seen with CEE was unexpected.[19,20] Further study of the relationship between different HT regimens and breast cancer is warranted.

APPENDIX References:

1. Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. *Obstet Gynecol.* May 2005;105(5 Pt 1):1063-1073.

2. Brunner RL, Aragaki A, Barnabei V, et al. Menopausal symptom experience before and after stopping estrogen therapy in the Women's Health Initiative randomized, placebo-controlled trial. *Menopause.* Sep-Oct 2010;17(5):946-954.

3. Ockene JK, Barad DH, Cochrane BB, et al. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA.* Jul 13 2005;294(2):183-193.

4. Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. *Arthritis Rheum.* Oct 2006;54(10):3194-3204.

5. Michael YL, Gold R, Manson JE, et al. Hormone therapy and physical function change among older women in the Women's Health Initiative: a randomized controlled trial. *Menopause.* Mar 2010;17(2):295-302.

6. Bray PF, Larson JC, Lacroix AZ, et al. Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. *Am J Cardiol.* Jun 1 2008;101(11):1599-1605.

7. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med.* Aug 7 2003;349(6):523-534.

8. Wild RA, Wu C, Curb D, et al. Coronary heart disease events in the Women's Health Initiative hormone trials: effect modification by metabolic syndrome: A nested case-control study within the Women's Health Initiative randomzied clinical trials. *Menopause.* 2013;20.

9. Rossouw JE, Prentice RL, Manson JE, et al. Relationships of coronary heart disease with 27-hydroxycholesterol, low-density lipoprotein cholesterol, and menopausal hormone therapy. *Circulation.* Sep 25 2012;126(13):1577-1586.

10. Prentice RL, Chlebowski RT, Stefanick ML, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am J Epidemiol.* May 15 2008;167(10):1207-1216.

11. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* Oct 1 2003;290(13):1729-1738.

12. Jackson RD, Wactawski-Wende J, LaCroix AZ, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. *J Bone Miner Res.* Jun 2006;21(6):817-828.

13. Chlebowski RT, Anderson G, Pettinger M, et al. Estrogen plus progestin and breast cancer detection by means of mammography and breast biopsy. *Arch Intern Med.* Feb 25 2008;168(4):370-377; quiz 345.

14. Chlebowski RT, Anderson GL. Changing concepts: Menopausal hormone therapy and breast cancer. *J Natl Cancer Inst.* Apr 4 2012;104(7):517-527.

15. Chlebowski RT, Manson JE, Anderson GL, et al. Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in the Women's Health Initiative Observational Study. *J Natl Cancer Inst.* Mar 29 2013 (in press).
16. Chlebowski RT, Anderson GL. The influence of time from menopause and mammography on hormone therapy-related breast cancer risk assessment. *J Natl Cancer Inst.* Feb 16 2011;103(4):284-285.
17. Beral V, Reeves G, Bull D, Green J. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst.* Feb 16 2011;103(4):296-305.
18. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA.* Oct 20 2010;304(15):1684-1692.
19. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA.* Apr 12 2006;295(14):1647-1657.
20. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol.* May 2012;13(5):476-486.