Title

Contributions of the Womens Health Initiative to Cardiovascular Research: JACC State-of-the-Art Review.

Journal

Journal of the American College of Cardiology, 80(3)

Authors

LaMonte, Michael

Manson, JoAnn

Anderson, Garnet

et al.

Publication Date

2022-07-19

DOI

10.1016/j.jacc.2022.05.016

Peer reviewed

HHS Public Access

Author manuscript

J Am Coll Cardiol. Author manuscript; available in PMC 2023 July 19.

Published in final edited form as:

J Am Coll Cardiol. 2022 July 19; 80(3): 256–275. doi:10.1016/j.jacc.2022.05.016.

Contributions of the Women's Health Initiative to Cardiovascular Research: JACC State-of-the-Art Review

Michael J. LaMonte, PhD, MPH[a,*,†], **JoAnn E. Manson, MD, DrPH**[b,*], **Garnet L. Anderson, PhD**[c], **Laura D. Baker, PhD**[d], **Jennifer W. Bea, PhD**[e], **Charles B. Eaton, MD, MS**[f], **Shawna Follis, PhD**[g], **Kathleen M. Hayden, PhD**[h], **Charles Kooperberg, PhD**[c], **Andrea Z. LaCroix, PhD**[i], **Marian C. Limacher, MD**[j], **Marian L. Neuhouser, PhD**[c], **Andrew Odegaard, PhD**[k], **Marco V. Perez, MD**[l], **Ross L. Prentice, PhD**[c], **Alexander P. Reiner, MD, MSc**[m], **Marcia L. Stefanick, PhD**[g], **Linda Van Horn, PhD**[n], **Gretchen L. Wells, MD, PhD**[o], **Eric A. Whitsel, MD, MPH**[p], **Jacques E. Rossouw, MD**[q],

WHI Investigators

[a.]Department of Epidemiology and Environmental Health, University at Buffalo – SUNY, Buffalo, NY, USA.

[b.]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

[c.]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA.

[d.]Department of Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA.

[e.]Department of Health Promotion Science, University of Arizona, Tucson, AZ, USA.

[f.]Department of Family Medicine and Epidemiology, Brown University, Providence, RI, USA.

[g.]Stanford Prevention Research Center, Department of Medicine, Stanford University, Stanford, CA, USA.

[h.]Department of Social Sciences and Health Policy, Wake Forest University School of Medicine, Winston-Salem, NC, USA.

[i.]Division of Epidemiology, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, USA.

[j.]Department of Internal Medicine, University of Florida, Gainesville, FL, USA.

[k.]Department of Epidemiology, University of California, Irvine, USA.

[†]Correspondence: Michael J. LaMonte, PhD, MPH, 270 Farber Hall, 3435 Main St., Buffalo, NY, 14214. Phone:716-829-5379; mlamonte@buffalo.edu.

[*]Denotes co-equal first author.

DISCLOSURES: None of the authors have any relationship with industry, known conflicts of interest, or disclosures relevant to this work.

[l.]Department of Medicine, Stanford University, Palo Alto, CA, USA.

[m.]Department of Epidemiology, University of Washington, Seattle, WA, USA.

[n.]Department of Preventive Medicine, Northwestern University, Chicago, IL, USA.

[o.]Department of Medicine, University of Alabama, Birmingham, USA.

[p.]Department of Epidemiology, Gillings School of Global Public health, University of North Carolina, Chapel Hill, NC, USA.

[q.]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA.

Abstract

The Women's Health Initiative (WHI) enrolled 161,808 racially and ethnically diverse postmenopausal women, aged 50–79 years, from 1993 to 1998 at 40 clinical centers across the U.S. In its clinical trial component, WHI evaluated three randomized interventions (menopausal hormone therapy; diet modification; and calcium/vitamin D supplementation) for the primary prevention of major chronic diseases, including cardiovascular disease (CVD), in older women. In the WHI observational study, numerous clinical, behavioral, and social factors have been evaluated as predictors of incident chronic disease and mortality. Although the original interventions have been completed, the WHI data and biomarker resources continue to be leveraged and expanded through ancillary studies to yield novel insights regarding CVD prevention and healthy aging in women.

CONDENSED ABSTRACT:

The landmark Women's Health Initiative (WHI) enrolled 161,808 U.S. postmenopausal women, ages 50–79 years at baseline in 1993–1998. WHI provided robust randomized trial results on three distinct interventions (menopausal hormone therapy; diet modification; calcium/vitamin supplementation) for the primary prevention of major diseases affecting aging women, including CVD. The WHI observational study provided important information on chronic disease rates and risk factors in a large community-based cohort of racially and ethnically diverse older women. Through a series of extension studies and targeted ancillary studies, the WHI data resource has grown and continued to yield novel insights regarding CVD prevention in women.

Keywords

Women's Health; Menopause; Cardiovascular Disease; Prevention; Randomized Trial; Epidemiology

INTRODUCTION

In 1991, one year after establishment of the National Institutes of Health (NIH) Office of Research on Women's Health, NIH director Dr. Bernadine Healy proposed the largest and most definitive study on women's health ever conducted in the United States, *The Women's Health Initiative* (WHI)[1]. Funding to support development of the WHI was obtained from Congress beginning in 1992. Administration of the WHI program was

moved in 1997 from the NIH Director's Office to the National Heart, Lung, and Blood Institute, in collaboration with other NIH institutes. Informed by input from a Trans-NIH scientific panel regarding key knowledge gaps in women's health research, the WHI was established to investigate intervention strategies for the prevention of leading causes of death, disability, and poor quality of life in postmenopausal women, including heart disease, breast and colorectal cancer, and osteoporosis. Although use of menopausal hormone therapy (HT) and certain dietary practices were highly prevalent in the U.S. at that time, the full range of clinical benefits and risks of these interventions had not been tested in rigorous large-scale randomized trials in postmenopausal women. The WHI framework evolved through extensive planning meetings and feasibility studies, and with much needed support from political, social, and scientific stakeholders[2]. To this day, WHI is one of the most complex and ambitious population-based prevention research investigations ever undertaken. Although several diseases relevant to women's health were studied in WHI, cardiovascular disease (CVD) was a major priority, including a definitive evaluation of the potential benefits and risks of menopausal hormone therapy on CVD and other chronic disease outcomes.

ORIGINAL GOALS AND STUDY DESIGN

Details of the WHI study aims, design, and implementation have been extensively reported[3] including a special issue of *Annals of Epidemiology* (2003, Vol 13, Supplement 9) containing articles that summarize recruitment and enrollment and that details each WHI study component. The core component of WHI was a partial factorial randomized clinical trial (RCT) designed to test three chronic disease prevention hypotheses in 68,132 postmenopausal women, aged 50–79 at randomization[3]. Specifically, would menopausal hormone therapy (HT), one of the most commonly used prescription drugs at WHI inception, reduce the risk of coronary heart disease (CHD) and provide overall health benefits? The primary safety concern for HT was breast cancer. The dietary modification trial (DMT) was designed to determine whether a low-fat dietary eating pattern that encouraged additional fruit, vegetable and grain consumption would prevent breast cancer and colorectal cancer. CHD was a prespecified secondary outcome. The third trial, testing calcium and vitamin D (CaD) supplementation, was designed to test whether these dietary supplements reduced hip fracture rates, with colorectal cancer prevention as a secondary aim. Each trial component was motivated by a substantial body of epidemiological and biological literature sufficient to justify a full-scale trial[3]. But by allowing women to participate in more than one trial, when eligible, the cost of the study was significantly reduced. Furthermore, the partial overlap allowed for some examination of potential interactions between interventions.

Recognizing both the paucity of high-quality epidemiological studies of chronic diseases in representative cohorts of postmenopausal women and the large number of women who would be screened but not enrolled in the WHI trials, the WHI leveraged this effort to form an observational study (OS) cohort of 93,676 postmenopausal women, aged 50–79 years, to support a range of efforts, including studies of disease risk factors and biomarkers and expanding the inference from the clinical trials beyond the specific interventions tested to

the broader range of exposures outside of the trial. Figure 1 summarizes the WHI study components.

Participants were recruited from the general population of postmenopausal women, primarily by mass mailings to those residing in proximity to the 40 clinical centers throughout a broad geographic distribution of the United States with targeted recruitment in underserved areas and among underrepresented racial/ethnic groups[3,4]. Enrollment into the WHI began in 1993 and was completed in 1998. A target age-distribution was implemented for the clinical trial component to ensure adequate power for the range of age-related health conditions of interest (10% aged 50–54 years, 20% for 55–59, 45% for 60–69, and 25% for 70–79). The age distribution (Table 1) provided a range in time since menopause including older menopausal women, a unique characteristic of WHI compared to previous studies on menopausal health which tended to focus on younger women in early menopause. WHI enrollment of underrepresented racial and ethnic groups was proportionally similar to the U.S. population in the age range at that time – Black (8.9%), Hispanic (4.5%), Asian/Pacific Islander (2.6%), and American Indian/Alaska Native (0.5%) -- making WHI one of the largest and most diverse cohorts of U.S. women ever assembled.

All participants provided extensive questionnaire information on demographics, personal and family medical history, reproductive history, medication and supplement usage, psychosocial constructs, and lifestyle habits including a detailed food frequency questionnaire developed for the WHI. Brief clinical examinations included fasting blood collection and storage; anthropometrics (weight, height, waist and hip circumferences); and resting blood pressure and heart rate. Among RCT participants a resting electrocardiogram and clinical breast exam was performed and a subset of women over age 65 had both physical and cognitive function assessments. Gynecological examinations were required for HT trial participants. The brief clinical examinations were completed annually in the RCT and at baseline and year 3 in the OS. Baseline and follow-up blood samples were collected and archived on all participants.

During the original protocol period, initial ascertainment of disease outcomes was obtained by semi-annual (RCT) or annual (OS) health updates questionnaires, with adjudication of primary trial outcomes by centrally-trained physicians using standardized methods[5]. Vital status for the small fraction lost-to follow-up was obtained through the National Death Index. Intervention activities in the estrogen plus progestin trial ended early in 2002, when accumulated evidence indicated the health risks exceeded the benefits. The intervention component of the estrogen-alone trial also ended early (see HT Trial section). Intervention activities in the other two trials ended as planned on March 31, 2005[6,7].

Nonintervention follow-up for consenting women from both the RCT and OS has been ongoing through a series of Extension Studies (ES) beginning in 2005 through the current 2020–2027 funding cycle (Figure 2). Approximately 77% and 87% of participants in active follow-up consented to ES 1 and 2, respectively. The ES 2 consent allows continued health follow-up without further active consent. To reduce costs in ES 2, documentation and adjudication of health outcomes were limited to Black and Hispanic Women and those who were formerly HT trial participants, referred to as the Medical Records Cohort.

The remaining women (the Self-Report Cohort) provide the same annual health updates with selected adjudication activities supported by supplemental funding. The NHLBI, the National Institute for Neurologic Diseases and Stroke, and the National Cancer Institute and have funded these efforts for selected heart failure reports, strokes, and all incident cancers, respectively. Regular linkages to Medicare data supplements this information with claims-based health information for a large fraction of participants.

In 2012, the WHI Long Life Study was conducted as part of ES 2 and included in-home examinations on a subcohort of 7,875 women in all 50 states to support research on factors associated with healthy aging and CVD biomarkers. Selected aspects of the baseline clinical examination were repeated (anthropometrics, resting blood pressure/heart rate, physical function, fasting blood collection). A second administration of the home visit protocol among surviving Long Life Study cohort members is planned for 2022–2024.

MENOPAUSAL HORMONE THERAPY: THE WHI CLINICAL TRIALS

Recognized for decades as an effective treatment for vasomotor symptoms of menopause and associated with lower rates of CHD in observational studies, estrogen therapy had become one of the most widely prescribed medications in the world by the 1980s and early 1990s[8,9]. Moreover, a larger role for systemic menopausal HT in the prevention of CVD, cognitive decline, osteoporosis, and other chronic diseases of aging began to emerge at that time, also fueled by observational research[8,9].

In view of a high prevalence of HT use[8] and its expanding use for chronic disease prevention, confirmation of these purported benefits in RCTs became imperative. In the early 1990s, the NIH secured funding from congress for the large-scale WHI, including a trial of estrogen alone (oral conjugated equine estrogens [CEE], 0.625 mg/d, among women with hysterectomy)[10] and a parallel trial of combination estrogen-progestin therapy (CEE 0.625 mg/d + medroxyprogesterone acetate [MPA], 2.5 mg/d, among women with an intact uterus)[11]. The two HT trials (N=27,347 women overall, aged 50–79 [mean age 63] at enrollment), were designed to assess the overall balance of benefits and risks of HT, including effects on rigorously adjudicated CVD and cancer endpoints, and slated to last 8 years.

In 2002, the CEE+MPA trial was stopped 3 years early because risks exceeded benefits, including increased risks of breast cancer, pulmonary embolism, stroke, and CHD[10]. The findings shocked the medical and lay communities, leading to a seismic shift in clinical practice and a 70–80% reduction in HT prescriptions[8]. In 2004, the WHI CEE-alone trial was stopped 1 year early due to similar increases in stroke and an absence of clear benefit for CHD[11].

Following publication of the WHI's main findings, questions arose about how observational studies and randomized trials of HT could have yielded such divergent findings[8,9,12]. Clinical trials are less susceptible to confounding and may be better able to capture early increases in risk[9,12]. The observational studies of HT, however, tended to include women in early menopause who typically were seeking treatment for vasomotor symptoms. This

motivated in-depth analyses within WHI by age group and years since menopause[13–15] to assess a potential modifying effect by these variables, which tend to correlate with underlying atherosclerotic burden. Absolute rates of CHD, stroke, and other incident chronic disease outcomes, as well as the rate differences due to HT (attributable risks), varied markedly by age group, with much lower absolute rates in the younger compared to older women[13,15] (Figure 3). Hazard ratios (HR) for HT and several, but not all, clinical outcomes tended to be more favorable in the younger than older women, especially in the estrogen-alone trial (Table 2). Effects of CEE-alone on CHD, myocardial infarction (MI), all-cause mortality, and the global index (composite endpoint of risks and benefits) tended to be favorable in the 50–59 year age group compared to older age groups. When examined by years since menopause, similar trends emerged for CHD, MI, and all-cause mortality with CEE+MPA[13,15]. Other intriguing signals for better HT outcomes in early menopause and in lower-risk women included lower post-trial levels of coronary artery calcification among women aged 50–59 randomized to CEE-alone vs placebo[16], more favorable CHD outcomes on HT for women with lower LDL-cholesterol levels[17] and without metabolic syndrome[18], compared to those at higher cardiometabolic risk, and greater benefits of CEE-alone among women with early bilateral oophorectomy[19].

The WHI HT trials overturned dogma and transformed menopause management by challenging the routine prescription of HT. WHI highlighted HT's complex matrix of effects, the important influence of age, time since menopause, and underlying risk factor status, and helped to clarify appropriate candidates for treatment. HT remains appropriate for menopausal symptom management, especially in early menopause, but is no longer routinely recommended for CVD or chronic disease prevention[8]. Individualized patient care and shared decision-making regarding HT are essential.

CORONARY HEART DISEASE

WHI has made extensive contributions to our understanding of CHD in postmenopausal women, a previously understudied topic. The roles of HT, diet, physical activity, and body composition in CHD are covered elsewhere in this manuscript. Here we review other key CHD findings from the WHI. Long-term follow-up has confirmed that CVDs comprise the most common causes of death among the postmenopausal women enrolled in the WHI. Of 47,723 deaths reported in the WHI studies through March 6, 2021, 14,745 (30.9%) were from CVD, with 5869 deemed atherosclerotic CVD, 2465 definite CHD and 3359 probable CHD[20].

In addition to the main WHI study, several important separately funded ancillary studies have been undertaken. The WHI Coronary Artery Calcification Study (WHI-CACS) enrolled women aged 50–59 at entry into the E-alone trial, who then underwent coronary artery calcium imaging and scoring with subsequent follow-up for clinical outcomes. Women with CAC =0, comprising 54% of the 1020 participants enrolled, had very low age-adjusted rates (per 1000 person-years) of CHD (0.91), CVD (5.56), and mortality (3.45) compared with women with any CAC (>0), whose rates for these endpoints were approximately two-fold higher[21].

WHI also evaluated risk-prediction models of CHD. The algorithm in the 2007 Update to the American Heart Association Guidelines for CVD in Women predicted coronary events with similar accuracy as the commonly-used Framingham equation (C-statistic: Framingham 0.665 vs AHA 0.664, P = 0.94) (Table 3) thus validating this simplified scoring system for women[22]. In a later investigation, The Reynolds Risk Score was found to be a more accurate predictor of 10-year risk than Framingham models (C-statistic 0.765 vs 0.757, P = 0.03), with a net reclassification index (NRI) of 12.9%[23]. Early studies of the AHA/ACC Pooled Cohort Equations (PCE) suggested that CVD risk was overestimated, a finding confirmed in a WHI subcohort of ~20,000 women using adjudicated CVD outcomes[24]. Further assessment, that added events confirmed through Medicare, however, found that the PCE discriminated risk well in postmenopausal women (C-statistic 0.726).

Reproductive factors have been evaluated as CHD predictors in WHI. In a model adjusted for CHD risk factors, novel reproductive factors (including number of pregnancy losses, number of stillbirths, and absence of breast feeding) were associated with postmenopausal CHD (25). However, when added to established risk factors, these reproductive risk factors did not appreciably improve overall CHD risk stratification in this population.

ECG findings among WHI participants with history of CHD at study enrollment demonstrated that left (LBBB) and right bundle branch block (RBBB) were predictive of CHD death (HR 2.92), but only LBBB was predictive of all-cause death (HR 1.43). In women without known CHD, only LBBB was predictive of CHD death (HR 2.17) and neither BBB predicted all-cause death[26].

Incident CVD, total and cause-specific death rates have been compared between WHI women with (n = 4,340) and without (n = 97,576) incident invasive breast cancer stratified by three age groups (50–59, 60–69 and 70–79 years). CVD was the leading cause of death over 10 years of follow up post-diagnosis for women with localized breast cancer diagnosed at age 70 years and older (27). Thus, WHI is contributing to the emerging field of cardio-oncology. WHI is also large enough to look at the relationship between inflammatory conditions, such as rheumatoid arthritis and CHD, documenting multivariable–adjusted HRs of 1.46 for incident CHD and 2.55 for fatal CVD among women with compared to women without rheumatoid arthritis[28].

It is widely acknowledged that conventional risk factors, such as smoking, hypertension, and hyperlipidemia, do not comprehensively identify all women who will develop CHD events. WHI remains an important ongoing resource for studying the incidence and determinants of cardiac disease in aging women, including the testing of promising novel interventions in embedded RCTs. Future investigations may include psychological interventions and the role of pain control as potential CHD risk-reducing modalities in this population[28,29].

HEART FAILURE AND ITS SUBTYPES

WHI has contributed uniquely to the epidemiology of heart failure (HF) in a racially and ethnically diverse cohort of older postmenopausal women. In the RCT, we showed that randomization to menopausal HT[30] or to CaD supplementation[31] was not associated with

HF risk. Among all WHI women, we revealed racial and ethnic variation in age-standardized incidence rates (per 100,000 person-years) for overall HF among White (274), Black (380), Hispanic (193), and Asian/Pacific Islander (103) subgroups[32]. Compared to White women, the excess HF risk in Black women (age-adjusted HR 1.45) was substantially attenuated when adjusted for socioeconomic status (SES) (HR 1.19) and traditional risk factors (HR 0.76); whereas, after adjusting for SES and risk factors the lower risks persisted in Hispanic (HR 0.54) and Asian/Pacific Islander (HR 0.49) participants. Racial and ethnic variation in HF with preserved (HFpEF) and reduced (HFrEF) ejection fraction also was evident with age-standardized incidence rates (per 100 person-years) in White, Black and Hispanic women of 0.20, 0.15, 0.08 for HFpEF, and 0.10, 0.10, and 0.05 for HFrEF, respectively[33]. When adjusted for SES, traditional and nontraditional risk factors, risks of HFpEF and HFrEF were lower in Black (HRs 0.59 and 0.77) and Hispanic (HRs 0.47 and 0.54) women relative to White women. Hypertension carried the highest population attributable risk for HFpEF (40.9%) and HFrEF (42.7%) in the overall cohort and across race and ethnic subgroups. WHI results provided clear evidence that some of the racial and ethnic differences in risk of HF and its subtypes is attributed to SES differences.

In WHI, healthy lifestyle factors, individually and as a composite score, were associated with lower risks of overall HF, HFpEF, and HFrEF[34], findings especially relevant in HFpEF for which effective therapies are currently limited. There is increasing interest in pregnancy-related complications and reproductive-related factors as predictors of CVD risk in later life. We studied several such factors in relation to HF risk, as summarized in Table 4[35–38]. Pregnancy-related hypertension, number of pregnancies and live births, and infertility were positively associated with overall HF, whereas hypertension, nulliparity, and infertility were positively associated with HFpEF.

ATRIAL FIBRILLATION

Although atrial fibrillation (AF) is more common in men than in women, women with AF have a higher risk of stroke and death compared to men with AF but have traditionally been understudied. While AF was not one of the primary outcomes in the main WHI study, we have subsequently linked most participants to Centers for Medicare & Medicaid Services data allowing us to create one of the largest multi-ethnic cohorts on AF including nearly 20,000 incident AF cases. In WHI, we learned that traditional modifiable risk factors were significantly associated with incident AF[39], and these associations were similar across race and ethnic subgroups[40]. However, because of the variable prevalence of risk factors among race and ethnic subgroups, hypertension had a much higher population attributable risk in Black (38.3%) and Hispanic (29.2%) women, compared to White (24.3%) and Asian (18.3%) women[40] (Table 5).

We have explored in depth the relationship of physical activity, obesity, and body composition with AF in the WHI. We found that self-reported physical activity was significantly inversely associated with AF incidence, an association that was more pronounced in obese women[41] (Figure 4). Conversely, we found that greater sedentary time measured objectively by accelerometry was associated with increased AF risk[42]. One of the most surprising observations regarding AF came from a study on women who had their body

composition measured by dual-energy x-ray absorptiometry (DXA). Lean body mass was more strongly related to AF than fat mass, and the risk of AF associated with BMI was largely attributable to its association with lean body mass[43]. We are currently evaluating the effect of an exercise intervention on the primary prevention of AF in the WHI Strong and Healthy (WHISH) trial[44] (NCT02425345), where we hope to continue gaining insights into arrhythmic disease in older women.

DIETARY INTAKE AND CVD RISK

The WHI DMT has contributed important findings related to the relevance of diet for cardiovascular health in postmenopausal women. The low-fat DMT in n=48,835 participants targeted breast/colon cancer reduction as primary outcomes and CHD was the secondary outcome. The intervention aimed to reduce total fat intake to 20% of energy without focusing on specific subtypes of fat, and also recommended increases in vegetables, fruits, and grains. Food frequency questionnaire assessments one year post-randomization estimated lower total fat and higher carbohydrate intakes each of about 10% of energy in the intervention versus comparison groups, along with modestly higher plant-based protein in the intervention group. Reductions in both saturated and unsaturated fatty acids in the intervention group were equivalent. After 8.1 years (median) CHD incidence did not differ between randomized groups, although LDL cholesterol was modestly lower in the intervention group[6]. CHD outcomes were unfavorable among participants who reported a history of CVD, but there was evidence for post-randomization confounding by statin use among participants with either prior CVD or baseline hypertension[45]. Among normotensive participants at baseline (n= 23,248), the intervention versus comparison group risk for CHD was reduced (HR 0.70, 95% confidence interval [CI]: 0.56, 0.87). Further, the shift from fat to carbohydrate occurred without accompanying weight gain as there was an initial 2 kg weight reduction in the intervention group that largely dissipated by the end of the intervention period. Energy expenditure (assessed by doubly-labeled-water in a subgroup) did not differ between randomization groups[46], and dietary changes among the intervention group participants were generally consistent with current dietary pattern recommendations[47].

Leveraging both the WHI DMT and OS, WHI's recent dietary research has focused on biomarkers to calibrate self-reported diet for measurement error and, using calibrated intakes, for association with clinical outcomes. These studies indicate lower risk of CHD, stroke, and HF among WHI participants who reported diets that were relatively lower in total energy, sodium to potassium ratio, and relatively higher in dietary fiber. Table 6 shows estimated HRs for 20% increments in these dietary variables from four WHI study reports[48–51]. A recent review paper[52] expands upon these results by presenting findings for additional clinical outcomes.

CaD SUPPLEMENTATION AND CVD RISK

In the WHI CaD RCT, 36,282 women were randomly assigned to calcium carbonate (1000 mg elemental calcium daily) plus vitamin D3 (400 IU daily) or to placebo, for a mean intervention period of 7 years[7]. Hip fracture and colorectal cancer were targeted as

co-primary outcomes and CVD was a secondary outcome. The HR for hip fracture was 0.88 (95% CI: 0.72, 1.08) and for colorectal cancer was 1.06 (95% CI: 0.85, 1.32)[7,53]. Results for incident CVD outcomes were null, including myocardial infarction (HR 1.03, 95% CI: 0.90, 1.19), CHD (HR 1.03, 95% CI: 0.90, 1.17) and stroke (HR 0.95, 95% CI: 0.82, 1.10)[53]. WHI participants were generally replete in calcium at baseline (only 33% self-reported intakes <800 mg/d at enrollment) and mean vitamin D intake at baseline was 367 IU/d. Although the HR for fracture was lower in the women with high adherence to study pills and those without personal use of calcium or vitamin D supplements, the results for CVD did not change appreciably when restricted to these groups. Moreover, an ancillary study to the CaD trial determined that there were no differences in coronary artery calcification (CAC) scores between intervention (Agatston CAC score, mean 91.6) and placebo (mean 100.5; P = 0.74) groups at the end of the intervention period[54]. Although CaD supplementation was generally safe and well tolerated, the risk of renal calculi was slightly increased (HR 1.17, 95% CI: 1.02, 1.34).

PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR

Epidemiologic research on physical activity (PA) and CVD has been based largely on self-reported PA exposures, including early results in WHI[55]. Because self-report questionnaires have limited accuracy and completeness for assessing movement in older adults, especially for light PA (<3 metabolic equivalent [MET] intensity) and sedentary behavior, the Objective Physical Activity and Cardiovascular Health in Older Women (OPACH) Study was launched. OPACH obtained data from triaxial accelerometers (Actigraph GT3X), worn at the hip for seven consecutive 24-hour days, in 6,489 women aged 63–99 years, 92% of deployed devices[56]. In a laboratory calibration study of 200 OPACH women – *the first of its kind specifically in older adults* – we showed that commonly-used intensity cutpoints (e.g., as in NHANES) developed in younger adults result in substantial underestimation of older women's time spent in moderate-to-vigorous PA (MVPA)[56]. In the OPACH cohort, >75% of daily PA time was spent in light intensity PA; <25% was in MVPA, the intensity level emphasized in current guidelines. Using the calibrated OPACH cutpoints, Table 7 summarizes findings for sedentary time, light PA and MVPA, and shows that steps per day were strongly inversely associated with mortality and CVD events[57–59]. Physical functioning, as measured by the Short Physical Performance Score (SPPB) has been identified as a hallmark of aging resiliency, yet few studies have evaluated this in relation to CVD risk. In OPACH, a lower SPPB score was shown to be a strong predictor of higher CVD incidence, including in women classified at low CVD risk by the Reynold's Risk Score, independent of accelerometer-measured PA[60] (Figure 5). Similar results were found for incident HF[61]. An ongoing pragmatic, RCT embedded within the current WHI Extension Study, the WHISH trial launched in 2015, is testing the hypothesis that increased PA, based on the 2008 and 2018 national PA recommendations for older adults, and decreased sedentary behavior will reduce major CVD events[44]. The WHISH trial will provide the first RCT evidence regarding the causal roles of increasing PA levels, including light PA, and reducing sedentary behavior in the *primary prevention* of incident clinical CVD events.

ADIPOSITY, BODY COMPOSITION, AND CARDIOMETABOLIC HEALTH

WHI has made seminal contributions to the evidence on adiposity, body composition, and cardiometabolic health in postmenopausal women. An unparalleled scientific resource, 11,020 older women completed DXA measures of body composition at three clinical examination sites chosen to enhance subcohort diversity regarding race, ethnicity, and age. These women underwent whole body DXA scans at baseline, year 1 (RCT only), and years 3, 6, and 9 (RCT and OS), which generated regional and total body composition measurements of adipose tissue and lean body mass. Availability of objectively and serially measured adiposity and other body composition parameters in such a large cohort is an enormously valuable data resource, particularly given the challenges of classifying obesity using traditional anthropometric measures in older women[62].

WHI studies have demonstrated higher levels of trunk fat predicted risk for incident type 2 diabetes in a strong, positive, monotonic fashion, with greater magnitude than seen for anthropometric predictors of risk[63]. Accounting for leg fat levels was particularly predictive of diabetes risk in Black women. A separate study confirmed a stronger association with incident diabetes for DXA measured overall body fat, and particularly trunk fat, as compared to anthropometric indices[64]. Furthermore, DXA adiposity measures more strongly discriminated incidence of diabetes and atherosclerotic CVD endpoints than did anthropometric measures[64]. Even in analyses restricted to women defined as normal weight (BMI ≤ 25 kg/m^2), those with higher trunk fat and lower amounts of leg fat had a higher risk for incident CHD and stroke[65] (Figure 6). We also examined incident lower extremity arterial disease, observing a strong positive association with greater trunk fat (Quartile 4 vs 1: HR 2.56, trend P = 0.008) and an inverse association with higher leg fat (HR 0.25, trend P <0.001) controlling for demographic and lifestyle factors[66]. Further adjustment for CVD risk factors attenuated the trunk fat relation (HR 1.33, trend P = 0.49), whereas the inverse association with leg fat persisted (HR 0.41, trend P = 0.008). The WHI will make additional significant future scientific contributions by examining recently derived DXA-measured abdominal visceral and subcutaneous adipose tissue in relation to clinical cardiometabolic outcomes in the WHI DXA subcohort[67].

COGNITION, SLEEP, AND CARDIOMETABOLIC HEALTH

Risk factors for poor cardiometabolic health are closely tied to sleep parameters, including sleep quality, duration, intermittent hypoxia, and sleep apnea. The relationship between sleep and CVD appears to be bidirectional. In WHI, only 27% of women reported sleeping 8 hours or more per night[68]. WHI participants with insomnia had a 27% higher risk for incident CVD, and a 38% higher risk for incident CHD[69]. Both short (≤5 hours) and long (≥ 10 hours) sleep duration was also associated with higher risks of CHD and CVD. For WHI participants, obtaining suboptimal sleep has also been associated with higher incidence of ischemic stroke[70] and all-cause mortality[71]. In a study of 7,444 WHIMS (WHI Memory Study) participants, obtaining ≤6 hours or ≥8 hours of sleep per night was associated with 35% higher risk of cognitive decline, irrespective of CVD status[72]; elevated risks of both mild cognitive impairment (MCI) and dementia also were found. Given the national prioritization to understand the interrelationships between cognitive

status and cardiovascular resilience in later life[73], understanding the extent to which sleep might represent a modifiable intervention target in older adults has profound public health relevance.

The WHI findings regarding sleep and women's health led to the development of the WHI Sleep HyPoxia Effects on Resilience (WHISPER) study to prospectively evaluate associations between objective sleep parameters including hypoxia, sleep duration and fragmentation, and outcomes of CVD events, cancer, and cognitive function and decline in older women. The study has enrolled over 4,990 WHI women (mean age 80.5 ± 4.8 years) who completed a home-based sleep study with multiple objective metrics, and baseline and follow-up cognitive assessments. These women are also prospectively followed for incident CVD and mortality. In WHISPER, sleep was evaluated using the WatchPat (Itamar Medical, Atlanta, GA) to measure oxygen desaturations and peripheral arterial tonometry, and the ActiGraph Link (ActiGraph, Inc. Pensacola, FL) to measure activity-dependent total sleep time, sleep efficiency and fragmentation. This WHI ancillary study is expected to shed critically needed light on the association between objective sleep measures, CVD, and trajectories of cognitive function in older women within a community-setting.

GENOMICS, EPIGENOMICS, CHIP, AND CVD

WHI is an active participant and often leader in many genetic and genomic cardiovascular consortia, including TOPMed (Trans-Omics for Precision Medicine)[74] and PAGE (Population Architecture using Genomics and Epidemiology)[75]. WHI contributes the largest number of incident clinical CVD endpoints for analysis in many of these data pooling projects, particularly among women. WHI has genome-wide SNP or whole genome sequencing data on ~50,000 participants, DNA methylation on ~10,000 participants, and RNA-seq, metabolomics and proteomics data on several thousand participants. The DNA methylation data, for example, have contributed to the development or validation of several epigenetic biomarkers of aging ("epigenetic clock"), some of which are highly predictive of incident CHD and mortality[76].

WHI investigators are currently leading research in clonal hematopoiesis of indeterminate potential (CHIP), an aging-related phenomenon due to the acquisition of somatic mutations in hematopoiesis-related genes (e.g., *TET2, DNMT3A, ASXL1, JAK2*). The mutations associated with CHIP lead to clonal expansion of a genetically distinct subpopulation of blood cells in the absence of overt hematologic disease[77]. CHIP increases with age, with a prevalence >20% among those aged 70 years or older. Animal models suggest CHIP has pro-inflammatory effects, which may contribute to the observed association of CHIP with increased risk of CHD[77]. Through a current NHLBI-funded R01 and WHI ancillary study, and in collaboration with NHLBI TOPMed and UKBiobank investigators, WHI investigators have identified germline genetic variants associated with CHIP[78] and assessed the relationship of CHIP to various CVD risk factors and clinical outcomes. For example, Honigberg et al identified a novel association between premature menopause, CHIP, and incident CVD risk[79]. Although a healthy-lifestyle composite score was not related to CHIP among WHI postmenopausal women[80], specific score components including smoking status and obesity showed associations. CHIP was associated with increased risk of total stroke

(HR 1.14, 95% CI: 1.03,1.27; P = 0.01), particularly hemorrhagic stroke and small vessel ischemic stroke subtypes[81]. CHIP was also associated with ~25% increased risk of incident HF in a meta-analysis (HR 1.25, 95% CI: 1.13, 1.38), with consistent associations across the individual cohorts including WHI[82].

ENVIRONMENTAL AND SOCIAL DETERMINANTS

WHI has made important contributions to the understanding of environmental and social determinants of health (SDOH) relevant to cardiovascular risk among U.S. postmenopausal women. Factors allowing it to do so include its large size and geographically and socially diverse study population; its early adoption of geographic information systems methods and data to characterize its participants; and its long-standing support of active Scientific Interest Groups dedicated to those ends. The geocoding has provided the foundation for spatiotemporal estimation of environmental exposures, exposure-outcome associations, and their neighborhood socioeconomic contexts over three decades of cohort follow-up. The resulting estimates have been featured in seminal reports describing the cardiovascular health effects of ambient air pollution[83,84], the pathophysiologic mechanisms underlying such effects[85], and the contextual socioeconomic factors that modify susceptibility to them[86]. Moreover, the reports have contributed to key meta-analyses and U.S. EPA *Integrated Science Assessments* that have provided the basis for tightening *National Ambient Air Quality Standards*, improving air quality, and thereby reducing U.S. population-wide CVD risks.

WHI also has contributed intersectional understanding of pathways that connect individual-level SDOH (e.g., stressful life events; social strain) to incident CHD and stroke through behavioral risk factors (e.g., unhealthy diet), as well as personal resources (e.g., resilience; social support) that buffer the adverse behavioral effects of such stress. Indeed, resilient women in WHI have 22% and 56% greater odds of a healthy diet and recommended physical activity levels, respectively[87]. Moreover, WHI has contributed to understanding structural-level SDOH by highlighting significant socioeconomic risk gradients in cardiovascular outcomes. For example, neighborhood disadvantage in SES and food environments are associated with greater rates of obesity and hypertension[88], and differences in income and prevalent diabetes largely explain the excess HF risk among Black women as compared with White women in WHI[32]. More recently, we identified persistent race and income disparities in coronary revascularization following acute MI, despite the national Healthy People initiative to ameliorate disparities in clinical cardiac interventions by 2020[89]. WHI investigators, therefore, remain committed to utilizing the unique and extensive data resource for ongoing structural-level SDOH research[90].

FUTURE RESEARCH DIRECTIONS

WHI findings have had a major impact on both a clinical and public health level. Moving forward, WHI is poised to contribute to several emerging topics. Cardio-oncology is of increasing importance as female cancer survivors live longer and face a greater burden of clinical cardiometabolic sequalae[91]. The WHI Life and Longevity After Cancer study (LILAC, U01 CA173642) is following a cohort of WHI participants diagnosed with any

of eight common cancers[92]. The cardiovascular risk factors and clinical endpoints available through WHI in this cancer survivor cohort provide unique opportunities to understand the impact of cancer and its treatment on CVD and aging in later life women where data are sparse.

Continuing WHI investigations using DXA-measured body composition, particularly visceral adiposity, in relation to cardiometabolic risk factors, clinical CVD events, and mortality in postmenopausal women (R01 AG055018) will also advance knowledge on age-related patterns and changes in lean and fat tissue, factors that contribute to these patterns, and how they influence CVD and healthy aging in older women.

Long-term follow-up of the original WHI RCT interventions continues to yield informative and exciting findings[13,45,93]. Novel nutritional biomarkers studies[46,52] that have progressed over 14 years in WHI will advance understanding on the importance of diet and dietary patterns in CVD prevention. New embedded pragmatic clinical trials, including the WHISH RCT on physical activity and CVD prevention[44], its ancillary studies focused on HF (R01 HL130591; NCT03099889) and atrial fibrillation (R01 HL136390) endpoints are ongoing, and the COcoa Supplement and Multivitamin Outcomes Study (COSMOS; NCT02422745) has recently completed[94,95].

The NHLBI is investing in large-scale collaborative science initiatives to leverage substantial existing phenotypic and genotypic resources[73,96,97]. WHI investigators will contribute to important new discovery efforts on the etiology, prevention, and management of HF as part of the Cross-Cohort Collaboration in CVD (R01 HL150170) and the newly formed NHLBI HeartShare Initiative. The current NHLBI-funded WHI extension study (2020–2025) includes an emphasis on deeper understanding of stroke in postmenopausal women. Vascular brain health and HF are major current public health challenges[73,96] that WHI will rigorously focus on in future studies.

WHI has collected repeated survey information on SARS-CoV-2 infections, vaccinations, COVID-19 hospitalizations, and long-term symptoms, as well as experiences with protective policies and behaviors, which will contribute to understanding of the physical and emotional/mental health impact of the COVID-19 pandemic on aging women in the U.S[98]. An initiative during the current WHI extension study is a second Long Life Study in-home examination (LLS2) in 4,000 women aged 73–105 who participated in the first LLS in-home exam 10 years earlier. The exam includes a fasting blood sample, resting blood pressure and pulse, anthropometrics, and physical functioning tests. Up to 2000 LILAC women also will complete the in-home exam protocol, providing an exceptional opportunity to further characterize CVD-related phenotypes in older cancer survivors. In an associated study, the D-3 creatine dilution method will be used for remote assessment of skeletal muscle mass[99] in both cancer survivors and cancer free women to understand its relevance to healthy aging, preservation of lean mass and physical function. Other planned LLS2 sub-studies will add accelerometry assessments and cardiac ECG patch wear over consecutive free-living days. Remote blood pressure monitoring has been piloted in WHI women and is planned for more widespread utilization to understand the relationship between several blood pressure parameters (diurnal variation, short-term systolic and diastolic variability)

and cardiovascular aging. WHI resources have been used in genomics and other omics-platforms to explore CVD-related associations such as the metabolomics of CHD100 and mortality[101], predictors and clinical sequelae of CHIP[78], and the association of the microbiome with incident hypertension[102]. The WHI database and large biorepository, with additional biological sample collection, will continue to support a broad range of discovery, validation, and mechanistic studies of CVD.

CONCLUSIONS

The WHI is the largest and most comprehensive investigation ever conducted on the prevention of CVD and other chronic diseases in postmenopausal women. Unlike most other population studies on CVD, WHI included a set of randomized prevention trials that provided definitive tests of hypotheses pertaining to the effect of menopausal HT, dietary modification, and CaD supplementation on rigorously adjudicated clinical CVD outcomes, in addition to a large community-based prospective observational cohort study (Central Illustration). Several funded extension studies have provided continuing annual follow-up for incident disease outcomes and have supported ancillary studies to collect additional new data through in-home examinations, wearable devices and mobile health technology, and remote biospecimen collection adding to the already extensive WHI biorepository. Use of these data resources in ongoing or planned studies aimed at deeper phenotyping through -omics platforms and artificial intelligence, such as machine learning, will lead to enhanced understanding of physiological and biochemical mechanisms of CVD and other diseases of aging. WHI also has served as a well-defined population base from which to recruit older women into novel randomized prevention trials testing behavioral and nutritional interventions. Training and career development of epidemiological, statistical, and clinical scientists has been strongly supported by the WHI program and is one of its most important legacies in cardiovascular science and public health that will continue for years to come. WHI has been a culmination of many years of scientific maturation, motivated by medical, public health, and societal imperatives to fill major knowledge gaps in women's health. WHI has helped to address several important issues summarized in the 2019–2023 Trans-NIH Strategic Plan for Women's Health Research, but additional research is needed to address disparities in evidence-based disease prevention and treatment tailored to women's needs, circumstances, and goals[103]. WHI is a unique scientific resource that continues to evolve and provide new insights into cardiovascular resiliency and healthy aging among women.

ACKNOWLEDGMENTS:

The authors thank the WHI participants, clinical sites, investigators, and staff for their dedicated efforts.

FUNDING:

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D0004, 75N92021D00005; with additional funding by HL151885 (WHISH Trial), HL130591 (WHISH-2-Prevent Heart Failure), HL136398 (WHISH-STAR), HL150170 (Cross-Cohort Consortium Heart Failure), HL148565 (CHIP), HL133684 (WHISPER), HL105065 and HL153462 (OPACH), and AG050657 (COSMOS-Mind). The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

ABBREVIATIONS

CaD	Calcium and Vitamin D Supplementation
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
DMT	Diet Modification Trial
HF	Heart Failure
HT	Menopausal Hormone Therapy
HR	Hazard Ratio
NIH	National Institutes of Health
OS	Observational Study
WHI	Women's Health Initiative

REFERENCES

1. Department of Health and Human Services. Healy proposes historic Women's Health Initiative. The NIH Reporter 1991;43:1, 4–5.
2. Rossouw JE, Finnegan LP, Harlan WR, Pinn VW, Clifford C, McGowan JA. The evolution of the Women's Health Initiative: perspectives from the NIH. J Am Med Womens Assoc 1995;50:50–5.
3. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Controlled Clinical Trials 1998;19:61–109. [PubMed: 9492970]
4. Hays J, Hunt JR, Hubbell FA et al. The Women's Health Initiative recruitment methods and results. Annals Epidemiol 2003;13:S18–77.
5. Curb JD, McTiernan A, Heckbert SR et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Annals Epidemiol 2003;13:S122–8.
6. Howard BV, Van Horn L, Hsia J et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:655–66. [PubMed: 16467234]
7. Jackson RD, LaCroix AZ, Gass M et al. Calcium plus vitamin D supplementation and the risk of fractures. New Engl J Med 2006;354:669–83. [PubMed: 16481635]
8. North American Menopause Society. The 2017 hormone therapy position statement of the Noth American Menopause Society. Menopause 2017;24:728–753. [PubMed: 28650869]
9. Manson JE, Bassuk SS. Menopause and menopausal hormone therapy. In: Jameson JL, Fauci AS, Kasper DL, Hauser S, Longo DL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw-Hill, 2018.
10. Rossouw JE, Anderson GL, Prentice RL et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33. [PubMed: 12117397]
11. 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;291:1701–12. [PubMed: 15082697]
12. Rossouw JE. Reconciling the divergent findings from clinical trials and observational studies of menopausal hormone therapy for prevention of coronary heart disease. Sem Reproductive Med 2014;32:426–32.

13. 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;310:1353–68. [PubMed: 24084921]
14. Prentice RL, Manson JE, Langer RD et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. Am J Epidemiol 2009;170:12–23. [PubMed: 19468079]
15. Rossouw JE, Prentice RL, Manson JE et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465–77. [PubMed: 17405972]
16. Manson JE, Allison MA, Rossouw JE et al. Estrogen therapy and coronary-artery calcification. New Engl J Med 2007;356:2591–602. [PubMed: 17582069]
17. 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;126:1577–86. [PubMed: 22932256]
18. 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;20:254–60. [PubMed: 23435021]
19. Manson JE, Aragaki AK, Bassuk SS et al. Menopausal Estrogen-Alone Therapy and Health Outcomes in Women With and Without Bilateral Oophorectomy: A Randomized Trial. Annals Intern Med 2019;171:406–414.
20. Women's Health Initiative Annual Progress Report. www.whi.org. 2021.
21. Poornima IG, Mackey RH, Allison MA et al. Coronary Artery Calcification (CAC) and Post-Trial Cardiovascular Events and Mortality Within the Women's Health Initiative Estrogen-Alone Trial. J Am Heart Assoc 2017;6.
22. Hsia J, Rodabough RJ, Manson JE et al. Evaluation of the American Heart Association cardiovascular disease prevention guideline for women. Circ Cardiovasc Qual Outcomes 2010;3:128–34. [PubMed: 20160160]
23. Cook NR, Paynter NP, Eaton CB et al. Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women's Health Initiative. Circulation 2012;125:1748–56, S1–11. [PubMed: 22399535]
24. Mora S, Wenger NK, Cook NR et al. Evaluation of the Pooled Cohort Risk Equations for Cardiovascular Risk Prediction in a Multiethnic Cohort From the Women's Health Initiative. JAMA Intern Med 2018;178:1231–1240. [PubMed: 30039172]
25. Parikh NI, Jeppson RP, Berger JS et al. Reproductive Risk Factors and Coronary Heart Disease in the Women's Health Initiative Observational Study. Circulation 2016;133:2149–58. [PubMed: 27143682]
26. Zhang ZM, Rautaharju PM, Soliman EZ et al. Mortality risk associated with bundle branch blocks and related repolarization abnormalities. Am J Cardiol 2012;110:1489–95. [PubMed: 22858187]
27. Park NJ, Chang Y, Bender C et al. Cardiovascular disease and mortality after breast cancer in postmenopausal women: Results from the Women's Health Initiative. PLoS One 2017;12:e0184174. [PubMed: 28934233]
28. Mackey RH, Kuller LH, Deane KD et al. Rheumatoid Arthritis, Anti-Cyclic Citrullinated Peptide Positivity, and Cardiovascular Disease Risk in the Women's Health Initiative. Arthritis Rheumatol 2015;67:2311–22. [PubMed: 25988241]
29. Tindle HA, Chang YF, Kuller LH et al. Optimism, cynical hostility, and incident coronary heart disease and mortality in the Women's Health Initiative. Circulation 2009;120:656–62. [PubMed: 19667234]
30. Liu L, Klein L, Eaton C et al. Menopausal Hormone Therapy and Risks of First Hospitalized Heart Failure and its Subtypes During the Intervention and Extended Postintervention Follow-up of the Women's Health Initiative Randomized Trials. J Card Fail 2020;26:2–12. [PubMed: 31536806]
31. Donneyong MM, Hornung CA, Taylor KC et al. Risk of heart failure among postmenopausal women: a secondary analysis of the randomized trial of vitamin D plus calcium of the women's health initiative. Circ Heart Fail 2015;8:49–56. [PubMed: 25398967]

32. Eaton CB, Abdulbaki AM, Margolis KL et al. Racial and ethnic differences in incident hospitalized heart failure in postmenopausal women: the Women's Health Initiative. Circulation 2012;126:688–96. [PubMed: 22753306]
33. Eaton CB, Pettinger M, Rossouw J et al. Risk Factors for Incident Hospitalized Heart Failure With Preserved Versus Reduced Ejection Fraction in a Multiracial Cohort of Postmenopausal Women. Circ Heart Fail 2016;9(10):e002883. [PubMed: 27682440]
34. Noel CA, LaMonte MJ, Roberts MB et al. Healthy lifestyle and risk of incident heart failure with preserved and reduced ejection fraction among post-menopausal women: The Women's Health Initiative study. Prev Med 2020;138:106155. [PubMed: 32473271]
35. Hall PS, Nah G, Howard BV et al. Reproductive Factors and Incidence of Heart Failure Hospitalization in the Women's Health Initiative. JACC 2017;69:2517–2526. [PubMed: 28521890]
36. Hansen AL, Sondergaard MM, Hlatky MA et al. Adverse Pregnancy Outcomes and Incident Heart Failure in the Women's Health Initiative. JAMA Netw Open 2021;4:e2138071. [PubMed: 34882182]
37. Lau ES, Wang D, Roberts M et al. Infertility and Risk of Heart Failure: Insights from the Women's Health Initiative. JACC 2022;79:1594–1603. [PubMed: 35450577]
38. Tison GH, Avram R, Nah G et al. Predicting Incident Heart Failure in Women With Machine Learning: The Women's Health Initiative Cohort. Can J Cardiol 2021;37:1708–1714. [PubMed: 34400272]
39. Perez MV, Wang PJ, Larson JC et al. Risk factors for atrial fibrillation and their population burden in postmenopausal women: the Women's Health Initiative Observational Study. Heart 2013;99:1173–8. [PubMed: 23756655]
40. Rodriguez F, Stefanick ML, Greenland P et al. Racial and ethnic differences in atrial fibrillation risk factors and predictors in women: Findings from the Women's Health Initiative. Am Heart J 2016;176:70–7. [PubMed: 27264222]
41. Azarbal F, Stefanick ML, Salmoirago-Blotcher E et al. Obesity, physical activity, and their interaction in incident atrial fibrillation in postmenopausal women. J Am Heart Assoc 2014;3(4):e001127. [PubMed: 25142057]
42. Boursiquot BC, Bellettiere J, LaMonte MJ, LaCroix AZ, Perez MV. Sedentary Behavior and Atrial Fibrillation in Older Women: the Objective Physical Activity and Cardiovascular Health (OPACH) Study. J Am Heart Assoc 2022;11(6):e023833. [PubMed: 35253465]
43. Azarbal F, Stefanick ML, Assimes TL et al. Lean body mass and risk of incident atrial fibrillation in post-menopausal women. Eur Heart J 2016;37:1606–13. [PubMed: 26371115]
44. Stefanick ML, King AC, Mackey S et al. Women's Health Initiative Strong and Healthy Pragmatic Physical Activity Intervention Trial for Cardiovascular Disease Prevention: Design and Baseline Characteristics. J Gerontol Biol Sci A Med B 2021;76:725–734.
45. Prentice RL, Aragaki AK, Van Horn L et al. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. Am J Clin Nutr 2017;106:35–43. [PubMed: 28515068]
46. Neuhouser ML, Tinker L, Shaw PA et al. Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. Am J Epidemiol 2008;167:1247–59. [PubMed: 18344516]
47. Van Horn L, Aragaki AK, Howard BV et al. Eating Pattern Response to a Low-Fat Diet Intervention and Cardiovascular Outcomes in Normotensive Women: The Women's Health Initiative. Curr Dev Nutr 2020;4:nzaa021.
48. Prentice RL, Huang Y, Neuhouser ML et al. Associations of Biomarker-Calibrated Sodium and Potassium Intakes With Cardiovascular Disease Risk Among Postmenopausal Women. Am J Epidemiol 2017;186:1035–1043. [PubMed: 28633342]
49. Prentice RL, Pettinger M, Neuhouser ML et al. Biomarker-Calibrated Macronutrient Intake and Chronic Disease Risk among Postmenopausal Women. J Nutr 2021;151:2330–2341. [PubMed: 33880504]
50. Prentice RL, Pettinger M, Zheng C et al. Biomarkers for Components of Dietary Protein and Carbohydrate with Application to Chronic Disease Risk Among Postmenopausal Women. J Nutr 2022;152:1107–1117. [PubMed: 35015878]

51. Zheng C, Beresford SA, Van Horn L et al. Simultaneous association of total energy consumption and activity-related energy expenditure with risks of cardiovascular disease, cancer, and diabetes among postmenopausal women. Am J Epidemiol 2014;180:526–35. [PubMed: 25016533]
52. Prentice RL, Howard BV, Van Horn L et al. Nutritional epidemiology and the Women's Health Initiative: a review. Am J Clin Nutr 2021;113:1083–1092. [PubMed: 33876183]
53. Prentice RL, Pettinger MB, Jackson RD et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clincal trial and cohort study. Osteoporosis Int 2013;24:567–580.
54. Manson JE, Allison MA, Carr JJ et al. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. Menopause 2010;17:683–691. [PubMed: 20551849]
55. Manson JE, Greenland P, LaCroix AZ et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. New Engl J Med 2002;347:716–25. [PubMed: 12213942]
56. LaCroix AZ, Rillamas-Sun E, Buchner D et al. The Objective Physical Activity and Cardiovascular Disease Health in Older Women (OPACH) Study. BMC Public Health 2017;17:192. [PubMed: 28193194]
57. Bellettiere J, LaMonte MJ, Evenson KR et al. Sedentary behavior and cardiovascular disease in older women: The Objective Physical Activity and Cardiovascular Health (OPACH) Study. Circulation 2019;139:1036–1046. [PubMed: 31031411]
58. LaCroix AZ, Bellettiere J, Rillamas-Sun E et al. Association of Light Physical Activity Measured by Accelerometry and Incidence of Coronary Heart Disease and Cardiovascular Disease in Older Women. JAMA Netw Open 2019;2:e190419. [PubMed: 30874775]
59. LaMonte MJ, Buchner DM, Rillamas-Sun E et al. Accelerometer-Measured Physical Activity and Mortality in Women Aged 63 to 99. J Am Geriatr Soc 2018;66:886–894. [PubMed: 29143320]
60. Bellettiere J, LaMonte MJ, Unkart J et al. Short Physical Performance Battery and Incident Cardiovascular Events Among Older Women. J Am Heart Assoc 2020;9:e016845. [PubMed: 32662311]
61. Bellettiere J, Nguyen S, Eaton CB et al. The short physical performance battery and incident heart failure among older women: the OPACH study. Am J Prev Cardiol 2021;8:100247. [PubMed: 34553186]
62. Banack HR, Wactawski-Wende J, Hovey KM, Stokes A. Is BMI a valid measure of obesity in postmenopausal women? Menopause 2018;25:307–313. [PubMed: 29135897]
63. Luo J, Hendryx M, Laddu D et al. Racial and Ethnic Differences in Anthropometric Measures as Risk Factors for Diabetes. Diabetes Care 2019;42:126–133. [PubMed: 30352893]
64. Laddu DR, Qin F, Hedlin H et al. DXA Versus Clinical Measures of Adiposity as Predictors of Cardiometabolic Diseases and All-Cause Mortality in Postmenopausal Women. Mayo Clin Proc 2021;96:2831–2842. [PubMed: 34479738]
65. Chen GC, Arthur R, Iyengar NM et al. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. Eur Heart J 2019;40:2849–2855. [PubMed: 31256194]
66. Chen GC, Arthur R, Kamensky V et al. Body Fat Distribution, Cardiometabolic Traits, and Risk of Major Lower-Extremity Arterial Disease in Postmenopausal Women. Diabetes Care 2022;45:222–231. [PubMed: 34732526]
67. Bea JW, Chen Z, Blew RM et al. MRI based validation of abdominal adipose tissue measurements from DXA in postmenopausal women. J Clin Densitom 2022;25:189–197. [PubMed: 34404568]
68. Kripke DF, Brunner R, Freeman R et al. Sleep Complaints of Postmenopausal Women. Clin J Womens Health 2001;1:244–252. [PubMed: 21461131]
69. Sands-Lincoln M, Loucks EB, Lu B et al. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the Women's Health Initiative. J Womens Health 2013;22:477–86.
70. Chen JC, Brunner RL, Ren H et al. Sleep duration and risk of ischemic stroke in postmenopausal women. Stroke 2008;39:3185–92. [PubMed: 18635832]

71. Kripke DF, Langer RD, Elliott JA, Klauber MR, Rex KM. Mortality related to actigraphic long and short sleep. Sleep Med 2011;12:28–33. [PubMed: 20870457]
72. Chen JC, Espeland MA, Brunner RL et al. Sleep duration, cognitive decline, and dementia risk in older women. Alzheimers Dement 2016;12:21–33. [PubMed: 26086180]
73. Goff DC Jr., Buxton DB, Pearson GD et al. Implementing the National Heart, Lung, and Blood Institute's Strategic Vision in the Division of Cardiovascular Sciences. Circ Res 2019;124:491–497. [PubMed: 31031412]
74. Taliun D, Harris DN, Kessler MD et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature 2021;590:290–299. [PubMed: 33568819]
75. Wojcik GL, Graff M, Nishimura KK et al. Genetic analyses of diverse populations improves discovery for complex traits. Nature 2019;570:514–518. [PubMed: 31217584]
76. Levine ME, Lu AT, Quach A et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging 2018;10:573–591. [PubMed: 29676998]
77. Libby P, Sidlow R, Lin AE et al. Clonal Hematopoiesis: Crossroads of Aging, Cardiovascular Disease, and Cancer. JACC 2019;74:567–577. [PubMed: 31345432]
78. Bick AG, Weinstock JS, Nandakumar SK et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. Nature 2020;586:763–768. [PubMed: 33057201]
79. Honigberg MC, Zekavat SM, Niroula A et al. Premature Menopause, Clonal Hematopoiesis, and Coronary Artery Disease in Postmenopausal Women. Circulation 2021;143:410–423. [PubMed: 33161765]
80. Haring B, Reiner AP, Liu J et al. Healthy Lifestyle and Clonal Hematopoiesis of Indeterminate Potential: Results From the Women's Health Initiative. J Am Heart Assoc 2021;10:e018789. [PubMed: 33619969]
81. Bhattacharya R, Zekavat SM, Haessler J et al. Clonal Hematopoiesis Is Associated With Higher Risk of Stroke. Stroke 2022;53:788–797. [PubMed: 34743536]
82. Yu B, Roberts MB, Raffield LM et al. Supplemental Association of Clonal Hematopoiesis With Incident Heart Failure. JACC 2021;78:42–52. [PubMed: 34210413]
83. Miller KA, Siscovick DS, Sheppard L et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. New Engl J Med 2007;356:447–58. [PubMed: 17267905]
84. Shih RA, Griffin BA, Salkowski N et al. Ambient particulate matter air pollution and venous thromboembolism in the Women's Health Initiative Hormone Therapy trials. Environ Health Perspect 2011;119:326–31. [PubMed: 21036692]
85. Women's Health Initiative Investigators. Pathophysiologic mechanisms underlying the cardiovascular health effects of ambient air pollution in the Women's Health Initiative, 2009–2021. Available at: https://tarheels.live/mechanisms. Accessed April 29, 2022.
86. Chi GC, Hajat A, Bird CE et al. Individual and Neighborhood Socioeconomic Status and the Association between Air Pollution and Cardiovascular Disease. Environ Health Perspect 2016;124:1840–1847. [PubMed: 27138533]
87. Springfield S, Qin F, Hedlin H et al. Resilience and CVD-protective Health Behaviors in Older Women: Examining Racial and Ethnic Differences in a Cross-Sectional Analysis of the Women's Health Initiative. Nutrients 2020;12(17):2107. [PubMed: 32708626]
88. Dubowitz T, Ghosh-Dastidar M, Eibner C et al. The Women's Health Initiative: The food environment, neighborhood socioeconomic status, BMI, and blood pressure. Obesity 2012;20:862–71. [PubMed: 21660076]
89. Tertulien T, Roberts MB, Eaton CB et al. Association between race/ethnicity and income on the likelihood of coronary revascularization among postmenopausal women with acute myocardial infarction: Women's health initiative study. Am Heart J 2022;246:82–92. [PubMed: 34998968]
90. Garcia L, Follis S, Thomson CA et al. Taking action to advance the study of race and ethnicity: the Women's Health Initiative (WHI). Womens Midlife Health 2022;8(1):1. [PubMed: 34983682]
91. Campia U, Moslehi JJ, Amiri-Kordestani L et al. Cardio-Oncology: Vascular and Metabolic Perspectives: A Scientific Statement From the American Heart Association. Circulation 2019;139:e579–e602. [PubMed: 30786722]

92. Paskett ED, Caan BJ, Johnson L et al. The Women's Health Initiative (WHI) Life and Longevity After Cancer (LILAC) Study: Description and Baseline Characteristics of Participants. Cancer Epidemiol Biomarkers Prev 2018;27:125–137. [PubMed: 29378785]

93. Cauley JA, Chlebowski RT, Wactawski-Wende J et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. J Womens Health 2013;22:915–29.

94. Sesso HD, Manson JE, Aragaki AK et al. Effect of cocoa flavanol supplementation for prevention of cardiovascular disease events: The COSMOS randomized clinical trial. Am J Clin Nutr 2022;Mar 16 Online ahead of print. Doi:10.1093/ajcn/nqac055.

95. Sesso HD, Rist PM, Aragaki AK et al. Multivitamins in the prevention of cancer and cardiovascular disease: The COSMOS randomized trial. Am J Clin Nutr 2022;Mar 16 Online ahead of print. Doi:10.1093/ajcn/nqac056.

96. Goff DC Jr., Khan SS, Lloyd-Jones D et al. Bending the Curve in Cardiovascular Disease Mortality: Bethesda + 40 and Beyond. Circulation 2021;143:837–851. [PubMed: 33617315]

97. Sorlie P, Wei GS. Population-based cohort studies: still relevant? JACC 2011;58:2010–3. [PubMed: 22032715]

98. Shadyab AH, Larson JC, Rapp SR et al. Association of global cognitive function with psychological distress and adherence to public health recommendations during the COVID-19 pandemic: The Women's Health Initiative. J Gerontol A Biol Sci Med Sci 2022; Mar 2 Online ahead of print. Doi: 10.1093/gerona/glac053.

99. Zhu K, Wactawski-Wende J, Ochs-Balcom HM et al. The Association of Muscle Mass Measured by D3-Creatine Dilution Method With Dual-Energy X-Ray Absorptiometry and Physical Function in Postmenopausal Women. J Gerontol Biol Sci A Med B 2021;76:1591–1599.

100. Paynter NP, Balasubramanian R, Giulianini F et al. Metabolic Predictors of Incident Coronary Heart Disease in Women. Circulation 2018;137:841–853. [PubMed: 29459470]

101. Balasubramanian R, Paynter NP, Giulianini F et al. Metabolomic profiles associated with all-cause mortality in the Women's Health Initiative. Int J Epidemiol 2019;49:289–300.

102. LaMonte MJ, Gordon JH, Diaz-Moreno P et al. Oral Microbiome is Associated with Incident Hypertension Among Postmenopausal Women. J Am Heart Assoc 2022;11(6):e21930.

103. Stuenkel CA, Manson JE. Women's Health - Traversing Medicine and Public Policy. New Engl J Med 2021;384:2073–2076. [PubMed: 34080809]

HIGHLIGHTS

- The Women's Health Initiative (WHI) included three randomized trials and a parallel observational study addressing pivotal questions pertaining to the cardiovascular health of postmenopausal women.
- Data from wearable technologies, collected biological specimens, and embedded pragmatic trials will enrich the already extensive WHI resources.
- Long-term follow-up of women enrolled in the large WHI cohort provides insights into cardiovascular resiliency and healthy aging.

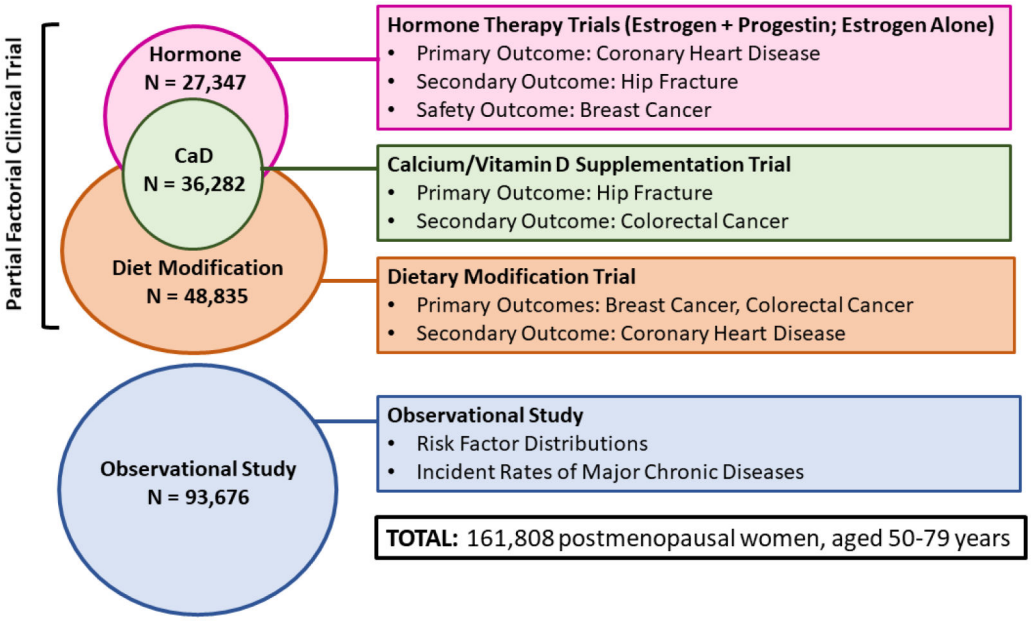


Figure 1. Original design of the WHI.

CaD, calcium and vitamin supplementation. WHI enrolled a total of 161,808 postmenopausal women, aged 50–79 years, at 40 clinical centers across the U.S. The randomized clinical trials component included three distinct interventions for primary prevention of major chronic diseases, whereas the observational study established a prospective cohort to evaluate rates and risk factors for aging-related diseases among older women in the community setting.

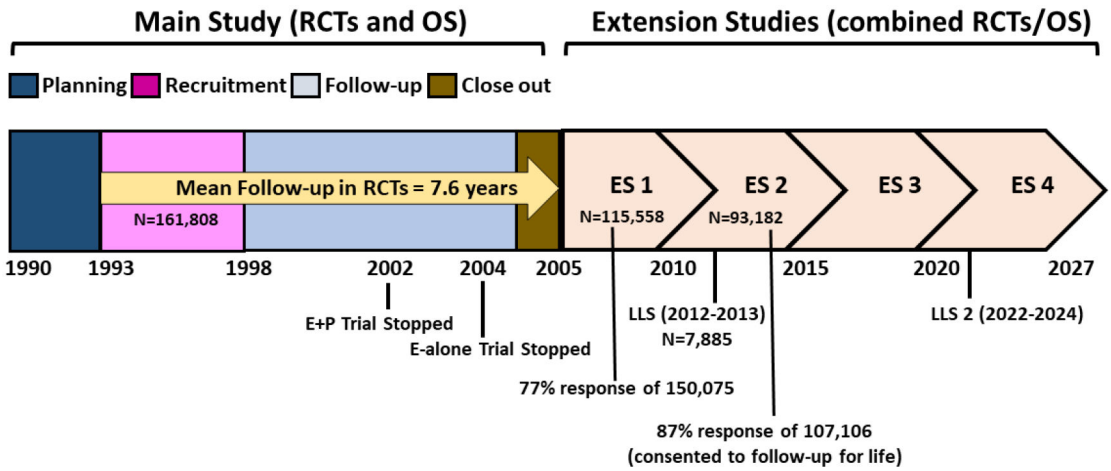


Figure 2. Timeline of the WHI studies.

E, estrogen; E+P, estrogen plus progestin; ES, extension study; LLS, long life study; OS, observational study; RCT, randomized clinical trial. Enrollment of the 161,808 women into the WHI was completed between 1993–1998. The main WHI study ended in 2005, with the hormone therapy trials stopping early in 2002 (E+P) and 2004 (E-alone). The diet modification and calcium/vitamin D trials ended in 2005 after the planned follow-up interval. A series of extension studies have continued longer-term annual follow-up for health outcomes and additional data collection, such as the Long Life Study in-home examination, in consenting women.

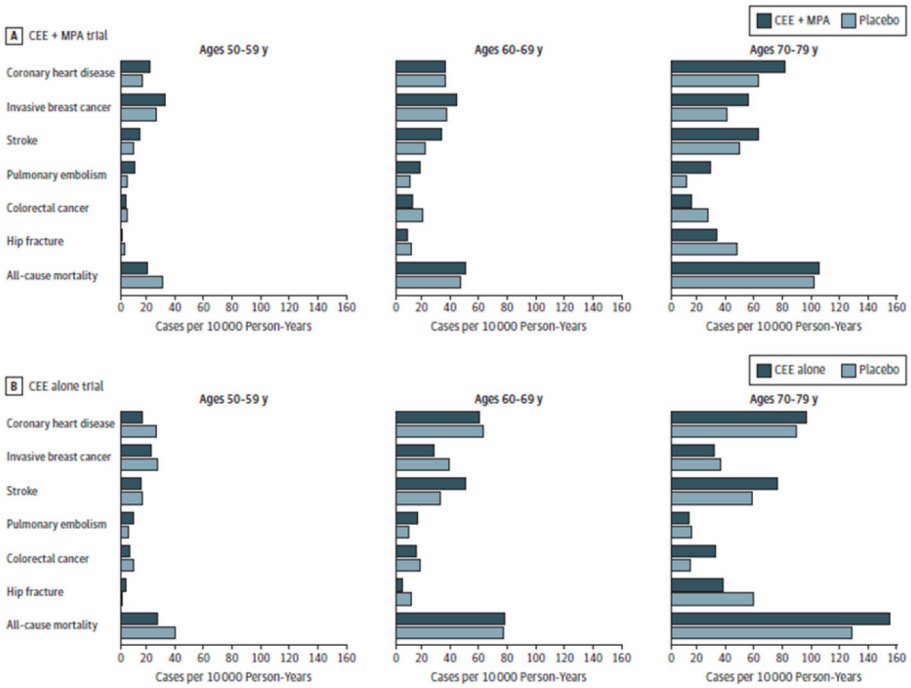


Figure 3. Absolute risks for major outcomes in the WHI hormone trials.

Absolute risks and risk differences for major health outcomes in the Women's Health Initiative estrogen-progestin and estrogen-alone trials, according to age at study entry, intervention phase. Absolute risks calculated as cases per 10,000 person-years for intervention and placebo groups in each trial. *CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate*. Considerably variability in the absolute risks of trial outcomes was evident when stratified on age at randomization for both the CEE-alone and CEE plus MPA hormone trial. *Used with permission from reference* 13.

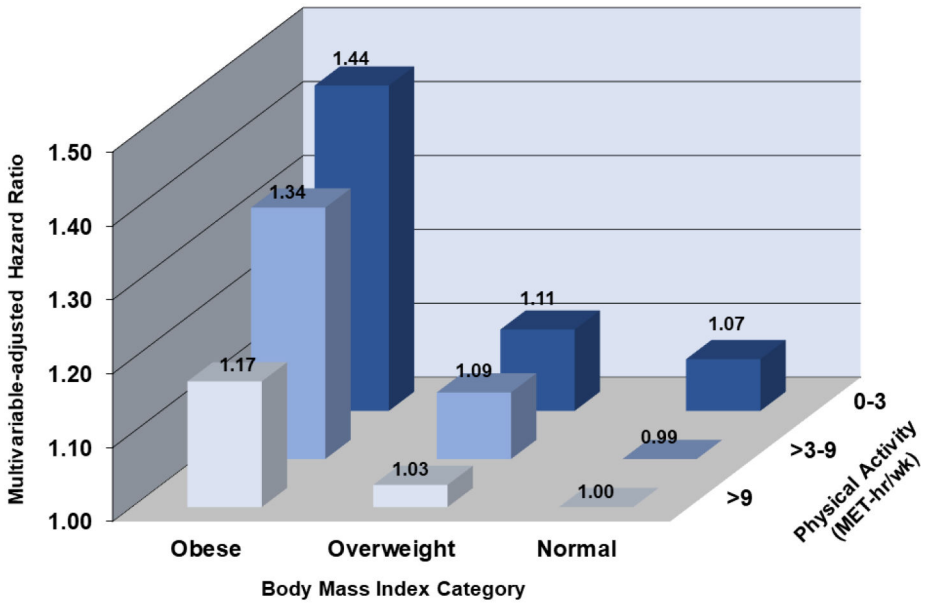


Figure 4. Risk of incident AF according to BMI and physical activity.

Multivariable hazard ratios for incident AF according to BMI and self-reported total recreational physical activity at WHI enrollment. *BMI, body mass index (<25 [normal], 25–29.9 [overweight], ≥30 kg/m^2 [obese]); MET-hr/wk, metabolic equivalent-hours per week (>9 achieves current guideline recommendations).* Both higher BMI and lower self-reported physical activity were associated with increased risk of incident AF, the highest relative risk seen in women who were both clinically obese and physically inactive. *Adapted from reference* 41.

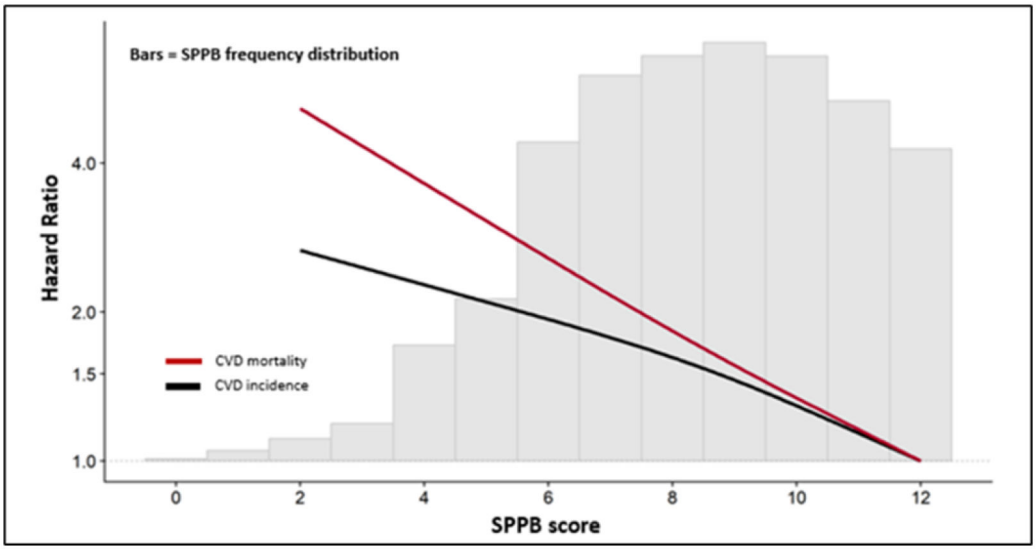


Figure 5. Dose-response association of SPPB physical function score and CVD incidence.

Dose-response for multivariable-adjusted risks of CVD incidence (MI, stroke, death) and mortality according to SPPB score in 5,043 women aged 61–99 years. Linear trend, P<0.001 each. *CVD, cardiovascular disease; SPPB, short physical performance battery*. Even after controlling for several CVD risk predictors, including accelerometer-measured physical activity, there is a strong inverse dose-response in CVD event risks across incremental levels of physical functioning measured using the objective SPPB score among ambulatory older women. Nearly a 4-fold higher relative risk of CVD mortality is evident for women whose SPPB score is 4 compared to those whose score is 12 (referent). *Adapted from reference* 60.

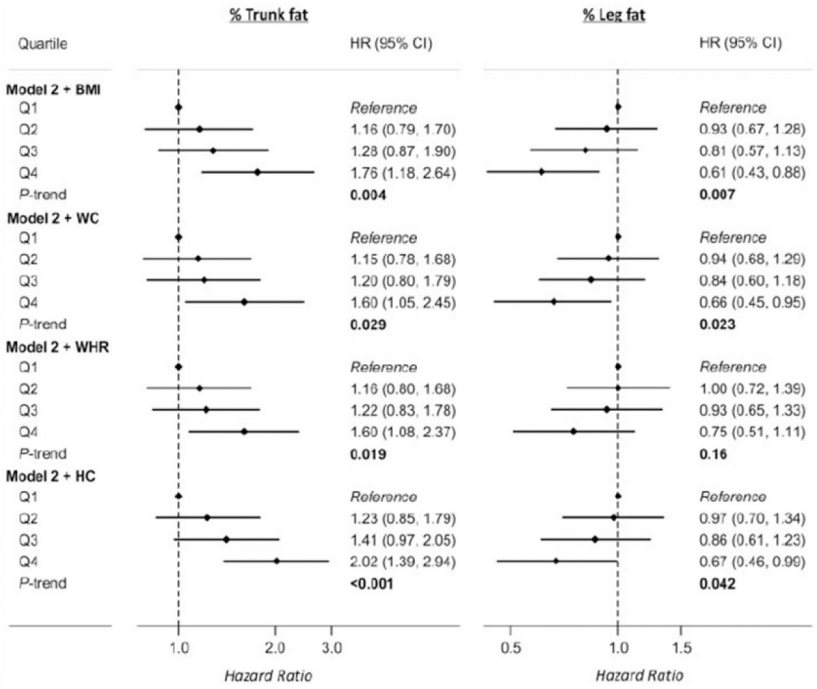
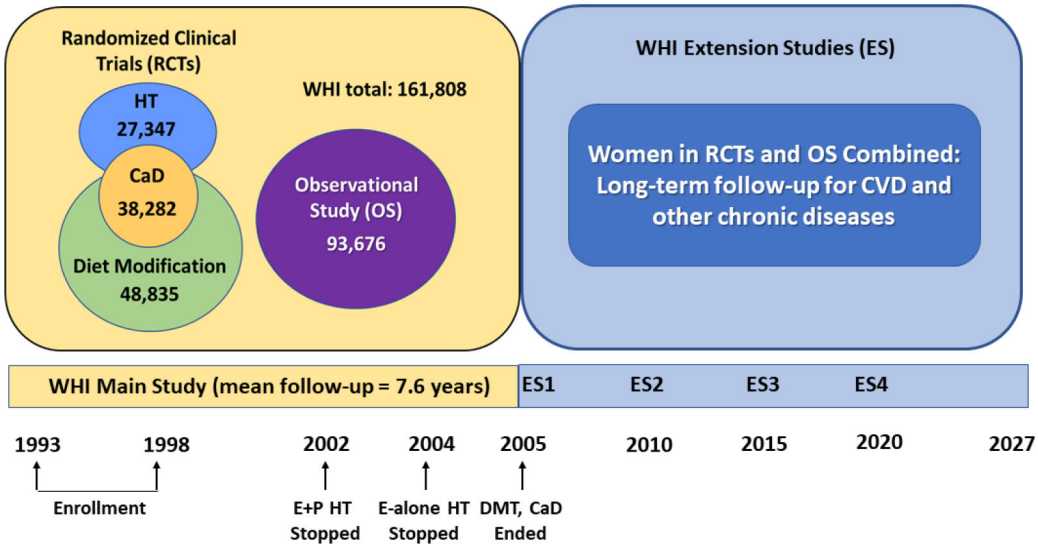


Figure 6. DXA-measured body fat and incident CVD in women with normal BMI.

Multivariable-adjusted associations of trunk or leg fat with incident CVD in women with normal BMI. *CI, confidence interval; BMI, body mass index; HC, hip circumference; HR, hazard ratio; Q, quartile; WC, waist circumference; WHR, waist-to-hip ratio*. When comparing the highest and lowest quartile of DXA measured trunk fat percentage, greater risks of CVD events is evident beyond the influence of commonly used anthropometric measures BMI, waist circumference, hip circumference, and waist-to-hip ratio. Greater DXA measured leg fat percentage appeared to be associated with lower CVD risk except when simultaneously controlling for waist-to-hip ratio. *Used with permission from reference* 65.



Central Illustration. Evolution of the WHI Study Program.

The unique study design of the population-based Women's Health Initiative (WHI) included a hybrid of three randomized clinical prevention trials in a partial factorial design and a large-scale observational cohort, each component targeting the prevention of major chronic diseases among postmenopausal women ages 50–79 years at enrollment. *HT, menopausal hormone therapy; CaD, calcium plus vitamin D trial; E+P, estrogen plus progestin; DMT, diet modification trial; CVD, cardiovascular disease*.

Table 1.

Sample sizes according to age group at enrollment into the Women's Health Initiative.

	Menopausal Hormone Therapy				
Age (years)	**Diet Modification**	**Estrogen + Progestin***	**Estrogen-Alone†**	**Calcium/Vitamin D**	**Observational Study**
50 – 59	18,004 (37)	5,521 (33)	3,312 (31)	13,422 (37)	29,707 (32)
60 – 69	22,713 (47)	7,512 (45)	4,852 (45)	16,520 (46)	41,196 (44)
70 – 79	8,118 (16)	3,575 (22)	2,575 (24)	6,340 (17)	22,773 (24)
Total	48,835	16,608	10,739	36,282	93,676

Data are N (%).

*Women with an intact uterus.

†Women who had hysterectomy.

J Am Coll Cardiol. Author manuscript; available in PMC 2023 July 19.

Table 2.

Cardiovascular, All-Cause Mortality, and Global Index Outcomes in the Women's Health Initiative Estrogen+Progestin and Estrogen-Alone HT Trials, according to Age at Study Entry – Results for the Intervention Phase of the Trials.

Outcome	E strogen+Progestin		Estrogen Alone	
	HR (95% CI)	P Trend*	HR (95% CI)	P Trend*
CHD				
50–59 y	1.34 (0.82, 2.19)	0.81	0.60 (0.35, 1.04)	0.08
60–69 y	1.01 (0.73, 1.39)		0.95 (0.72, 1.24)	
70–79 y	1.31 (0.93, 1.84)		1.09 (0.80, 1.49)	
Myocardial infarction				
50–59 y	1.32 (0.77, 2.25)	0.55	0.55 (0.31, 1.00)	0.02
60–69 y	1.05 (0.74, 1.47)		0.95 (0.69, 1.30)	
70–79 y	1.46 (1.00, 2.15)		1.24 (0.88, 1.75)	
Stroke				
50–59 y	1.51 (0.81, 2.82)	0.50	0.99 (0.53, 1.85)	0.77
60–69 y	1.45 (1.00, 2.11)		1.55 (1.10, 2.16)	
70–79 y	1.22 (0.84, 1.79)		1.29 (0.90, 1.86)	
Pulmonary embolism				
50–59 y	2.05 (0.89, 4.71)	0.61	1.53 (0.63, 3.75)	0.28
60–69 y	1.69 (1.01, 2.85)		1.72 (0.94, 3.14)	
70–79 y	2.54 (1.27, 5.09)		0.85 (0.39, 1.84)	
All-cause mortality				
50–59 y	0.67 (0.43, 1.04)	0.20	0.70 (0.46, 1.09)	0.04
60–69 y	1.07 (0.81, 1.41)		1.01 (0.79, 1.29)	
70–79 y	1.03 (0.78, 1.36)		1.21 (0.95, 1.56)	
Global index				
50–59 y	1.12 (0.89, 1.40)	0.99	0.84 (0.66, 1.07)	0.02
60–69 y	1.13 (0.97, 1.31)		0.99 (0.85, 1.15)	
70–79 y	1.12 (0.95, 1.32)		1.17 (0.99, 1.39)	

*P-value for trend across age groups. HT, hormone therapy. HR, hazard ratio. CI, confidence interval. CHD, coronary heart disease. Global index, a composite of CHD, breast cancer, stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture, and all-cause mortality. *Adapted from data in reference* 13.

Table 3.

Number of observed events and hazard ratios for cardiovascular endpoints according to risk category determined using the 2007 Update to the AHA Guidelines for Cardiovascular Disease Prevention in Women algorithm.

Endpoint	High risk		At risk		Optimal Risk		Not categorized	
	N (%10y)	HR (95% CI)	N (%10y)	HR (95% CI)	N (%10y)	HR (95% CI)	N (% 10y)	HR (95% CI)
MI	1141 (9.1)	10.58 (7.90, 14.16)	2224 (2.5)	2.86 (2.14, 3.81)	47 (0.9)	1.00 (ref)	178 (1.1)	1.21 (0.88, 1.67)
CHD death	631 (4.9)	19.46 (11.46, 33.05)	747 (0.8)	3.20 (1.89, 5.44)	14 (0.3)	1.00 (ref)	52 (0.3)	1.16 (0.64, 2.09)
Hospitalized angina	1902 (15.7)	12.19 (9.59, 15.50)	3011 (3.4)	2.62 (2.06, 3.33)	69 (1.3)	1.00 (ref)	267 (1.6)	1.24 (0.95, 1.62)
MI/CHD death	1568 (12.5)	11.63 (8.97, 15.09)	2749 (3.1)	2.81 (2.17, 3.64)	59 (1.1)	1.00 (ref)	217 (1.3)	1.17 (0.88, 1.56)
MI/CHD death/ angina	3204 (27.2)	11.76 (9.83, 14.06)	5575 (6.3)	2.70 (2.26, 3.23)	125 (2.3)	1.00 (ref)	473 (2.8)	1.21 (0.99, 1.47)
MI/CHD death/ stroke/angina	3868 (33.4)	9.78 (8.44, 11.33)	7642 (8.7)	2.52 (2.17, 2.91)	185 (3.5)	1.00 (ref)	688 (4.1)	1.19 (1.01, 1.40)

HR, hazard ratio. CI, confidence interval. % 10 yr, the 10-year observed probability (%) of an incident endpoint.

MI, myocardial infarction. CHD, coronary heart disease. *Adapted from reference* 22.

Table 4.

Reproductive factors and the risks of heart failure and its subtypes.

Risk Factor	Overall HF HR (95% CI)	HFpEF HR (95% CI)	HFrEF HR (95% CI)
Pregnancy-related Hypertension[36]	1.75 (1.22, 2.50)	2.06 (1.29, 3.27)	1.17 (0.59, 2.30)
Reproductive duration per year[35]	0.99 (0.98, 0.99)	1.00 (0.98, 1.01)	0.99 (0.98, 1.01)
Nulliparity[35]	1.70 (0.95, 3.03)	2.75 (1.16, 6.52)	1.27 (0.39, 4.17)
Infertility[37]	1.16 (1.04, 1.30)	1.27 (1.09, 1.48)	0.97 (0.80, 1.18)
Number of Pregnancies[38]	1.03 (1.00, 1.05)	N/A	N/A
Age at menopause[38]	0.99 (0.98, 0.99)	N/A	N/A
Number of live births[38]	1.23 (1.01, 1.50)	N/A	N/A

HR, hazard ratio. CI, confidence interval. HF, heart failure. HFpEF, heart failure with preserved ejection fraction. HFrEF, heart failure with reduced ejection fraction. N/A, the HF subtype was not evaluated in relation to the specified reproductive factor. *Adapted from references* 35–38.

Table 5.

Attributable risk (%) of incident atrial fibrillation for preventable or treatable risk factors.

Risk Factor	White	Black	Hispanic	Asian/Pacific Islander
Hypertension	24.3	38.2	29.2	18.3
Overweight/obesity *	13.1	18.9	15.7	6.9
Diabetes mellitus	2.6	8.7	3.6	4.9
Current smoking	4.3	5.4	9.1	4.2
Peripheral artery disease	1.6	3.4	1.6	0.2
Heart failure	0.9	2.9	2.0	1.1
Coronary heart disease	3.5	5.5	4.4	1.8
Total	50.3	83.1	65.6	37.4

* BMI ≥25 kg/m^2. Attributable risk (%) calculated as the difference between the AF rate in the entire race and ethnic subgroup minus the AF rate in the race-ethnic group without the risk factor, divided by the AF rate in the entire race-ethnic group, multiplied by 100. *Adapted from reference* 40.

Table 6.

Multivariable-adjusted hazard ratios and 95% confidence intervals for 20% increments in dietary variables that have been calibrated using intake biomarkers to correct self-report assessments for measurement error, from four analyses in WHI cohorts.

Outcome	Analysis 1: Total Energy[51]		Analysis 2: Sodium/ Potassium[48]		Analysis 3: Carbohydrate Density[49]		Analysis 4: Fiber Density Factor[50]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CHD	1.57	(1.19, 2.06)	1.13	(1.04, 1.22)	0.95	(0.92, 0.98)	0.80	(0.72, 0.89)
Stroke	1.36	(1.05, 1.76)	1.05	(0.98, 1.13)	0.96	(0.93, 0.99)	0.91	(0.82, 1.02)
Heart Failure	3.51	(2.12, 5.82)	1.20	(1.01, 1.42)	0.92	(0.88, 0.96)	0.87	(1.01, 1.08)
Total CVD	1.49	(1.23, 1.81)	1.10	(1.03, 1.18)	0.83	(0.73, 0.93)	0.89	(0.83, 0.94)

HR, hazard ratio. CI, confidence interval. CHD, coronary heart disease. CVD, cardiovascular disease *Adapted from references* 48–51. (See original manuscripts for details)

Table 7.

Multivariable-adjusted hazard ratios (95% CI) comparing quartile 4 (highest amount) with quartile 1 (lowest amount) of accelerometer-measured sedentary time, physical activity, and steps/day in women ages 63–99 years enrolled in the *OPACH Study*.

Outcome	Sedentary time	Light PA	MVPA	Steps per day*
All-cause Mortality[57]	1.83 (1.41, 2.37)	0.57 (0.42, 0.76)	0.46 (0.33, 0.65)	0.51 (0.40, 0.66)
CVD Mortality[57]	2.14 (1.32, 3.46)	0.33 (0.18, 0.59)	0.43 (0.23, 0.81)	0.52 (0.33, 0.81)
CHD incidence[55,56]	2.65 (1.34, 5.22)	0.58 (0.34, 0.99)	0.54 (0.30, 0.96)	0.61 (0.37, 0.99)
Total CVD incidence[55,56]	1.69 (1.27, 2.26)	0.78 (0.60, 1.00)	0.69 (0.53, 0.91)	0.74 (0.55, 1.01)
Heart Failure incidence *	2.18 (1.46, 3.27)	0.69 (0.48, 0.98)	0.39 (0.25, 0.59)	0.47 (0.30, 0.76)

CI, confidence interval. CVD, cardiovascular disease. CHD, coronary heart disease. PA, physical activity. *Adapted from references* 54–56.

*Adapted from presentations given at the Annual Meeting of the American Heart Association Epidemiology and Prevention Council by LaCroix AZ et al. (2020) and LaMonte MJ et al. (2019).