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# The timing hypothesis: Do coronary risks of menopausal hormone therapy vary by age or time since menopause onset?

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## Abstract

The Women's Health Initiative (WHI), a landmark randomized trial of menopausal hormone therapy (HT) for prevention of chronic disease in postmenopausal women aged 50–79, established that such therapy neither prevents coronary heart disease (CHD) nor yields a favorable balance of benefits and risks in such women as a whole. However, a nuanced look at the data from this trial, considered alongside other evidence, suggests that timing of HT initiation affects the relation between such therapy and coronary risk, as well as its overall benefit-risk balance. Estrogen may have a beneficial effect on the heart if started in early menopause, when a woman's arteries are likely to be relatively healthy, but a harmful effect if started in late menopause, when those arteries are more likely to show signs of atherosclerotic disease. However, even if HT-associated relative risks are constant across age or time since menopause onset, the low absolute risk of CHD in younger or recently menopausal women translates into low attributable risks in this group. Thus, HT initiation for relief of moderate to severe vasomotor symptoms in early menopausal patients who have a favorable coronary profile remains a viable option.

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### Keywords

coronary heart disease; cancer; epidemiology; estrogen; menopausal hormone therapy; mortality; randomized clinical trials; stroke; venous thromboembolism; women

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**Additional information**

A full list of all the investigators who have contributed to the WHI is at: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

## 1. Introduction

Menopausal hormone therapy (HT) has long been a mainstay of treatment for vasomotor symptoms of menopause, providing relief from the hot flashes and night sweats that affect many women during this stage of life (1). Until the early 2000s, HT was also promoted as an effective strategy for preventing coronary heart disease (CHD) and other chronic diseases of aging in postmenopausal women of all ages, particularly those at elevated coronary risk, and was increasingly taken for this purpose (2). This practice was unwise given the absence of conclusive data from large-scale randomized clinical trials on the balance of risks and benefits of HT used for chronic disease prevention.

Results from the large Women's Health Initiative (WHI) HT trials, the first of which were published in 2002 (3), and smaller trials have now shown that the risks of such therapy outweigh the benefits for many women (1). In response, the prevalence of HT use in the U.S., which peaked at >40% in 2001, declined sharply (4, 5). However, a closer look at the clinical trial findings indicates that it may be possible to identify women who are most likely to experience a favorable benefit-risk balance from HT when it is taken for a currently approved indication—treatment of moderate to severe vasomotor symptoms of menopause, and, in women at high fracture risk who cannot tolerate other therapies, prevention of osteoporosis (6). This article reviews the evidence from WHI and other randomized trials suggesting that women who are younger or more recently menopausal at HT initiation have more favorable coronary outcomes than their counterparts who are older or further past the menopausal transition—a theory that has been dubbed the 'timing hypothesis.' We also address non-human primate research testing this hypothesis.

## 2. Overview of the WHI HT trials

In the WHI HT trials, 27,347 healthy postmenopausal women aged 50–79 were randomized to oral estrogen (conjugated equine estrogens [CEE], 0.625 mg/d)—taken with or without oral progestin (medroxyprogesterone acetate [MPA], 2.5 mg/d) depending on hysterectomy status—or to placebo. Because progestin is known to counteract the elevation in endometrial cancer risk conferred by unopposed estrogen therapy, participants with an intact uterus (n=16,608) were enrolled in the estrogen-progestin trial (3), whereas participants with hysterectomy (n=10,739) were enrolled in the estrogen-alone trial (7). At enrollment, 32.3% of participants were aged 50–59 years, 42.2% were aged 60–69 years, and 22.5% were aged 70–79 years; the mean age was 63 years. The sample sizes were chosen to have sufficient power to detect an effect of HT on CHD (defined as nonfatal myocardial infarction [MI] or coronary death), should such an effect exist, and to assess the balance of benefits and risks over an 8.5-year treatment period (8). However, both trials were stopped—early the estrogen-progestin trial after a median of 5.6 years of treatment because of a significant increase in breast cancer risk and an unfavorable benefit-risk balance in the overall cohort (3), and the estrogen-alone trial after a median of 7.2 years because of an elevated stroke risk that was not counterbalanced by a reduced CHD risk (7). After the trials were stopped, the participants were followed observationally to determine whether and how quickly treatment effects dissipated. Unless noted, the WHI results reported here are from a comprehensive

overview of the findings published in 2013 by WHI investigators (9), or related publications (1, 10).

## 3. HT-associated health outcomes in the total WHI study population

Table 1 shows the associations between HT and health outcomes in the WHI study population as a whole.

### 3.1. Cardiovascular disease

Compared with those randomized to placebo, women randomized to 5.6 years of estrogen-progestin were 18% more likely to develop CHD, although this increase did not reach statistical significance. During the trial's first year, there was a significant 80% risk elevation, which tapered off with time on treatment (p, trend by time=0.03). Women randomized to 7.1 years of estrogen alone experienced neither an increase nor decrease in CHD risk. This pattern of results was similar for total MI. Neither HT regimen affected risk of coronary revascularization. Women randomized to estrogen-progestin or estrogen alone were about 35% more likely to suffer a stroke than those randomized to placebo. Estrogen-progestin was associated with an approximate doubling in risk for pulmonary embolism and deep vein thrombosis, and estrogen alone was associated with a 35–50% increase in these risks. Both HT regimens led to a significant 10–15% increase in risk of total cardiovascular events, a composite endpoint that included MI, stroke, coronary revascularization, angina, heart failure, carotid artery disease, peripheral vascular disease, pulmonary embolism, deep vein thrombosis, and cardiovascular death.

In absolute terms, an estimated additional 19 cardiovascular events, including 6 CHD events, 9 strokes, and 21 venous thromboembolisms (VTEs), would be expected to occur among every 10,000 women assigned to estrogen-progestin for one year, and an estimated additional 27 cardiovascular events, including 3 fewer CHD events, 11 more strokes, and 11 more VTEs, would be expected among every 10,000 women assigned to estrogen alone for one year.

### 3.2 Cancer

Women randomized to estrogen-progestin experienced a significant 24% increase in the risk of breast cancer compared with those randomized to placebo. In contrast, randomization to estrogen alone was unexpectedly associated with a risk reduction of 21% that approached statistical significance. Biologic explanations for the latter finding remain elusive (11). Assignment to estrogen-progestin was associated with a significant risk reduction of 38% for colorectal cancer and a nonsignificant 17% reduction in endometrial cancer, respectively, whereas assignment to estrogen alone was unrelated to risk of these cancers. Neither estrogen-progestin nor estrogen alone was associated with risk of total cancer.

The absolute risks of specific cancers per 10,000 women per year in the HT groups compared with placebo groups are shown in Table 1. Considering all cancer types, there would be 4 excess cancer cases per 10,000 women per year using estrogen-progestin. In contrast, with estrogen alone, there would be 8 *fewer* cancers of all types per 10,000 women per year.

### 3.3 Other endpoints

Significant reductions in risk of hip fracture, type 2 diabetes, and gallbladder disease were observed with both HT regimens. Estrogen-progestin doubled the risk of probable dementia (this outcome was assessed only in women aged ≥65), and estrogen alone led to a 47% increase in risk. Estrogen-progestin also appeared to increase ovarian cancer risk (relative risk [RR]=1.41, 95% confidence interval [0.75–2.66]), but the estimate was imprecise because of the small number of cases. Neither estrogen-progestin nor estrogen alone was associated with total mortality. WHI investigators created a global index consisting of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (estrogen-progestin only), hip fracture, and total mortality to summarize the overall balance of risks and benefits for each HT regimen. Analysis of this summary variable showed a net effect of 20 additional adverse outcomes per 10,000 estrogen-progestin users per year. In contrast, the health risks of estrogen alone were about equal to its benefits.

## 4. Health changes after discontinuation of HT

Many but not all of the risks and benefits of HT waned within 5 to 7 years after treatment was stopped. During a median cumulative 13.2-year follow-up (5.6 years of treatment plus 8.2 years of post-intervention observation) of the estrogen-progestin cohort, the cardiovascular risks associated with active HT use had greatly diminished (e.g., CHD: RR=1.09 [0.96–1.24]; stroke: RR=1.16 [1.00–1.35]; pulmonary embolism: RR=1.26 [1.00–1.59]); the excess breast cancer risk (RR=1.28 [1.11–1.48]) and hip fracture benefit (RR=0.81 [0.68–0.97]) persisted; and the endometrial cancer benefit became stronger and statistically significant (RR=0.67 [0.49–0.91]). During a median cumulative 13.0-year follow-up (7.2 years of treatment plus 6.6 years of post-intervention observation) of the estrogen-alone cohort, the breast cancer benefit became statistically significant (RR=0.79 [0.65–0.97]), and significant differences by age group (described in the next section) persisted for MI and the global index summary variable.

## 5. HT-associated health outcomes according to age and time since menopause onset

It is important to recognize that the findings summarized above are for the entire WHI cohort and are thus heavily weighted by the data from the two thirds of the participants who enrolled in the trial at age 60 or older (well past the age at which HT is typically started for vasomotor symptom relief). WHI investigators conducted exploratory subgroup analyses to determine whether a woman's age or time since menopause onset influences her balance of benefits and risks after initiation of HT.

### 5.1 CHD

These subgroup analyses do suggest that a woman's age (Table 2) and/or how many years past the menopausal transition she is when she starts HT are important determinants of whether such therapy has adverse coronary effects—i.e., the timing hypothesis. The data show that, although estrogen alone was unrelated to CHD risk in the overall study population, such therapy was associated with a borderline significant 40% reduction in CHD

among the youngest women (i.e., those aged 50–59), whereas there was no risk reduction or even a slight increase for their older counterparts (p, trend by age=0.08). Age differences were even more pronounced for total MI; for this outcome, estrogen alone was associated with a 45% risk reduction and a nonsignificant 24% risk increase among the youngest and oldest women, respectively (p, trend=0.02). For coronary revascularization, there was a risk reduction in the youngest women (p, trend by age=0.06). Although these age differences were not observed in the estrogen-progestin trial, cardiovascular risks associated with such therapy increased with years since menopause onset, with statistically significant elevations in those furthest from this transition. For CHD, the RRs associated with randomization to estrogen-progestin in women less than 10 years, 10 to 19 years, and 20 or more years past menopause onset were 0.90 (0.56–1.45), 1.19 (0.83–1.70), and 1.52 (1.07–2.17), respectively (p, trend=0.08). For total MI, these RRs were 0.91 (0.54–1.52), 1.16 (0.79–1.69), and 1.99 (1.32–3.02) (p, trend=0.01). Most importantly, the absolute risks of CHD and other CVD events were substantially lower in younger than older women (Table 2).

Why might estrogen therapy have a more favorable coronary effect if initiated early in the menopause but an adverse effect if started years later? The difference may result from underlying differences in the health of the vasculature between younger or recently menopausal women and those who are older or further past the menopausal transition (12). In relatively healthy blood vessels (more likely in a younger woman), estrogen is believed to increase nitric oxide synthesis and vasodilation and to decrease inflammatory cell adhesion and slow the development of atherosclerotic plaque. However, in vessels with substantial atherosclerotic plaque (more likely in an older woman), the estrogen receptors become less functional, and these benefits do not occur. Instead, estrogen may render established atherosclerotic lesions more susceptible to rupture and also increase risk of thrombotic occlusion of a stenotic blood vessel (13).

In the WHI, exploratory analyses of subgroups defined by established biomarkers of coronary risk lend credence to the timing hypothesis (Table 3). Among women with a favorable LDL/HDL cholesterol ratio (<2.5), estrogen with or without progestin led to a 40% lower risk for incident CHD, whereas among women with a less favorable ratio (≥2.5), such therapy resulted in a 73% higher risk (p, interaction=0.002) (14). Similarly, among women who entered the trial with a lower LDL cholesterol level (<130 mg/dl), estrogen with or without progestin led to a nonsignificantly lower risk for incident CHD, whereas among participants with a higher baseline cholesterol (≥130 mg/dl), such therapy resulted in a 46% higher risk (p, interaction=0.03) (14). The results were similar when users of statins and other cholesterol-lowering medications were excluded from the analysis. The presence or absence of the metabolic syndrome also influenced the relation between HT and incident CHD, especially in women without CVD, hypertension, or diabetes at trial entry. In these individuals, the presence of the metabolic syndrome more than doubled the HT-associated CHD risk, whereas no association between HT and CHD risk was observed among those without the syndrome (p, interaction=0.03) (15). The individual components of the metabolic syndrome (Table 3, footnote *a*) did not significantly affect the HT-CHD association, although there was a suggestive interaction for waist size.

WHI investigators conducted an exploratory ancillary study after the WHI estrogen-alone trial was halted to elucidate the basis for the lower risk of clinical CHD events observed among the younger hormone users in that trial. Specifically, the aim was to determine whether randomization to estrogen therapy was predictive of a lower level of coronary artery calcium (CAC) among women aged 50–59 years. High CAC indicates a greater atherosclerotic plaque burden and is associated with a higher risk of future coronary events (16). As hypothesized, CAC measurements were lower among women assigned to estrogen than among their counterparts assigned to placebo. Comparing the former with the latter group, odds ratios for increasingly high CAC prevalence cutpoints (CAC>0, ≥10, and ≥100) were 0.78 (0.58–1.04), 0.74 (0.55–0.99), and 0.69 (0.48–0.98), respectively (17). These findings support the hypothesis that estrogen therapy reduces progression of atherosclerosis and subclinical coronary artery disease in younger women who are closer to the onset of menopause.

Other data also support a potential interaction between HT and age or time since menopause onset on risk for CHD (18). For example, investigators with the long-running observational Nurses' Health Study reported in 2000 that current use of HT was associated with an ~40% reduction in CHD risk in their cohort of 70,000 postmenopausal women followed for up to 20 years (19). Upon re-examination of the data in light of the intriguing WHI age- and time-since-menopause subgroup analyses, the investigators subsequently reported that the coronary benefit was largely limited to women who began HT within 4 years of menopause onset (20). Of course, observational findings may be confounded by variables such as socioeconomic status, access to medical care, and lifestyle factors. Data from randomized trials provide more compelling support. Indeed, a 2006 meta-analysis that pooled data from 22 smaller randomized trials with data from WHI found that HT was associated with a 30–40% reduction in CHD risk in trials with predominantly younger participants (those aged<60 years or ≤10 years from menopause onset) but not in trials with predominantly older participants (21). Among the non-WHI trials included in this meta-analysis was the Heart and Estrogen/progestin Replacement Study (HERS), a 4-year randomized trial of CEE (0.625 mg/d) plus MPA (2.5 mg/d) for the prevention of recurrent CHD events in 2763 women with a mean age of 67 years (22), the results of which were published 4 years prior to the initial WHI estrogen-progestin findings and ended the practice of prescribing HT for women with known CHD. In a pattern similar to that subsequently observed in the total WHI estrogen-progestin study population, HERS reported a significant 50% increase in risk of recurrent CHD events during the first year of treatment that was offset by a decreased risk later on, leading to null results overall (22, 23).

Results from more recent randomized trials are also relevant. The U.K.-based Women's International Study of Long Duration Oestrogen after Menopause (WISDOM), which had a target sample size of 22,000 healthy postmenopausal women aged 50–69 and a target of 10 years of randomized treatment with HT (CEE with or without MPA) or placebo, was stopped prematurely upon publication of the initial WHI findings. Analyses of the available data—5692 participants with a mean age of 63 years were randomized to HT or placebo for 1 year—indicated a treatment-associated increase in CHD events (estrogen-progestin: n=7; estrogen alone: n=4; placebo: n=0; p, estrogen-progestin vs. placebo comparison=0.016) (24). Nine of the 11 CHD events occurred in participants who, at baseline, were aged>64

years and had at least one coronary risk factor. On the other hand, in a 10-year open-label trial in Denmark among 1000 healthy recently menopausal women aged 45–58 (mean age, 50) at enrollment, treatment with HT (estradiol with or without norethisterone acetate) led to a significant reduction in the primary endpoint of mortality, MI, or heart failure (16 vs. 33 events; RR=0.48 [0.26–0.87]) (25).

Findings of experiments in nonhuman primates are also in line with the timing hypothesis. In cynomolgus monkeys, conjugated estrogens with or without MPA had no effect on coronary artery plaque when started at 2 years (~6 human years) after oophorectomy and in the presence of established atherosclerosis, whereas such therapy reduced the extent of plaque by 70% when initiated immediately following oophorectomy, in the early stages of atherosclerosis (26). Similarly, human imaging trials in participants with significant coronary lesions at study entry have not found that estrogen slows the rate of arterial narrowing (27–30), whereas an imaging trial in which the presence of significant lesions was not required for study entry found that estrogen did do so (31).

Most recently, the Early versus Late Intervention Trial with Estradiol (ELITE), a 6-year randomized trial among 643 healthy postmenopausal women that was specifically designed to test whether effects of estrogen on the development and progression of atherosclerosis vary according to age at initiation of therapy, reported that HT—oral 17β-estradiol (1 mg/d), with or without vaginal micronized progesterone gel 4% (45 mg/d for 10 d/month)—significantly slowed carotid atherosclerotic progression in women within 6 years of menopause onset (mean age, 55.4 years) but not in women more than 10 years past menopause onset (mean age, 65.4 years) (p, interaction=0.007) (32). On the other hand, the Kronos Early Estrogen Prevention Study (KEEPS), a 4-year randomized trial among 729 healthy menopausal women who were all within 3 years of menopause onset at trial entry (mean age, 53 years), failed to find an effect of low-dose oral CEE (0.45 mg/d) or transdermal estradiol (50 mcg/d by weekly patch), administered in combination with oral micronized progesterone (200 mg/d for 12 d/month), on progression of carotid atherosclerosis, although a nonsignificant reduction in accrual of coronary calcium was noted (33). However, there was little progression of atherosclerosis in this low-risk study population, which may have curtailed power to detect a difference in this endpoint.

### 5.2 Other outcomes

In contrast to the CHD findings, the WHI results do not suggest that a woman's age (Table 2) and/or how many years past the menopausal transition she is at initiation of HT affect her treatment-associated risks of stroke, VTE, total cancer, breast cancer, or total fracture. This was also true for hip fracture, but a low incidence of this endpoint precluded precise age-stratified estimates (data not shown). For colorectal cancer, estrogen alone was associated with an increased risk in women aged 70–79 but not in younger women (p, trend by age=0.02). For diabetes, estrogen-progestin was associated with risk reductions in women aged 50–59 years and 60–69 years (in the latter group, the risk reduction was statistically significant) but a near-significant risk elevation in women aged 70–79 (p, trend=0.10). HT-associated RRs significantly increased with age for total mortality (p, trend=0.04) and the global index (p, trend=0.02) in the estrogen alone trial but not in the estrogen-progestin trial.

Viewing the global index results of the estrogen-alone trial from an absolute risk perspective, there were 19 fewer adverse events per 10,000 women per year in the youngest age group randomized to HT and 51 additional adverse events per 10,000 women per year among the oldest group, compared with their counterparts randomized to placebo. For the estrogen-progestin trial, the corresponding statistics were 12 additional adverse events associated with HT use in the youngest age group and 38 additional adverse events in the oldest age group.

Taken in aggregate, the evidence for differential health effects of HT by age and time since menopause onset appears compelling. Nonetheless, even if HT-associated relative risks do not vary according to these characteristics, the much lower absolute baseline risks of coronary and other events in younger or recently postmenopausal women means that they have much lower attributable risks of HT compared with their counterparts who are older or further past menopause.

## 6. Delivery route, dose, and formulation of HT

The WHI studied only one method of administration, dose, and formulation of estrogen and progestogen, so its results are not necessarily generalizable to other hormone preparations. Indeed, results of observational studies suggest that alternatives may offer a different balance of benefits and risks, particularly cardiovascular risks. For example, such studies show that transdermal estrogen products are less likely than oral ones to precipitate VTE (34–37). Small randomized trials of estrogen therapy in relation to hemostatic biomarkers find results consistent with these clinical results, with administration of oral but not transdermal estrogen associated with activation of blood coagulation and hypercoagulability (38). Observational research also suggests that lower estrogen doses (1/3 to 1/2 of that tested in the WHI) may be less likely to lead to stroke (39). However, there is a dearth of large trials on the long-term safety—as assessed by effects on risk of clinical cardiovascular events, breast cancer, and other clinical outcomes—of transdermal therapy and of lower estrogen doses, as well as of formulations other than CEE and MPA (e.g., estradiol and micronized progesterone, so-called ‘bioidentical’ hormones with the same molecular structure as those produced by the human body); progestogen-only therapies; and novel drug combinations (e.g., CEE and the estrogen-agonist bazedoxifene, which was approved by the FDA in 2013) (40).

## 7. Conclusion

The WHI established that, when used for chronic disease prevention, HT neither reduces risk of CHD nor yields a favorable balance of benefits and risks in postmenopausal women aged 50–79 as a whole. However, the findings for the entire cohort primarily reflect the experiences of participants aged 60 and older (two thirds of the WHI study population) and likely exaggerate the risks for younger women at low baseline risk of CVD and breast cancer who begin HT closer to menopause onset. A critical mass of data now suggests that these healthy younger women are likely to experience an acceptable benefit-risk balance while taking HT for the amelioration of moderate to severe vasomotor symptoms. Thus, the take-home message for clinicians is that HT remains a viable option in this scenario. That said, healthcare providers should keep informed of new developments in the field of personalized

risk assessment, as well as emerging treatment alternatives, to help their patients make optimal choices regarding the use of hormonal or nonhormonal treatments for management of vasomotor symptoms of menopause (40). Research to identify individual characteristics (other than age or time since menopause onset) that may affect HT-associated health outcomes in the WHI is ongoing; for a summary of recent results and future plans, see references (18, 41).

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## References

1. Manson, JE.; Bassuk, SS. Menopause and postmenopausal hormone therapy. In: Kasper, DL.; Fauci, AS.; Longo, DL., et al., editors. Harrison's Principles of Internal Medicine, Nineteenth Edition. New York: McGraw-Hill; 2015.
2. Heinemann K, Rubig A, Strothmann A, et al. Prevalence and opinions of hormone therapy prior to the Women's Health Initiative: a multinational survey on four continents. J Womens Health (Larchmt). 2008; 17(7):1151–66. [PubMed: 18774896]
3. 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):321–33. [PubMed: 12117397]
4. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004; 291(1):47–53. [PubMed: 14709575]
5. Sprague BL, Trentham-Dietz A, Cronin KA. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999–2010. Obstet Gynecol. 2012; 120(3):595–603. [PubMed: 22914469]
6. North American Menopause Society. The 2012 hormone therapy position statement of the North American Menopause Society. Menopause. 2012; 19(3):257–71. [PubMed: 22367731]
7. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004; 291(14):1701–12. [PubMed: 15082697]
8. Stefanick ML, Cochrane BB, Hsia J, et al. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol. 2003; 13(9 Suppl):S78–86. [PubMed: 14575940]
9. 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. 2013; 310(13):1353–68. [PubMed: 24084921]
10. Bassuk SS, Manson JE. Oral contraceptives and menopausal hormone therapy: relative and attributable risks of cardiovascular disease, cancer, and other health outcomes. Ann Epidemiol. 2015; 25(3):193–200. [PubMed: 25534509]
11. Chlebowski RT, Anderson GL. Changing concepts: Menopausal hormone therapy and breast cancer. J Natl Cancer Inst. 2012; 104(7):517–27. [PubMed: 22427684]
12. Manson JE. The 'timing hypothesis' for estrogen therapy in menopausal symptom management. Womens Health (Lond Engl). 2015; 11(4):437–40. [PubMed: 26237097]
13. Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences. Science. 2005; 308(5728):1583–7. [PubMed: 15947175]
14. 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):1599–605. [PubMed: 18489937]

15. Wild RA, Wu C, Curb JD, 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 randomized clinical trials. Menopause. 2013; 20(3):254–60. [PubMed: 23435021]
16. Hecht HS, Budoff MJ, Berman DS, et al. Coronary artery calcium scanning: Clinical paradigms for cardiac risk assessment and treatment. Am Heart J. 2006; 151(6):1139–46. [PubMed: 16781212]
17. Manson JE, Allison MA, Rossouw JE, et al. Estrogen therapy and coronary artery calcification. N Engl J Med. 2007; 356:2591–602. [PubMed: 17582069]
18. Bassuk SS, Manson JE. Menopausal hormone therapy and cardiovascular disease risk: utility of biomarkers and clinical factors for risk stratification. Clin Chem. 2014; 60(1):68–77. [PubMed: 24379312]
19. Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med. 2000; 133(12):933–41. [PubMed: 11119394]
20. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. J Womens Health. 2006; 15(1):35–44.
21. Salpeter SR, Walsh JM, Greyber E, et al. Brief report: Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. J Gen Intern Med. 2006; 21(4):363–6. [PubMed: 16686814]
22. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998; 280(7):605–13. [PubMed: 9718051]
23. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6. 8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002; 288(1):49–57. [PubMed: 12090862]
24. Vickers MR, Maclennan AH, Lawton B, et al. Main morbidities recorded in the Women's International Study of long Duration Oestrogen after Menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. BMJ. 2007; 335(7613)
25. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ. 2012; 345:e6409. [PubMed: 23048011]
26. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. Cardiovasc Res. 2002; 53:605–19. [PubMed: 11861031]
27. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med. 2000; 343(8):522–9. [PubMed: 10954759]
28. Hodis HN, Mack WJ, Azen SP, et al. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med. 2003; 349(6):535–45. [PubMed: 12904518]
29. Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. JAMA. 2002; 288(19):2432–40. [PubMed: 12435256]
30. Angerer P, Stork S, Kothny W, et al. Effect of oral postmenopausal hormone replacement on progression of atherosclerosis : a randomized, controlled trial. Arterioscler Thromb Vasc Biol. 2001; 21(2):262–8. [PubMed: 11156863]
31. Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001; 135(11):939–53. [PubMed: 11730394]
32. Hodis HN, Shoupe D, Azen SP, et al. Testing the menopausal hormone therapy timing hypothesis: the Early versus Late Intervention Trial with Estradiol. Circulation. 2014; 22(4):391–401.
33. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. Ann Intern Med. 2014; 161(4):249–60. [PubMed: 25069991]

34. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007; 115(7):840–5. [PubMed: 17309934]
35. Canonico M, Plu-Bureau G, Lowe GD, et al. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008; 336(7655):1227–31. [PubMed: 18495631]
36. Canonico M, Fournier A, Carcaillon L, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. Arterioscler Thromb Vasc Biol. 2010; 30(2):340–5. [PubMed: 19834106]
37. Sweetland S, Beral V, Balkwill A, et al. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012; 10(11):2277–86. [PubMed: 22963114]
38. Canonico M. Hormone therapy and hemostasis among postmenopausal women: a review. Menopause. 2014; 21(7):753–62. [PubMed: 24937030]
39. Grodstein F, Manson JE, Stampfer MJ, et al. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. Arch Intern Med. 2008; 168(8): 861–6. [PubMed: 18443262]
40. Kaunitz AM, Manson JE. Management of menopausal symptoms. Obstet Gynecol. 2015; 126(4): 859–76. [PubMed: 26348174]
41. Manson JE. The role of personalized medicine in identifying appropriate candidates for menopausal estrogen therapy. Metabolism. 2013; 62(Suppl 1):S15–9. [PubMed: 23018143]

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## Highlights

- Timing of initiation of hormone therapy affects the relation with coronary risk.
- Estrogen may provide coronary benefit in early menopause but harm if started later.
- Absolute risks of hormone therapy are lower in early than late menopause.
- Hormone therapy is appropriate for vasomotor symptom relief in early menopause.
- Hormone therapy is not recommended for chronic disease prevention.

**Table 1**

Health outcomes in the overall study population in the Women's Health Initiative hormone therapy trials during the intervention phase[a]

| | Estrogen-progestin trial | | | | | Estrogen-alone trial | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | E+P | Placebo | | | | E-alone | Placebo | | | |
| ***Outcome*** | **# events per 10,000 PY** | **# events per 10,000 PY** | **Difference[b] per 10,000 PY** | **RR (95% CI)** | **p** | **# events per 10,000 PY** | **# events per 10,000 PY** | **Difference[b] per 10,000 PY** | **RR (95% CI)** | **p** |
| ***Cardiovascular disease*** | | | | | | | | | | |
| Coronary heart disease[c] | 41 | 35 | 6 | 1.18 (0.95 – 1.45) | 0.13 | 55 | 58 | −3 | 0.94 (0.78 – 1.14) | 0.53 |
| Myocardial infarction | 35 | 29 | 6 | 1.24 (0.98 – 1.56) | 0.07 | 44 | 45 | −1 | 0.97 (0.79 – 1.21) | 0.97 |
| Coronary revascularization[d] | 42 | 45 | −3 | 0.95 (0.78 – 1.16) | 0.64 | 68 | 67 | 1 | 1.00 (0.83 – 1.19) | 0.96 |
| Stroke | 33 | 24 | 9 | 1.37 (1.07 – 1.76) | 0.01 | 45 | 34 | 11 | 1.35 (1.07 – 1.70) | 0.01 |
| Pulmonary embolism | 18 | 9 | 9 | 1.98 (1.36 – 2.87) | <0.001 | 14 | 10 | 4 | 1.35 (0.89 – 2.05) | 0.15 |
| Deep vein thrombosis | 25 | 14 | 12 | 1.87 (1.37 – 2.54) | <0.001 | 23 | 15 | 7 | 1.48 (1.06 – 2.07) | 0.02 |
| All cardiovascular events[e] | 170 | 152 | 19 | 1.13 (1.02 – 1.25) | 0.02 | 251 | 224 | 27 | 1.11 (1.01 – 1.22) | 0.03 |
| ***Cancer*** | | | | | | | | | | |
| Breast cancer | 43 | 35 | 9 | 1.24 (1.01 – 1.53) | 0.04 | 28 | 35 | −7 | 0.79 (0.61 – 1.02) | 0.07 |
| Colorectal cancer | 10 | 17 | −6 | 0.62 (0.43 – 0.89) | 0.009 | 17 | 15 | 2 | 1.15 (0.81 – 1.64) | 0.44 |
| Endometrial cancer | 6 | 7 | −1 | 0.83 (0.49 – 1.40) | 0.49 | NA | NA | NA | NA | NA |
| All cancer types[f] | 127 | 124 | 4 | 1.02 (0.91 – 1.15) | 0.69 | 109 | 117 | −8 | 0.93 (0.81 – 1.07) | 0.30 |
| ***Other outcomes*** | | | | | | | | | | |
| Hip fracture | 11 | 17 | −6 | 0.67 (0.47 – 0.95) | 0.03 | 13 | 19 | −6 | 0.67 (0.46 – 0.96) | 0.03 |
| All fracture | 161 | 212 | −51 | 0.76 (0.69 – 0.83) | <0.001 | 153 | 214 | −61 | 0.72 (0.64 – 0.80) | <0.001 |
| Diabetes | 72 | 88 | −16 | 0.81 (0.70 – 0.94) | 0.005 | 134 | 155 | −21 | 0.86 (0.76 – 0.98) | 0.02 |
| Gallbladder disease | 131 | 84 | 47 | 1.57 (1.36 – 1.80) | <0.001 | 164 | 106 | 58 | 1.55 (1.34 – 1.79) | <0.001 |
| Probable dementia[g] | 46 | 23 | 23 | 2.01 (1.19 – 3.42) | 0.01 | 44 | 29 | 15 | 1.47 (0.85 – 2.52) | 0.17 |
| Total mortality | 52 | 53 | −1 | 0.97 (0.81 – 1.16) | 0.76 | 80 | 77 | 3 | 1.03 (0.88 – 1.21) | 0.68 |
| Global index[h] | 189 | 168 | 20 | 1.12 (1.02 – 1.24) | 0.02 | 208 | 204 | 4 | 1.03 (0.93 – 1.13) | 0.63 |

[a]Median length of randomized treatment was 5.6 years for estrogen-progestin and 7.2 years for estrogen alone.

[b]Difference = # events per 10,000 women per year in the hormone therapy group - # events per 10,000 women per year in the placebo group. Numbers may not add precisely due to rounding error.

[c]Coronary heart disease is defined as nonfatal myocardial infarction or coronary death.

[d]Coronary revascularization is defined as coronary artery bypass grafting or percutaneous coronary intervention.

[e]All cardiovascular events is a composite outcome of myocardial infarction, stroke, coronary revascularization, angina, heart failure, carotid artery disease, peripheral vascular disease, venous thromboembolism (pulmonary embolism, deep vein thrombosis), and cardiovascular death.

[f]All cancer types except for non-melanoma skin cancer.

[g]Probable dementia was assessed in women aged ≥65.

[h]Global index=a composite outcome of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (in the estrogen-progestin trial), hip fracture, and mortality.

*Abbreviations:* CI, confidence interval; NA, not applicable (due to hysterectomy); PY, person-years; RR, relative risk.

*Data from*: Manson JE, et al. *JAMA* 2013;310:1353–68.

*Metabolism*. Author manuscript; available in PMC 2017 May 01.

**Table 2**

Health outcomes in the Women's Health Initiative hormone therapy trials, according to age at study entry, during the intervention phase[a]

| | Estrogen-progestin trial | | | | | Estrogen-alone trial | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | E+P | Placebo | | | | E alone | Placebo | | | |
| *Outcome* | # events per 10,000 PY | # events per 10,000 PY | Difference[b] per 10,000 PY | RR (95% CI) | p | # events per 10,000 PY | # events per 10,000 PY | Difference[b] per 10,000 PY | RR (95% CI) | p |
| ***Cardiovascular disease*** | | | | | | | | | | |
| Coronary heart disease[c] | | | | | | | | | | |
| 50–59 y | 23 | 17 | 5 | 1.34 (0.82 – 2.19) | 0.81 | 17 | 28 | −11 | 0.60 (0.35 – 1.04) | 0.08 |
| 60–69 y | 37 | 37 | 0 | 1.01 (0.73 – 1.39) | | 61 | 63 | −3 | 0.95 (0.72 – 1.24) | |
| 70–79 y | 82 | 63 | 19 | 1.31 (0.93 – 1.84) | | 97 | 90 | 7 | 1.09 (0.80 – 1.49) | |
| Myocardial infarction | | | | | | | | | | |
| 50–59 y | 19 | 15 | 4 | 1.32 (0.77 – 2.25) | 0.55 | 14 | 25 | −11 | 0.55 (0.31 – 1.00) | 0.02 |
| 60–69 y | 33 | 31 | 2 | 1.05 (0.74 – 1.47) | | 46 | 48 | −2 | 0.95 (0.69 – 1.30) | |
| 70–79 y | 69 | 47 | 21 | 1.46 (1.00 – 2.15) | | 83 | 69 | 14 | 1.24 (0.88 – 1.75) | |
| Coronary revascularization[d] | | | | | | | | | | |
| 50–59 y | 20 | 20 | 0 | 1.03 (0.63 – 1.68) | 0.67 | 24 | 41 | −17 | 0.56 (0.35 – 0.88) | 0.06 |
| 60–69 y | 43 | 52 | −9 | 0.85 (0.64 – 1.13) | | 79 | 69 | 11 | 1.13 (0.88 – 1.46) | |
| 70–79 y | 75 | 70 | +5 | 1.08 (0.77 – 1.51) | | 107 | 102 | 5 | 1.07 (0.79 – 1.43) | |
| Stroke | | | | | | | | | | |
| 50–59 y | 15 | 10 | 5 | 1.51 (0.81 – 2.82) | 0.50 | 16 | 17 | −1 | 0.99 (0.53 – 1.85) | 0.77 |
| 60–69 y | 34 | 23 | 11 | 1.45 (1.00 – 2.11) | | 51 | 33 | 18 | 1.55 (1.10 – 2.16) | |
| 70–79 y | 63 | 50 | 13 | 1.22 (0.84 – 1.79) | | 77 | 59 | 17 | 1.29 (0.90 – 1.86) | |
| Pulmonary embolism | | | | | | | | | | |
| 50–59 y | 11 | 5 | 6 | 2.05 (0.89 – 4.71) | 0.61 | 10 | 6 | 3 | 1.53 (0.63 – 3.75) | 0.28 |
| 60–69 y | 19 | 11 | 8 | 1.69 (1.01 – 2.85) | | 17 | 10 | 7 | 1.72 (0.94 – 3.14) | |
| 70–79 y | 30 | 12 | 18 | 2.54 (1.27 – 5.09) | | 14 | 16 | −2 | 0.85 (0.39 – 1.84) | |
| All cardiovascular events[e] | | | | | | | | | | |
| 50–59 y | 82 | 67 | 14 | 1.19 (0.92 – 1.53) | 0.92 | 108 | 123 | −16 | 0.84 (0.66–1.06) | 0.06 |
| 60–69 y | 176 | 161 | 15 | 1.10 (0.94 – 1.28) | | 280 | 236 | 44 | 1.18 (1.03 – 1.36) | |
| 70–79 y | 321 | 280 | 41 | 1.14 (0.96 – 1.35) | | 410 | 350 | 60 | 1.17 (0.99 – 1.37) | |

| | Estrogen-progestin trial | | | | | Estrogen-alone trial | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | E+P | Placebo | | | | E alone | Placebo | | | |
| *Outcome* | # events per 10,000 PY | # events per 10,000 PY | Difference[b] per 10,000 PY | RR (95% CI) | p | # events per 10,000 PY | # events per 10,000 PY | Difference[b] per 10,000 PY | RR (95% CI) | p |
| ***Cancer*** | | | | | | | | | | |
| Breast cancer | | | | | | | | | | |
| 50–59 y | 33 | 27 | 6 | 1.21 (0.81 – 1.80) | 0.68 | 24 | 29 | −5 | 0.82 (0.50 – 1.34) | 0.89 |
| 60–69 y | 45 | 38 | 8 | 1.20 (0.89 – 1.62) | | 28 | 39 | −10 | 0.73 (0.51 – 1.07) | |
| 70–79 y | 56 | 41 | 15 | 1.37 (0.90 – 2.07) | | 32 | 27 | −5 | 0.86 (0.52 – 1.43) | |
| Colorectal cancer | | | | | | | | | | |
| 50–59 y | 4 | 5 | −1 | 0.79 (0.29 – 2.18) | 0.66 | 7 | 10 | −3 | 0.71 (0.30 – 1.67) | 0.02 |
| 60–69 y | 13 | 21 | −8 | 0.61 (0.37 – 0.99) | | 16 | 19 | −2 | 0.88 (0.53 – 1.47) | |
| 70–79 y | 16 | 28 | −11 | 0.58 (0.31 – 1.08) | | 33 | 15 | 19 | 2.24 (1.16 – 4.30) | |
| All cancer[f] | | | | | | | | | | |
| 50–59 y | 83 | 84 | −1 | 0.97 (0.76 – 1.23) | 0.77 | 71 | 79 | −8 | 0.89 (0.66 – 1.19) | 0.39 |
| 60–69 y | 142 | 128 | 15 | 1.11 (0.93 – 1.31) | | 114 | 129 | −15 | 0.89 (0.73 – 1.08) | |
| 70–79 y | 171 | 182 | −11 | 0.94 (0.75 – 1.17) | | 152 | 147 | 6 | 1.04 (0.81 – 1.33) | |
| ***Other outcomes*** | | | | | | | | | | |
| All fracture | | | | | | | | | | |
| 50–59 y | 120 | 145 | −25 | 0.82 (0.68 – 1.00) | 0.83 | 133 | 149 | −16 | 0.90 (0.72 – 1.11) | 0.33 |
| 60–69 y | 160 | 226 | −66 | 0.70 (0.61 – 0.81) | | 139 | 218 | −80 | 0.63 (0.53 – 0.75) | |
| 70–79 y | 236 | 300 | −65 | 0.79 (0.66 – 0.95) | | 208 | 297 | −90 | 0.71 (0.58 – 0.87) | |
| Diabetes | | | | | | | | | | |
| 50–59 y | 74 | 85 | −11 | 0.85 (0.66 – 1.09) | 0.10 | 131 | 158 | −26 | 0.83 (0.67 – 1.04) | 0.99 |
| 60–69 y | 61 | 99 | −38 | 0.61 (0.49 – 0.77) | | 144 | 159 | −15 | 0.91 (0.76 – 1.09) | |
| 70–79 y | 95 | 70 | +24 | 1.35 (0.98 – 1.88) | | 119 | 114 | −27 | 0.82 (0.62 – 1.07) | |
| Total mortality | | | | | | | | | | |
| 50–59 y | 21 | 31 | −10 | 0.67 (0.43 – 1.04) | 0.20 | 29 | 40 | −11 | 0.70 (0.46 – 1.09) | 0.04 |
| 60–69 y | 51 | 47 | 5 | 1.07 (0.81 – 1.41) | | 78 | 77 | 0 | 1.01 (0.79 – 1.29) | |
| 70–79 y | 106 | 102 | 3 | 1.03 (0.87 – 1.36) | | 155 | 129 | 26 | 1.21 (0.95 – 1.56) | |
| Global index[g] | | | | | | | | | | |
| 50–59 y | 103 | 91 | 12 | 1.12 (0.89 – 1.40) | >0.99 | 98 | 117 | −19 | 0.84 (0.66 – 1.07) | 0.02 |

| | Estrogen-progestin trial | | | | | Estrogen-alone trial | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | E+P | Placebo | | | | E alone | Placebo | | | |
| *Outcome* | # events per 10,000 PY | # events per 10,000 PY | Difference[b] per 10,000 PY | RR (95% CI) | p | # events per 10,000 PY | # events per 10,000 PY | Difference[b] per 10,000 PY | RR (95% CI) | p |
| 60–69 y | 189 | 167 | 22 | 1.13 (0.97 – 1.31) | | 210 | 211 | −1 | 0.99 (0.85 – 1.15) | |
| 70–79 y | 342 | 303 | 38 | 1.12 (0.95 – 1.32) | | 367 | 316 | 51 | 1.17 (0.99 – 1.39) | |

[a]Median length of randomized treatment was 5.6 years for estrogen-progestin and 7.2 years for estrogen alone.

[b]Difference = # events per 10,000 women per year in the hormone therapy group - # events per 10,000 women per year in the placebo group. Numbers may not add precisely due to rounding error.

[c]Coronary heart disease is defined as nonfatal myocardial infarction or coronary death.

[d]Coronary revascularization is defined as coronary artery bypass grafting or percutaneous coronary intervention.

[e]All cardiovascular events is a composite outcome of MI, stroke, coronary revascularization, angina, heart failure, carotid artery disease, peripheral vascular disease, venous thromboembolism (pulmonary embolism, deep vein thrombosis), and cardiovascular death.

[f]All cancer types except for non-melanoma skin cancer.

[g]Global index=a composite outcome of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (in the estrogen-progestin trial), hip fracture, and mortality.

*Abbreviations:* CI, confidence interval; PY, person-years; RR, relative risk. *Data from*: Manson JE, et al. *JAMA* 2013;310:1353–68.

## Table 3

Coronary heart disease risk in the Women's Health Initiative estrogen-progestin and estrogen-alone trials, according to baseline levels of selected markers

| Marker | OR (95% CI) for HT treatment effect | p, interaction |
|---|---|---|
| LDL cholesterol (mg/dl) | | |
| <130 | 0.66 (0.34–1.27) | 0.03 |
| ≥130 | 1.46 (1.02–2.10) | |
| LDL/HDL cholesterol ratio | | |
| <2.5 | 0.60 (0.34–1.06) | 0.002 |
| ≥2.5 | 1.73 (1.18–2.53) | |
| C-reactive protein | | |
| <2.0 | 1.01 (0.63–1.62) | 0.16 |
| ≥2.0 | 1.58 (1.05–2.39) | |
| Metabolic syndrome[a, b] | | |
| No | 0.97 (0.58–1.61) | 0.03 |
| Yes | 2.26 (1.26–4.07) | |
| Waist circumference[b] | | |
| ≤88 cm | 1.03 (0.62–1.70) | 0.12 |
| >88 cm | 1.93 (1.08–3.44) | |

[a]Metabolic syndrome was defined as having three or more of the following: waist size >88 cm (>80 cm for Asians and Native Americans); systolic blood pressure >130 mm/Hg or diastolic blood pressure >85 mm Hg; fasting glucose >100 mg/dL; HDL cholesterol <50 mg/dL; triglycerides >150 mg/dL.

[b]The reported ORs are among participants without cardiovascular disease, hypertension, or diabetes at baseline.

*Abbreviations*: OR, odds ratio; CI, confidence interval.

*Sources*: Bray PF, et al. *Am J Cardiol* 2008;101(11):1599–605; Wild RA, et al. *Menopause* 2013;20(3):254–60.