

2020 WHI Investigator's Meeting | Poster Abstracts Selected for Webinar Presentation

Date of Presentation	Presenter	Institution	Title
April 27	Tracy E. Crane	University of Arizona	Dietary Patterns and Fatigue after a Cancer Diagnosis: Results for Women's Health Initiative
April 27	Mandana Kamgar, MD, MPH	Department of Medicine, Division of Oncology, Medical College of Wisconsin	Peripheral Neuropathy after Breast Cancer: an Analysis of Data from the Women's Health Initiative Life and Longevity After Cancer Cohort.
May 6	Emily Gower and Jonathan Fix	UNC	Risk Factors for Missed Influenza and Pneumococcal Vaccination amongst Participants in the Women's Health Initiative
May 6	Kathleen Hayden	Wake Health	Clonal Hematopoiesis of Indeterminate Potential and the Risk of Mild Cognitive Impairment or Probable Dementia in the Women's Health Initiative Memory Study
May 6	Iris Leng, MD, PhD	Wake Forest	Is there an association between baseline macro nutrients intake and changes in cognition? Results from the Women's Health Initiative Memory Study (WHIMS)
May 6	Margaret L. Scales	Wake Forest	Women's Health Initiative Sleep Hypoxia Effects on Resilience (WHISPER): Consent and Sleep Assessment Enrollment and Retention Success.
May 6	Chrisandra Shufelt, MD, MS, FACP, NCMP		Bilateral Oophorectomy vs Ovarian Conservation at the Time of Hysterectomy and All-cause Mortality: Women's Health Initiative Observational Study (WHI-OS)
May 7	Anna Batorsky / Nora Franceschini	NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium; TOPMed MESA Multi-Omics Working Group	Differential DNA Methylation associated with kidney function across three ethnic groups.
May 7	Bernhard Haring	University of Wurzburg, Germany	Blood Pressure Variability and Risk of Heart Failure in Postmenopausal Women. Results from the Women's Health Initiative

May 7	Purva Jain	UCSD	Standing time with and without ambulation and mortality over 6 years of follow-up: the WHI OPACH Study
May 7	Marian Neuhouser / Lesley Tinker	FHCRC	Understanding the role of nutrition in health promotion and disease prevention in the Women's Health Initiative (WHI) using biomarkers
May 7	Benjamin T. Schumacher, MPH		Accelerometer-Measured Daily Steps and Incident Fall Risk in Older Women: The OPACH Study
May 7	Sylvia Smoller	Einstein	Diastolic Blood Pressure Levels And Mortality Among Older Women: Results From The Women's Health Initiative Long Life Study

**Conference:** Women's Health Initiative annual meeting

**Due date:** February 25, 2020

**Character limit:** 2300 characters including spaces

**Title:** Dietary Patterns and Fatigue after a Cancer Diagnosis: Results for Women's Health Initiative

**Authors:** Tracy E. Crane<sup>1,2\*</sup>, Lindsay N. Kohler<sup>2,3</sup>, Meghan B. Skiba<sup>3</sup>, Cynthia A. Thomson<sup>2,3</sup>, Suzanna M. Zick<sup>4,5</sup>

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**Purpose of the study:** To explore the relationship between baseline dietary patterns and post-diagnosis fatigue among cancer survivors participating in the observation arm of the Women's Health Initiative (WHI).

**Methods:** Secondary data analysis was conducted within the WHI Observational Study (OS). Self-reported, validated questionnaires assessed dietary intake and post-diagnosis fatigue (vitality, score 0-100, higher score indicating lower fatigue) at baseline and year 3 follow-up, respectively. Dietary pattern scores were calculated for the Healthy Eating Index 2015 (HEI-2015, score 0-100), alternate Mediterranean Diet Score (aMED, score 0-9) and a literature-based, Fatigue Reducing Diet (FRD) score (0-10). Clinically relevant fatigue was considered as a score of  $\leq 45$ . Adjusted linear regression models were used to assess the relationship between dietary quality score at pre-cancer diagnosis (baseline) and post-diagnosis fatigue (year 3).

**Results:** Among 2,632 female cancer survivors the mean age at enrollment was  $65.2 \pm 7.0$  years with 22.5% of women reporting high levels of fatigue ( $\leq 45$ ) post-diagnosis. Women with higher levels of fatigue as compared to women with lower levels of fatigue ( $>45$ ), had a higher BMI and were significantly more likely to have an increased number of co-morbidities, report higher levels of pain and sleep disturbance at baseline (all p-values  $<0.001$ ). No significant differences were observed between fatigue levels and age. Average diet pattern scores at baseline were 1.1 (1.1), 4.1 (1.8), and 67.7 (10.0) for the FRD, aMED, and HEI-2015, respectively. In adjusted regression models assessing each baseline diet pattern scores on fatigue showed that HEI-2015 (B=0.46, 95% CI 0.05, 0.22) and aMED (B=0.55, 95% CI 0.01, 0.90) were associated with lower post-cancer diagnosis levels of fatigue. No significant association was seen between baseline

FRD and post-cancer diagnosis fatigue, likely influenced by the low number of women scoring high for this diet pattern.

**Conclusions:** Overall, greater adherence to HEI or a Mediterranean diet pattern were associated with lower post-cancer diagnosis fatigue. Dietary intake is a modifiable behavior and may hold potential for favorable modulation of fatigue levels in cancer survivors. Future trials testing the efficacy of a dietary intervention for the management of fatigue in cancer survivors are needed.

**Key words:** fatigue, diet quality, diet patterns, cancer

**Word count: 348**

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### **Peripheral Neuropathy after Breast Cancer: an Analysis of Data from the Women's Health Initiative Life and Longevity After Cancer Cohort.**

**Background:** There are over 3.8 million breast cancer survivors in the US, and many experience long-term side effects from chemotherapy. Factors associated with peripheral neuropathy (PN), one troubling side effect, following breast cancer among women are unknown.

**Methods:** We included 2,420 women enrolled in the Women's Health Initiative and diagnosed prospectively with local or regional stage breast cancer and followed in the Life and Longevity After Cancer (LILAC) study. PN was assessed by response to the baseline LILAC questionnaire regarding the presence of "nerve problems, tingling sensations" after treatment. Data were collected on initial course of therapy (surgery, radiation, and chemotherapy) through Medicare linkage or the LILAC staging and treatment form. Chi-square and Wilcoxon rank-sum tests were used for univariate comparison of socio-demographics, clinical and diagnosis characteristics associated with the presence or absence of PN.

**Results:** The sample included 1,913 women (79%) with local and 507 women (21%) with regional stage disease. Initial course of therapy included either surgery alone (21%), surgery and radiation (53%), or surgery and chemotherapy (+/- radiation) (26%). Seventeen percent of women reported experiencing PN days (30%), months (46%) or years (24%) following treatment. Three-quarters (74%) reported ongoing symptoms at the time of the LILAC survey. PN was reported by 33% of chemotherapy recipients, compared to 12% in the surgery alone group, and 11% in the group that received surgery and radiation ( $p < 0.0001$ ). The prevalence of PN was higher among women receiving regimens containing paclitaxel (52%) and docetaxel (39%), compared to those receiving other chemotherapy (17%) ( $p < 0.0001$ ).

**Conclusions:** PN is an important complication of taxane-based chemotherapy. Further analysis will explore the relationship between socio-demographic, clinical and treatment on the development and severity of PN after cancer directed therapy.

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## **Risk Factors for Missed Influenza and Pneumococcal Vaccination amongst Participants in the Women's Health Initiative**

Emily W. Gower and Jonathan Fix

**Background:** Increased susceptibility to infectious diseases at older ages makes vaccination against seasonal influenza and pneumococcal pneumonia vaccination among older adults critical to preventing disease and severe downstream outcomes. Vaccination rates among older adults have been reported to differ substantially by key demographic and health-related factors.

**Objectives:** To explore predictors of vaccine uptake among older women enrolled in the Women's Health Initiative (WHI).

**Methods:** We used self-reported demographic and health-related information from multiple WHI visits. Seasonal influenza and pneumococcal vaccination status were ascertained through a 2011 supplemental questionnaire. Separately for each vaccine, we completed univariate analyses to identify risk factors for missed vaccination. We then performed multivariable analyses, including all variables that were significant at a 0.10 alpha level in the univariate analyses.

**Results:** Among the 71,858 women who responded regarding influenza vaccination in the previous year, 11,280 (15.7%) reported being unvaccinated, while 10,030 (14.5%) of the 69,051 women who responded regarding pneumococcal vaccination in the previous 5 years reported being unvaccinated. For both vaccines, risk of missed vaccination was highest among Blacks (27%) and Hispanics (22% vs. 14% of Whites), those without health insurance (32% versus 15% of Medicare), and individuals living in rural settings (19% versus 16% in urban areas). Higher levels of education (13% among those with a 4 year degree versus 23% of those with less than a high school diploma and increased counts of co-morbid conditions (13% missed vaccination amongst individuals with 4+ comorbidities compared with 21% of those with no comorbid conditions) were associated with lower likelihood of being unvaccinated.

**Interpretation:** Our cohort has higher vaccination rates compared to the national averages for older adults, however, even with high rates of vaccination overall, we identified important characteristics predictive of missed influenza and/or pneumococcal vaccination. These findings support previous research and reinforce the need to enact policy and implement programs that will improve access to, education and awareness about, and provider recommendations regarding these critical disease prevention tools among older adults.

**MS4067/A1406 Title:** Clonal Hematopoiesis of Indeterminate Potential and the Risk of Mild Cognitive Impairment or Probable Dementia in the Women's Health Initiative Memory Study

**Authors:**

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**Background:**

Clonal Hematopoiesis of Indeterminate Potential (CHIP) occurs when hematopoietic stem cells in bone marrow undergo somatic mutations and yield genetically distinct leukocyte subpopulations with increased expression of inflammatory genes in innate immune cells. Genes commonly mutated in CHIP are associated with DNA methylation, inflammation, generation of reactive oxygen species, and DNA damage response. Factors associated with CHIP, including inflammation, cardiovascular disease (CVD), metabolic disorders, and stroke are risks for Alzheimer's disease and other dementias, however the association between CHIP and dementia is unknown. We examined the association between CHIP and the incidence of MCI or probable dementia over 22 years of follow-up in the Women's Health Initiative Memory Study (WHIMS). We also examined these associations by common driver mutations for CHIP.

**Method:**

Women without a baseline (1993-1998) history of stroke, who participated in WHIMS and had baseline blood sample, were followed with annual cognitive assessments, adjudication of MCI or probable dementia, and provided self-report of dementia diagnoses for up to 22 years. CHIP was defined by whole genome sequencing through TOPMed. Proportional hazards models were used to examine survival to onset of cognitive impairment (mild cognitive impairment (MCI), probable dementia, or self-reported dementia).

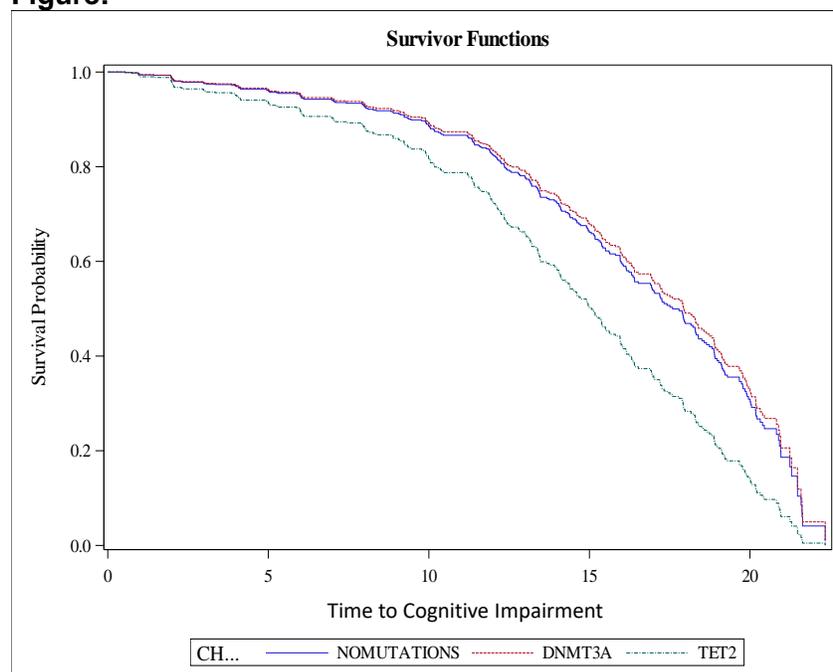
**Result:**

We classified 934 women into two groups, CHIP (11%) and no CHIP (89%). A total of 300 women developed cognitive impairment by Year 22. Survival analyses for time to cognitive impairment was adjusted for baseline age, education, 3MS score, hypertension, diabetes, and BMI. There was no difference in risk of cognitive impairment between the women with and without CHIP ( $p = 0.63$ ). When CHIP was categorized by gene-specific driver mutations, survival free of impairment among women with *DNMT3A* mutations was not different from those without CHIP. Risk for impairment was higher among women with *TET2* (HR 1.75,  $p=0.19$ ). Overall results were not statistically significant, however power was limited by low numbers of women with CHIP (see Figure).

**Conclusion:**

CHIP was not associated with cognitive outcomes overall but when stratified by the primary CHIP mutations (*DNMT3A* or *TET2*), different trends emerged. Future work in WHIMS will explore the cognitive performance over time by different CHIP mutations.

**Figure:**



MS 397

(Is there an association between baseline macro nutrients intake and changes in cognition?  
Results from the Women's Health Initiative Memory Study (WHIMS))

Baseline Composition of Macronutrients is Associated with Risk of Mild Cognitive Impairment or Dementia: Results from the Women's Health Initiative Memory Study (WHIMS)

Xiaoyan Leng, MD, PhD; Martha Payne PhD, MPH, RD; Stephen Rapp PhD; and Mara Vitolins PhD

Background: Total energy intake is determined by the calories derived from macronutrients. It has been shown that a dietary pattern with relatively high caloric intake from carbohydrates and low caloric intake from fat and protein may increase the risk of MCI or dementia in an elderly person. The purpose of this paper is to investigate the relationship between baseline composition of macronutrients and the risk for cognitive decline among the women in the Women's Health Initiative Memory Study (WHIMS).

Methods: A total of 8 components of macro nutrients were considered: carbohydrate (sugar and non-sugar), protein (animal and plant protein), and fat (total saturated fatty acid (SFA), total monounsaturated fatty acids (MFA), total polyunsaturated fatty acids (PFA); and total trans fatty acids (TFA)). Compositional data analysis based on isometric log-ratio transformation (ilr) is applied to construct compositional independent variables to model the macro nutrients simultaneously. Linear mixed effect models were used to model trajectories of Modified Mini Mental State Exam (3MSE) and Cox proportional hazard regressions were used to model time to MCI or Dementia in the WHIMS main clinical trials and the extension phase of the studies. All models adjusted for age, race/ethnicity, education, income, years since menopause, smoking status, physical activity, dietary modification arm, calcium and vitamin D arm, hormone treatment arm, hypertension, diabetes, depressive symptoms, BMI, history of stroke, and history of cardiovascular disease .

Results: A total of 5821 WHIMS women ( $\geq 60$ ) free of MCI and dementia at baseline were followed for an average 7.5 years. Among the 8 components of macronutrients studied, higher sugar intake and lower plant protein intake was associated with lower 3MSE trajectories over time ( $p = 0.0005$ ). Higher sugar intake may increase the risk of MCI or dementia ( $p = 0.0072$ ), however this effect is alleviated when baseline 3MSE was also adjusted ( $p = 0.0761$ ).

Conclusions: Higher sugar intake might have negative impact on cognitive function, while higher plant protein might have positive impact on cognitive function in older women.

## **Women's Health Initiative Sleep Hypoxia Effects on Resilience (WHISPER): Consent and Sleep Assessment Enrollment and Retention Success.**

Margaret L. Scales, Jonna E. Daniel, Leslie Tinker, Susan Redline, Katie L. Stone, David M. Reboussin, Beverly M. Snively, Stephen R. Rapp, Sally A. Shumaker, and Laura D. Baker for the WHISPER study group.

**Background.** The Women's Health Initiative Sleep Hypoxia Effects on Resilience (WHISPER) is a national, prospective observational study that includes over 5,000 women from the WHI Extension Cohort. WHISPER is the first study of its kind: using only telephone and mail-based communication to enroll and follow geographically and racially diverse older women to complete (1) consenting, (2) home-based objective sleep assessments using two wrist-worn devices (WatchPAT for oximetry, ActiGraph for actigraphy), and (3) cognitive assessments. The sleep assessment involved the collection of continuous oximetry data for one night to assess sleep-disordered breathing using measures such as the Apnea Hypopnea Index (AHI) and the Oxygen Desaturation Index (ODI), and actigraphy data to quantify other measures of sleep quality including total duration and fragmentation. The use of well-validated, low cost and low burden methodology in WHI has produced a unique and rich dataset that could have important and innovative implications for science and for clinical care.

**Objectives.** To describe WHISPER's partnerships between the Wake Forest School of Medicine (Coordinating Center; WFSM CC), the WHI CCC, and Sleep Reading Centers at Brigham and Women's Hospital and California Pacific Medical Center that were instrumental for the successful completion of study enrollment and N=5000 sleep assessments within 24 months.

**Results.** Using a data-driven approach, the WHI CCC projected a need for N=13,000 mailings to WHI participants meeting WHISPER eligibility criteria to permit planned enrollment of N=6,000 to obtain N=5000 valid sleep assessments. Consistent with projections, WHISPER successfully enrolled N=5,929 from N=12,903 who were approached by the WHI CCC, representing a 46% enrollment success rate using this strategy.

Of those who consented, N=4,882 have completed a valid sleep assessment so far (final 140 assessments are in the final stages of completion). Mean age [SD] of the WHISPER sample is 80.42[4.90] years (range: 70.6-100.6). WHISPER participants with completed valid sleep assessments are diverse with regard to geographic region (48 states represented), race and ethnicity (~30% from communities of color), and in education (High school/GED or less: 33.7%).

**Implications.** Our enrollment and sleep assessment completion rates demonstrate that data-driven approaches and successful partnerships with experts in the field result in efficient and cost effective recruitment for large ancillary studies such as WHISPER from the WHI Extension cohort. Data generated from such large and representative studies have the potential to provide better tools to inform clinical care and future research focused on characterizing and possibly treating sleep disturbances in older women.

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## **Bilateral Oophorectomy vs Ovarian Conservation at the Time of Hysterectomy and All-cause Mortality: Women's Health Initiative Observational Study (WHI-OS)**

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**Background:** Bilateral salpingo-oophorectomy (BSO) decreases the risk of ovarian and breast cancers, however in premenopausal women, BSO results in abrupt declines in endogenous sex hormones and induces menopause. Studies have indicated that women who undergo BSO at a young age (i.e., before age 45) and who do not use estrogen therapy after BSO have higher risk of cardiovascular disease, cardiovascular death and all-cause mortality. Using the Women's Health Initiative Observational Study (WHI-OS) data, we evaluated the association of BSO vs. ovarian conservation with long-term all-cause mortality among women with hysterectomy. We further determined if the association is modified by age at BSO, hormone therapy (HT) use, or race.

**Methods:** This is a prospective cohort of 26,151 postmenopausal women enrolled in the WHI-OS who had a history of hysterectomy and BSO (n=14,639) or hysterectomy with ovarian conservation (n=11,512). Women with a prior history of cancer were excluded. Multivariable Cox regression models were used to examine the association between BSO and all-cause mortality, comparing BSO with ovarian conservation. Models were adjusted for race/ethnicity, BMI, waist-to-hip ratio, smoking, alcohol intake, total physical activity, and income. Effect modification was assessed separately by age at hysterectomy with BSO or age at hysterectomy with ovarian conservation (<40 yrs, 40-44 yrs, 45-49 yr, 50-54 yr and  $\geq$ 55 yrs), HT use (ever/never), and race (black/white).

**Results:** Average age at enrollment was 63.5 yrs (7.3) for women with BSO and 63.4 yrs (7.3) for women with ovarian conservation. Roughly half had hysterectomy with or without BSO before age 45 yrs. During 18 years of follow up, mortality rates were 19.6 deaths per 1,000 person-yrs for all women with hysterectomy and BSO and 20.3 per 1,000 person-yrs in those with ovarian conservation. Among women younger than 40 years at the time of hysterectomy with or without BSO, BSO was associated with a significantly increased risk of all-cause mortality rate [Adjusted HR 1.14 (95% CI, 1.05-1.24); p-interaction= $\leq$ 0.001]. Among women who never used HT, BSO compared with ovarian conservation was significantly associated with increased risk of all-cause mortality [Adjusted HR 1.13 (95% CI, 1.04-1.22), p-interaction=0.002]; no interaction was observed by race.

**Interpretation:** In these preliminary analyses, women <40 years of age at the time of hysterectomy, BSO compared to ovarian conservation was associated with significantly increased risk of all-cause mortality. Furthermore, women < 40 yrs at the time of BSO who never used HT had significantly increased risk of mortality when compared to women <40 yrs who had hysterectomy with ovarian conservation and never took HT. Planned analyses include evaluating these findings by cause-specific mortality and according to duration of HT use.

**Presenter:**

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Differential DNA Methylation associated with kidney function across three ethnic groups.

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**Background:** Epigenetic alterations such as differential DNA methylation (DNAm) influence gene expression and regulation, and may contribute to chronic kidney disease (CKD). CKD, defined by low estimated glomerular filtration rate (eGFR), is more common among U.S. Hispanics and African Americans.

**Objectives:** The main goal of this study is to identify shared- and ethnic-specific DNAm differences associated with eGFR using epigenome-wide association studies (EWAS).

**Methods:** We use data from up to 5,456 participants (2,887 African Americans, 818 Hispanics, and 1750 European Americans) from the Women's Health Initiative, Jackson Heart Study and Multi-Ethnic Study of Atherosclerosis to examine associations between eGFR and DNAm patterns in whole blood. DNAm beta values obtained using Illumina 450K or EPIC arrays were normalized and adjusted for technical variables. EWAS was performed in ethnic-stratified samples using linear regression or mixed models adjusted for age, smoking, and study-specific variables, principal components, and cell type composition. Summary results were meta-analyzed across ethnicities using fixed effect models.

**Results:** We identified 93 unique CpGs associated with eGFR at FDR of 0.05, including 78 CPGs in trans-ethnic analysis, 23 CPGs among African Americans, 5 CPGs among Hispanics/Latinos and 5 CpGs among European Americans. Fifteen CpGs were unique to one ancestry (11 CpGs for African Americans, 3 CpGs for Hispanics/Latinos, and 1 CpG for European Americans). We replicated the published association at the *ZNF788/ZNF20* locus (cg17944885) and 7 of our novel loci in data from this prior publication. eFORGE analysis of the top 1000 eGFR-associated GpGs for European Americans showed significant enrichment at DNaseI hypersensitivity sites in kidney cells.

**Interpretation:** We identified shared- and ethnic-specific CpGs associated with eGFR that were enriched for genomic regions related to regulatory function in kidney cells. These findings suggest epigenetic mechanisms regulating eGFR across populations.

\*Presenters

## Abstract for WHI meeting (May 2020, Washington DC)

### Blood Pressure Variability and Risk of Heart Failure in Postmenopausal Women. Results from the Women's Health Initiative

**Bernhard Haring**, Rebecca Hunt, Daichi Shimbo, Michael J. LaMonte, Klein Liviu, Matthew Allison, Robert A Wild, Robert Wallace, Aladdin H. Shadyab, Khadijah Breathett, JoAnn E. Manson, Sylvia Wassertheil-Smoller and Charles Eaton

**Objective:** To examine the relationship between systolic and diastolic blood pressure variability (BPV) and incident hospitalized heart failure (HF) and its subtypes of HF with preserved (HFpEF) and reduced (HFrEF) ejection fraction in postmenopausal women.

**Methods:** The analytic study sample consisted of 24,047 postmenopausal women [mean age: 63 years] enrolled in the Women's Health Initiative Hormone Therapy Trials. Blood pressure (BP) readings were taken at baseline and at each annual follow-up visit. BPV was defined as the standard deviation (SD) associated with a participant's mean BP across visits. Hospitalized acute decompensated HF diagnosis was self-reported on annual health surveys. HF diagnosis was adjudicated by trained physician review of medical records through March 01, 2018. HF with an ejection fraction < 45% was considered HFrEF, HF with an ejection fraction  $\geq$  45% was considered HFpEF. Cox regression models with covariate adjustment were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for HF, HFpEF and HFrEF.

**Results:** During a mean (SD) 15.8 (5.7)-year follow-up, 1,679 incident cases of total HF, 430 and 931 cases of HFrEF and HFpEF were identified. Compared with participants in the lowest quartile of systolic BPV, participants in the highest quartile had a higher risk of incident HF (HR 1.80; 95% CI 1.37,2.37; P-trend < 0.0001), higher risk of HFrEF (HR 2.14; 95%CI 1.18, 3.88; P-trend = 0.003), and higher risk of HFpEF (HR 2.13; 95%CI 1.46, 3.12; P-trend < 0.001) after adjusting for age, race/ethnicity, Hormone Therapy trial randomization arm, income, education, BMI, alcohol intake, left ventricular hypertrophy on 12-lead electrocardiogram, physical activity, smoking status, prior hormone therapy use, high cholesterol, history of diabetes, history of CVD, history of cancer, history of atrial fibrillation, mean heart rate across visits (time-dependent variable), mean SBP across visits (time-dependent variable), mean DBP across visits (time-dependent variable) and antihypertensive medication use across visits (time-dependent variable). Similarly, compared with participants in the lowest quartile of diastolic BPV, participants in the highest quartile had a higher risk of incident HF (HR 1.41; 95% CI 1.10,1.82; P-trend = 0.0001), higher risk of HFrEF (HR 2.70; 95%CI: 1.36, 5.33; P-trend = 0.005), and higher risk of HFpEF (HR: 1.44; 95%CI: 1.02, 2.04; P-trend < 0.01).

**Conclusions:** In postmenopausal women greater visit-to-visit systolic and diastolic BPV was associated with higher risk of developing HF, HFpEF and HFrEF. Additional research is needed to understand the influence BPV over shorter time intervals has on HF risk, and how these results might be translated to clinical practice guidelines and public health screening programs.

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**Standing time with and without ambulation and mortality over 6 years of follow-up:  
the WHI OPACH Study**

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**ABSTRACT**

**Background:** Previous studies have shown that self-reported time spent standing is associated with reduced risk of mortality. No previous studies have examined this association using objectively measured standing.

**Methods:** This was a prospective cohort study of 5,878 older (median age=80 years), racially diverse, community-dwelling women in the Objective Physical Activity and Cardiovascular Health Study. This study used a valid machine learning algorithm to categorize up to 7 days of ActiGraph GT3X+ accelerometer data into time spent standing with and without ambulation. (1) Multivariable Cox proportional hazards models estimated mortality risk overall and effect modification by age, BMI, MVPA, sedentary time, physical functioning, and race-ethnicity.

**Results:** There were 691 deaths in 26,649 person-years of follow-up through March 31, 2018. In fully adjusted models, mortality risk was lower among those with more standing (quartile (Q) 4 vs. Q1 HR=0.63; 95% CI=0.49-0.81, p-trend=0.003) and more standing with ambulation (Q4 vs. Q1 HR=0.50; 95% CI=0.35-0.71, p-trend<0.001). Associations of standing with ambulation and mortality were also stronger only among women with above-median sedentary time (HR=0.51; 95% CI=0.38-0.68) compared to women with below-median sedentary time (HR=0.80; 95% CI=0.59-1.07; p-interaction=0.02).

**Conclusions:** Our results suggest that greater time spent standing with or without ambulation is associated with lower risk of mortality among older women. Older women can be encouraged to increase their movement at this end of spectrum. Standing, specifically for older adults, is a safe and feasible behavior that can contribute to a healthy lifestyle and should be promoted as an exercise target.

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**Understanding the role of nutrition in health promotion and disease prevention in the Women's Health Initiative (WHI) using biomarkers**

**Co-Presenters: Marian L Neuhouer and Lesley F Tinker**

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**Title: Understanding the role of nutrition in health promotion and disease prevention in the Women's Health Initiative (WHI) using biomarkers.**

**Authors:** Marian L Neuhouser\*, Lesley F Tinker\*, Johanna W Lampe, Mary Pettinger, Shirley Beresford, Dan Raftery, Nagana Gowda, Dale Schoeller, Diane O'Brien, Ying Huang, Cheng Zheng, and Ross L. Prentice.

\* Co-Presenters

**Background:** Nutritional habits play a critical role in health promotion and chronic disease prevention in postmenopausal women. However, dietary assessment methods relying on self-report are subject to substantial, systematically biased measurement error, yielding inaccurate and unreliable estimates of dietary intake that distorts diet-disease associations.

**Objectives:** Since 2004, we have been conducting a suite of studies within the WHI to identify and use nutritional biomarkers of dietary intake. These biomarkers have been used for nutritional biomarker discovery, statistical methods development and for important diet-disease association studies in the WHI.

**Methods:** Over 1000 WHI participants from both the WHI-Dietary Modification Trial (DMT) through the Nutritional Biomarkers Study (NBS) and the WHI-Observational Study (OS) through the Nutrition and Physical Activity Assessment Study (NPAAS) have completed biomarker protocols including two-week doubly labeled water protocols, 24-hour and spot urine collections, indirect calorimetry, blood draws, anthropometry, and several self-reported assessments of physical activity, diet, and lifestyle habits such as smoking, dietary supplement use and body image. A subset of women from the Seattle WHI clinical center also completed a two-week controlled feeding study. Blood and urine specimens have been assayed for total energy (kcal), protein (computed from nitrogen), vitamins, minerals, fatty acids, carotenoids, metabolomics and stable isotope ratios of carbon and nitrogen. Multivariate regression models have been developed to calibrate self-reported dietary intake based on biomarkers, self-reports, and participant characteristics, and utilized in WHI diet-disease association studies. Statistical methods development is ongoing, as we continue to analyze the concentration biomarkers, metabolomics data and the feeding study data.

**Results:** Since its inception, NBS and NPAAS data have been used in 54 WHI-related publications. Notable results include confirmation that all forms of standard dietary assessment (food frequency questionnaires, 24-hour recalls and multiple-day food records) are subject to systematic measurement error, and that underreporting of diet is common and is influenced by participant characteristics. Because measurement error in self-reported diet is so common, we have used the nutritional biomarkers to calibrate the self-report, leading to several noteworthy findings in the larger WHI cohorts. These include: **1)** a 20% increase in biomarker-calibrated sodium intake was associated with increased risk of hypertension (OR=1.29, 95%CI 1.11-1.51) as well as increased risks for CAPG and PCI (HR=1.17, 95%CI 1.02-1.34) and heart failure (HR=1.36, 95%CI 1.02-1.82). A 20% increase in biomarker-calibrated potassium was associated with decreased risk for CHD (HR=0.85, 95% CI 0.73-0.99), non-fatal MI (HR=0.83, 95%CI 0.72-0.96), coronary death (HR=0.84, 95%CI 0.74-0.98) CABG and PCI (HR=0.85, 95%CI 0.75-0.98), ischemic stroke (HR=0.84, 95%CI 0.73-0.98) and total CVD (HR=0.86, 95%CI 0.75-0.98). **2)** a 20% increase in biomarker-calibrated energy intake was associated with increased risk change n for total CVD (HR=1.49, 95%CI 1.22-1.81), total invasive cancer (HR=1.43, 95%CI 1.17-1.73) and diabetes (HR=4.17, 95%CI 2.68-6.49) while biomarker-calibrated physical activity was inversely associated with these outcomes (16%-40% reduced risk). **3)** a doubling of carotenoid intake was associated with reduced risk of invasive breast cancer ( $\beta$ -carotene only, HR=0.68, 95%CI 0.51-0.91), diabetes, CABG/PCI ( $\alpha$ - and  $\beta$ - carotene - HR ranges= 0.72-0.86), stroke (lutein +zeaxanthin only - HR=0.83 95%CI 0.71-0.98) and total CVD ( $\alpha$ -carotene and lutein+zeaxanthin - HR ranges: 0.83-0.92). A doubling of tocopherol intake was associated with a 15% increased risk of CABG/PCI. **4)** a 20% increase in biomarker-calibrated protein intake was not associated with impaired renal function but was associated with a decreased risk of frailty (HR=0.32, 95%CI 0.23-0.50). Most of these associations were not observed using uncalibrated measures of diet.

**Interpretation:** Nutrition is an important and modifiable risk factor for multiple chronic diseases and conditions in postmenopausal women such as cardiovascular disease, diabetes, frailty and some cancers. This body of work illustrates the importance of using biomarkers to correct for measurement error in self-reported diet. Further information and guidance can be found at [www.whi.org](http://www.whi.org). This suite of WHI ancillary studies – NBS and NPAAS – has made lasting contributions in furthering science to improve postmenopausal women's health.

**Funding:** NIH/NCI R01 CA119171 and WHI contract funds. **WHI Ancillary Studies:** W8, W27, 218, 272, 423, 498, 525

**Accelerometer-Measured Daily Steps and Incident Fall Risk in Older Women: The OPACH Study**

**Authors:** Benjamin T. Schumacher\*, John Bellettiere, Michael J. LaMonte, Chongzhi Di, Andrea Z. LaCroix

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**Background:** Women have experienced a threefold increase in falls since 1970, and, given the aging population, the number of fatal falls are expected to quadruple by 2030. Higher physical activity levels may reduce fall risk, but no study has assessed fall risk in association with steps per day (steps/d), a measure that is ubiquitously captured by smartphones and wearable devices. Further, as steps/d are easily understood by the public, thorough examination of this association may contribute to the development of translatable fall risk reduction guidelines for older adults.

**Objectives:** To 1) quantify the association between accelerometer-measured steps/d and subsequent fall risk and 2) to assess the role physical functioning may have on this association.

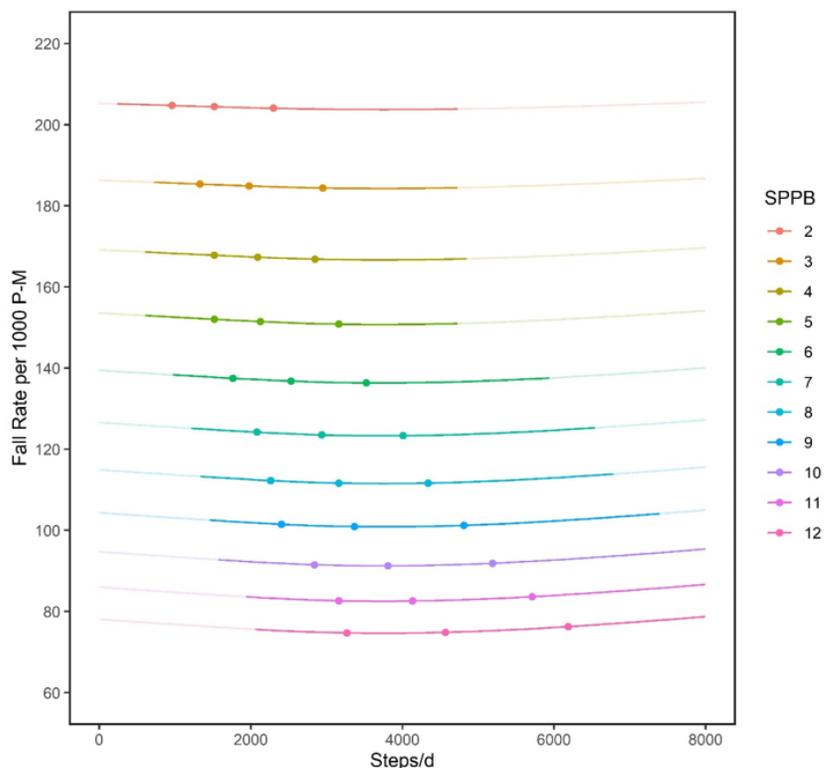
**Methods:** Accelerometer-measured steps/d and 13 months of falls calendars were collected from 5,537 participants of the Objective Physical Activity and Cardiovascular Health Study (OPACH). Parametric negative binomial regressions were specified using quartiles of steps/d regressed on rates of subsequent falls (computed as number of reported falls per 1,000 falls calendar months) adjusting for: demographics alone (Model 1), demographics and fall risk factors (Model 2), and demographics, fall risk factors, and physical functioning as scored by the Short Physical Performance Battery (SPPB) (Model 3). Nonparametric generalized additive models (GAMs), adjusting for model 3 covariates, were specified to allow for nonlinear associations between steps/d and the risk of falling across continuum of steps/d.

**Results:** Crude fall rates per 1,000 calendar months decreased as quartiles of steps/d increased from quartile 1 (Q1) to Q4, respectively: 125.6, 85.4, 76.1, and 72.2. Model 1 quartile regression results showed a similar pattern that had a significant linear trend ( $P$ -trend <0.001). Compared to quartile 1, respective incidence rate ratios (IRRs) and 95% confidence intervals for Q2, Q3, and Q4 were 0.68 (0.54–0.86), 0.63 (0.49–0.80), and 0.60 (0.46–0.78). Additional

adjustment for fall risk factors (Model 2) and physical functioning (Model 3) attenuated the observed IRRs and associations were no longer statistically significant. Model 3 IRRs for Q2, Q3, and Q4, with Q1 as the reference, were as follows: 0.80 (0.60–1.05), 0.84 (0.62–1.13), and 0.88 (0.63–1.24) ( $P$ -trend = 0.45). The predicted probabilities from restricted cubic splines (**Figure**) indicated that within strata of SPPB, variation in women's steps/d was not associated with subsequent falls, however, the strong dose-response association of increased fall risk with lower SPPB scores is notable.

**Interpretation:** The number of steps taken per day was not significantly associated with fall risk in older women after adjustment for physical functioning. While there is no optimum number of steps to recommend for reducing fall risk, more steps have been shown to be protective against other aging-related outcomes such as CVD, diabetes, and mortality. Lastly, targeted fall risk-reduction interventions that focus on improving physical functioning could have huge public health implications and need to be tested.

**Figure.** Dose-response trajectories of associations\* between steps/day and incident falls risk by level of the Short Physical Performance Battery



\*Associations are adjusted for age, race/ethnicity, education, vision, body pain, alcohol use, sleep aid use, body mass index, and number of chronic conditions. SPPB = Short Physical Performance Battery. SPPB scores range from 0 (lowest functioning) – 12 (highest functioning). SPPB 0, 1, and 2 are collapsed due to small sample sizes in these strata. Dots are at the 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentile of the SPPB-specific step distribution. The highlighted portion represents the 5<sup>th</sup> to the 95<sup>th</sup> percentile of each stratum's distribution.

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## Diastolic Blood Pressure Levels And Mortality Among Older Women: Results From The Women's Health Initiative Long Life Study

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**Background:** Systolic blood pressure targets of 120-140 mmHg often do not take into account the impact of concomitantly lowering diastolic blood pressure to achieve these targets, especially in older people.

**Objective:** To examine prospectively the relationship of attained diastolic blood pressure levels to all-cause mortality in older women in the Women's Health Initiative Long Life Study (WHI-LLS).

**Design and Methods:** Participants in the LLS are 7,875 women who are part of the WHI, who were over 70 years old at time of LLS and had an in-person visit conducted in 2012-2013 which consisted of a blood draw, a brief clinical assessment, including blood pressure measurement, and an assessment of functional status. These women also had other data available from the Women's Health Initiative baseline and follow-up questionnaires, including medications. Outcomes are ascertained from annual follow-up questionnaires, and reports from participants and third parties as well as the National Death Index, and are centrally adjudicated by trained physicians.

**Results:** Average age at LLS baseline was 79 years; 52% were 80 years or older. After 5 years follow-up, all-cause mortality occurred in 7.8% of participants. Diastolic blood pressure had a u-shaped relationship to mortality with the nadir at 72 mmHg. Relative risk of death compared to the nadir was 1.44 (95%CI: 1.36-1.52) for a DBP of 50mmHg and 1.82 (95%CI: 1.72-1.93) or a DBP of 100mmHg, controlling for age, race/ethnicity, and systolic blood pressure. There was no such relationship for attained systolic blood pressure, controlling for diastolic pressure.

**Conclusions:** In this cohort of older women, the risk of mortality increased with an attained diastolic blood pressure both lower and higher than the nadir of 73mmHg. These findings suggest that in older persons, when attempting to control systolic hypertension, consideration should be given to potential adverse effects of lowering diastolic pressure below approximately 70 mHg. The balance of benefits between lowering systolic pressure and concomitantly excess lowering of diastolic blood pressure needs further research of that specific question.

